PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Nivolumab (Opdivo) for Non-Small Cell Lung Cancer

June 3, 2016

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1 GUIDANCE IN BRIEF

1.1 Background

The purpose of this review is to evaluate the safety and efficacy of nivolumab (Opdivo) as monotherapy compared to appropriate comparators, on patient outcomes in the treatment of adult patients with advanced or metastatic non-small cell lung cancer (NSCLC) who progressed on or after chemotherapy.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included two randomized, open-label, phase 3 studies comparing nivolumab to Docetaxel in adult patients with non-squamous[5] or squamous[1] NSCLC who have progressed during or after platinum-based doublet chemotherapy. Generally, baseline characteristics were balanced between the two groups in the two studies.

- CheckMate 057 (non-squamous) enrolled patients with a median age of 62 and who had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 (31%) or 1 (69%). The trial eligibility criteria did not allow patients with an ECOG PS >1. Patients enrolled in the study also had stage IV disease (92%) and were mostly current or former smokers (79%) with a minority who had never smoked (20%). Patients were eligible for the trial if brain metastases have been treated and were stable. EGFR mutation positivity was present in 14% of patients, ALK mutation in 4% and KRAS mutation in 11% of patients.
- CheckMate 017 (squamous) enrolled patients with a median age of 63 and who had an ECOG PS of 0 (24%) or 1 (76%). The trial eligibility criteria did not include patients with an ECOG PS >1 or patients with untreated CNS metastases. Patients enrolled in the study also had stage IV cancer (80%), were current or former smokers (92%), and were mostly white (93%). Driver mutation status was not reported in the trial.

Patients were randomised 1:1 in both studies to receive nivolumab at 3 mg/kg of body weight every 2 weeks or Docetaxel at 75 mg/per m^2 of body-surface area every 3 weeks administered intravenously over 60 minutes. While the Health Canada approved dose for Docetaxel is 100mg/m^2, the 75mg/m^2 dose is supported by trials that demonstrated superiority in median overall survival (OS), one year survival and reduced toxicity with the lower dose.[2,3] Treatment beyond initial progression was allowed with nivolumab at the investigator's discretion, whereas treatment with Docetaxel beyond disease progression was not permitted. A total of 24% and 21% of patients continued treatment beyond progression in CheckMate 057 and 017, respectively. Crossover was allowed in both trials only after they were stopped by the data monitoring committee. Less than 1% and <5% of patients from the Docetaxel group in CheckMate 057 and 017, respectively crossing over to receive nivolumab upon disease progression.

Efficacy

The primary outcome in both studies was OS. Both studies were stopped early, having met the pre-specified threshold for superiority by demonstrating superior overall survival with nivolumab versus Docetaxel. In CheckMate 057, median OS was 12.2 months versus 9.4 months with a hazard ratio (HR) of 0.73 (96%CI, 0.59 to 0.89), P=0.002. Results from a follow-up analysis for OS supported the results from the interim analysis with a statistically significant improvement in median OS in favour of nivolumab [with a hazard ratio of 0.72(95%CI, 0.60 to 0.88), P<0.001)]. At 12 months, the survival rate was 51% versus 39% in the nivolumab versus Docetaxel groups,

respectively. In CheckMate 017 median OS was 9.2 months versus 6.0 months with a HR of 0.59 (95%CI, 0.44 to 0.79), P<0.001. Results from an updated OS analysis support the results from the interim analysis, with a statistically significant difference in OS in favour of nivolumab [with a hazard ratio of 0.62(95%CI, 0.48 to 0.81), P=0.0004]. At 12 months, survival rate was 42% versus 24% in the nivolumab versus Docetaxel groups, respectively.

Key secondary outcomes included progression free survival (PFS), objective response rate (ORR), patient-reported outcomes and safety. In CheckMate 057, ORR was higher with nivolumab [19% versus 12%, with an odds ratio of 1.7 (95%CI, 1.1 to 2.6); *P* =0.02], while no difference in PFS was observed between the two groups (median PFS of 2.3 versus 4.2 months in the nivolumab compared to Docetaxel groups, respectively, with a HR of 0.92 (95%CI, 0.77 to 1.11; *P*=0.39). Among patients achieving ORR 52% versus 14% of patients in the nivolumab versus Docetaxel groups, respectively had an ongoing response. Similarly, in CheckMate 017 ORR was higher with nivolumab (20% versus 9%). Among patients achieving ORR 63% versus 33% of patients in the nivolumab versus Docetaxel groups, respectively had an ongoing response. A statistically significant difference in PFS was observed between the two groups (median PFS of 3.5 versus 2.8 months in the nivolumab compared to Docetaxel groups, respectively 0.62 (95%CI, 0.47 to 0.81), *P*<0.001.[4]

Patient-reported outcomes were measured using the lung cancer symptom scale (LCSS) in both studies. The proportion of patients experiencing a clinically meaningful improvement (defined as a change in ≥10 points) in symptoms by week 12 according to the LCSS average symptom burden index (ASBI) was the objective of the patient-reported outcomes assessment for both studies. This outcome was achieved in 17.8% versus 19.7% in CheckMate 057 and 20.0% vs 21.9% in CheckMate 017 among the nivolumab and Docetaxel groups, respectively. Results also suggested that quality of life did not deteriorate over time for both groups in the two studies. Comparisons across groups demonstrated numerical differences in favour of the nivolumab group but no clinically meaningful differences over time was demonstrated in most instances.

Harms

In CheckMate 057, grade 3-4 treatment related adverse events (TRAEs) were less frequent in the nivolumab compared to the Docetaxel group (10% versus 54%). One death was attributed to nivolumab (encephalitis); however, causality was later changed after the database lock and the death was no longer attributed to nivolumab. The association of one death (from encephalitis) in a patient in the nivolumab group was changed from not related to treatment to treatment-related after the database lock.[5]

In CheckMate 017, grade 3-4 TRAEs were less frequent in the nivolumab compared to the Docetaxel group (8% versus 56%).[1] At the time of the interim analysis, no deaths were attributed to nivolumab and three deaths were attributed to Docetaxel (interstitial lung disease, pulmonary hemorrhage, and sepsis).[4]

1.2.2 Additional Evidence

Provincial Advisory Group Input

pCODR received input on nivolumab for the treatment of adult patients with advanced or metastatic non-small cell lung cancer (NSCLC) who progressed on or after chemotherapy. Provincial Advisory Group (PAG) input was obtained from nine of the nine provinces participating in pCODR.

In addition, one supplemental question was identified during the review as relevant to the pCODR review of nivolumab (Opdivo) and is discussed as supporting information:

- Critical appraisal of a manufacturer-submitted indirect treatment comparison (ITC) of the relative efficacy and safety of nivolumab versus pemetrexed among advanced non-squamous cell NSCLC patients.

1.2.3 Interpretation and Guidance

Burden of Illness and Need

Despite advances in therapies over the last few decades, lung cancer remains the most common cause of cancer specific mortality globally and in Canada with a five year survival rate of < 5%.[6-8] The majority of lung cancers are diagnosed at an advanced stage. NSCLC is the most common subtype of lung cancer and typically accounts for 85% of all lung cancers. Non-squamous cell lung cancer comprises about 70% of NSCLC while squamous cell cancer comprises 30%.

The typical treatment approach for those patients with NSCLC who do not have a driver mutation and who have received first line chemotherapy is to receive second line chemotherapy if a good performance status is maintained and patients are willing to receive additional chemotherapy. Single agent therapy with pemetrexed or Docetaxel in this situation is based on a modest improvement in survival as well as quality of life when compared to best supportive care.[9,10] For those patients who receive biomarker driver therapy initially, later lines of systemic therapy typically consist of second line platinum-based chemotherapy and pemetrexed in third line for those who maintain performance status. For patients with non-squamous disease most available agents have limited efficacy or are directed at specific molecular alterations that are rarely found in this histology.[11]

Effectiveness

Based on the results of CheckMate 057 and CheckMate 017 nivolumab demonstrated statistically significant and clinically meaningful superiority in overall survival representing a 27% and 41% reduction in the risk of death in the non-squamous and squamous populations, respectively when compared to Docetaxel. Among patients achieving objective response, clinically meaningful and durable objective response rates of 52% and 63% were also reported in the non-squamous and squamous population, respectively when compared to 14% and 33% in the Docetaxel groups respectively for the two populations.

Based on the results of patient reported outcomes in the two trials, there is evidence for a delay in symptom deterioration and better global HRQoL with the LCSS 3-item index.

Safety

The tolerability profile with nivolumab was also superior to Docetaxel in both studies. Grade 3 and 4 TRAE's were lower in the nivolumab groups for both trials and immune related adverse events were manageable in both trials.

1.3 Conclusions

The pCODR Lung Clinical Guidance Panel concluded that that there is an overall net clinical benefit to nivolumab in the treatment of patients with advanced or metastatic NSCLC following platinum doublet combination chemotherapy. This was based on two open label randomised clinical trials that demonstrated clinically meaningful and superior overall survival, durable objective responses and a tolerability profile with nivolumab that was superior to docetaxel after patients progressed on a platinum containing chemotherapy regimen.

In making this recommendation, the Clinical Guidance Panel considered:

- The improvement in survival with nivolumab compared to docetaxel, as well as the potential for durable responses in both the squamous and non-squamous populations was clinically meaningful and represented a potentially significant therapeutic option for a group of patients for whom therapeutic options are both limited and toxic.
- Based on the results of patient reported outcomes in the two trials, there is evidence for a delay in symptom deterioration and better global HRQoL with the LCSS 3-item index.
- The clinical trials that lead to this conclusion have some potential for bias due to their open label design, as well as some imbalances in the distribution of patients between groups.
- The available data support the use of this agent in patients following treatment with a platinum doublet, irrespective of prior lines of treatment. There are ongoing first line trials to clarify efficacy in treatment naïve patients.
- Based on the current evidence, the Clinical Guidance Panel would support the use nivolumab in patients with adequately treated CNS metastasis as long as patients had neurologically returned to baseline except for treatment related toxicities at least 2 weeks prior to enrollment and had to have been titrated down to a steroid dose equivalent of ≤ 10 mg daily prednisone.
- There remains considerable uncertainty concerning the role of PD-L1 testing and whether there is a cut off level below which patients should not be treated. It is notable that PD-L1 testing will not be required in the current population under review given that benefit with nivolumab was demonstrated regardless of PD-L1 status.
- The indirect treatment comparison of nivolumab to pemetrexed failed to provide a definite answer on the comparative efficacy of these two treatments due to methodological deficiencies.
- The optimal duration of therapy is currently unknown. Based on the results of the two clinical trials, it is not clear as to whether there is clinical benefit in continuing to treat beyond progression. The Clinical Panel agreed that continuation of treatment beyond disease progression should be at the discretion of the treating physician. Whether therapy should be continued until disease progression or be discontinued after 1 year with the option to reinitiate therapy on progression is being assessed in a phase IIIb/IV trial.
- Nivolumab can be safely administered at community centers but immune-related toxicities should be carefully monitored using safety algorithms

2 CLINICAL GUIDANCE

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 (OPDIVO) for the treatment of patients with advanced or metastatic non-small cell lung cancer (NSCLC) who progressed on or after chemotherapy. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance is based on: a systematic review of the literature regarding nivolumab (OPDIVO) for the treatment of patients with advanced or metastatic non-small cell lung cancer who progressed on or after chemotherapy conducted by the Lung Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; 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 on nivolumab and NSCLC and a summary of submitted Provincial Advisory Group Input on nivolumab (OPDIVO) for the treatment of patients with advanced or metastatic non-small cell lung cancer who progressed on or after chemotherapy are provided in Sections 3, 4 and 5 respectively.

2.1 Context for the Clinical Guidance

2.1.1 Introduction

On February 26, 2016 nivolumab was approved by Health Canada for the treatment of patients with advanced or metastatic NSCLC who progressed on or after platinum based chemotherapy.[12]

The recommended dose, as it appears in the Product Monograph, is 3 mg/kg administered intravenously over 60 minutes every 2 weeks. Treatment is continued as long as clinical benefit is observed or until it is no longer tolerated by the patient. Nivolumab is a fully human monoclonal immunoglobulin G4 antibody.[12]

2.1.2 Objectives and Scope of pCODR Review

To evaluate the effectiveness and safety of nivolumab (Opdivo) for the treatment of patients with advanced or metastatic NSCLC who progressed on or after chemotherapy.

See section 6.2.1 for details on PICO question and review protocol.

2.1.3 Highlights of Evidence in the Systematic Review

CheckMate 057 (Non-Squamous NSCLC)

Trial Design:

CheckMate 057 is a randomized open-label, phase 3 study comparing nivolumab to Docetaxel in patients with non-squamous NSCLC that have progressed during or after platinum-based doublet chemotherapy. Patients were randomized in a 1:1 ratio to receive 3 mg of nivolumab per kg of body weight every 2 weeks or 75 mg of Docetaxel per m^2 of body-surface area every 3 weeks dosed intravenously over 60 minutes. Randomization was stratified by prior maintenance treatment (yes versus no) and line of therapy (second line versus third line). Details on key inclusion and exclusion criteria can be found in Section 6 of this report. Treatment with nivolumab

beyond initial disease progression was permitted at the investigator's discretion, whereas treatment with Docetaxel beyond disease progression was not permitted. A total of 24% patients in the nivolumab group (n=71 out of 292) continued treatment after initial progression, as defined by RECIST, version 1.1.[5] The median, range, mean, and standard deviation of the duration of treatment after initial progressive disease was 1.2 months (0-20.5 months) and 2.8 months (±3.9 months).[13]

An interim analysis was performed after the data cut-off date of March 18, 2015.[5] Updated efficacy analysis with additional follow-up was performed after the data cut-off date of July 2, 2015.[5]

Although the study allowed patients to crossover from the Docetaxel to nivolumab group upon disease progression after the trial as part of a nivolumab extension phase,[14,15] less than 1% (0.7%, 2 out of 292) of patients who had received Docetaxel crossed over to receive nivolumab at the time of July 2, 2015 cut-off date.[14,16] Most patients in the trial had an ECOG performance status of 1 (69%), were current or former smokers (79%), had one prior systemic therapy (88%), had stage IV cancer (92%), and were white (92%). A small proportion of patients were epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), and Kirsten rat sarcoma viral oncogene homologue (KRAS) mutation positive (14%, 4%, and 11% respectively). Patients were balanced between the two groups, with the exception of the percentage of males (52% versus 58%).

Results:

Details of the summary of key outcomes are listed in Table 2.1. CheckMate 057 was stopped early because it met the pre-specified threshold for superiority in the primary outcome, demonstrating superior overall survival with nivolumab versus Docetaxel. Overall survival, the primary endpoint of the trial, was prolonged with nivolumab compared with Docetaxel (the median OS was 12.2 months versus 9.4 months; at one year, the survival rate was 51% versus 39%). Results from a follow-up analysis (minimum follow-up of 17.2 months) for OS supported the results from the interim analysis; a statistically significant difference in OS was found in favour of nivolumab [hazard ratio for death: 0.72(95% CI, 0.60 to 0.88)]. The median OS was 12.2 months versus 9.4 months for the nivolumab group compared to the Docetaxel group, respectively. At 18 months, the OS rate for the nivolumab group was 39% compared to 23% for the Docetaxel group.**[5]**

In the interim analysis, the median PFS, a secondary outcome, was 2.3 months in the nivolumab group compared with 4.2 months in the Docetaxel group. The PFS rate at 1 year was 19% in the nivolumab group compared with 8% in the Docetaxel group. The hazard ratio for disease progression and death was not statistically significant [0.92(95%CI, 0.77 to1.11), *P*=0.39].**[5]**

The proportion of patients experiencing a clinically meaningful improvement (defined as a change in ≥10 points) in symptoms by week 12 according to the Lung Cancer Symptom Scale (LCSS) average symptom burden index (ASBI) was the objective of the patient-reported outcome measurement. This outcome was achieved in 17.8% of patients in nivolumab group versus 19.7% of patients in the Docetaxel group. It appears that quality of life was maintained over time for the nivolumab and Docetaxel groups, since the LCSS ASBI change scores appeared stable over time [nivolumab: never equivalent to or exceeded the minimally important difference (MID - a 10 point or greater decrease) from baseline (n at risk=210) to week 66(n at risk=27),Docetaxel: never equivalent or exceeded the MID from baseline (n at risk=212) to week 54 (n at risk=7)].**[17]** While the estimates were not reported, according to the submitter, the hazard rate estimated in the analysis of time to deterioration (TTD) in the LCSS ASBI showed that nivolumab was associated with a delay in deterioration of average symptom burden, with the corresponding descriptive p-value less than 0.05. Similarly, the submitter indicated that the hazard rate estimates from each of the separate TTD analyses of the individual symptoms demonstrated a delay in deterioration of

these symptoms in favour of nivolumab treatment relative to Docetaxel treatment; however, these estimates were not reported. [16]

ORR, another secondary outcome, was higher with nivolumab (19% versus 12%, with an odds ratio of 1.7 (95%CI, 1.1 to 2.6; *P* =0.02). The median duration of response was also in favour of nivolumab (17.2 months versus 5.6 months; p value not reported). The median time to response was fairly similar in both groups (2.1 months versus 2.6 months; p value not reported). Among patients achieving ORR, a total of 52% of patients in the nivolumab group (29 of 56 patients) had an ongoing response compared with 14% of patients in the Docetaxel group (5 of 36 patients) who had an ongoing response.

Grade 3-4 TRAEs were less frequent in the nivolumab group compared with the Docetaxel group (10% versus 54%). The association of one death (from encephalitis) in a patient in the nivolumab group was changed from not related to treatment to treatment-related after the database lock(March 18, 2015). One death was attributed to Docetaxel (febrile neutropenia).[5]

CheckMate 017 (Squamous NSCLC)

Trial Design:

CheckMate 017, is a randomized open-label, phase 3 study comparing nivolumab to Docetaxel in patients with squamous NSCLC that have progressed during or after prior platinum-based doublet chemotherapy. Patients were randomized in a 1:1 ratio to receive 3 mg of nivolumab per kg of body weight every 2 weeks or 75 mg of Docetaxel per m^2 of body-surface area every 3 weeks administered intravenously over 60 minutes. Randomization was stratified by prior use of paclitaxel therapy (yes versus no) and geographical region. [4] Details on key inclusion and exclusion criteria can be found in Section 6 of the report. Treatment with nivolumab beyond initial disease progression was permitted at the investigator's discretion, whereas treatment with Docetaxel beyond disease progression was not permitted. A total of 21% (n=28 out of 135) patients in the nivolumab group continued treatment after initial progression, as defined by RECIST, version 1.1. [4] The median, range, mean, and standard deviation of the duration of treatment after initial progressive disease was 1.3 months (0-16.3 months) and 2.9 months (±4.1 months).

The interim analysis was performed after the data cut-off date of December 15, 2014.[4] Updated efficacy (OS) analysis with additional follow-up was performed after the data cut-off date of August 2015.[1] Updated safety (selected TRAEs) analysis was performed after the data cut-off date of June 2015.[1]

The study allowed patients to crossover from the Docetaxel to nivolumab group upon disease progression after the trial as part of a nivolumab extension phase.[15] Less than 5% (4.4%, 6 out of 137) of patients who had received Docetaxel crossed over to receive nivolumab at the time of data cut-off August 2015.[16]

Most patients included in the trial were males (76%), had an ECOG performance status of 1(76%), had stage IV cancer (80%), were current or former smokers (92%), and were white (93%). All except for one patient received only a single line of cancer therapy prior to study drug (which could have included multiple agents or a switch of agents within the first-line regimen). The proportion of patients that were ALK or KRAS mutation positive was not reported. Patients were generally balanced between the two groups, with the exception of the percentage of males (82% versus 71%) and ECOG performance status 0 (20% versus 27%) in the nivolumab compared to Docetaxel groups, respectively.[4,18]

Results:

Details of the summary of key outcomes are listed in Table 2.1.

CheckMate 017 was stopped early because it met the pre-specified threshold for superiority in the primary outcome, demonstrating superior overall survival with nivolumab versus Docetaxel.[19] Overall survival, which was the primary endpoint, was prolonged with nivolumab compared with Docetaxel (median OS was 9.2 months versus 6.0 months, respectively, and the one-year survival rate was 42% versus 24%). Results from updated OS analysis (minimum follow-up 18 months) supported the results from the interim analysis; a statistically significant difference in OS was found in favour of nivolumab [hazard ratio for death: 0.62 (95% CI, 0.48 to 0.81), P=0.0004. The median OS was 9.2 months for the nivolumab group compared with 6.0 months for the Docetaxel group. At 18 months, the OS rate for the nivolumab group was 28% compared with 13% for the Docetaxel group.[1]

In the interim analysis, the median PFS, a secondary endpoint, was 3.5 months in the nivolumab group compared to 2.8 months in the Docetaxel group. The PFS rate at 1 year was 21% compared with 6%. The hazard ratio for disease progression and death was 0.62 (95%CI, 0.47 to 0.81), *P*<0.001.[4]

The proportion of patients experiencing a clinically meaningful improvement (defined as a change in ≥10 points) in symptoms by week 12 according to the LCSS ASBI was the objective of the patient-reported outcome measurement. This outcome was achieved in 20.0% of patients in nivolumab group versus 21.9% of patients in the Docetaxel group. Quality of life trended towards clinical improvement from week 40 through 54 (where the LCSS ASBI change scores exceeded the MID threshold - a 10 point or greater decrease) for the nivolumab group; however, the number at risk from week 36 and onward was 20 or less for the nivolumab group. The number at risk then dropped to less than 10 patients after week 54. The quality of life data suggested maintenance from baseline to week 18 for the Docetaxel group, after which the number at risk dropped to fewer than 10 patients. Based on results presented in an oral presentation for the TTD analysis of the LCSS ASBI and its components (i.e., fatigue, cough, dyspnea, pain) except for anorexia, no statistically significant difference in time to first-disease-related deterioration was observed. In the TTD analysis of the 3-item index and the TTD analyses of each of its components (symptom distress, interference with activity level, QoL) a statistically significant difference in time to first-disease-related deterioration was found in favour of nivolumab.[20] For EQ-5D analysis, the authors reported a clinical improvement at weeks 24-36, and week 48 [where the EQ-5D Utility Index change scores exceeded the MID (0.08)] in the nivolumab group. The number at risk then dropped to less than 10 patients after week 54. Similar improvements were found in the nivolumab group using the EQ-5D VAS change scores [where the EQ-5D VAS change scores exceeded the MID threshold (7) at week 42 to week 54]. The authors indicated that the EQ-5D Utility Index and VAS scores did not differ from baseline to week 18 in the Docetaxel group; after which the number at risk dropped to fewer than 10 patients.[21]

The ORR, a secondary outcome in the trial, was higher with nivolumab [20% versus 9%, with an odds ratio of 2.6 (95%CI, 1.3 to 5.5), *P*=0.008]. The median duration of response was not reached in the nivolumab group, while the median duration of response was 8.4 months in the Docetaxel group. Time to response was similar in both groups (2.2 months versus 2.1 months; p-value not reported). Among patients achieving ORR, a total of 63% of patients in the nivolumab group (17 of 27 patients) had an ongoing response compared with 33% of patients in the Docetaxel group (4 of 12 patients) who had an ongoing response.

Grade 3-4 TRAEs were less frequent in the nivolumab group compared with the Docetaxel group (7% versus 55%; interim analysis database locked on December 15, 2014).[4] At the time of the interim analysis (database locked on December 15, 2014), no deaths were attributed to nivolumab and three deaths were attributed to Docetaxel (interstitial lung disease, pulmonary hemorrhage,

and sepsis).[4] Updated safety data were similar to interim safety data (8% versus 56%; updated analysis database locked on June 2015).[1]

Overall, the risk of bias appeared moderate for both trials, with the greatest concern being that secondary endpoints (PFS and ORR) were measured by the investigator and not confirmed by an independent review committee. Overall survival was unlikely influenced by subjective bias.

Table 2.1 Summary of Key Outcomes of Pivotal Trials for Nivolumab in NSCLC

	Non-squamous NSCLC CheckMate 057[a,b] [5,13]		Squamous NSCLC CheckMate 017[c,d] [1,4]	
	Nivolumab (n=292)	Docetaxel (n=290)	Nivolumab (n=135)	Docetaxel (n=137)
Interim Analysis				
Median OS, months	12.2(95%CI:9.7-15.0)	9.4(95%CI:8.1-10.7)	9.2(95%CI:7.3-13.3)	6.0(95%CI:5.1-7.3)
Hazard ratio	0.73(96%CI:0.59-0.89), *P*=0.002		0.59(95%CI:0.44-0.79), *P*<0.001	
OS rate, 1 year	51%	39%	42%	24%
No. at risk, at 1 year	146	111	52	30
Median PFS, months	2.3(95%CI:2.2-3.3)	4.2(95%CI:3.5-4.9)	3.5(95%CI:2.1-4.9)	2.8(95%CI:2.1-3.5)
PFS rate, 1 year	19%	8%	21%	6%
No. at risk	46	18	21	6
Objective response, n(%)	56(19%)	36(12%)	27(20%)	12(9%)
Odds Ratio	1.7(95%CI:1.1-2.6), *P* =0.02		2.6(95%CI:1.3-5.5), *P*=0.008	
Follow-up Analysis				
Median OS, months	12.2(95%CI:9.7-15.1)	9.4(95CI%:8.1-10.7)	9.2(95%CI:7.33-12.62)	6.0(95%CI:5.29-7.39)
Hazard ratio	0.72(95%CI:0.60-0.88), *P*<0.001		0.62(95%CI:0.48-0.81), *P*=0.0004	
OS rate,18 months	39%	23%	28%	13%
No. at risk, at 18 months	107	61	37	17
Median PFS, months	NR	NR	3.5(95%CI:2.14-5.06)	2.8(95%CI:2.14-3.52)
Hazard ratio	NR		0.63(95%CI:0.48-0.83), *P*=0.0008	
PFS rate,18 months	NR	NR	17%	3%
No. at risk, at 18 months	NR	NR	16	1

CI = confidence interval; NR = not reported; NSCLC = non-small cell lung cancer; PFS = progression-free survival; OS = overall survival.
[a]Interim analysis database locked on March 18, 2015
[b]Follow-up analysis database locked on July 2, 2015 (Follow-up of minimum 17.2 months)
[c]Interim analysis database locked on December 15, 2014
[d]Follow-up analysis database locked on August 2015 (Follow-up of minimum 18 months)
*Performed with data from all patients who had a response

2.1.4 Comparison with Other Literature

One ongoing trial did not meet the inclusion criteria for the systematic review, however, the review team felt that the trial, an RCT, was relevant in light of the breath of therapies being investigated.

Lung-MAP (SWOG S1400) is a multi-drug, multi-sub-study, randomized phase II/III biomarker-driven squamous cell lung cancer trial that uses genomic profiling to match patients to sub-studies testing investigational treatments.[22,23] The study began in June 2014 and is currently enrolling patients (estimated to enrollment 10 000) with an estimated primary completion date of April 2022.[22,23]

Of note, the master protocol may be amended (as needed) as drugs enter and exit the trial, rather than developing and launching a separate protocol for each new drug.[22,23] Therefore, the current list of comparisons in Table 2.2 may expand as new drugs are introduced.

The primary objective of each Lung-MAP trial sub-study is to determine whether targeted therapy that matched the genomic makeup of a patient's lung cancer tumor is more effective than the current standard therapy. The secondary objective of each trial sub-study is to compare the tumor response rates and the frequency and severity of toxicities experienced by patients on the targeted-therapy versus the standard-of-care.[22,23]

For enrollment in the trial, patients are tested once according to a "master protocol" and randomised into one of multiple trial sub-studies, each testing a different drug. With respect to nivolumab, patients that are non-matched to a sub-study (i.e., screened patients not eligible for any of the biomarker-driven sub-studies) are assigned to either nivolumab monotherapy or nivolumab in combination with ipilimumab.[23]

Table 2.2 Summary of Ongoing Clinical Trial - A Biomarker-Driven Master Protocol for Previously Treated Squamous Cell Lung Cancer (Lung-MAP) [22,23]

Trial Design	Eligibility Criteria	Comparisons	Outcomes
Lung-MAP NCT02154490 Screening and multi-sub-study randomized phase II/III trial Study Start Date: June 2014 Status: currently recruiting participants (Last verified March 8, 2016) Estimated Enrollment: 10 000 Estimated Primary Completion Date: April 2022 (final data collection date for primary outcome measure) Locations: 783 study locations in the USA Study Sponsor: Southwest Oncology Group Collaborator: National Cancer Institute	**Key Eligibility Criteria for Screening** • pathologically proven squamous cell carcinoma lung cancer • eligible to be screened at progression on prior treatment or to be pre-screened prior to progression on current treatment; • adequate tumor tissue available • not have a known EGFR mutation or ALK fusion • ECOG performance status 0-1 **Key Eligibility Criteria for Sub-Study** • patients whose biomarker profiling results indicate the presence of an EGFR mutation or EML4/ALK fusion were not eligible • progressed per RECIST 1.1 following the most recent line of therapy • not have received any prior systemic therapy (systemic chemotherapy, immunotherapy or investigational drug) within 21 days prior to sub-study registration • measurable disease documented by CT or MRI	Durvalumab vs. Docetaxel Taselisib vs. Docetaxel* Palbociclib vs. Docetaxel* FGFR Inhibitor AZD4547 vs. Docetaxel* Erlotinib Hydrochloride vs. Docetaxel Nivolumab/ipilimumab vs. nivolumab	Screen success rate† Investigator-assessed progression-free survival Overall survival Response rate Duration of response Frequency and severity of toxicities

ALK = anaplastic lymphoma kinase; CT = computed tomography; EGFR = epidermal growth factor receptor; EML4 = echinoderm microtubule-associated protein-like 4; /MRI = magnetic resonance imaging; RECIST = Response Evaluation Criteria In Solid Tumors; ECOG = Eastern Cooperative Oncology Group
†defined as the percentage of screened patients that register for a therapeutic sub-study
*Amended and now single arm Phase II trial of the targeted treatments only

2.1.5 Summary of Supplemental Questions

The manufacturer submitted an ITC with the primary objective of assessing the relative efficacy (measured by PFS, OS, and ORR, where available) of nivolumab versus pemetrexed, and an exploratory objective of assessing the relative safety of nivolumab versus pemetrexed among the second and third line non-squamous cell NSCLC population.

The following are reasons for which this critical appraisal was necessary:

- Pemetrexed was identified as a relevant comparison in the protocol,
- No available direct comparison of nivolumab to pemetrexed,
- The manufacturer submitted an economic evaluation which included pemetrexed as a comparator.

Along with the indirect comparison of nivolumab versus pemetrexed in the non-squamous cell NSCLC population, the manufacturer included an ITC of nivolumab versus erlotinib in both the squamous cell and non-squamous cell NSCLC populations. However, this critical appraisal was focused only on the comparison of nivolumab versus pemetrexed in the non-squamous cell NSCLC population, as the CGP considered that erlotinib has limited clinical use in this patient population.

Summary of Critical Appraisal

The validity of the manufacturer's ITC hinges on three important assumptions: (1) homogeneity; (2) transitivity/similarity; and, (3) consistency. There is a high uncertainty with this NMA since the differences in the trial characteristics may have affected the treatment effects observed in each trial, thus violating the similarity assumption and confounding these comparisons. Statistical heterogeneity among the pairwise comparisons in the network was not explored formally with statistical tests. The Methods team acknowledged the authors' rule of thumb (at least four trials) to perform a Cochran's Q-test, but felt that with the Docetaxel versus pemetrexed pairwise direct comparison, a Cochran's Q-test could have been performed.

The Methods team noted a lack of a systematic approach in trial selection and limited details on the literature review approach. For instance, the literature review was performed in two phases, and the databases searched and search terms used were expanded for phase II of the literature review, but not applied in phase I.

The Methods team noted that the sensitivity analyses (based on ITT only and non-squamous cell NSCLC or ITT) did not serve its purpose to validate the base case analysis (based on non-squamous cell NSCLC only), and felt that the results from the sensitivity analysis did not add value.

The Methods team agreed that the Bucher method was appropriate; however, it noted that a Bayesian random effects or fixed effect model could have been applied to the network in addition to the applied Bucher Method. The results from a random effects or fixed effect model may have supported the findings and resulted in the Methods team being more confident in the results.

The Methods team emphasised that although it may appear that nivolumab shows trends of having better efficacy compared pemetrexed, there is much uncertainty in the reported results. Therefore, the reported results should be interpreted with caution.

Details of the summary and critically appraisal of the methods and findings of the manufacturer-submitted ITC can be found in Section 7 Supplemental Questions.

2.1.6 Other Considerations

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

Patient Advocacy Group Input

From a patient perspective, respondents who had experience with nivolumab reported that the side effects of nivolumab are more tolerable than chemotherapy and that the most common side effect was fatigue. Respondents also stated that most of the fatigue appeared to be manageable and did not interfere with daily activity. According to LCC, respondents reported that their quality

of life is higher with nivolumab compared to chemotherapy. LCC stated that all patients interviewed agreed that nivolumab infusions are less stressful (e.g., nivolumab treatment is 1-hour every two weeks whereas chemotherapy ranged from 3–6 hours every three weeks). They also reported nivolumab treatment to be less tiring, having fewer side effects, and less of a burden, while giving them more time, and more quality of life than chemotherapy infusions. Respondents also reported stability of their disease and shrinkages in their tumours with the use of nivolumab.

PAG Input

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

Clinical factors:

- Indication creep into first line setting
- Indication creep into second-line or beyond for patients who have not received platinum-based doublet chemotherapy
- Unknown treatment duration

Economic factors:

- Drug wastage
- Frequency of administration

Please see Section 5 for more details on the PAG input.

2.2 Interpretation and Guidance

Burden of illness and indication for improved treatment:
Lung cancer is the most common cancer both in Canada and globally.[6,24] Non-small cell lung cancer (NSCLC) is the most common subtype and typically account for 85% of all lung cancers. The majority of lung cancers are diagnosed at advanced stage. Despite advances in therapies over the last few decades, it remains the most common cause of cancer specific mortality globally and in Canada with a five year survival rate of < 5%.[6,24,25] The median age at diagnosis and the associated comorbidities mean that many patients with advanced NSCLC are not candidates for treatment due to their inability to tolerate current standard chemotherapy options. Therapy following platinum doublet therapy typically consists of single agents. Most commonly, docetaxel is used for squamous cell cancer, as well as in non-squamous cell cancer for those patients who have previously received pemetrexed therapy as maintenance therapy following a platinum doublet. Docetaxel has shown improved response rates, longer time to progression and improved progression free survival when compared to both older single agent chemotherapy, as well as best supportive care. The difference in terms of median survival (7 months vs. 4.6 months; $p<0.05$) and one year survival (32% vs. 19%; $p<0.05$) were most pronounced and statistically significant with a docetaxel dose of 75mg/m^2 when compared to best supportive care or older single agent regimens respectively. [9,26] Serious hematological toxicity including treatment- related mortality from febrile neutropenia, as well as some non-hematological toxicity was greater with the docetaxel regimen. Toxicity and treatment related deaths were greater with docetaxel at a dose of 100mg/m^2 when compared to a dose of 75mg/m^2.[9,26] In patients with poor performance status or other co-morbidities that preclude the use of chemotherapy, treatment alternatives include targeted agents such as EGFR tyrosine kinase inhibitors or best supportive care.[27-30]

The role of the immune system in surveillance and eradicating malignancy as well as the processes used by tumor cells to evade immunoregulation is being elucidated. NSCLC has previously been considered a non-immunogenic tumour. Improved understanding of immune activation and checkpoint inhibition coupled with promising results from phase I and II studies point to an important role for checkpoint inhibiting therapies in the treatment of NSCLC. The Programmed Death (PD)-1 receptor is an important player in the checkpoint pathways. Nivolumab is a fully humanized monoclonal antibody that blocks the interaction of the PD-1 receptor with its ligands, namely PD-L1 and PD-L2 to restore antitumor immune responses.[31]

Efficacy and Safety of Nivolumab in Squamous Cell Lung Cancer:
Squamous cell lung cancer comprises about 30% of NSCLC. Most available agents have limited efficacy in this population or are directed at specific molecular alterations that are rarely found in this histology.[32] The Checkmate 017 was an open label, randomized, phase 3 trial comparing nivolumab to docetaxel following treatment with a platinum doublet chemotherapy in patients with squamous cell lung cancer. The dose of nivolumab used was 3 mg/kg every 2 weeks intravenously. This dose was selected based on the superior efficacy and comparable toxicity results obtained from the Checkpoint 003 phase 1 trial. Docetaxel was dosed at 75mg/m^2 every 3 weeks intravenously. Two hundred and sixty patients received treatment with a minimum follow up of 11 months.

The primary endpoint of overall survival was significantly longer with nivolumab and represented a 41% reduction in the risk of death when compared to docetaxel (HR: 0.59; p<0.001). Furthermore, responses were durable with >60% of responders demonstrating a sustained response. The median duration of response has not been reached when compared to 8.4 months with docetaxel. Confirmed objective responses were superior with nivolumab (20% vs. 9%; P=0.008). The time to response was comparable to that of docetaxel at just over 2 months. Severe treatment related adverse events were lower with nivolumab when compared to the docetaxel group (>/Gr 3 AE: 7% vs. 55%). There were no deaths attributable to adverse events with nivolumab compared to three treatment related deaths with docetaxel. Furthermore, immune related adverse events related to nivolumab were manageable.

A treatment effect favoring nivolumab was noted across most pre-specified subgroups including those stratified for PD-L1 expression, except for patients over the age of 75 years and those patients treated outside of North American and European centers. This was attributed to small numbers of patients in these subgroups as well as an imbalance in ECOG PS favoring the docetaxel group in the elderly and a hence a definite conclusion that would warrant exclusion of this group of patients cannot be made.

Efficacy and Safety of Nivolumab in Non - Squamous Cell Lung Cancer:
Non-squamous cell lung cancer comprises about 70% of NSCLC. Phase I and pre-clinical data suggested durable antitumor activity of nivolumab in all histological subtypes of NSCLC. The Checkmate 057 was an open label, randomized, phase 3 trial comparing nivolumab to docetaxel following systemic therapy with a platinum doublet in patients with non-squamous cell lung cancer. The dose of nivolumab used was 3 mg/kg every 2 weeks intravenously. This dose was selected based on the superior efficacy and comparable toxicity results obtained from the Checkpoint 003 phase 1 trial. Docetaxel was dosed at 75mg/m^2 every 3 weeks intravenously. Five hundred and fifty five of 582 randomized patients received treatment with a minimum follow up of 17 months.

The primary endpoint of overall survival was significantly longer with nivolumab (12.2 months vs. 9.4 months) and represented a 27% reduction in the risk of death when compared to docetaxel (HR:0.73; P=0.002). One year survival was superior with nivolumab when compared to docetaxel (51% vs. 39%). The responses were durable with >50% of responders demonstrating a sustained

response and a superior 18 month survival rate of 39% (vs. 23% with docetaxel). The median duration of response with nivolumab was superior (17.2 months vs. 5.6 months) to docetaxel. Confirmed objective responses were superior with nivolumab (19% vs. 12%; P=0.02). Time to response was slightly better than docetaxel at just over 2 months. Severe treatment related adverse events were lower with nivolumab when compared to the docetaxel group (≥Gr 3 AE: 10% vs. 54%). There was one death attributable to adverse events with both treatments (encephalitis with nivolumab and febrile neutropenia with docetaxel). Immune related adverse events related to nivolumab were manageable.

A treatment effect favoring nivolumab was noted across most pre-specified subgroups except for those who were receiving third line therapy, those treated in centers outside of North America or Europe, those with CNS metastases, never smokers and patients with EGFR mutation positive tumours. The limited sample size within these subgroups makes interpretation of this data difficult. While several studies have called into question the suitability of PD-L1 expression as a reliable biomarker for response to PD-1 axis inhibitor therapy, PD-L1 expression appeared to be predictive of clinical outcome across 3 different pre-specified cut-off levels with patients with as little as ≥1% PD-L1 expression showing improved overall survival with nivolumab when compared to docetaxel.

An indirect treatment comparison (ITC) of nivolumab compared to pemetrexed was submitted. The results were limited by deficiencies in the systematic approach to trial selection and differences in the trial characteristics that may have impacted treatment effects. The statistical heterogeneity among the pairwise comparisons in the network was not explored formally with statistical tests, limiting the interpretation and applicability of these results.

Concerns about the toxicity profile of this new modality of therapy and the ability of smaller community centers to adequately monitor and manage these toxicities exist. Early results from an ongoing phase IIIb/IV safety trial of nivolumab in the treatment of advanced or metastatic NSCLC following at least one line of systemic therapy suggest that immune-related toxicities will be manageable in community practice settings that use safety algorithms.[33]

Currently available randomized data demonstrates a role for nivolumab in platinum doublet pre-treated patients, irrespective of the number of prior lines of treatment. There is a paucity of randomized data to argue for or against the use of Nivolumab in patients who have progressed following treatment with single agent therapy (due to having discontinued the platinum portion of their therapy). If single agent therapy has been utilized in their last treatment regimen due to poorer performance status, where a platinum double would have been used, there is limited data from a community practice based clinical trial that treatment related adverse events (with Nivolumab) were comparable in patient with ECOG PS 2 and those with ECOG PS 0-1. [82]

Other relevant information

In patients who appeared to be deriving clinical benefit from the therapy but showed evidence of progression per RECIST criteria radiologically, demonstrating pseudoprogression, the Checkmate 017 and 057 clinical trials allowed continuation of therapy for an additional 6 weeks with plan for repeat CT scan. True progression was defined as an additional 10% in tumor burden volume from time of initial PD. A minority of these patients, in the range of 5-7% were identified to have a non-conventional response.

Table 2.3 Assessment of generalizability of evidence for nivolumab in NSCLS				
Domain	**Factor**	**Evidence (CheckMate 017, CheckMate 057, PAG Input, Submitter ITCs)**	**Generalizability Question**	**CGP Assessment of Generalizability**
Population	ECOG performance status	PAG identified that in both trials, patients with ECOG PS of 2 or greater were excluded.	Do trial results apply to patients with ECOG PS of 2 or greater? If so, why?	The phase 1 checkmate 003 clinical trial included a small proportion of patients with ECOG PS 2. Furthermore, the post marketing phase IIIb/IV trial evaluating the safety profile of this drug in mostly community practice settings also included a small proportion of ECOG PS 2 patients. The small numbers in these cohorts of patients preclude a definite conclusion regarding the applicability of these results to patients with ECOG PS 2. Following a more in depth discussion, it is the opinion of the clinical guidance panel that the applicability of these results would be determined by the factors that determine a poorer PS and would depend on the clinical judgement of the health care provider.
	Previously untreated with platinum-based doublet chemotherapy	PAG identified that patients who were not previously treated with platinum-based doublet chemotherapy were excluded.	Do trial results apply to patients who were not previously treated with platinum-based doublet chemotherapy? If so, why?	The available data support the use of this agent in patients following treatment with a platinum doublet. There are ongoing first line trials to clarify efficacy in treatment naïve patients.
	Patients with Brain Metastasis	CheckMate 057 and 017: Patients with brain metastases were eligible if the metastases have been treated and were stable. Proportion of patients with treated/stable brain mets in the	Do trial results apply to patients with brain metastasis	Patients with controlled CNS metastases, defined as those who were adequately treated and had neurologically returned to baseline except for treatment related toxicities at least 2 weeks prior to enrollment, were eligible. Furthermore, they had to have been titrated down to a

Table 2.3 Assessment of generalizability of evidence for nivolumab in NSCLS				
Domain	**Factor**	**Evidence (CheckMate 017, CheckMate 057, PAG Input, Submitter ITCs)**	**Generalizability Question**	**CGP Assessment of Generalizability**
		trial, 6% in CheckMate 017 and 12% in CheckMate 057		steroid dose equivalent of ≤ 10 mg daily prednisone. Patients with carcinomatous meningitis were excluded. Based on the current evidence, the clinical guidance panel would support the use of patients with adequately treated CNS metastasis as long as the aforementioned criteria are met.
Intervention	NA	No factors were identified at this moment.		
Comparator	Relevant comparator	PAG identified that Docetaxel and tyrosine kinase inhibitors are standards of care in second-line treatment of advanced or metastatic lung cancer; and that patients may also be treated with crizotinib, if ALK mutation positive, or pemetrexed, if non-squamous NSCLC. In both studies, nivolumab was compared to Docetaxel. One ITC from the Submitter compared nivolumab to pemetrexed and erlotinib in the non-squamous NSCLC population. One ITC from the Submitter compared nivolumab to erlotinib in the squamous NSCLC population.	Is the comparator used in each trial / ITC reflective of Canadian practice? If so, how?	The Delta trial established that there was no significant difference in PFS between the Docetaxel and erlotinib groups in epidermal growth factor receptor (EGFR)-unselected NSCLC, while Docetaxel was better than erlotinib in EGFR wild type tumors. The TAILOR trial demonstrated the superiority of Docetaxel over erlotinib as second line treatment for patients who were EGFR wild type. Therefore, the comparator used in this trial would be appropriate and is reflective of Canadian practice for this line of therapy.
	Dosage	According to the Docetaxel product monograph, the recommended	Is the dosage used in each trial	Docetaxel has shown improved response rates, longer time to progression and

Table 2.3 Assessment of generalizability of evidence for nivolumab in NSCLS				
Domain	**Factor**	**Evidence (CheckMate 017, CheckMate 057, PAG Input, Submitter ITCs)**	**Generalizability Question**	**CGP Assessment of Generalizability**
		dosage of Docetaxel for injection is 100 mg/m^2 and when used in combination, 75mg/m^2. In both studies, Docetaxel was given 75mg/m^2 every 3 weeks.[34]	reflective of Canadian practice? If so, how?	improved progression free survival when compared to both older single agent chemotherapy regimens as well as best supportive care. The difference in terms of median survival (7 months versus 4.6 months; p<0.05) and one year survival (32% versus 19%; p<0.05) were most pronounced and statistically significant with a dose of Docetaxel at 75mg/m^2 when compared to best supportive care or older single agent regimens respectively. Toxicity and treatment related deaths were greater with Docetaxel at a dose of 100mg/m^2 when compared to a dose of 75mg/m^2
Outcome	NA	No factors were identified at this moment.		
Setting	Study centres	CheckMate 017 was conducted at 92 sites in 21 countries (Argentina, Australia, Austria, Canada, Chile, Czech Republic, France, Germany, Hungary, Ireland, Italy, Mexico, Netherlands, Norway, Peru, Poland, Romania, Russian Federation, Spain, United Kingdom, and United States). CheckMate 057 was conducted in centres in USA/Canada, Europe, South America, Asia, and Australia.	Do the trial results apply to patients from Canadian centres?	Canadian centers participated in the CheckMate 017 and CheckMate 057.

CGP = clinical guidance panel; ECOG PS = Eastern Cooperative Oncology Group performance status; ITC = indirect treatment comparison NA = not applicable; PAG = Provincial Advisory Group.

2.3 Conclusions

The pCODR Lung Clinical Guidance Panel concluded that that there is an overall net clinical benefit to nivolumab in the treatment of patients with advanced or metastatic NSCLC following platinum doublet combination chemotherapy. This was based on two open label randomised clinical trials that demonstrated clinically meaningful and superior overall survival, durable objective responses and a tolerability profile with nivolumab that was superior to docetaxel after patients progressed on a platinum containing chemotherapy regimen.

In making this recommendation, the Clinical Guidance Panel considered:

- The improvement in survival with nivolumab compared to docetaxel, as well as the potential for durable responses in both the squamous and non-squamous populations was clinically meaningful and represented a potentially significant therapeutic option for a group of patients for whom therapeutic options are both limited and toxic.
- Based on the results of patient reported outcomes in the two trials, there is evidence for a delay in symptom deterioration and better global HRQoL with the LCSS 3-item index.
- The clinical trials that lead to this conclusion have some potential for bias due to their open label design, as well as some imbalances in the distribution of patients between groups.
- The available data support the use of this agent in patients following treatment with a platinum doublet, irrespective of prior lines of treatment. There are ongoing first line trials to clarify efficacy in treatment naïve patients.
- Based on the current evidence, the Clinical Guidance Panel would support the use nivolumab in patients with adequately treated CNS metastasis as long as patients had neurologically returned to baseline except for treatment related toxicities at least 2 weeks prior to enrollment and had to have been titrated down to a steroid dose equivalent of ≤ 10 mg daily prednisone.
- There remains considerable uncertainty concerning the role of PD-L1 testing and whether there is a cut off level below which patients should not be treated. It is notable that PD-L1 testing will not be required in the current population under review given that benefit with nivolumab was demonstrated regardless of PD-L1 status.
- The indirect treatment comparison of nivolumab to pemetrexed failed to provide a definite answer on the comparative efficacy of these two treatments due to methodological deficiencies.
- The optimal duration of therapy is currently unknown. Based on the results of the two clinical trials, it is not clear as to whether there is clinical benefit in continuing to treat beyond progression. The Clinical Panel agreed that continuation of treatment beyond disease progression should be at the discretion of the treating physician. Whether therapy should be continued until disease progression or be discontinued after 1 year with the option to reinitiate therapy on progression is being assessed in a phase IIIb/IV trial.
- Nivolumab can be safely administered at community centers but immune-related toxicities should be carefully monitored using safety algorithms

3 BACKGROUND CLINICAL INFORMATION

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

3.1 Description of the Condition

In Canada, 2 out of every 5 people are expected to develop cancer in their lifetime. Furthermore, 1 out of 4 Canadians are expected to die of cancer. Lung cancer is the most common type of cancer in Canada. In 2015, it was estimated that 26,600 new cases of lung cancer would be diagnosed and 20,900 deaths from lung cancer would occur. The incidence and mortality rates for lung cancer were 51.9/100,000 and 40.2/100,000 respectively.[6] Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, comprising 85% of lung cancers. The majority of new cases of lung cancer are expected to arise in people over 60 years of age, with an estimated 16,300 new cases in the age group between 60 years and 79 years and 12,300 deaths.[6,7] The advanced age group and advanced stage population contain a disproportionately greater number of patients with poor performance status, as well as a higher likelihood of significant co-morbidities that impact patients' ability to tolerate conventional chemotherapy regimens.[8]

3.2 Accepted Clinical Practice

Introduction: The two main histological subtypes of NSCLC are squamous cell carcinoma and adenocarcinoma. Squamous cell carcinomas account for 30-40% of all NSCLC, and are more common in men than women.[35] Adenocarcinomas are the most common non-squamous cell carcinoma, and occur more frequently in women than men. The goals of treatment for patients with advanced stage NSCLC are primarily palliative; namely to prolong life while maintaining or improving quality of life. Factors that influence the choice of initial therapy depend on the clinical condition (performance status, co-morbidities, etc.) of the patient, the histological subtype of NSCLC and the presence of driver mutations for which a specific inhibitor may be available.

First-line systemic therapy in tumors without identified driver mutations: In the setting of NSCLC without an eligible driver mutation, platinum based doublet chemotherapy combinations remain the mainstay of first life systemic treatment. Platinum combinations provide palliative benefit with modest a incremental improvement in median survival measured in months over the course of the last few decades.[2,3,36,37] A variety of first-line platinum doublets have shown comparable efficacy in terms of response rates, survival improvement and improvement in quality of life. Third generation cytotoxic agents such as vinorelbine, gemcitabine, pemetrexed, paclitaxel and Docetaxel, when paired with platinum agents, have shown modest incremental gains over older regimens.[37-39] Histological sub classifications of NSCLC have proven to have implications for therapy. The use of pemetrexed combinations appears to preferentially benefit patients with non-squamous histologies. Alternatively, this agent appears to be inferior to gemcitabine in the first line treatment of squamous NSCLC when combined with a platinum agent.[40] This difference has been attributed to differential levels of thymidylate synthase expression.[41,42] The addition of maintenance therapy following first line therapy with pemetrexed or the Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor (EGFR TKI), erlotinib, have demonstrated modest incremental gains in survival.[43,44] Platinum doublets in combination with targeted therapy in the form of bevacizumab have demonstrated an improvement in progression free survival without consistently translating into an overall survival benefit in the first line setting.[11,45] While a meta-analysis identified an improvement in overall survival with this strategy, there remains uncertainty as to whether the identified survival gains are superior to those provided by the addition of maintenance chemotherapy to the first-line

setting.[46,47] Furthermore, the cost of bevacizumab and its associated toxicities has dissuaded its widespread adoption in clinical practice.

Systemic therapy in tumors with identified driver mutations: Activating mutations have been increasingly recognized as key drivers in certain histological subtypes. Epidermal Growth Factor Receptor (EGFR) activating mutations and Echinoderm microtubule associated protein like-4/anaplastic lymphoma kinase (EML4-ALK) mutations have well elucidated roles in the pathogenesis of NSCLC.[48,49] Agents that selectively target these pathways have been shown to induce superior response rates and progression free survival benefits in patients whose cancers harbor these mutations. Several trials and a meta-analysis have confirmed the benefit of EGFR TKI therapy in the first line, second line and maintenance therapy in patients with EGFR mutated tumors without demonstrating an advantage to overall survival - attributed to the extensive cross over in this population.[50] In patients with EML4-ALK mutated tumors, crizotinib — an oral small molecule inhibitor of ALK, MET and ROS1 kinase - has demonstrated superior Objective Response Rates (ORR) and Progression Free Survival (PFS) when compared to standard first line platinum doublet therapy and second line chemotherapy.[51,52] The second generation ALK inhibitor, ceritinib, has demonstrated the ability to overcome resistance to crizotinib. Data from phase I and phase II trials suggests that this drug induces durable responses and meaningful benefit in terms of progression free survival in both crizotinib resistant and crizotinib naive patients.[53-55] The exact sequencing of these agents in relation to chemotherapy is not yet clearly established.[56] Nevertheless, there is increasing clinical consensus that the utilization of these agents upfront provides improved quality of life and delays the necessity of initiating cytotoxic chemotherapy with its inferior tolerability profile in well-selected populations.

Second-line systemic therapy: The typical treatment approach for those patients with NSCLC who do not have a driver mutation and who have received first line chemotherapy is to receive second line chemotherapy if they maintain a good performance status and are willing to receive additional chemotherapy. Single agent therapy with pemetrexed or Docetaxel in this situation is based on a modest improvement in survival as well as quality of life when compared to best supportive care.[9,10] For those patients who receive biomarker driver therapy initially, second line systemic therapy typically consists of second line platinum-based chemotherapy and pemetrexed in third line for those who maintain a performance status. While erlotinib may be used in some patients, in whom it is difficult to determine mutation status due to inaccessibility of tissue for testing, it has less importance in clinical practice compared to Docetaxel and pemetrexed as most patients are now assessed for mutation status before first line is initiated and receive treatments based on their mutation status.

Third-line and subsequent systemic therapy: In this population, antineoplastic systemic therapy is typically dependent on patient performance status as well as patient motivation. In the era of targeted therapies, Gefitinib demonstrated non-inferiority to Docetaxel in the second or subsequent line of treatment.[27] Erlotinib has shown improved survival and symptom control in the second line or later line treatment when compared to best supportive care.[28] More recently, afatinib has been shown to provide greater benefit than erlotinib in the treatment of squamous cell cancers.[29] A trial of a previously unused agent is reasonable in the absence of contraindications and if a suitable clinical trial is unavailable. Supportive care therapy including palliative radiation and early referral to the palliative care team along with psychosocial and spiritual supportive care are considered appropriate throughout the spectrum of treatment and have been shown to improve survival[30,57].

Elderly and poor performance status patients: In patients who are elderly or have poor performance status, chemotherapy can increase the risk of serious adverse events. Phase III trials have suggested a clinically meaningful benefit including improved overall survival with chemotherapy. Hence, the choice of therapy needs to be tailored to the patient's overall condition and performance status. Subset analysis of a trial comparing pemetrexed and Docetaxel in the second line treatment of non-small cell lung cancer identified a similar survival

advantage with acceptable toxicity profile in patients who were elderly compared to those who were younger than 70 years of age.[58] **Patient population and attrition with subsequent lines of therapy:** Retrospective analyses have suggested that there is an attrition in the number of patients who receive systemic therapy as they proceed from first line therapy to second or subsequent lines of therapy. For second line therapy, it is estimated that close to 50% of patients receiving first line therapy will receive second line therapy and approximately 30% of patients receiving first line therapy will proceed to third line regimens.[59,60] These studies nevertheless are limited in terms of their generalizability because they have typically been retrospective and single institution in nature. These and other factors may make the results less relevant to the Canadian context.

3.3 Evidence-Based Considerations for a Funding Population

Immunotherapy: Innate immunity and immunoediting are becoming increasingly recognized as key aspects in the development and persistence of cancer cells in the body. The programmed cell death 1 (PD-1) receptor on activated T cells interacts with ligands, PD-L1 and PD-L2, expressed by tumor cells and infiltrating immune cells. NSCLC tumor cells have been noted to over express PD-L1. Interaction between PD-L1 on tumor cells with PD-1 receptors on T cells inhibits T cell activation and promotes tumor immune escape and avoids elimination by the immune system. Nivolumab is a Programmed Cell Death Receptor 1 (PD-1) antibody. A promising role for nivolumab in the treatment of advanced NSCLC was suggested by activity observed in the phase I Checkpoint 003 clinical trial that demonstrated durable responses in heavily pretreated patients with advanced NSCLC. At dose levels of 3mg/kg, durable responses were seen with survival at 1 year, 2 years and 3 years, which appeared better than with prior systemic therapies across all tumor histologies.[61]

These promising results subsequently resulted in two phase III randomized clinical trials, evaluating a role for immunotherapy in the second line setting for patients with advanced NSCLC that have published their interim analysis data. The Checkmate 017 trial evaluates the efficacy of Nivolumab when compared to Docetaxel chemotherapy in the treatment of patients with squamous cell lung cancer who have previously been treated with a platinum doublet. The Checkmate 057 trial evaluates the efficacy of Nivolumab, when compared to Docetaxel chemotherapy in the treatment of patients with non-squamous cell lung cancer and who have previously been treated with a platinum doublet.[4,5]

The optimal duration of therapy with nivolumab is currently being defined. Most trials have allowed continuation of nivolumab therapy until progression, death or unacceptable toxicity. A median of 6 and 8 doses were administered in the Checkmate 057 and 017 trial respectively. A phase IIIb/IV study is evaluating the safety of administering nivolumab in community centers as well as exploring the option of continuing therapy until progression compared to discontinuing therapy after 1 year of treatment with the option to reinitiate therapy on progression. This trial may provide better insight into the optimal duration of treatment with nivolumab.[33]

Another phase I study has suggested impressive and durable responses with another PD-1 inhibitor, pembrolizumab, in a subset of patients with high levels of PD-L1 expression.[62] In 2015, based on the results of these trials, the FDA granted approval for use of nivolumab and pembrolizumab in the treatment of advanced (metastatic) NSCLC. Trials combining immunotherapies are ongoing, attesting to the increasingly significant role of immunotherapy in lung cancer.[63]

Pseudoprogression:

Tumor pseudoprogression is characterized by an increase of lesion size related to treatment that simulates progressive disease. In the context of Nivolumab and other immune checkpoint inhibitors, 'pseudo-progression' may be due to peritumoral lymphocyte infiltration or delayed immune activity. Limitations of evaluating tumor responses utilizing current RECIST criteria have been documented and an immune-related response criterion has been created.[81] Nevertheless, these criteria are not yet widely utilized in the context of routine clinical management. A small proportion of patients on trials with Nivolumab monotherapy in NSCLC continued to receive treatment beyond progression to account for the phenomenon of "pseudoprogression".

Biomarker: A reliable biomarker has not yet been elucidated for use with nivolumab therapy. While, there is some data from clinical trial evaluation of PD-1 and PD-L1 blocking antibodies in NSCLC to suggest an enhanced benefit in tumors with increased immunohistochemical expression of PD-L1, the data has not been clear or consistent. Diagnostic PD-L1 immunohistochemistry assays vary between pharmaceutical companies and different thresholds for PD-L1 positivity ranging between 1 and 50 percent have been evaluated in clinical trials. Furthermore, there appears to be considerable heterogeneity in PD-L1 expression within tumors and between tumor sites, as well as a potential for this expression to change over time and with other therapies. Moreover, responses to PD-1 inhibition have been identified in small subsets of patients reported to be PD-L1 negative across trials. These factors have called into question the suitability of PD-L1 expression as a reliable biomarker for response to PD-1 axis inhibitor therapy.

3.4 Other Patient Populations in Whom the Drug May Be Used

Currently, nivolumab is approved for use in previously untreated, unresectable or metastatic BRAF V600 wild-type melanoma by Health Canada as well as the FDA. Furthermore, the FDA have approved its use in metastatic renal cell carcinoma and advanced lung cancer. There are several ongoing trials evaluating its role in a variety of other tumor types such as Head and Neck Squamous Cell Cancers, Gastrointestinal and hepatobiliary cancers, sarcomas, brain tumors, as well as hematological malignancies. The wide availability of these trials allows for a broad population to access this and similar agents in the controlled setting of a clinical trial without the need for off label use.

Currently available randomized data demonstrates a role for Nivolumab in platinum doublet pre-treated patients. In 2 phase 1 studies,[83, 84] patients who had received >/ 3 lines of therapy were enrolled. In a more recent publication,[85] approximately 54% of patient had received >/ 3 lines of previous therapies. These therapies included pre-treatment with Tyrosine Kinase inhibitors. Objective and durable responses were identified in the entire cohort. While, there are no phase III data to guide use in this line, there are no data to suggest that it would be inappropriate to use these agents in carefully selected eligible pre-treated populations.

4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

One patient advocacy group, Lung Cancer Canada (LCC), provided input on the nivolumab (Opdivo) submission as treatment for patients with advanced or metastatic non-small cell lung cancer who progressed on or after chemotherapy, and their input is summarized below.

Lung Cancer Canada conducted a national survey of lung cancer patients and caregivers in August 2015. Ninety one (91) patients and seventy-two (72) caregivers completed the survey. All of the patients who completed the survey have or have had lung cancer, and all of the caregivers are currently caring for, or have previously cared for patients with lung cancer. Specifically for this submission, there were six (6) patients and three (3) caregivers who had experience with nivolumab. In addition, LCC conducted an environmental scan of online forums to gather patient and caregiver feedback on nivolumab. The thoughts of five (5) patients and two (2) caregivers from the forums were included. To provide context around patients' experiences with lung cancer and their treatments, LCC included information from fourteen (14) patients with an ALK+ mutation and ten (10) caregivers who were interviewed regarding their thoughts on chemotherapy and patient/caregiver needs from previous focus groups and individual interviews conducted by LCC for first-line crizotinib and second line ceritinib. LCC also provided an updated literature review from previous submissions.

According to LCC, the key symptoms associated with lung cancer include fatigue, loss of appetite, shortness of breath, cough, pain, and blood in sputum. LCC found that loss of appetite, cough, pain, and shortness of breath were found to be significant quality of life predictors.

LCC reported that most Canadians with NSCLC get chemotherapy for first-line treatment and for those patients who do not have EGFR or ALK+ mutations, it can be the only type of treatment. Response rates are approximately 20%-30%, with temporary improvement in symptoms and quality of life in up to two thirds of patients.

LCC reported that chemotherapy is associated with severe side effects including nausea, vomiting, hair loss, fatigue and the risk of fever and infection. In addition, people can also experience dehydration, kidney damage, hearing loss and nerve damage. LCC also reported that patients felt burdened with the inconvenience of multiple blood tests, intravenous treatment and multiple visits (with long wait times) to hospital for chemotherapy. LCC stated that this poses a tremendous burden on patients and their caregivers, who must take time off from work to receive treatment, and then additional time off to manage chemotherapy toxicity, including frequent admission to hospital (>10%).

From a patient perspective, respondents who had experience with nivolumab reported that the side effects of nivolumab are more tolerable than chemotherapy and that the most common side effect was fatigue. Respondents also stated that most of the fatigue appeared to be manageable and did not interfere with daily activity. According to LCC, respondents reported that their quality of life is higher with nivolumab compared to chemotherapy. LCC stated that all patients interviewed agreed that nivolumab infusions are less stressful (e.g., nivolumab treatment is 1-hour every two weeks whereas chemotherapy ranged from 3–6 hours every three weeks). They also reported nivolumab treatment to be less tiring, having fewer side effects, and less of a burden, while giving them more time, and more quality of life than chemotherapy infusions. Respondents also reported stability of their disease and shrinkages in their tumours with the use of nivolumab.

Please see below for a summary of specific input received from Lung Cancer Canada (LCC). 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.

4.1 Condition and Current Therapy Information

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

LCC highlighted that lung cancer is the leading cause of death in Canadian men and women, killing more Canadians than breast, prostate, and colorectal cancer combined.

LCC conducted a literature search and found a US study, which underlined that a high proportion of patients experienced the following lung cancer symptoms: fatigue (100 %), loss of appetite (97 %), shortness of breath (95 %), cough (93 %), pain (92 %), and blood in sputum (63 %). Loss of appetite, cough, pain, and shortness of breath were found to be significant quality of life predictors.

LCC reported on the significant challenges experienced by lung cancer patients. LCC stated that in a survey of Canadian patients with advanced lung cancer, two-thirds of patients feel their symptoms interfere with daily activities, that anxiety or worry is common, and was reported as "frequent" or "constant" in 27% of patients. LCC also reported that depression rates in advanced lung cancer patients vary from 16-50%, and are consistently higher than other cancer sites.

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

LCC indicated that lung cancer patients and their families also carry a heavy burden of stigma related to smoking.

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

LCC reported that most Canadians with advanced lung cancer receive chemotherapy for first-line treatment of NSCLC, and for those patients without the EGFR and ALK+ mutation, it can be the only type of treatment. Response rates are approximately 20%-30%, with temporary improvement in symptoms and quality of life in up to two thirds of patients.

LCC stated that chemotherapy is associated with severe side effects including nausea, vomiting, hair loss, fatigue and the risk of fever and infection. In addition, other side effects may include dehydration, kidney damage, hearing loss and nerve damage. There is an added inconvenience of multiple blood tests, intravenous treatment and multiple visits (with long wait times) to hospital for chemotherapy. LCC indicated that this poses a tremendous burden on patients and their caregivers, who must take time off from work to receive treatment, and then additional time off to manage chemotherapy toxicity, including frequent admission to hospital (>10%).

LCC also stated that the cost of travel is an additional burden, more so in rural communities. Hospital appointments are difficult to obtain and access to chemotherapy suites is limited even in urban areas, and more so in outlying areas. Also, some patients may be deemed unsuitable of chemotherapy, for reasons such as performance status, age or other illnesses. As a result, this further shortens their survival and ability to fight their advanced lung cancer.

According to respondents, the burden of chemotherapy was felt during all stages of the treatment.

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

2. Infusion: The infusions themselves presented challenges beyond travel time and hospital visits. During the infusion, some patients were asked to wear "*ice*" mittens and socks to in an attempt to minimize the effects of chemotherapy on finger and toe nails. This made the experience of chemotherapy even more challenging and as one respondent described it "*painful*".

3. Recovery: Significant recovery time was needed after each chemotherapy infusion. For one respondent, this meant "*two bad weeks and one good week.*" "*Walking and activity were difficult. I was so so sick on infusion chemo. I wasn't functional*," stated another respondent. According to LCC, all of the patients who were on chemotherapy mentioned that chemotherapy took away precious time that they could spend with loved ones due to the side effects. Even when the more acute side effects subsided, their susceptibility to infections due to low white blood counts made spending time with friends and family difficult. The effects were cyclical for many. One respondent stated: "*I had one good week and then the next two were in bed."*

4. Lasting effects of chemotherapy: One respondent that was on chemotherapy felt that you never recover. To this date, 4 years after chemotherapy she still experiences fatigue and has not yet been able to return to work.

5. "Looking sick": LCC reported that not only did respondents feel sick on chemotherapy, they also looked sick. On chemotherapy, they tended to stay at home and some experienced hair loss. Hair loss was a major issue for female respondents. In contrast, LCC reported that nivolumab did not cause hair loss and allowed patients to "*look and feel great*".

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

LCC received input from caregivers that were interviewed for two previous submissions to pCODR-CADTH, for both first line crizotinib and second line ceritinib. There were ten (10) caregivers in total who were interviewed for both these previous submissions. An additional three (3) caregivers were interviewed specifically for their thoughts relating to this submission.

According to LCC, caregivers play an important role in making decisions about treatment and care. The demands of providing transportation, scheduling and making hospital visits, arranging for home nursing and oxygen support, and managing family finances are physically and emotionally devastating for both cancer patients and their caregivers. Persistent psychological distress and role adjustment problems experienced by caregivers have been reported up to a year after patients have completed treatment for cancer, with levels of distress far higher than those found in healthy controls.

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

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

2) Lung cancer is further handicapped by late diagnosis.

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

3) Lung cancer carries a significant economic toll on household finances.

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

4) High symptom burden of lung cancer is difficult to manage for both patients and caregivers.

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

To help illustrate the caregivers' experiences, LCC included the following quotations from respondents:

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

  Survey respondent

- "I was putting together pictures for Dad's funeral and the person at the photolab asked what they are for. I explained and then felt I had to rush to add, "But he didn't smoke", before she could even ask. It was maddening that he was continuing to be judged even after he passed."

  Daughter of victim of lung cancer

4.2 Information about the Drug Being Reviewed

4.2.1 Patient Expectations for and Experiences To Date with nivolumab (Opdivo)

According to LCC, patients and their families expect that nivolumab will help them live longer and keep families together for a longer period of time in comparison to traditional therapies.

Below are key findings and comments that were reported by LCC based on patients' expectations with having access to nivolumab:

- Nivolumab represents hope realized and there are patients that are able to see great shrinkages in their tumour. Anecdotally, LCC reported that one patient was in hospice care but "at the last moment" was able to receive nivolumab. After several cycles, he experienced 96% shrinkage in his tumours.
- Based on literature review, LCC noted that nivolumab is backed up scientifically and is recognized by various approving bodies, and therefore supports patients' expectations that nivolumab could prolong their life over standard chemotherapy treatment.
- One respondent stated: "I was diagnosed in April 2008. By October 2010, I had exhausted all options. Every stage I was told I would not see Christmas".

Below are additional comments reported by respondents who have experience with using nivolumab:

- Nivolumab works! LCC reported that 7 of the respondents whose cancer journey contributed to this submission have had at least a first scan after being on nivolumab. LCC stated that they all now have stable disease. With the exception of one person, all have experienced dramatic shrinkages in their tumours. One respondent stated: "*Jan 2011 was my first infusion of nivolumab. I was patient 96. The spots in my liver have disappeared and the tumours in my lymph node has shrank."*

- Quality of life is higher on nivolumab compared to chemotherapy and one respondent stated: "*My quality of life is better on nivolumab than on chemotherapy and they can't compare."*

- LCC reported that both nivolumab and chemotherapy are in-hospital infusions but are very different. Respondents stated that less is more with nivolumab. All respondents interviewed agreed that nivolumab infusions are less stressful, less tiring, less side effects, and less burdensome, while giving them more time, more feeling well, more effective, more quality of life than chemotherapy infusions. These factors alleviate the burden of lung cancer affecting both patients and caregivers.

- Respondents also noted that nivolumab saves time in-hospital. According to LCC, respondents reported that nivolumab treatment is 1-hour every two weeks whereas chemotherapy ranged from 3 – 6 hours every three weeks. Many respondents needed to also go to the hospital every week to check blood counts when they were on chemotherapy, whereas doctor visits on nivolumab ranged from twice a month to monthly. All patients agreed that the nivolumab regimen is easier to tolerate.

- Patients are functional immediately post-treatment. LCC indicated that this is in direct contrast to chemotherapy. All the patients experienced tiredness, fatigue, nausea immediately after chemotherapy. Some had flu like symptoms. Chemotherapy immediately, "knocked me out", as one respondent stated. Someone needed to accompany them to chemotherapy appointments. However most of the respondents interviewed felt "fine" after an infusion of nivolumab. 2 of the respondents interviewed go to the appointments by themselves.

- Recovery time is faster after a nivolumab infusion versus chemotherapy. One respondent stated: "*3- 4 days after [a chemotherapy] infusion, I was slammed. It hit my very hard emotionally as well. Dragged me down some. Go into chemo knowing that I was going to die."*

- According to LCC, patients reported at least 2 weeks of intense and "nonfunctional" recovery time after chemotherapy. One respondent stated: "On chemo the first week I was so nauseous that for three days could not function. There was many times where I really, really wondered if this was worth it or not". Patients then had "one good week" before having to go back for another treatment. Many interviewed experienced some stress this "good week" knowing that the process would start all over again next week, and they would again be sick. Another respondent stated: "*The third week I started to feel better but would get depressed because I knew the cycle was going to start again"*

- Respondents recognized that immunotherapy carries risks of side effects that differ from traditional chemotherapy or targeted therapy. However, respondents that were interviewed were not concerned as they stressed that they had trust in the experience of their oncology team – their oncology team had developed a protocol to address these potential scenarios.

- LCC reported that respondents felt the side effects on nivolumab were more tolerable than chemotherapy. Most patients reported minimal or no side effects with nivolumab. One respondent stated: "*I feel great*!' When side effects were reported, the most common side effect was fatigue. However most of the fatigue appeared to be manageable and did not interfere with daily activity. Only one patient reported to be bedridden. Other side effects were reported to a lesser degree and included, "tiny bumps" or rash (n=2), thyroid disturbances (n=2), GI disturbances (n=2), loss of appetite or weight loss (n=1), flu like symptoms (n=1).

- Nivolumab allowed normal. One respondent stated:
  "For my husband Opdivo has made the biggest difference. He was not used to doing groceries, cooking and other things related to running the household. Now he can go back to his normal self and not do any of the chores," For others it meant returning to work or hobbies that they enjoyed before cancer. One respondent returned to work full time. Another returned to competitive swimming. And another returned to dog showing. For those that have seen results on nivolumab, it meant returning to a quality of life before

cancer. For caregivers returning to normal meant less time off work and moments to enjoy with their loved one.

- LCC stated that several factors combined have changed the way patients perceive treatment. One respondent was from a small town in northern Alberta. His mother, his grandfather, and two of his aunts have passed from lung cancer. He and his twin brother both have lung cancer. One respondent stated: "*Chemotherapy was just to make life a bit better and maybe add a few weeks of life. By the end I didn't want to go to the hospital anymore. Now [on nivolumab] I look forward to my hospital visits." "It's almost like going to see friends now".*

- LCC interviewed two respondents who have been using nivolumab for two years. One respondent reported the following:

    - The patient is a family doctor in Quebec. She had an active practice, was a non-smoker that lead an active healthy lifestyle. She swam in Masters competitions. She learned of her diagnosis between patients. She has EGFR+ squamous cell carcinoma – with bony lesions. When chemo stopped working she was told to stop working - that she was going to die. Due to her the nature of her cancer, she did not qualify for many clinical trials. Nivolumab was an opportunity that couldn't come soon enough. Today she is alive.

    - Another respondent stated: "Cancer has gone from fatal to chronic. I was dead or dying in October 2010." The patient started nivolumab in Jan 2011. Today he still has tumours but they are stable. As of October 2015, he has off treatment for 2 years and 10 months. Another respondent stated: "*You put up with chemo because you hope that chemo will keep you in alive. People are dying - on nivolumab they are living. What more do you need?"*

LCC reported that one respondent had to wait nine weeks for nivolumab, "*To wait nine weeks can be devastating. If you are changing treatments it means the other is not working. You know lung cancer is not good. There is a 25% chance of living 2 years, 17% chance of living 5 years. Nine weeks is really long in that context*."

Another respondent who is the primary caregiver for her mother stated the following, "Every day waiting for treatment is a stolen day."

LCC recognizes that since nivolumab is a new treatment, there are many questions about side effects. In the scan of the blogs, there seemed to be some uncertainty on how to differentiate between a nivolumab side effect and something else. For example, one patient developed hip pain after infusions and questioned whether it was treatment related. Another developed a cough mid-cycle. LCC, therefore, recommends both healthcare professional and patient education in order to increase awareness of this new class of therapy.

4.3 Additional Information

LCC believes that the chance to recover life is lessened if you do not have a molecular target that has an approved drug. LCC submits that nivolumab gives lung cancer patients an effective weapon. It is an efficacious treatment that fights the cancer, makes patients feel better and thus alleviates the toll of lung cancer on caregivers and patients. It will help to fill a significant unmet need.

5 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The following issues were identified by the Provincial Advisory Group as factors that could affect the feasibility of implementing a funding recommendation for nivolumab NSCLC. 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 (www.cadth.ca/pcodr).

Overall Summary

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

Clinical factors:

- Indication creep into first line setting
- Indication creep into second-line or beyond for patients who have not received platinum-based doublet chemotherapy
- Unknown treatment duration

Economic factors:

- Drug wastage
- Frequency of administration

Please see below for more details.

5.1 Factors Related to Comparators

Docetaxel and tyrosine kinase inhibitors are standard of care in second-line treatment of advanced or metastatic lung cancer. Patients may also be treated with crizotinib, if ALK mutation positive, or pemetrexed, if non-squamous NSCLC.

5.2 Factors Related to Patient Population

There is a large number of patients with lung cancer.

PAG had questions regarding the generalizability of data. Specifically, PAG noted that the trials included patients who were previously treated with platinum-based doublet chemotherapy and who have ECOG performance status of 0 or 1. PAG is seeking information on the use of nivolumab in patients who

1. were not previously treated with platinum-containing chemotherapy (e.g. patients treated first-line with oral target therapies)
2. have ECOG performance status of 2 or greater
3. have failed two or more lines of therapy

If nivolumab is recommended for funding, PAG indicated that the funding criteria for oral targeted therapies would need to be re-evaluated as there would be a shift of current

second and third-line treatments to third and fourth-line. PAG is seeking information on sequencing of the currently available treatments for lung cancer in all lines of therapy.

5.3 Factors Related to Accessibility

PAG identified that the infusion time for nivolumab is similar to Docetaxel. However, nivolumab is administered every 2 weeks, whereas the current standard of care with Docetaxel is administered every 3 weeks, and increased use of chemotherapy chair time may be a challenge in some cancer centres given the large number of patients with lung cancer.

5.4 Factors Related to Dosing

PAG has concerns about the incremental costs due to drug wastage, specifically in centers where vial sharing would be difficult because there could only be one patient in the day. Dose is based on weight and there are two vial sizes available to help address drug wastage. However, any unused portion would be discarded as the stability of reconstituted drug is poor.

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

The unknown treatment duration is also a factor since nivolumab is administered until progression, which ranged from 1 to 48 months in the trial.

5.5 Factors Related to Implementation Costs

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

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

5.6 Other Factors

The high cost and large potential budget impact of nivolumab will be barriers to implementation.

PAG noted that nivolumab is undergoing trials for numerous other tumour sites and is seeking information to drug access, either through manufacturer's access program or clinical trials, for these other indications.

6 SYSTEMATIC REVIEW

6.1 Objective

To evaluate the effectiveness and safety of nivolumab (OPDIVO) for the treatment of patients with advanced or metastatic non-small cell lung cancer (NSCLC) who progressed on or after chemotherapy.

A supplemental question relevant to the pCODR review and the Provincial Advisory Group was identified while developing the review protocol and is outlined in Section 7.

- Critical appraisal of a manufacturer-submitted indirect treatment comparison (ITC) of the relative efficacy and safety of nivolumab versus pemetrexed among advanced non-squamous cell NSCLC patients.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

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

Table 6.1 Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*†	Outcomes
Published or unpublished RCTs	Patients with advanced or metastatic NSCLC who progressed on or after chemotherapy Subgroups: • Histologic type (squamous versus non-squamous) • EGFR mutation status • ALK mutation status • Age • Sex • Smoking status • ECOG PS	Nivolumab monotherapy at the dose of 3 mg/kg administered intravenously over 60 minutes every 2 weeks	Docetaxel Pemetrexed Erlotinib	• Overall survival • Progression-free survival • **Quality of life** • Response rate (CR, PR) • Duration of response • Time to response • Serious adverse events • Adverse events ▪ Immune-related • Withdrawal due to adverse events

ALK = anaplastic lymphoma kinase; CR = complete response; ECOG PS = Eastern Cooperative Oncology Group performance survival; EGFR = epidermal growth factor receptor; NSCLC = non-small cell lung cancer; PR = partial response; RCT = randomized controlled trial.
*Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)
†With a main focus on Docetaxel and pemetrexed, given that erlotinib is relevant to a limited number of NSCLC patients

6.2.2 Literature Search Methods

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

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946 - Nov 5, 2015) with in-process records & daily updates via Ovid; Embase (1974-2015 November 05) via Ovid; EBM Reviews - Cochrane Central Register of Controlled Trials (September 2015) 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 nivolumab, Opdivo and non-small cell lung cancer.

No filters were applied to limit 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 March 3, 2016.

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

6.2.3 Study Selection

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

6.2.4 Quality Assessment

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

6.2.5 Data Analysis

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

6.2.6 Writing of the Review Report

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

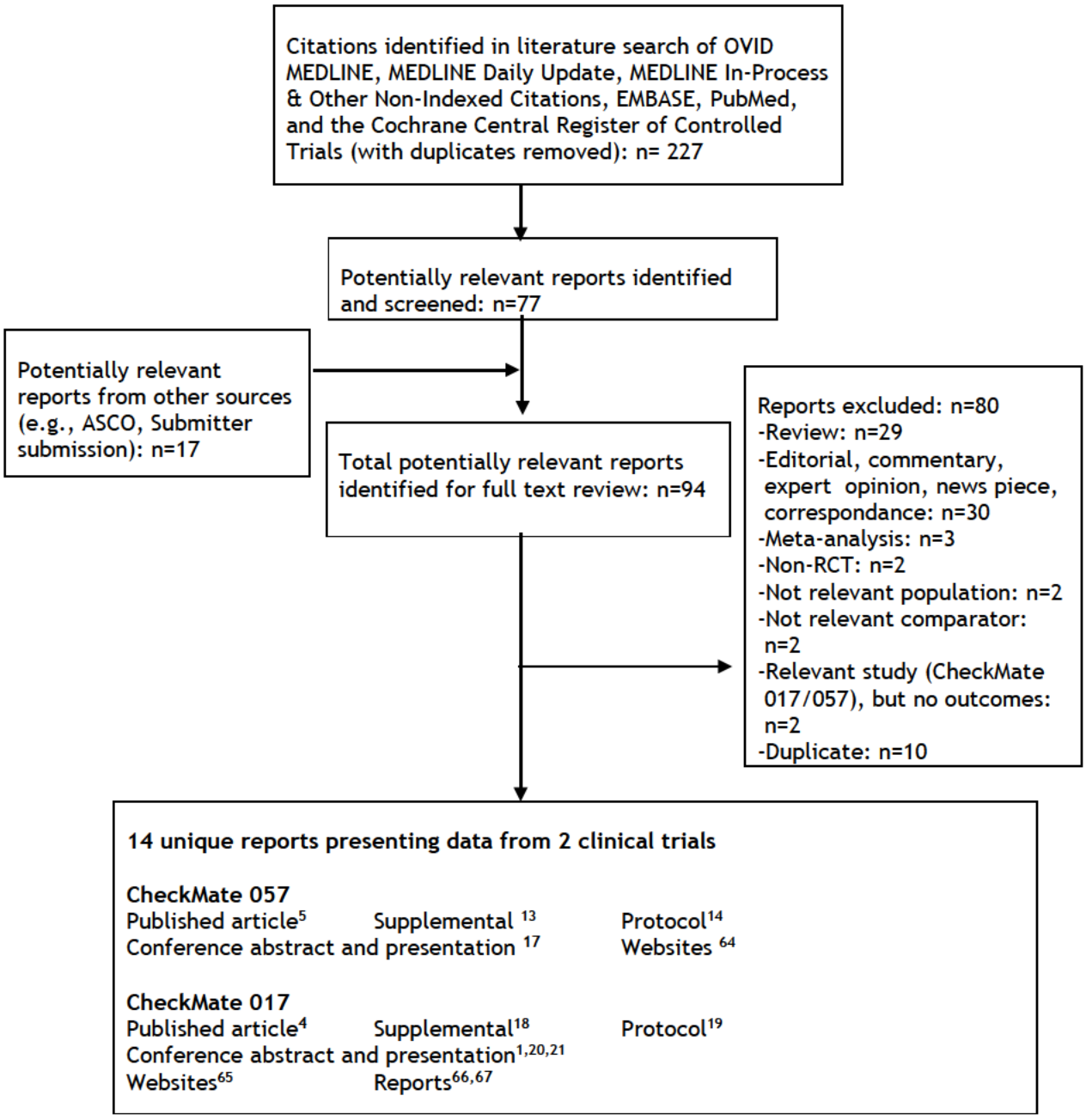
- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental issues.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information, the interpretation of the systematic review and wrote the guidance and conclusions for the report.
-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

6.3 Results

6.3.1 Literature Search Results

Of the 227 citations identified in the literature search, two studies (CheckMate 057 and CheckMate 017) were included in the systematic review.

Figure 6.1 QUOROM Flow Diagram for Inclusion and Exclusion of Studies



Note: Additional data related to CheckMate 057 and CheckMate 017 were also obtained through requests to the Submitter by pCODR[15,16]

6.3.2 Summary of Included Studies

6.3.2.1 Detailed Trial Characteristics

Table 6.2 Summary of Trial Characteristics of the Included Studies[4,5,14,19,64,65]

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
CheckMate 057 (NCT01673867) Randomized, open-label, multicentre international phase III study Enrolment: November 2012 - December 2013 N enrolled = 792 Interim analysis data cut-off date: March 18, 2015 Updated OS data cut-off date: July 2, 2015 Estimated study completion date: May 2016 Randomized 1:1 ratio, stratified by prior maintenance treatment (yes vs. no) & line of therapy (second line vs. third line) N randomized = 582 Funded by Bristol-Myers Squibb	• Men and women ≥ 18 years of age • ECOG performance status of ≤ 1 • Histologically- or cytologically-documented non-squamous cell NSCLC with stage IIIB/stage IV disease or with recurrent progressive disease following multimodal therapy. • Measurable disease by CT or MRI per RECIST 1.1 criteria • disease progression during or after one prior platinum-containing chemotherapy regimen • Tumor tissue available for biomarker evaluation • Prior palliative radiotherapy must have been completed at least 2 weeks prior to randomization <u>Key Exclusion Criteria</u> • Ongoing treatment with >10 mg of prednisone/day (or steroid equivalent, excluding inhaled or topical steroids) • Prior treatment with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody • Prior treatment with Docetaxel • Active, known or suspected autoimmune disease or recent history of a syndrome that required systemic corticosteroids/immunosuppressive medications	<u>Intervention</u> nivolumab 3 mg/kg every 2 weeks <u>Comparator</u> Docetaxel 75 mg/m^2 every 3 weeks dosed intravenously over 60 minutes until disease progression, unacceptable toxicity or other reasons specified in the protocol treatment with nivolumab beyond initial disease progression was permitted at the investigator's discretion, whereas treatment with Docetaxel beyond disease progression was not permitted	<u>Primary</u> OS <u>Secondary</u> ORR DOOR TTOR PFS PD-L1 expression as a predictive biomarker for OS and ORR Patient-reported outcomes
Trial Design	**Key Inclusion Criteria**	**Intervention and Comparator**	**Outcomes**
CheckMate 017 (NCT01642004) Randomized, open-label, multicentre	• Men and women ≥ 18 years of age • ECOG performance status ≤ 1 • Histologically- or cytologically-documented squamous cell	<u>Intervention</u> nivolumab 3 mg/kg every 2 weeks <u>Comparator</u>	<u>Primary</u> OS <u>Secondary</u> ORR

Table 6.2 Summary of Trial Characteristics of the Included Studies[4,5,14,19,64,65]			
Trial Design	**Key Inclusion Criteria**	**Intervention and Comparator**	**Outcomes**
international phase III study Enrolment: October 2012 - December 2013 N enrolled = 352 Interim analysis data cut-off date: December 15, 2014 Updated safety data cut-off date: June 2015 Update OS and PFS data cut-off date: August 2015 Estimated study completion date: January 2017 Randomized 1:1 ratio, stratified by prior use of paclitaxel therapy (Yes vs. No) and geographical region (USA or Canada vs. Europe vs. rest of world*) N randomized = 272 Funded by Bristol-Myers Squibb	NSCLC with Stage IIIB/ Stage IV disease or with recurrent or progressive disease following multimodal therapy • Disease recurrence or progression during or after one prior platinum doublet-based chemotherapy regimen for advanced or metastatic disease. • Measurable disease by CT or MRI per RECIST 1.1 criteria; radiographic tumor assessment performed within 28 days of randomization • Tumor sample available for biomarker evaluation <u>Key Exclusion Criteria</u> • Untreated CNS metastases Carcinomatous meningitis • Active, known or suspected autoimmune disease • Require systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomization • Prior treatment with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody • Prior treatment on the first-line study CA184104 • Prior treatment with Docetaxel	Docetaxel 75mg/ m^2 every 3 weeks • dosed intravenously over 60 minutes • until disease progression, unacceptable toxicity or other reasons specified in the protocol • treatment with nivolumab beyond initial disease progression was permitted at the investigator's discretion, whereas treatment with Docetaxel beyond disease progression was not permitted	DOOR TTOR PFS PD-L1 expression as a predictive biomarker for OS and ORR Patient-reported outcomes
CNS = central nervous system; CT = computed tomography; CTLA-4 = cytotoxic T-lymphocyte-associated protein 4; DOOR = duration of objective response; ECOG = Eastern Cooperative Oncology Group; MRI = magnetic resonance imaging; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PD-1 = programmed cell death protein 1; PD-L1 = programmed death-ligand 1; PD-L2 programmed cell death 1 ligand 2; RECIST = Response Evaluation Criteria in Solid Tumours; TTOR = time to objective response; vs. = versus. *Argentina, Australia, Chile, Mexico, Peru			

a) Trials

Trial details are summarized in Table 6.2.

CheckMate 057 (Non-Squamous NSCLC)

CheckMate 057 is a randomized open-label, phase 3 study comparing nivolumab to Docetaxel in patients with non-squamous NSCLC whose disease progressed during or after platinum-based doublet chemotherapy.

The study was sponsored by Bristol-Myers Squibb. The study enrolled 797 patients with stage IIIB or IV or recurrent non-squamous NSCLC after radiation therapy or surgical resection and whose disease had progressed during or after one prior platinum-based doublet chemotherapy regimen. Patients were randomized in a 1:1 ratio to receive 3 mg of nivolumab per kg of body weight every 2 weeks or 75 mg of Docetaxel per m^2 of body-surface area every 3 weeks dosed intravenously over 60 minutes. Randomization was stratified by prior maintenance treatment (yes versus no) and line of therapy (second line versus third line). Inclusion criteria were as follows: ≥18 years of age, ECOG performance status of 0-1, and adequate hematologic, hepatic, and renal function. Patients with central nervous system (CNS) metastases were eligible if the metastases have been treated and were stable. Exclusion criteria included: autoimmune disease, symptomatic interstitial lung disease, systemic immunosuppression, prior treatment with immune-stimulatory antitumor agents including checkpoint-targeted agents, and prior use of Docetaxel.

The primary endpoint was overall survival. Secondary endpoints included ORR (including DOOR, TTOR), PFS, PD-L1 expression as a predictive biomarker for OS and ORR, and patient-reported outcomes. The study design required a minimum of 442 deaths, with an interim analysis after 380 deaths (86% of total deaths needed for final analysis) to ensure 90% power to detect a treatment effect.[14] The boundary for declaring superiority with respect to overall survival at the interim analysis was a P value of less than 0.0408.[5]

The interim analysis was performed after the data cut-off date of March 18, 2015.[5] Updated efficacy analysis with additional follow-up was performed after the data cut-off date of July 2, 2015.[5]

Patients were followed for survival continuously while they received treatment and every 3 months after treatment was discontinued.[5] Tumour response was assessed at week 9, and then every 6 weeks until disease progression.[5] Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.[5] The assessment of patient reported outcomes using the LCSS was a secondary objective, while the assessment of the general health status using the EQ-5D utility index and VAS was an exploratory objective.[14]

CheckMate 057 was stopped early because it met the pre-specified threshold for superiority in the primary outcome, demonstrating superior overall survival with nivolumab versus Docetaxel. The study was amended (Amendment 8, on April 22, 2015) to provide a mechanism for eligible patients originally randomized to the Docetaxel group to receive subsequent nivolumab therapy as part of a nivolumab extension phase.[14,15]

CheckMate 017 (Squamous NSCLC)

CheckMate 017, is a randomized open-label, phase 3 study comparing nivolumab to Docetaxel in patients with squamous NSCLC whose disease had progressed during or after first-line platinum-based doublet chemotherapy.

The study was sponsored by Bristol-Myers Squibb. The study enrolled 352 patients with stage IIIB or IV squamous-cell NSCLC who had disease recurrence after one prior platinum-containing.

Patients were randomized in a 1:1 ratio to receive 3 mg of nivolumab per kg of body weight every 2 weeks or 75 mg of Docetaxel per m^2 of body-surface area every 3 weeks dosed intravenously over 60 minutes. Randomization was stratified by prior use of paclitaxel therapy (yes versus no) and geographical region (USA or Canada versus Europe versus rest of world which included Argentina, Australia, Chile, Mexico, and Peru).[4] Inclusion criteria were as follows: ≥18 years of age, ECOG performance status of 0-1, and submitted pre-treatment tumour-tissue specimen available for biomarker evaluation. Patients with central nervous system (CNS) metastases were eligible if the metastases have been treated and were stable. Exclusion criteria included: autoimmune disease, symptomatic interstitial lung disease, systemic immunosuppression, prior treatment with T-cell costimulation or checkpoint-targeted agents, and prior use of Docetaxel. As well, patients who received more than one prior systemic therapy for metastatic disease were excluded. Prior maintenance therapy (including tyrosine kinase inhibitor) was permitted.

The primary endpoint was overall survival. Secondary endpoints included ORR (including DOOR, TTOR), PFS, PD-L1 expression as a predictive biomarker for OS and ORR, and patient-reported outcomes.[19] The study was design required a minimum of 231 deaths, with an interim analysis after 196 deaths (85% of total deaths needed for final analysis) to ensure 90% power to detect a treatment effect.[19] The boundary for declaring superiority for overall survival at the interim analysis was a P value of less than 0.03.[4] The interim analysis was performed after the data cut-off date of December 15, 2014.[4] Updated safety (selected TRAEs) analysis was performed after the data cut-off date of June 2015.[1]Updated efficacy (OS) analysis with additional follow-up was performed after the data cut-off date of August 2015.[1]

Patients were followed for survival continuously while they received treatment and every 3 months after treatment was discontinued.[4] Tumour response was assessed at week 9 and then every 6 weeks until disease progression. [4] Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.[4] The assessment of patient reported outcomes using the LCSS was a secondary objective, while the assessment of the general health status using the EQ-5D utility index and VAS was an exploratory objective.[19]

CheckMate 017 was stopped early because it met the pre-specified threshold for superiority in the primary outcome, demonstrating superior overall survival with nivolumab versus Docetaxel.[19] The study was amended (Amendment 11, on January 26, 2015) to provide a mechanism for eligible patients originally randomized to the Docetaxel group to receive subsequent nivolumab therapy as part of a nivolumab extension phase.[15]

b) Populations

Details of baseline characteristics for both trials are listed in Table 6.3.

CheckMate 057 (Non-Squamous NSCLC)

A total of 582 patients were randomized to receive nivolumab (n=292) or Docetaxel (n=290). The median age was 62. Most patients had an ECOG performance status of 1 (69%), were current or former smokers (79%), had one prior systemic therapy (88%), had stage IV cancer (92%), and were white (92%). A small proportion of patients were EGFR, ALK, and KRAS mutation positive (14%, 4%, and 11% respectively). Patients were balanced between the two groups, with the exception of the percentage of males (52% versus 58%).[5] Approximately 12% of patients included in both arms had treated and stable CNS metastasis.

CheckMate 017 (Squamous NSCLC)

A total of 272 patients were randomized to receive nivolumab (n=135) or Docetaxel (n=137). The median age was 63. Most patients were male (76%), had an ECOG performance status of 1(76%), had stage IV cancer (80%), were current or former smokers (92%), and were white (93%). All but

one patient received only one line of prior cancer therapy (which could have included multiple agents or a switch of agents within the first-line regimen). The proportion of patients that were ALK or KRAS mutation positive was not reported. Patients were balanced between the two groups, with the exception of the percentage of males (82% versus 71%) and ECOG performance status 0 (20% versus 27%). Approximately 6% of patients included in both arms had treated and stable CNS metastasis.

Table 6.3 Baseline Characteristics of Pivotal Trials of Nivolumab in NSCLC

	Non-squamous NSCLC CheckMate 057[5,13]			Squamous NSCLC CheckMate 017[4,18]		
	Nivolumab (n=292)	Docetaxel (n=290)	Total (N=582)	Nivolumab (n=135)	Docetaxel (n=137)	Total (N=272)
Age, median(range)	61(37-84)	64(21-85)	62(21-85)	62(39-85)	64(42-84)	63(39-85)
Sex, male	151(52%)	168(58%)	319(55%)	111(82%)	97(71%)	208(76%)
Race						
White	267(91%)	266(92%)	533(92%)	122(90%)	130(95%)	252(93%)
Asian	9(3%)	8(3%)	17(3%)	4(3%)	2(1%)	6(2%)
ECOG performance status						
0	84(29%)	95(33%)	179(31%)	27(20%)	37(27%)	64(24%)
1	208(71%)	194(67%)	402(69%)	106(79%)	100(73%)	206(76%)
NR	0	1(<1%)	1(<1%)	2(1%)	0	2(1%)
Smoking status						
Current or former	231(79%)	227(78%)	458(79%)	121(90%)	129(94%)	250(92%)
Never smoked	58(20%)	60(21%)	118(20%)	10(7%)	7(5%)	17(6%)
Unknown	3(1%)	3(1%)	6(1%)	4(3%)	1(1%)	5(2%)
Disease stage						
IIIB	20(7%)	24(8%)	44(8%)	29(21%)	24(18%)	53(19%)
IV	272(93%)	266(92%)	538(92%)	105(78%)	112(82%)	217(80%)
NR	0	0	0	1(1%)	1(1%)	2(1%)
Prior maintenance therapy	122(42%)	111(38%)	233(40%)	NR	NR	NR
Prior systemic therapy						
1	256(88%)	259(89%)	515(88%)	134(99%)	137(100%)	272(<100%)
2	35(12%)	31(11%)	66(11%)	1(1%)[†]	0	1(<1%)
Other	1(<1%)	0	1(<1%)	-	-	-
Type of prior systemic therapy[‡]						
Platinum-based therapy	292(100%)	290(100%)	582(100%)	135(100%)	137(100%)	272(100%)
ALK inhibitor	1(<1%)	2(1%)	3(1%)	NR	NR	NR
EGFR TKI	29(10%)	24(8%)	53(9%)	0	3(2%)	3(1%)
Other chemotherapy	NR	NR	NR	135(100%)	136(99%)	271(<100%)
Other—experimental therapy	23(8%)	18(6%)	41(7%)	9(7%)	2(1%)	11(4%)
Mutation status						
EGFR positive	44(15%)	38(13%)	82(14%)	NR	NR	NR
ALK positive	13(4%)	8(3%)	21(4%)	NR	NR	NR
KRAS positive	28(10%)	34(12%)	62(11%)	NR	NR	NR

ALK = anaplastic lymphoma kinase; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; KRAS = Kirsten rat sarcoma viral oncogene homologue; NA= not applicable; NR = not reported; NSCLC = non-small cell lung cancer; TKI = tyrosine kinase inhibitor.

Table 6.3 Baseline Characteristics of Pivotal Trials of Nivolumab in NSCLC						
	Non-squamous NSCLC CheckMate 057[5,13]			Squamous NSCLC CheckMate 017[4,18]		
	Nivolumab (n=292)	Docetaxel (n=290)	Total (N=582)	Nivolumab (n=135)	Docetaxel (n=137)	Total (N=272)
†one patient received only one line of prior cancer therapy, which could have included multiple agents or a switch of agents within the first-line regimen ‡Patients may have been treated with more than one type of therapy						

c) Interventions

CheckMate 057 (Non-Squamous NSCLC)

Treatment was administered in both groups as described in Table 6.2. Treatment beyond initial disease progression (beyond initial RECIST 1.1 defined progressive disease) was permitted for the nivolumab group, as long as the following criteria were met: investigator-assessed clinical benefit and no rapid disease progression; tolerance of study drug; stable performance status; patients continue to meet all other study protocol eligibility criteria; treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases) and Subjects will be re-consented with an ICF describing any reasonably foreseeable risks or discomforts, or other alternative treatment options. A radiographic assessment/ scan should be performed within six (6) weeks of original progressive disease to determine whether there has been a decrease in the tumor size, or continued PD. Treatment with Docetaxel beyond initial disease progression was not permitted. Dose modification (escalation or reduction) was not permitted for the nivolumab group; however, dose reduction was allowed for the Docetaxel group. Dose delay was permitted for both groups.[14]

A total of 71 patients (24%) in the nivolumab group continued treatment after initial progression, of which 23% (n=16) had a nonconventional pattern of benefit (i.e. reduction in size and/or number of target lesions with simultaneous appearance of new lesions or initial progression followed by either tumor reduction or no further progression for at least two tumor assessments).[5] The median, range, mean, and standard deviation of the duration of treatment after initial progressive disease was 1.2 months (0-20.5 months) and 2.8 months (±3.9 months).[13]

CheckMate 017 (Squamous NSCLC)

Treatment was administered in both groups as described in Table 6.2. Treatment beyond initial disease progression (beyond initial RECIST 1.1 defined progressive disease) was permitted for the nivolumab group, as long as the following criteria were met: investigator-assessed clinical benefit, and no rapid disease progression; tolerance of study drug; and stable performance status, treatment beyond progression not to delay an imminent intervention to prevent serious complications of disease progression (e.g., CNS metastases); and written informed consent prior to receiving additional nivolumab. A radiographic assessment/ scan should be performed within six (6) weeks of original progressive disease to determine whether there has been a decrease in the tumor size, or continued PD. Treatment with Docetaxel beyond initial disease progression was not permitted. Dose modification (escalation or reduction) was not permitted for the nivolumab group; however, dose reduction was allowed for the Docetaxel group. Dose delay was permitted for both groups.[19]

A total of 28 patients (21%) in the nivolumab group continued treatment after initial progression, of which 32% (n=9) had a nonconventional pattern of benefit (i.e. reduction in size and/or number of target lesions with simultaneous appearance of new lesions or initial progression followed by either tumor reduction or no further progression for at least two tumor assessments).[4] The

median, range, mean, and standard deviation of the duration of treatment after initial progressive disease was 1.3 months (0-16.3 months) and 2.9 months (±4.1 months).[18]

d) Patient Disposition

Details of the patient disposition in both studies can be found in Table 6.4.

Table 6.4 Patient Disposition

	Non-squamous NSCLC CheckMate 057[a13]		Squamous NSCLC CheckMate 017[b16,18]	
Enrolled	792		352	
Randomized	582		272	
Allocation	**Nivolumab**	**Docetaxel**	**Nivolumab**	**Docetaxel**
Randomized	292	290	135	137
Received treatment	287	268	131	129
Did not receive allocated treated (reasons below)	5	22	4	8
• withdrew consent	0	12	1	6
• no longer met study criteria	4	5	2	2
• requested to discontinue	0	4	0	0
• adverse event unrelated to study drug	1	0	1	0
• lost to follow-up	0	1	0	0
Disposition	**Nivolumab**	**Docetaxel**	**Nivolumab**	**Docetaxel**
Still on treatment	43	0	21	2
Discontinued treatment (reasons below)	244	268	110	127
• disease progression	194	179	88	80
• study drug toxicity	17	42	5	13
• death	1	1	1	0
• adverse events unrelated to study drug	19	11	6	13
• requested to discontinue study drug	5	16	2	4
• withdraw consent	4	6	3	5
• maximum clinical benefit	0	10	2	7
• poor/non-compliance	0	0	1	0
• patient no longer met study criteria	2	0	1	2
• other	2	3	1	2
• not reported	0	0	0	1
In post-treatment follow-up	55	63	28	20
Analysis	**Nivolumab**	**Docetaxel**	**Nivolumab**	**Docetaxel**
Efficacy	292	290	135	137
Safety[†]	287	268	131	129

ITT = intent-to-treat; NSCLC = non-small cell lung cancer; NR = not reported.
[a]Database locked on March 18, 2015
[b]Database locked on December 15, 2014
[†]all the patients who received at least 1 dose of study drug

e) Limitations/Sources of Bias

Overall, the risk of bias appeared moderate in both trials, with the greatest concern being that secondary endpoints (PFS and ORR) were measured by the investigator and not confirmed by an independent review committee. Details are provided below.

1. Randomization and allocation concealment

CheckMate 057 (Non-Squamous NSCLC)

Patients were randomized via permuted blocks within each stratum (by prior use of maintenance therapy versus no maintenance therapy, and second-line patients versus third-line patients) and allocated in a 1:1 fashion.[14]

Patients were balanced between the two groups, with the exception of the percentage of males. There was a slightly lower proportion of males in the nivolumab group compared with the Docetaxel group (52% versus 58%).[5]

CheckMate 017 (Squamous NSCLC)

Patients were randomized via permuted blocks within each stratum (by prior paclitaxel versus other prior treatment, and region) and allocated in a 1:1 fashion.[19]. Patients were balanced between the two groups, with the exception of the percentage of males and ECOG performance status 0. There was a higher proportion of males and a lower proportion of patients with an ECOG performance status of 0 in the nivolumab group compared with the Docetaxel group (82% versus 71%, 20% versus 27% respectively).

2. Blinding

CheckMate 057 (Non-Squamous NSCLC)

Blinding was not applicable; CheckMate 057 was an open label study. The rationale for an open label study as opposed to a blinded study was the following: the management of similar adverse events differed between treatment groups; different dose modification rules applied to the two agents being studied and different drug-drug interaction profiles were expected. These complexities precluded a blinding strategy.[14] The open label design of CheckMate 057 is acceptable given the different dosing frequencies.

PFS and ORR were measured by the investigator and were not confirmed by an independent review committee. This open label design may introduce moderate-high risk of bias in the assessment of measures such as PFS, ORR, patient-reported outcomes, and reporting of adverse events. Overall survival is unlikely to be influenced by subjective bias.

CheckMate 017 (Squamous NSCLC)

Blinding was not applicable; CheckMate 017 was an open label study. This rationale for an open label study as opposed to blinded study was the following: the management of similar adverse events differed between treatment groups; different dose modification rules applied to the two agents being studied and different drug-drug interaction profiles were expected. These complexities precluded a blinding strategy.[19]The open label design of CheckMate 057 is acceptable given the different dosing frequencies.

PFS and ORR were measured by the investigator and were not confirmed by an independent review committee. This open label design may introduce moderate-high risk of bias in the assessment of measures such as PFS, ORR, patient-reported outcomes, and reporting of adverse events. Overall survival is unlikely to be influenced by subjective bias.

3. Attrition

CheckMate 057 (Non-Squamous NSCLC)

After randomization, a small proportion of patients did not receive study treatment (2% for the nivolumab group and 8% for the Docetaxel group).The primary reason for discontinuation of treatment in both groups was disease progression. The efficacy outcomes were analyzed according to the intention to treat principle. Safety outcome analyses used the as-treated population, which included 98% of patients randomized to the nivolumab group and 92% of patients randomized in the Docetaxel group. The LCSS completion rate at baseline was 82% in the nivolumab group (n=240 out of 292) compared with 77% in the Docetaxel group (n=222 out of 290). As a result, LCSS baseline data were not available for a total 52 of patients in the nivolumab group (18%) and a total of 68 of patients in the Docetaxel group (23%), and therefore not included in the analysis since the completion rate at Week 12 was calculated using the number of patients with non-missing LCSS data at baseline and data from at least one post-baseline visit, divided by the number of patients in the study at each respective time point.

CheckMate 017 (Squamous NSCLC)

After randomization, a small proportion of patients did not receive study treatment (3% for the nivolumab group and 6% for the Docetaxel group).The primary reason for discontinuation of treatment in both groups was disease progression. The efficacy outcomes were analyzed according to the intention to treat principle. Safety outcomes analyses used the as-treated population, which included 97% of patients randomized to the nivolumab group and 94% of patients randomized in the Docetaxel group. The LCSS completion rate at baseline was 78% in the nivolumab group (n=105 out of 135) compared to 77% in the Docetaxel group (n=105 out of 137). As a result, LCSS baseline data were not available for a total 30 of patients in the nivolumab group (22%) and a total of 32 of patients in the Docetaxel group (23%), and therefore not included in the analysis since the completion rate at Week 12 was calculated using the number of patients with non-missing LCSS data at baseline and data from at least one post-baseline visit, divided by the number of patients in the study at each respective time point.

4. Reporting of outcomes

CheckMate 057 (Non-Squamous NSCLC)

The updated OS analysis (data-cut off July 2, 2015) was performed after Amendment 8 (Nivolumab Extension Phase, on April 22, 2015).[15] which allowed eligible patients originally randomized to the docetaxel group to receive subsequent nivolumab therapy. Given less than 1% (0.7%, 2 out of 292) of patients who had received docetaxel crossed over to receive nivolumab, the risk of confounding the updated OS results was low.[16] Given all the relevant outcomes were reported, the risk of reporting bias was low.

CheckMate 017 (Squamous NSCLC)

The updated OS analysis (data-cut off August 2015) was performed after the Amendment 11 (Nivolumab Extension Phase, on January 26, 2015), allowing eligible patients originally randomised to Docetaxel to receive subsequent nivolumab.[15] Given less than 5% (4.4%, 6 out of 137) of patients who had received docetaxel crossed over to receive nivolumab, the risk of confounding the updated OS results was low.[16] The results from the patient-reported outcome assessment using the EQ-5D should be interpreted with caution, since the data were found in abstract format only and were limited regarding important critical appraisal points. Overall for the CheckMate 017 trial, the risk of reporting bias was low, given that all of the relevant outcomes were reported.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

a) Efficacy Outcomes

Overall Survival

Details of OS data for both trials are listed in Table 6.5a. Figure 6.2 illustrates the interim OS analysis results from CheckMate 017 in the form of a Kaplan-Meier plot.

CheckMate 057 (Non-Squamous NSCLC)

In the interim analysis, there was a statistically significant difference in OS in favour of nivolumab [hazard ratio for death: 0.73(96% CI, 0.59 to 0.89). The median OS was 12.2 months for patients in the nivolumab group compared with 9.4 months for patients in the Docetaxel group. There was a 12% improvement in one year survival (OS rate at 1 year: 51% versus 39%).[5]

The study was not powered to detect a difference in different subsets, rather pre-specified subgroup analyses were conducted to assess consistency of treatment effects in different subsets.[14] Among the subgroups of interest to the CGP, results from the subgroup analyses relating to age, sex, ECOG performance status were consistent with the overall OS results, showing treatment effect in favour of nivolumab. Results from the subgroup analyses relating to smoking status (in never smokers) and EGFR mutation status (in mutation positive) were not consistent in showing treatment effect in favour of nivolumab; and wide confidence intervals were likely attributed to small size.

With additional follow-up (minimum 17.2 months), the median OS was 12.2 months for the nivolumab group compared to 9.4 months for the Docetaxel group. At 18 months, the OS rate for the nivolumab group was 39% compared with 23% for the Docetaxel group. Results from a follow-up analysis for OS supported the results from the interim analysis; a statistically significant difference in OS was found in favour of nivolumab [hazard ratio for death: 0.72(95% CI, 0.60 to 0.88)].[5]

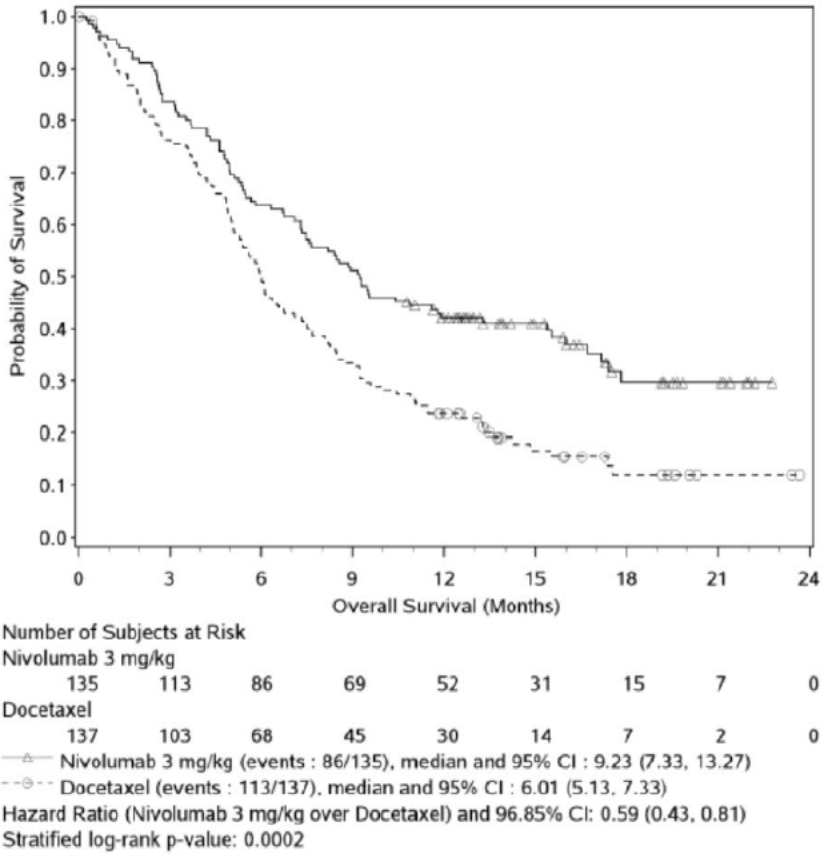
CheckMate 017 (Squamous NSCLC)

In the interim analysis, there was a statistically significant difference in OS in favor of nivolumab [hazard ratio for death: 0.59(95%CI, 0.44 to 0.79). The median OS was 9.2 months for patients in the nivolumab group compared with 6.0 months for patients in the Docetaxel group. There was an 18% improvement in one year survival (OS rate at 1 year: 42% versus 24%).[4]

The study was not powered to detect a difference in different subsets, rather pre-specified subgroup analyses were conducted to assess consistency of treatment effects in different subsets.[19] Among the subgroups of interest to the CGP, results from the subgroup analyses relating to sex, ECOG performance status, and smoking status were consistent with the overall OS results, showing treatment effect in favour of nivolumab. Results from the subgroup analysis relating to age (in ≥ 75 years) were not consistent in showing treatment effect in favour of nivolumab; and wide confidence intervals were likely attributed to small size.

With additional follow-up (minimum 18 months), the median OS was 9.2 months for the nivolumab group compared with 6.0 months for the Docetaxel group. At 18 months, the OS rate for the nivolumab group was 28% compared with 13% for the Docetaxel group. [1] Results from updated OS analysis supported the results from the interim analysis; a statistically significant difference in OS was found in favour of nivolumab [hazard ratio for death: 0.62(95%CI, 0.48 to 0.81), P=0.0004.[1]

Figure 6.2 CheckMate 017 – Kaplan-Meier Plot of Overall Survival[66]



Source:[66]

Table 6.5a. Overall Survival of Pivotal Trials for Nivolumab in NSCLC				
	Non-squamous NSCLC CheckMate 057[a,b 5,13]		Squamous NSCLC CheckMate 017[c,d1,4,18]	
Interim Analysis	**Nivolumab (n=292)**	**Docetaxel (n=290)**	**Nivolumab (n=135)**	**Docetaxel (n=137)**
Median OS, months	12.2(95%CI:9.7-15.0)	9.4(95CI%:8.1-10.7)	9.2(95%CI:7.3-13.3)	6.0(95%CI:5.1-7.3)
Hazard ratio	0.73(96%CI:0.59-0.89), *P*=0.002		0.59(95%CI:0.44-0.79), *P*<0.001	
OS rate, 1 year	51%	39%	42%	24%
No. at risk at 1 year	146	111	52	30
Follow-up Analysis	**Nivolumab (n=292)**	**Docetaxel (n=290)**	**Nivolumab (n=135)**	**Docetaxel (n=137)**
Median OS, months	12.2(95%CI:9.7-15.1)	9.4(95%CI:8.1-10.7)	9.2(95%CI:7.33-12.62)	6.0(95%CI:5.29-7.39)
Hazard ratio	0.72(95%CI:0.60-0.88), *P*<0.001		0.62(95%CI:0.48-0.81), *P*=0.0004	
OS rate,18 months	39%	23%	28%	13%
No. at risk at 18 months	107	61	37	17
Subgroup[†]	**No. of Patients**	**Unstratified Hazard Ratio[a] (95%CI)**	**No. of Patients**	**Unstratified Hazard Ratio[c] (95%CI)**
Interim Analysis, Overall	582	0.75(0.62-0.91)	272	0.59(0.44-0.78)
Age				

Table 6.5a. Overall Survival of Pivotal Trials for Nivolumab in NSCLC				
<65 years	339	0.81(0.62-1.04)	152	0.52(0.35-0.75)
≥65 to <75 years	200	0.63(0.45-0.89)	91	0.56(0.34-0.91)
≥75 years	43	0.90(0.43-1.87)	29	1.85(0.76-4.51)
Sex				
Male	319	0.73(0.56-0.96)	208	0.57(0.41-0.78)
Female	263	0.78(0.58-1.04)	64	0.67(0.36-1.25)
ECOG performance status				
0	179	0.64(0.44-0.93)	64	0.48(0.24-0.99)
1	402	0.80(0.63-1.00)	206	0.54(0.39-0.74)
Smoking Status				
Current or former smoker	458	0.70(0.56-0.86)	250	0.59(0.44-0.80)
Never smoked	118	1.02(0.64-1.61)	NR	NR
EGFR mutation status				
Positive	82	1.18(0.69-2.00)	NA‡	NA‡
Not detected	340	0.66(0.51-0.86)	NA‡	NA‡
Not reported	160	0.74(0.51-1.06)	NA‡	NA‡

CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; NA = not applicable; NR = not reported; NSCLC = non-small cell lung cancer; OS = overall survival.
[a]Interim analysis database locked on March 18, 2015
[b]Follow-up analysis database locked on July 2, 2015 (follow-up of minimum 17.2 months)
[c]Interim analysis database locked on December 15, 2014
[d]Follow-up analysis database locked on August 2015; (follow-up of minimum 18 months)
[†]Hazard ratios for death were not computed for subgroups that included a treatment group with fewer than 10 patients (i.e.: unreported ECOG performance status, unknown smoking status)
[‡]based on clinical input, EGFR mutation is limited to non-squamous histology and mutually exclusive to ALK and KRAS mutations.

Progression-free survival

Details of PFS results for both trials are listed in Table 6.5b.

CheckMate 057 (Non-Squamous NSCLC)

In the interim analysis, no statistically significant difference in PFS was found. The hazard ratio for disease progression and death: 0.92(95%CI, 0.77 to1.11), *P*=0.39.[5] The median PFS was 2.3 months in the nivolumab group and 4.2 months in the Docetaxel group. The PFS rate at 1 year was 19% in the nivolumab group and 8% in the Docetaxel group.

CheckMate 017 (Squamous NSCLC)

In the interim analysis, a statistically significant difference in PFS was found. The hazard ratio for disease progression and death was 0.62 (95%CI, 0.47 to 0.81), *P*<0.001.[4]the median PFS was 3.5 months in the nivolumab group compared with 2.8 months in the Docetaxel group. The PFS rate at 1 year was 21% compared with 9%.

Results from an updated PFS analysis were reported; only a small number of patients were at risk at 18 months (n=16 for the nivolumab group and n=1 for the Docetaxel group). [1]

Table 6.5b. Progression Free Survival of Pivotal Trials for Nivolumab in NSCLC				
	Non-squamous NSCLC CheckMate 057[a,b] [5,74]		Squamous NSCLC CheckMate 017[c,d] [1,4]	
	Nivolumab (n=292)	Docetaxel (n=290)	Nivolumab (n=135)	Docetaxel (n=137)
Interim Analysis				
Median PFS, months	2.3(95%CI:2.2-3.3)	4.2(95%CI:3.5-4.9)	3.5(95%CI:2.1-4.9)	2.8(95%CI:2.1-3.5)
Hazard ratio	0.92(95%CI:0.77-1.11), *P*=0.39		0.62(95%CI:0.47-0.81), *P*<0.001	
PFS rate, 1 year	19%	8%	21%	6%
No. at risk at 1 year	46	18	21	6
Follow-up Analysis				
Median PFS, months	NR	NR	3.5(95%CI:2.14-5.06)	2.8(95%CI:2.14-3.52)
Hazard ratio	NR		0.63(95%CI:0.48-0.83), *P*=0.0008	
PFS rate,18 months	NR	NR	17%	3%
No. at risk at 18 months	NR	NR	16	1

CI = confidence interval; NR = not reported; NSCLC = non-small cell lung cancer; PFS = progression-free survival.
[a]Interim analysis database locked on March 18, 2015
[b]Follow-up analysis database locked on July 2, 2015
[c]Interim analysis database locked on December 15, 2014
[d]Follow-up analysis database locked on August 2015; minimum follow-up survival: 18 months

Quality of Life

CheckMate 057 (Non-Squamous NSCLC)

Patient-reported outcomes were measured using the LCSS (as a secondary outcome) and EQ-5D (as an exploratory outcome). The objective of the patient-reported outcome assessment using the LCSS was to evaluate the proportion of patients that experienced disease-related symptom improvement by 12 weeks in the nivolumab and Docetaxel groups (defined as the proportion of randomized patients who had 10 points or more decrease from baseline in ASBI score at anytime between randomization and week 12).[14]

LCSS is a valid and reliable instrument [68] and is used in several studies for assessing quality of life.[69]

Notwithstanding, LCSS does have its limitations, as noted by Anant et al[69] that the LCSS ignores important components of quality of life such as the social and emotional aspects, which are important aspects to patients. As noted by Lung Cancer Canada, anxiety or worry was common, reporting that depression rates are consistently higher with lung cancer than other cancer sites.

The LCSS completion rate at baseline (any baseline data with no-post-baseline data requirement) was 82.2% in the nivolumab group (n=240 out of 292) compared with 76.6% in the Docetaxel group (n=222 out of 290).[16] At week 12, the LCSS completion rate was 77.2% in the nivolumab group compared (n=112 out of 145) with 75.8% in the Docetaxel group (n=100 out of 132). According to the submitter, the completion rate at Week 12 was calculated using the number of patients with non-missing LCSS data at baseline and data from at least one post-baseline visit, divided by the number of patients in the study at each respective time point.

The MID used for LCSS ASBI was a 10 point or greater decrease. The mean LCSS ASBI scores at baseline were similar between nivolumab and Docetaxel groups (24.8, ±15.9 versus 24.4, ±15.8).[17]

The proportion of patients experiencing a clinically meaningful improvement in symptoms by week 12 according to the LCSS ASBI was similar in the nivolumab group (17.8%; 95% CI [13.6, 22.7]; 52 out of 292 patients) and the Docetaxel group (19.7%; 95% CI [15.2, 24.7]; 57 out of 290 patients) groups.[16,17]

Mean change in symptoms for patients remaining on treatment

According to the submitter, the description of the within-patient changes from baseline while on treatment in the LCSS ASBI by treatment group was a pre-specified exploratory endpoint in CheckMate 057. The data suggests that quality of life was maintained over time for both the nivolumab and Docetaxel groups, since the LCSS ASBI change scores appeared stable over time [Nivolumab: never equivalent to or exceeded the MID from baseline(n at risk=210) to week 66(n at risk=27), Docetaxel: never equivalent or exceeded the MID from baseline(n at risk=212) to week 54(n at risk=7)].[17] Comparisons across treatment groups, when 10 or more patients were available in both treatment groups at common assessment time points (weeks 12, 24, 30, 36, 42, and 48), showed numerical improvements for patients on nivolumab in changes from baseline score relative to changes from baseline scores for Docetaxel patients, with the descriptive p-value less than 0.05 at weeks 12, 24, 30, and 42, and the difference at week 42 larger than the MID.[16]

Mean changes from baseline while on treatment at Week 12

The submitter indicated that for the assessment of the mean change from baseline for patients remaining on treatment at week 12, the estimated changes in LCSS ASBI for both nivolumab and Docetaxel were less than the MID, with descriptive p-value greater than 0.05. Among individual symptoms, for anorexia, cough, hemoptysis, and pain, in each group the estimated changes from baseline at week 12 were less than the MID and the descriptive p-value exceeded 0.05 for each symptom for each treatment group. For fatigue and dyspnea, the estimated changes from baseline at week 12 were also less than the MID (for nivolumab - fatigue: p-value < 0.05; dyspnea: p-value > 0.05; for Docetaxel p-value < 0.05 for both symptoms).[16]

The LCSS 3-item index is the sum of its component measures (symptom distress, interference with activities and global HRQoL). For the LCSS 3-item index at week 12, the estimated changes from baseline were less than the MID for nivolumab and Docetaxel, with p-values exceeding 0.05. Results were consistent for both the symptom distress and interference with activities components and the global health-related quality of life component of the LCSS 3-item index (the changes from baseline at week 12 for each treatment group were less than the MID, and the corresponding p-values of the estimates were greater than 0.05).[16]

Individual symptoms and 3-item index and its components: differences from baseline after week 12

The submitter stated that following the assessment at week 12, for both nivolumab and Docetaxel, the on-treatment individual symptoms and 3-item index and its components followed the general pattern of the LCSS ASBI, with differences from baseline being less than the MID (either with or without p-values less than 0.05) for the assessments while there were at least 10 patients remaining in the treatment group. The submitter noted that there were some instances of within-treatment group estimated differences from baseline that exceeded the MID while also having descriptive p-values less than 0.05; these included improvement in cough and global HRQoL for nivolumab patients at certain assessments and deterioration in symptom distress for Docetaxel patients at certain assessments. Across treatment groups at common assessments up to week 48, there were some estimates of the difference in change from baseline (favouring nivolumab) at one or more assessments that exceeded the MID and had descriptive p-values of less than 0.05 for the following scales: the 3-item index, symptom distress, global HRQoL, anorexia, dyspnea, and pain.[16]

Time to deterioration in symptoms

According to the submitter, CheckMate 057 included a series of pre-specified exploratory Time to Deterioration (TTD) analyses for the LCSS average symptom burden index (ASBI), each of the 6 LCSS symptoms, the LCSS 3-item index and each its components (symptom distress, limitations in activities, and global HRQoL). First deterioration was defined as time to the first assessment where the difference from the baseline score indicated a deterioration equal to or exceeding the MID.[16]

The submitter stated that the hazard rate estimated in the analysis of TTD in the LCSS ASBI showed that nivolumab was associated with a delay in deterioration of average symptom burden [estimates not reported], with the corresponding descriptive p-value less than 0.05. The hazard rate estimates from each of the (separate) TTD analyses of the individual symptoms were also consistent with a delay in deterioration of these symptoms related to nivolumab treatment relative to Docetaxel treatment [estimates not reported]. Four of 6 of the corresponding p-values across these analyses were less than 0.05. The TTD analysis of the 3-item index and the TTD analyses of each of its components estimated hazard ratios were consistent with delay in deterioration in patients treated with nivolumab relative to Docetaxel; in each of these analyses, the descriptive p-value corresponding to the estimated hazard ratio was less than 0.05 [estimates not reported].[16]

The exploratory objective of the patient-reported outcome assessment using the EQ-5D was to assess patients' overall health status using the EQ-5D Index and visual analog scale.[14] Results from the overall health status assessment using the EQ-5D were not reported in the presentation.

CheckMate 017 (Squamous NSCLC)

Patient-reported outcomes were measured using the LCSS (as a secondary outcome) and EQ-5D (as an exploratory outcome). The objective of the patient-reported outcome assessment using the LCSS was to evaluate the proportion of patients that experienced disease-related symptom improvement by 12 weeks in the nivolumab and Docetaxel groups.[19]

The results from the patient-reported outcome assessment using the LCSS were reported in a presentation at the International Association for the Study of Lung Cancer. The patient-reported outcome assessment using LCSS was performed at baseline (cycle 1, day 1 visit), followed by every 4 weeks for nivolumab and every 3 weeks for Docetaxel for the first 6 months on treatment, then every 6 weeks for the remainder of the treatment period for both study groups; followed by two follow-up visits (after treatment discontinuation). The MID used for LCSS ASBI was a 10 point or greater decrease and the MID used for LCSS 3-Item Index was a change of 30 points of greater.[20]

At baseline, the LCSS completion rate was 77.8% in the nivolumab group (n=105 out of 135) compared with 76.6% in the Docetaxel group (n=105 out of 137). The LCSS completion rate at baseline plus at least one follow-up assessment was 68.9% in the nivolumab group (n=93 out of 135) compared with 62.8% in the Docetaxel group (n=86 out of 137). At week 12, the LCSS completion rate for patients on-treatment was 67.6% in the nivolumab group compared (n=48 out of 71) to 66.7% in the Docetaxel group (n=30 out of 45). According to the author, the completion rate was calculated using the number of patients with non-missing LCSS data at baseline and data from ≥1 post-baseline visit, divided by the number of patients in the study at each respective time point.[20]

Table 6.5c and 6.5d summarize baseline and changes in symptoms and in global QoL measures between nivolumab and Docetaxel over the treatment period. The mean baseline characteristics were similar between nivolumab and Docetaxel (29.6, ± 16.4 versus 29.6, ± 14.7). The proportion

of patients experiencing a clinically meaningful improvement in symptoms by week 12 according to the LCSS ASBI was 20.0% (95% CI, 13.6 to 27.7) in the nivolumab group (n=27 out of 135) compared to 21.9% (95% CI, 15.3 to 29.8) in the Docetaxel group (n=30 out of 137). It appeared that quality of life may be trending to clinical improvement from week 40 through 54 (where the LCSS ASBI change scores exceeded the MID threshold) for the nivolumab group; however, the number at risk from week 36 and onward was 20 or less for the nivolumab group. The number at risk then dropped to less than 10 patients after week 54. It appears that quality of life was maintained from baseline to week 18 for the Docetaxel group; after which the number at risk dropped to fewer than 10 patients.[20]

Table 6.5c CheckMate 017 - Baseline and difference in symptoms between nivolumab and Docetaxel over treatment period: mixed-effect model results[16,20]

	Mean(SD) Baseline Score Nivolumab	Change From Baseline Nivolumab	Mean(SD) Baseline Score Docetaxel	Change From Baseline Docetaxel
Symptom Burden Index	29.6(±16.4)	-4.4[a,b]	29.6(±14.7)	1.1
Anorexia	33.3 ±27.7	-7.2[a]	31.2 ±26.0	-0.1
Fatigue	44.8 ±29.4	-8.6[a,b]	42.8 ±29.9	7.3[a]
Cough	33.3 ±28.2	-10.6[a]	39.0 ±29.0	-7.4[a]
Dyspnea	34.0 ±29.7	-2.7	34.0 ±26.5	4.1
Hemoptysis	3.4 ±9.3	0.2	5.5 ±13.1	0.8
Pain	29.0 ±27.3	-4.0	25.4 ±28.8	0.3

[a]P< 0.05 vs. Baseline
[b]P<0.05 for Nivolumab vs. Docetaxel
†Negative change from baseline indicates improvement.
MID consists of a change of ≥ 10 points.
Covariates included: baseline PRO score, region, and prior paclitaxel usage

Table 6.5d CheckMate 017 - Difference in global measure between nivolumab and Docetaxel over treatment period: mixed-effect model results[16,20]

	Mean(SD) Baseline Score Nivolumab	Change From Baseline Nivolumab	Mean(SD) Baseline Score Docetaxel	Change From Baseline Docetaxel
3-Item Index	193.1(±63.0)	9.9[b]	192.7(±69.8)	-12.2
Symptom Distress	67.9 ±25.7	2.3	69.3 ±27.4	0.2
Interference with Activity	62.3 ±28.5	4.6[b]	61.5 ±27.8	-5.4
QoL	62.9 ±23.4	6.7[a,b]	61.9 ±27.2	-5.5

[a]P< 0.05 vs. Baseline
[b]P<0.05 for Nivolumab vs. Docetaxel
Positive change from baseline indicates improvement.
MID consists of a change of ≥ 30 points.
Covariates included: baseline PRO score, region, and prior paclitaxel usage

Details of Time to First Disease-Related Deterioration data are listed in Table 6.5e. Only patients with one or more follow-up assessments were included in the time to first disease-related deterioration analysis. In the TTD analysis of the LCSS ASBI and its components (i.e., fatigue, cough, dyspnea, pain) except anorexia, no statically significant difference in time to first-disease-related deterioration was found. In the TTD analysis of the 3-item index and the TTD analyses of

each of its components (symptom distress, interference with activity level, QoL) a statically significant difference in time to first-disease-related deterioration was found.[20]

Table.6.5e CheckMate 017 - Time to First Disease-Related Deterioration for LCSS Measures [a20]		
LCSS Measures	**Hazard Ratio (95% CI)[b]**	***P* value**
Average Symptom Burden Index	0.67(0.43 -1.03)	NS
• Anorexia	0.57(0.37-0.87)	0.009
• Fatigue	0.74(0.50-1.10)	NS
• Cough	0.70(0.46-1.06)	NS
• Dyspnea	0.84(0.58-1.22)	NS
• Hemoptysis	0.59(0.28-1.24)	NS
• Pain	0.78(0.51-1.19)	NS
3-Item Index	0.57(0.38-0.85)	0.005
• Symptom distress	0.65(0.44-0.95)	0.026
• Interference with activity level	0.57(0.39-0.84)	0.004
• QoL	0.58(0.39-0.86)	0.007

CI = confidence interval; QoL = health related quality of life; LCSS = lung cancer symptom scale; NS = not significant.
[a]Reproduced and adapted from Gralla[20] slide 15
[b]Cox proportional hazard model, treating baseline PRO scores as a covariate. Hazard ratio is nivolumab over Docetaxel.

The exploratory objective of the patient-reported outcome assessment using the EQ-5D was to assess patients' overall health status using the EQ-5D Index and visual analog scale.[19]

The results from the patient-reported outcome assessment using the EQ-5D were reported in an abstract at the ESMO European Cancer Congress 2015. The patient-reported outcome assessment using EQ-5D was performed at baseline (cycle 1, day 1 visit), followed by every 4 weeks for nivolumab and every 3 weeks for Docetaxel for the first 6 months on treatment, then every 6 weeks for the remainder of the treatment period for both study groups; followed by two follow-up visits (after treatment discontinuation).[21]

The completion rate at baseline were similar between treatment groups (77.8% in the nivolumab group compared to 76.6% in the Docetaxel group).[67] The EQ-5D completion rate at baseline plus at least one follow-up assessment was 71.9% in the nivolumab group (n=97 out of 135) compared with 64.2% in the Docetaxel group (n=88 out of 137).[21]

The mean baseline EQ-5D Utility Index and VAS scores were similar between nivolumab (0.683, ±0.208; 63.7, ± 18.2) and Docetaxel (0.663, ±0.284; 66.3, ± 20.5). The authors reported a clinical improvement at weeks 24-36, and week 48 [where the EQ-5D Utility Index change scores exceeded the MID (0.08)] in the nivolumab group. The number at risk then dropped to less than 10 patients after week 54. Similar improvements were found in the nivolumab group using the EQ-5D VAS change scores [where the EQ-5D VAS change scores exceeded the MID threshold (7) at week 42 to week 54]. The authors indicated that the EQ-5D Utility Index and VAS scores did not differ from baseline to week 18 in the Docetaxel group; after which the number at risk dropped to fewer than 10 patients.[21]

Response rate, duration of response, and time to response

Details of response rate, duration of response, and time to response for both trials are listed in Table 6.5f.

CheckMate 057 (Non-Squamous NSCLC)

The overall response rate, which was assessed by the investigator, was greater in the nivolumab group compared with the Docetaxel group [19% versus 12%, with an odds ratio of 1.7 (95%CI, 1.1 to 2.6), *P* =0.02]. The complete response rate was minimal in both groups (1% and <1% respectively). The median duration of response was higher in the nivolumab group compared with the Docetaxel group (17.2 versus 5.6 months, no p-value reported). The median time to response was fairly similar in both groups (2.1 versus 2.6 months, no p-value reported). A total of 52% of patients in the nivolumab group (29 of 56 patients) had an ongoing response compared with 14% of patients in the Docetaxel group (5 of 36 patients) who had an ongoing response.[5]

CheckMate 017 (Squamous NSCLC)

The overall response rate, which was also assessed by the investigator, was greater in the nivolumab group compared with the Docetaxel group [20% versus 9%, with an odds ratio of 2.6 (95%CI, 1.3 to 5.5), P=0.008]. The complete response rate was minimal to none in both groups (1% and 0% respectively). The median duration of response was not reached in the nivolumab group, while the median duration of response was 8.4 months in the Docetaxel group. The median time to response was similar in both groups (2.2 versus 2.1 months, no p-value reported). A total of 63% of patients in the nivolumab group (17 of 27 patients) had an ongoing response compared with 33% of patients in the Docetaxel group (4 of 12 patients) who had an ongoing response.[4]

Table 6.5f Response Rate, Duration of Response, and Time to Response

	Non-squamous NSCLC CheckMate 057[a 5,13]		Squamous NSCLC CheckMate 017[c1,4]	
	Nivolumab (n=292)	Docetaxel (n=290)	Nivolumab (n=135)	Docetaxel (n=137)
Objective response rate[†], n(%)	56(19%)	36(12%)	27(20%)	12(9%)
Odds Ratio	1.7(95%CI:1.1-2.6), *P* =0.02		2.6(95%CI:1.3-5.5), *P*=0.008	
Complete response, n(%)	4(1%)	1(<1%)	1(1%)	0
Partial response, n(%)	52(18%)	35(12%)	26(19%)	12(9%)
Median duration of response, months(range)*	17.2(1.8-22.6+)	5.6(1.2+-15.2+)	Not reached (2.9-20.5+)	8.4(1.4+-15.2+)
Median time to response, months(range)*	2.1(1.2-8.6)	2.6(1.4-6.3)	2.2(1.6-11.8)	2.1(1.8-9.5)

CI = confidence interval; NR = not reported; NSCLC = non-small cell lung cancer;
[a]Interim analysis database locked on March 18, 2015
[c]Interim analysis database locked on December 15, 2014
[†]Assessed by the investigator
*Performed with data from all patients who had a response
+Censored value. The value of 1.2+ was censored because the patient discontinued treatment without disease progression. The value of 1.4 was censored because of the start of subsequent therapy in one patient, and the other values were censored because the response was ongoing at the time of the analysis.

b) Harms Outcomes

Details of harms outcomes reported in both trials are listed in Table 6.6.

Serious adverse events

CheckMate 057 (Non-Squamous NSCLC)

Grade 3-4 TRAEs were much less frequent in the nivolumab group compared with the Docetaxel group (10% versus 54%).[5] The association of one death (from encephalitis) in a patient in the nivolumab group was changed from not related to treatment to treatment-related after the database lock.. One death was attributed to Docetaxel (febrile neutropenia).

CheckMate 017 (Squamous NSCLC)

Grade 3-4 TRAEs were less frequent in the nivolumab group compared with the Docetaxel group (7% versus 55%; interim analysis database locked on December 15, 2014).[4] At the time of the interim analysis (database locked on December 15, 2014), no deaths were attributed to nivolumab and three deaths were attributed to Docetaxel (interstitial lung disease, pulmonary hemorrhage, and sepsis).[4] Updated safety data were similar **(**8% versus 56%; updated analysis database locked on June 2015).[1]

Immune related adverse events and treatment related adverse events of special interest

CheckMate 057 (Non-Squamous NSCLC)

Immune related adverse events were reported in CheckMate 057 for diarrhea (8% versus 23%), pruritus (8% versus 1%), rash (9% versus 3%), increased ALT (3% versus 1%), increased AST (3% versus 1%), and pneumonitis (3% versus <1%).The following TRAEs (any grade) of special interest were only reported in the nivolumab group: hypothyroidism (7%), hyperthyroidism (1%), colitis (1%). The following TRAEs (any grade) of special interest were reported in the nivolumab group and docetaxel group: fatigue (16% versus 29%), nausea (12% versus 26%), neutropenia (<1% versus 31%).[5,13]

CheckMate 017 (Squamous NSCLC)

Immune related adverse events were reported in CheckMate 057 for diarrhea (8% versus 20%), rash (4% versus 6%), increased ALT (2% versus 1%), increased AST (2% versus 1%). The following TRAEs (any grade) of special interest were only reported in the nivolumab group: pneumonitis (5%), hypothyroidism (4%), pruritus (2%) colitis (1%). The following TRAEs (any grade) of special interest were reported in the nivolumab group and docetaxel group: fatigue (16% versus 33%), neutropenia (1% versus 33%), nausea (9% versus 23%).[1,4,18]

Withdrawal due to adverse events

CheckMate 057 (Non-Squamous NSCLC)

Discontinuation of study drug due to TRAE was less frequently reported in patients in nivolumab group compared with patients in the Docetaxel group (5% versus 15%).[5] The most common TRAE which led to discontinuation of study drug was pneumonitis in the nivolumab group (1%) and fatigue in the Docetaxel group (3%).[13]

CheckMate 017 (Squamous NSCLC)

Discontinuation of study drug due to TRAE was less frequently reported in patients in nivolumab group compared with patients in the Docetaxel group (3% versus 10%).[4] At the time of the interim analysis (database locked on December 15, 2014), the most common TRAE which led to discontinuation of study drug was pneumonitis in the nivolumab group (2%) and peripheral neuropathy in the Docetaxel group (3%).[18] Two additional patients in the nivolumab group discontinued treatment due to pneumonitis (one for whom causality was changed from not-related

to treatment-related after database lock (December 15, 2014), and one who was discontinued greater than 30 days after the most recent nivolumab dose).[18]

Table 6.6 Harms Outcomes								
	Non-squamous NSCLC CheckMate 057[a5,13]				Squamous NSCLC CheckMate 017[b1,4,18]			
	Nivolumab (n=287)		Docetaxel (n=268)		Nivolumab (n=131)		Docetaxel (n=129)	
	Any	Grade 3 or 4	Any	Grade 3 or 4	Any	Grade 3 or 4	Any	Grade 3 or 4
Any TRAEs	199(69%)	30(10%)	236(88%)	144(54%)	NR(59%)[c] 76(58%)	NR(8%)[c] 9(7%)	NR(87%)[c] 111(86%)	NR(56%)[c] 71(55%)
Skin								
Pruritus	24(8%)	0	4(1%)	0	3(2%)	0	0	0
Rash	27(9%)	1(<1%)	8(3%)	0	5(4%)	0	8(6%)	2(2%)
Gastrointestinal								
Diarrhea	22(8%)	2(1%)	62(23%)	3(1%)	NR(8%)[c] 10(8%)	NR(1%)[c] 0	NR(20%)[c] 26(20%)	NR(2%)[c] 3(2%)
Colitis	2(1%)	1(<1%)	0	0	1(1%)	1(1%)	0	0
Nausea	34(12%)	2(1%)	70(26%)	2(1%)	NR(9%)[c] 12(9%)	NR(0%)[c] 0	NR(23%)[c] 30(23%)	NR(2%)[c] 2(2%)
Hepatic								
Increase in ALT	9(3%)	0	4(1%)	1(<1%)	2(2%)	0	1(1%)	1(1%)
Increase in AST	9(3%)	1(<1%)	2(1%)	0	2(2%)	0	1(1%)	1(1%)
Endocrine								
Hypothyroidism	19(7%)	0	0	0	5(4%)	0	0	0
Hyperthyroidism	4(1%)	0	0	0	NR	NR	NR	NR
Pulmonary								
Pneumonitis	8(3%)	3(1%)	1(<1%)	1(<1%)	6(5%)	1(1%)	0	0
General								
Fatigue	46(16%)	3(1%)	78(29%)	13(5%)	NR(16%)[c] 21(16%)	NR(1%)[c] 1(1%)	NR(33%)[c] 42(33%)	NR(8%)[c] 10(8%)
Neutropenia	1(<1%)	0	83(31%)	73(27%)	NR(1%)[c] 1(1%)	NR(0%)[c] 0	NR(33%)[c] 42(33%)	NR(30%)[c] 38(30%)
TRAEs leading to discontinuation	14(5%)	11(4%)	40(15%)	18(7%)	4(3%)	2(2%)	13(10%)	8(6%)
Death due to toxic effect of study drug	1[†]	-	1*	-	0	-	3[‡]	-

ALT = alanine aminotransferase; AST = aspartate aminotransferase, NSCLC = non-small cell lung cancer; NR = not reported; TRAE = treatment-related adverse events

[a]Interim analysis database locked on March 18, 2015, events reported between the first dose and 30 days after last dose of study drug.

[b]Interim analysis database locked on December 15, 2014, events reported between the first dose and 30 days after last dose of study drug.

[c]Updated TRAEs database locked on June 2015, events reported between the first dose and 30 days after last dose of study drug.

[†]1 death attributed to nivolumab (encephalitis), causality was later changed after the database lock. *1 death attributed to Docetaxel (febrile neutropenia).

[‡]3 deaths attributed to Docetaxel (interstitial lung disease, pulmonary hemorrhage, and sepsis).

6.4 Ongoing Trials

Details of relevant ongoing trials are listed in Table 6.7. One ongoing trial that met our inclusion criteria was identified in our search. The purpose of the phase III, multinational, randomized, open label study is to determine whether nivolumab improves life expectancy compared to Docetaxel in subjects with advanced or metastatic NSCLC who have failed prior platinum-based doublet chemotherapy.[70] The study start date was December 2015 and the estimated complete date for primary outcome measure is April 2018. As of March 7, 2016, the study is not yet open for participant recruitment; centre locations are not report, nor are nivolumab and Docetaxel dose and schedule.

Table 6.7 Ongoing Trial of Nivolumab for NSCLC [70]

Trial Design	Eligibility Criteria	Intervention and Comparator	Outcomes
CheckMate 078 NCT02613507 Phase III, Multinational, Randomized, Open Label Study Study Start Date: December 2015 Status: Not yet open for participant recruitment (Last verified March 7, 2016) Estimated Enrollment: 500 Estimated Study Completion Date: December 2018 Estimated Primary Completion Date: April 2018 (Final data collection date for primary outcome measure) Sponsor: Bristol-Myers Squibb	Inclusion Criteria: • Disease progression experienced during or after one prior platinum containing doublet chemotherapy • Stage IIIb/IV or recurrent disease • Male and female ≥ 18 years of age • Measurable disease per RECIST 1.1 • Performance status ≤ 1 Exclusion Criteria: • History of Carcinomatous meningitis • Active central nervous system metastases • History of auto immune diseases • Prior treatment with Docetaxel • Prior treatment with ipilimumab or any drug targeting T-Cell costimulation or checkpoint pathways	Intervention: Nivolumab intravenous infusion specified dose on specified days† Comparator: Docetaxel intravenous infusion specified dose on specified days‡	Primary: • OS[a] Secondary: • ORR[b] • PFS[c] • Rate of disease-related symptom improvement[d]

ORR = objective response rate; OS = overall survival; PFS = progression free survival; RECIST = Response Evaluation Criteria in Solid Tumours.
† As of March 7, 2016 nivolumab specified dose on specified days were not reported
‡ As of March 7, 2016 Docetaxel specified dose on specified days were not reported
[a] defined as the time from randomization to the date of death
[b] defined as the number of subjects whose best overall response of complete response or partial response divided by the number of randomized subjects.
[c] defined as the time from randomization to the date of the first documented tumor progression as determined by investigators per RECIST 1.1, or death due to any cause
[d] Proportion of subjects exhibiting disease related symptoms improvements as measured by Lung Cancer Symptom Scale

7 SUPPLEMENTAL QUESTIONS

The following supplemental questions were identified as relevant to the pCODR review of nivolumab for the treatment of patients with advanced or metastatic NSCLC who progressed on or after chemotherapy:

- Critical appraisal of a manufacturer-submitted indirect treatment comparison (ITC) of the relative efficacy and safety of nivolumab versus pemetrexed among advanced non-squamous cell NSCLC patients.

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

7.1 Critical Appraisal of Indirect Treatment Comparison of Nivolumab versus Pemetrexed

7.1.1 Objective

The objective of this section is to summarize and critically appraise the methods and findings of the manufacturer-submitted ITC of relative efficacy and safety of nivolumab versus pemetrexed among advanced non-squamous cell NSCLC patients receiving second-line or higher-line therapy.

The following are reasons for which this critical appraisal was necessary:

- Pemetrexed was identified as a relevant comparison in the protocol,
- No available direct comparison of nivolumab to pemetrexed,
- The manufacturer-submitted an economic evaluation which included a pemetrexed as a comparator.

It is worth noting that along with the indirect comparison of nivolumab versus pemetrexed in the non-squamous cell NSCLC population, the manufacturer included an ITC of nivolumab versus erlotinib in the squamous cell and non-squamous cell NSCLC populations. However, given that that erlotinib is relevant to a subgroup of NSCLC patients, the focus of this critical appraisal was on the comparison of nivolumab versus pemetrexed in the non-squamous cell NSCLC population.

7.1.2 Findings

The manufacturer submitted an ITC with the primary objective of assessing the relative efficacy (measured by PFS, OS, and ORR, where available) of nivolumab versus pemetrexed, and an exploratory objective of assessing the relative safety of nivolumab versus pemetrexed among the second and third line non-squamous cell NSCLC population.

Systematic Literature Review

A detailed systematic review report was provided by the submitter.[71] The submitter commissioned a systemic literature review in two phases. Phase I included relevant RCTs published before June 2014 and it appeared that PubMed, the Cochrane Systematic Literature Reviews, and ClinicalTrials.gov were searched.[71] Phase II included relevant RCTs published from June 2014 to May 2015 and the authors stated that additional databases were searched (EMBASE, Cochrane Central Register of Controlled Trials, as Web of Science) and that search terms were broadened. In the ITC report, the authors also stated that reports from unpublished sources such as abstracts from conferences were included; however, upon review of the detailed systematic review report provided by the submitter, it is unclear which conferences were searched and if the abstracts from conferences were searched in both phases.

Inclusion was limited to studies that:

- assessed patients with advanced or recurrent NSCLC (i.e., stage IIIB or IV);
- included patients 18 years or older and tested the drug of interest as a second-line/third-line treatment;
- were phase II or phase III RCTs;
- presented the results of the trial (not trial rationale and design);
- were published through May 2015 and in English language.

Studies were excluded if the tested drug of interest was in combination with radiotherapy; and did not present the outcomes of interest (i.e., response rate, OS, or PFS).

Data Preparation

Additional inclusion criteria for data synthesis included:

- a common comparator drug with a similar dose (i.e., Docetaxel dose of 75mg/m^2) in the treatment group or a comparator therapy that could be linked through another study to CheckMate 057;
- and efficacy data on OS and PFS.

As noted above, the authors stated that a common comparator drug with a similar dose was an additional inclusion criterion. Upon assessment of the detailed systematic review provided by the submitter,[71] patients were given Docetaxel dose of 60 mg/m^2 [not Docetaxel dose of 75mg/m^2] or erlotinib dose of 150 mg every day in one included study.

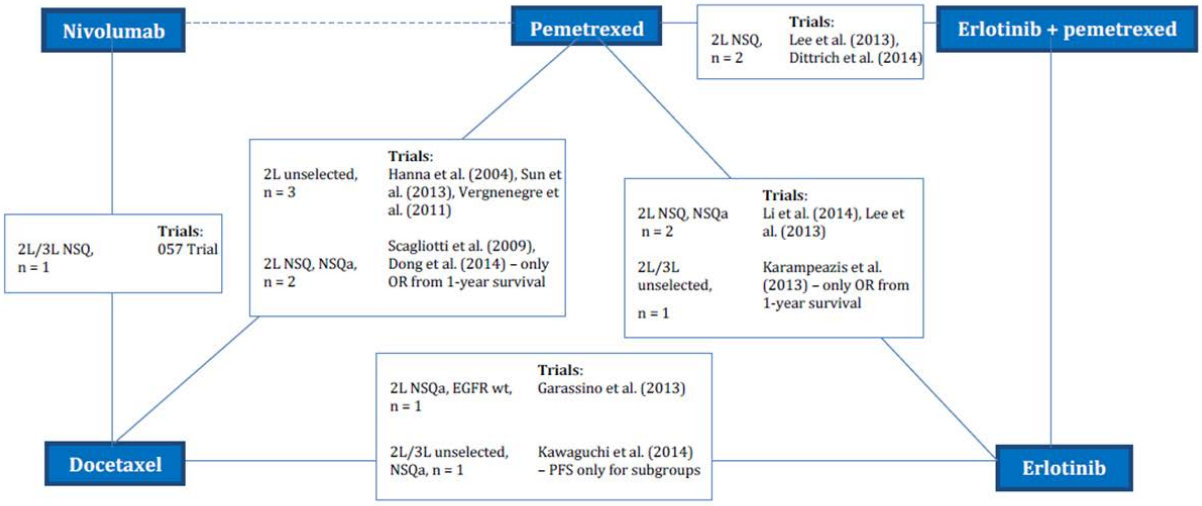
The authors also stated that in the absence of an ideal comparator trial for a particular comparator, inclusion criteria were expanded to capture studies that reported on patients with unselected NSCLC, adenocarcinoma or non-squamous cell NSCLC patients receiving interventions as a second line therapy or higher therapy.

If more than one comparator trial existed for the same pair of treatments, the authors pooled the efficacy data using a random effects model (from the meta-analysis approach) prior to performing the ITC.

Indirect Treatment Comparison

The network diagram included in the indirect treatment comparison provided by the manufacturer can be found in Figure 7.1. In addition to CheckMate 057, a total of 10 unique trials (from 11 sources) were identified as relevant for the nivolumab versus pemetrexed comparison.

Figure 7.1 Overview of indirect treatment comparisons between nivolumab and pemetrexed



Populations included in ITCs: EGFR = Epidermal growth factor receptor; NSQ = Non-squamous; NSQa = Non-squamous adenocarcinoma; unselected = NSCLC patients of all histologies; wt = Wild type.
Line of therapy: 2L = Second-line; 2L/3L = Second- or third-line.
Outcomes: OR = Odds ratio; PFS = Progression-free survival.
n = number of trials; dashed line indicates indirect comparison and solid line indicates direct comparison.

For each comparator for which at least one comparable trial was found, the Bucher method was applied to conduct the ITC. The authors stated that when appropriate, the Bucher method was expanded to create a more complex network where a series of common comparators were used to connect nivolumab to the comparator of interest.

The base case ITC analysis included trials that included data on the non-squamous cell NSCLC only population, regardless of whether data were reported at the subgroup or ITT population level. For some trials, subgroup data were reported for non-squamous cell NSCLC or non-squamous adenocarcinoma histologies, and for other trials the entire intent-to-treat (ITT) population consisted of non-squamous cell NSCLC patients.

Two sensitivity analyses were conducted: (i) ITT only, also referred to as the unselected NSCLC population (which included data reported on the ITT population for all trials, and therefore for most trials, both squamous and non-squamous cell NSCLC populations were included) and (ii) non-squamous cell NSCLC or ITT (which included data reported from the non-squamous cell NSCLC population regardless of whether data were reported at the subgroup or ITT population level, and data from the unselected NSCLC population, if data were not reported separately for the non-squamous cell NSCLC population).

Although the results of the sensitivity analyses (based on ITT and non-squamous cell NSCLC or ITT) were consistent with the results from the base case analysis (based on non-squamous cell NSCLC only), it appears that the sensitivity analyses were not able to validate the base case analysis, given that a mixed population of squamous and non-squamous cell NSCLC patients were included in the sensitivity analyses. As a result, further details on the sensitivity analysis results are not reported in this appraisal.

Similarly, grade 3 or 4 adverse event results (i.e., the pooled risk ratios of pemetrexed versus Docetaxel, the risk ratio estimates of nivolumab versus pemetrexed) are not reported in this appraisal, given that the safety data from the ITC included the ITT population rather than the

non-squamous cell NSCLC only population (and therefore for most trials, both the squamous and non-squamous cell NSCLC populations were included).

A summary of the objective, trial type, outcomes of the studies included in the base case analysis, as well as the population used in the base case analysis can be found in Table 7.1a. Also a summary of selected baseline characteristics of trials included in the base case analysis can be found in Table 7.1b.

There are significant differences in the baseline characteristics of the studies included in the base case analysis. For example, the majority of studies included in the base case analysis had only second-line patients, whereas CheckMate 057 included second- and third-line patients. In CheckMate 057, the majority of patients were white; however, in two studies included in the base case analysis, there were no white patients. In CheckMate 057, patients with an ECOG performance status of 2 or greater were excluded; however, it appears that the studies in the base case analysis included patients with an ECOG performance status of 2 or greater. Most patients in CheckMate 057 were current or former smokers; in one study included in the base case analysis, only never smokers were included. Between 13.1%-15.1% of patients included in CheckMate 057 were EGFR mutation positive, one study in the base case analysis only included EGFR wild-type patients. In addition to significant differences in the baseline characteristics, there is added uncertainty in the reported results given that for some studies included in the base case analysis, certain baseline characteristics were not reported.

Table 7.1a Summary of Trials Included in the Base Case ITC Analysis

Trials Included	Objective of Included Trial/Study	Type of Trial	Outcomes of Trial	Population in Base Case Analysis
CheckMate 057 Borghaei[5]	To compare nivolumab with Docetaxel in patients with non-squamous cell NSCLC that had progressed during or after platinum-based doublet chemotherapy.	Phase III, open label RCT (N=582)	Primary: OS Secondary: PFS, ORR, PD-L1 expression, HRQoL	2L/3L non-squamous cell NSCLC (N=582)
Scagliotti[72]	To review the differential efficacy of pemetrexed according to histology in two large, phase III NSCLC trials (the relevant trial was a study that tested pemetrexed versus Docetaxel in previously treated patients).	Phase III, RCT (n=571)	Primary: OS Secondary: PFS, TTP, TTF, tumour RR, duration of response, toxicity	2L non-squamous cell NSCLC (n=399)
Dong[73]	To compare the therapeutic effects and adverse reactions of pemetrexed and Docetaxel as salvage chemotherapy in patients with NSCLC after the failure of EGFR-TKI.	Phase I,I RCT (N=109)	Primary: survival Secondary: response rate	2L non-squamous adenocarcinoma (n=104)
Garassino[74]	To compare erlotinib with Docetaxel in patients who failed first-line platinum-based chemotherapy and who had the wild-type EGFR gene.	RCT (N=222)	Primary: OS Secondary: PFS, ORR, QoL	2L non-squamous adenocarcinoma, EGFR wild-type (n=152)
Kawaguchi[75]	To investigate the efficacy of erlotinib versus Docetaxel in previously treated patients with advanced NSCLC in EGFR-unselected patient population.	Phase III, open-label RCT (N=301)	Primary: PFS Secondary: OS, response rate, safety, and analyses on *EGFR*	2L/3L non-squamous adenocarcinoma (n=207)

Table 7.1a Summary of Trials Included in the Base Case ITC Analysis				
Trials Included	**Objective of Included Trial/Study**	**Type of Trial**	**Outcomes of Trial**	**Population in Base Case Analysis**
			wild-type tumors.	
Li[76]	To assess the efficacy and safety of erlotinib compared with pemetrexed as second-line treatment of patients with EGFR wild-type and EGFR FISH-positive lung adenocarcinoma.	Phase II, open label RCT (N=123)	Primary: PFS Secondary: ORR, OS, and safety and tolerability	2L non-squamous adenocarcinoma (N=123)
Lee[77]	To compared pemetrexed and erlotinib in combination with either agent alone in terms of efficacy and safety as second-line treatment in a clinically selected population of never-smokers with non-squamous cell NSCLC	Phase II, open label RCT(N=240)	Primary: PFS Secondary: OS, Tumour response rate, disease control rate	2L non-squamous cell NSCLC (N=240)
Dittrich[78]	To evaluate PFS of pemetrexed and pemetrexed plus erlotinib in an overall advanced NSCLC patient population. In this paper, authors focused on the analyses of the enrolled non-squamous cell NSCLC patients. To assess efficacy and safety of pemetrexed versus pemetrexed + erlotinib in patients with advanced non-squamous cell NSCLC.	Phase II, open label RCT (N=211)	Primary: PFS Secondary: OS, TTF, response rate and toxicity	2L non-squamous cell NSCLC (n=165)

EGFR = epidermal growth factor receptor; NSCLC = non small cell lung cancer; OS = overall survival; PFS = progression-free survival; RCT = randomized controlled trial; TKI = tyrosine kinase inhibitors; TTP = time to progression; TTF: time to failure.

Table 7.1b Selected Baseline Characteristics Trials Included in Base Case Analysis†							
Trials Included	**Range (Yrs) of Median Age**	**Range(%) of Males**	**Range(%) of White**	**Range(%) ECOG PS of 2**	**Range(%) of Current or Former Smoker**	**Range(%) of EGFR Mutation Positive**	**Range(%) of Stage IV**
Borghaei_CheckMate 057[5]	61.0-64.0	51.7-57.9	91.4-91.7	0.0	78.3-79.1	13.1-15.1	91.7-93.2
Scagliotti[72] Dong[73] Garassino[74] Li[76] Lee[77] Dittrich[78] Kawaguchi[75]	53.9-67 Scagliotti[72] Median age NR	25.6-70.6	0.0-99.1 Dong[73] Li[76] Race NR	4.0-13.2 Lee[77] Reported ECOG PS 2 or 3	0.0-86.8 Scagliotti[72] Dong[73] Smoking Status NR	0.0-21.9 Scagliotti[72] Dong[73] Li[76] Lee[77] Dittrich[78] EGFR Mutation Status NR	61.3-92.3 Garassino[74] Stage not reported

ECOG PS = Eastern Cooperative Oncology Group performance status; EGFR = epidermal growth factor receptor; NR = not reported.
†Adapted from manufacturer-submitted ITC

In the base case analysis, reported hazard ratio or odds ratio estimates of nivolumab versus Docetaxel (direct comparison) for efficacy outcomes and pooled hazard ratio or odds ratio estimates of pemetrexed versus Docetaxel (direct and indirect comparison) for efficacy outcomes are listed in Table 7.2.

Table 7.2 Pooled estimates of reported OS and PFS hazard ratio, and overall response odds ratio for nivolumab and pemetrexed versus Docetaxel among previously treated NSCLC population†

Outcome	Study Populations from Trials Included for Comparison	Drug (versus Docetaxel)	Trials Included	Pooled or Reported Hazard Ratio or Odds Ratio (95%CI)
OS	Second-line/third-line non-squamous cell NSCLC	nivolumab	1	0.73(0.59,0.89)
OS	Second-line/third-line non-squamous cell NSCLC, non-squamous adenocarcinoma EGFR wild-type	pemetrexed	6	0.92(0.66,1.29)
PFS	Second-line/third-line non-squamous cell NSCLC	nivolumab	1	0.92(0.77,1.11)
PFS	Second-line/third-line non-squamous cell NSCLC, non-squamous adenocarcinoma EGFR wild-type	pemetrexed	6	1.01(0.64,1.59)
Overall Response	Second-line/third-line non-squamous cell NSCLC	nivolumab	1	1.67(1.06,2.64)
Overall Response	Second-line/third-line non-squamous cell NSCLC, non-squamous adenocarcinoma EGFR wild-type	pemetrexed	2	1.16(0.68,1.95)

CI = confidence interval; EGFR = epidermal growth factor receptor; NSCLC = non small cell lung cancer; OS = overall survival; PFS = progression-free survival.
†Adapted from manufacturer-submitted ITC

In the base case analysis, OS and PFS hazard ratio estimates, and overall response odds ratio estimates of nivolumab versus pemetrexed for efficacy outcomes are listed in Table 7.3.

Table 7.3 OS and PFS hazard ratio estimates, and overall response odds ratio estimates from indirect comparison of nivolumab versus pemetrexed among previously treated NSCLC population†

Outcome	Trials Included	Hazard Ratio or Odds Ratio (95%CI)
Overall Survival	7	0.79(0.54,1.17)
Progression Free Survival	7	0.91(0.56,1.48)
Overall Response	2	1.45(0.72,2.89)

CI = confidence interval; NSCLC = non small cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival.
†Adapted from manufacturer-submitted ITC

Limitations

The credibility of the manufacturer-submitted ITC was assessed in accordance with the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparison.[79,80] Details and commentary with respect to the manufacturer-submitted ITC for each items identified by the ISOR Task Force are provided in Table 7.4.

Table 7.4 ISPOR Questionnaire to Assess the Credibility of an Indirect Treatment Comparison or Network Meta-Analysis[†]	
ISPOR Questions	**Details and Comments[‡]**
1. Is the population relevant?	Yes. Second-line/third-line non-squamous cell NSCLC population.
2. Are any critical interventions missing?	No.
3. Are any relevant outcomes missing?	**Yes, in part.** OS, PFS, response rate and safety outcomes were considered. Time to response, duration of response, and HRQoL were not considered. However, the most relevant outcome, OS, was considered.
4. Is the context (e.g., settings and circumstances) applicable to your population?	Yes.
5. Did the researchers attempt to identify and include all relevant randomized controlled trials?	Yes. In the ITC report, a summary of the systematic literature review process was provided and this included the information sources, search strategy, study selection criteria, and data extraction process. A detailed systematic review report was also provided by the submitter.[71]
6. Do the trials for the interventions of interest form one connected network of randomized controlled trials?	Yes. Anchored indirect treatment comparison.
7. Is it apparent that poor quality studies were included thereby leading to bias?	No. Within the detailed systematic review provided by the submitter, key study characteristics of each RCT such as method of randomization, treatment allocation concealment, blinding of outcome assessor, and dropout were reported.
8. Is it likely that bias was induced by selective reporting of outcomes in the studies?	No. The Methods team performed a "check" to identify whether any of the selected studies did not report some of the outcomes of interest and were therefore not included in some of the network meta-analyses of the different end points. Selected studies did report outcomes of interest when appropriate. The Methods team performed a "check" on the reasons studies were excluded and no eligible studies were excluded only because the outcome of interest. The stated reasons for exclusion were the following: first line use, Phase 1, economic modeling, studies on biomarkers, concomitant radiotherapy, terminated studies, maintenance therapy, single group studies, editorials and letters to editors.
9. Are there systematic differences in treatment effect modifiers (i.e. baseline patient or study characteristics that impact the treatment effects) across the different treatment comparisons in the network?	**Yes.** (see Table 7.1a and Table 7.1b) The authors provided a qualitative assessment of heterogeneity; however, the Methods team felt that both quantitative and qualitative assessment of the heterogeneity would have been helpful. The Methods team acknowledged the authors' rule of thumb used (at least four trials) to perform a Cochran's Q-test; however, it felt that with the Docetaxel versus pemetrexed pairwise direct comparison, a Cochran's Q-test could have been performed given that a total of 5 trials were included.
10. If yes (i.e. there are such systematic differences in treatment effect modifiers), were these imbalances in effect modifiers across the different treatment comparisons identified prior to comparing individual study results?	**Not reported.** The authors of the report stated that they used qualitative approaches to assess patient baseline characteristics such as age, gender, ECOG performance status, histology, and line of therapy, across the trials for similarities and notable differences. However, **it is unclear if the effect modifiers across the different treatment comparisons were identified prior to comparing individual study results.**
11. Were statistical methods used that preserve within-study randomization? (No naïve comparisons)	Yes. Bucher Method.
12. If both direct and indirect comparisons are available for pairwise contrasts (i.e. closed loops), was agreement in treatment effects (i.e. consistency) evaluated or discussed?	Not applicable.

Table 7.4 ISPOR Questionnaire to Assess the Credibility of an Indirect Treatment Comparison or Network Meta-Analysis[†]	
ISPOR Questions	**Details and Comments[‡]**
13. In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the network meta-analysis?	Not applicable.
14. With inconsistency or an imbalance in the distribution of treatment effect modifiers across the different types of comparisons in the network of trials, did the researchers attempt to minimize this bias with the analysis?	**No.** There were imbalances in the distribution of treatment effect modifiers across the different types of comparisons in the network of trials (see Table 7.1b). Meta-regression analysis or models with inconsistency factors were not performed.
15. Was a valid rationale provided for the use of random effects or fixed effect models?	Not applicable. Bayesian random effects or fixed effect model was not used for the network.
16. If a random effects model was used, were assumptions about heterogeneity explored or discussed?	Not applicable.
17. If there are indications of heterogeneity, were subgroup analyses or meta-regression analysis with pre-specified covariates performed?	**No.** Subgroup analysis or meta-regression analysis was not performed.
18. Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison?	Yes. Refer to Figure 7.1.
19. Are the individual study results reported?	**No.** The submitter did not provide the individual study results in the ITC report.
20. Are results of direct comparisons reported separately from results of the indirect comparisons or network meta-analysis?	**No.** Although the results (i.e., overall hazard ratio, odds ratio, and risk ratio estimates) of the direct comparison of nivolumab versus Docetaxel were provided, only the pooled results of pemetrexed versus Docetaxel (which included direct and indirect comparison) were reported. The pooled or reported results from the direct comparisons of pemetrexed versus Docetaxel, Docetaxel versus erlotinib, pemetrexed versus erlotinib, and pemetrexed versus erlotinib were not reported.
21. Are all pairwise contrasts between interventions as obtained with the network meta-analysis reported along with measures of uncertainty?	**No.** Although the results and measures of uncertainty of the direct comparison of nivolumab versus Docetaxel were provided, only the pooled results and measures of uncertainty for pemetrexed versus Docetaxel (which included direct and indirect comparison) were reported. The pooled or reported results and measures of uncertainty from the direct comparisons of pemetrexed versus Docetaxel, Docetaxel versus erlotinib, pemetrexed versus erlotinib, pemetrexed versus erlotinib were not reported.
22. Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome?	Not applicable.
23. Is the impact of important patient characteristics on treatment effects reported?	Yes.
24. Are the conclusions fair and balanced?	The Methods team would like to emphasise that although it may appear that nivolumab shows trends of having better efficacy compared to pemetrexed, **there is much uncertainty in the reported results. Differences in the trial characteristics may have affected the treatment effects observed in each trial, thus violating the similarity assumption.**
25. Were there any potential conflicts of interest?	**Not reported.**
26. If yes, were steps taken to address these?	Not applicable.

Table 7.4 ISPOR Questionnaire to Assess the Credibility of an Indirect Treatment Comparison or Network Meta-Analysis[†]	
ISPOR Questions	**Details and Comments[‡]**
HRQoL = health-related quality of life; ISPOR = International Society For Pharmacoeconomics and Outcomes Research; ITC = indirect treatment comparison; ITT = intent to treat; NSCLC = non small cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival. [†] Adapted from Jansen et al [79,80]. [‡]Bolded comments are considered a weakness of the ITC.	

7.1.3 Summary and Interpretation

The validity of manufacturer's ITC hinges on three important assumptions: (1) homogeneity; (2) transitivity/similarity; and, (3) consistency. There is a high uncertainty with this NMA since the differences in the trial characteristics may have affected the treatment effects observed in each trial, thus violating the similarity assumption and confounding these comparisons. Statistical heterogeneity among the pairwise comparisons in the network was not explored formally with statistical tests. The Methods team acknowledged the authors' rule of thumb (at least four trials) to perform a Cochran's Q-test, but felt that with the Docetaxel versus pemetrexed pairwise direct comparison, a Cochran's Q-test could have been performed.

The Methods teams felt there was a lack of a systematic approach in trial selection and limited details on the literature review approach. For instance, the literature review was performed in two phases and the databases searched and the search terms used were expanded for phase II of literature review, but not applied in phase I.

The Methods teams felt that the sensitivity analyses (based on ITT only and non-squamous cell NSCLC or ITT) did not serve its purpose to validate the base case analysis (based on non-squamous cell NSCLC only), and felt that the results from the sensitivity analysis did not add value.

The Methods teams agreed that the Bucher method was appropriate; however, it felt that a Bayesian random effects or fixed effects model could have been applied to the network in addition to the applied Bucher Method. The results from a random effects or fixed effects model may have supported the findings and resulted in the Methods team being more confident in the results.

The Methods team would like to emphasise that although it may appear that nivolumab shows trends of having better efficacy compared pemetrexed, there is much uncertainty in the reported results. Therefore, the reported results should be interpreted with caution.

8 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Lung Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on nivolumab and NSCLC. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the CADTH website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report. Note that no revision was made in between posting of the Initial and Final Clinical Guidance Reports.

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

APPENDIX A: LITERATURE SEARCH STRATEGY

See section 6.2.2 for more details on literature search methods.

1. Literature search via OVID platform

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** September 2015, **Embase** 1974 to 2015 November 05, **Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present
Search Strategy:

#	Searches	Results
1	(Opdivo* or nivolumab* or 946414-94-4 or MDX 1106 or MDX1106 or BMS936558 or BMS 936558 or ONO4538 or ONO 4538 or UNII-31YO63LBSN).ti,ot,ab,rn,hw,nm,kf.	1533
2	Carcinoma, Non-Small-Cell Lung/ or NSCLC.ti,ab.	87552
3	(exp Adenocarcinoma/ or Carcinoma, Large Cell/ or exp Carcinoma, Squamous Cell/ or Carcinoma, Adenosquamous/ or Carcinoma/) and (lung* or pulmonary or bronchial).ti,ab.	78754
4	((non-small cell or nonsmall cell or large cell or squamous or bronchoalveolar or bronchiolo alveolar) and (neoplasm* or cancer* or carcinoma* or tumor* or tumour* or adenocarcinoma*) and (lung* or pulmonary or bronchial)).ti,ab.	139547
5	or/2-4	199896
6	1 and 5	312
7	6 use pmez	85
8	6 use cctr	4
9	7 or 8	89
10	*nivolumab/ or (Opdivo* or nivolumab* or MDX 1106 or MDX1106 or BMS936558 or BMS 936558 or ONO4538 or ONO 4538 or UNII-31YO63LBSN).ti,ab.	656

11	Non small cell lung cancer/ or NSCLC.ti,ab.	90325
12	(exp Adenocarcinoma/ or Large cell carcinoma/ or exp Squamous cell carcinoma/ or Carcinoma/) and (lung* or pulmonary or bronchial).ti,ab.	78359
13	((non-small cell or nonsmall cell or large cell or squamous or bronchoalveolar or bronchiolo alveolar) and (neoplasm* or cancer* or carcinoma* or tumor* or tumour* or adenocarcinoma*) and (lung* or pulmonary or bronchial)).ti,ab.	139547
14	or/11-13	200916
15	10 and 14	224
16	15 use oemezd	156
17	9 or 16	245
18	limit 17 to english language	243
19	remove duplicates from 18	181

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

Search	Query	Items found
#10	**Search #6 OR #9**	6
#9	**Search #1 AND(#2 OR #3 OR #4) Filters: Publication date from 2015/11/02 to 2015/11/06; English**	1
#8	**Search #1 AND(#2 OR #3 OR #4) Filters: English**	76
#7	**Search #1 AND(#2 OR #3 OR #4)**	77
#6	**Search #5 AND publisher[sb]**	6

Search	Query	Items found
#5	Search #1 AND (#2 OR #3 OR #4)	77
#4	Search (non-small cell[tiab] OR nonsmall cell[tiab] OR large cell[tiab] OR squamous[tiab] OR bronchoalveolar[tiab] OR bronchiolo alveolar[tiab]) AND (neoplasm*[tiab] OR cancer*[tiab] OR carcinoma*[tiab] OR tumor*[tiab] OR tumour*[tiab]) AND (lung*[tiab] OR pulmonary[tiab] OR bronchial[tiab])	55298
#3	Search (Adenocarcinoma[mh] OR Carcinoma, Large Cell[mh] OR exp Carcinoma, Squamous Cell[mh] OR Carcinoma, Adenosquamous[mh] OR Carcinoma[mh:noexp]) AND (lung*[tiab] OR pulmonary[tiab] OR bronchial[tiab])	38719
#2	Search Carcinoma, Non-Small-Cell Lung[mh] OR NSCLC[tiab]	41533
#1	Search nivolumab[Supplementary Concept] OR nivolumab*[tiab] OR Opdivo*[tiab] OR 946414-94-4[rn] OR MDX 1106[tiab] OR MDX1106[tiab] OR BMS936558[tiab] OR BMS 936558[tiab] OR ONO4538[tiab] OR ONO 4538[tiab]	293

3. Cochrane Central Register of Controlled Trials (Central)

   Searched via Ovid

4. Grey Literature search via:

Clinical trial registries:

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

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

Search terms: Opdivo/nivolumab + NSCLC

Select international agencies including:

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

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

Search terms: Opdivo/nivolumab + NSCLC

Conference abstracts:

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

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

Search terms: Opdivo/nivolumab + NSCLC, the last 5 years

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