CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Durvalumab (Imfinzi) for Non-Small Cell Lung Cancer

May 3, 2019

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TABLE OF CONTENTS

DISCLAIMER ii

FUNDING ii

INQUIRIES iii

TABLE OF CONTENTS iv

1 GUIDANCE IN BRIEF 1
1.1 Introduction 1
1.2 Key Results and Interpretation 1
1.2.1 Systematic Review Evidence 1
1.2.2 Additional Evidence 3
1.2.3 Factors Related to Generalizability of the Evidence 5
1.2.4 Interpretation 10
1.3 Conclusions 13

2 BACKGROUND CLINICAL INFORMATION 15
2.1 Description of the Condition 15
2.2 Accepted Clinical Practice 15
2.3 Evidence-Based Considerations for a Funding Population 17
2.4 Other Patient Populations in Whom the Drug May Be Used 17

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT 19
3.1 Condition and Current Therapy Information 20
3.1.1 Experiences Patients have with NSCLC 20
3.1.2 Patients' Experiences with Current Therapy for NSCLC 21
3.1.3 Impact of NSCLC and Current Therapy on Caregivers 22
3.2 Information about the Drug Being Reviewed 22
3.2.1 Patient Expectations for and Experiences To Date with NSCLC 22
3.3 Additional Information 24

4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT 25
4.1 Currently Funded Treatments 25
4.2 Eligible Patient Population 25
4.3 Implementation Factors 26
4.4 Sequencing and Priority of Treatments 26
4.5 Companion Diagnostic Testing 26
4.6 Additional Information 26

5 SUMMARY OF REGISTERED CLINICIAN INPUT 27

5.1 Current Treatment(s) for NSCLC 27

5.2 Eligible Patient Population 27

5.3 Relevance to Clinical Practice 28

5.4 Sequencing and Priority of Treatments with Durvalumab 29

5.5 Companion Diagnostic Testing 29

5.6 Additional Information 29

6 SYSTEMATIC REVIEW 31
6.1 Objectives 31
6.2 Methods 31
6.3 Results 32

6.3.1 Literature Search Results 32
6.3.2 Summary of Included Studies 33
6.4 Ongoing Trials 57
7 SUPPLEMENTAL QUESTIONS 58
8 COMPARISON WITH OTHER LITERATURE 59
9 ABOUT THIS DOCUMENT 58
APPENDIX A: LITERATURE SEARCH STRATEGY AND DETAILED METHODOLOGY 59
REFERENCES 66

1 GUIDANCE IN BRIEF

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding durvalumab (Imfinzi) NSCLC. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance is based on: a systematic review of the literature regarding durvalumab (Imfinzi) NSCLC conducted by the Lung Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; input from Registered Clinicians; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. A background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on durvalumab (Imfinzi) NSCLC a summary of submitted Provincial Advisory Group Input on durvalumab (Imfinzi) NSCLC and a summary of submitted registered clinician input on durvalumab (Imfinzi) NSCLC, and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

The purpose of this review is to evaluate the safety and efficacy of durvalumab (Imfinzi) for the treatment of patients with locally advanced, unresectable NSCLC following curative intent platinum-based chemoradiation therapy, for up to a maximum of 12 months.

The Health Canada approved indication is for the treatment of patients with locally advanced, unresectable NSCLC whose disease has not progressed following platinum-based chemoradiation therapy. The recommended dose of durvalumab for locally advanced, unresectable NSCLC is 10 mg/kg administered as an intravenous infusion over 60 minutes every 2 weeks for one year or until disease progression or unacceptable toxicity. Durvalumab has been issued marketing authorization with conditions, pending the results of trials to verify its clinical benefit. Durvalumab is available as 50 mg durvalumab/mL in 120 mg and 500 mg single-use vials.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included one trial, PACIFIC, a randomized, double blind, placebo controlled, international phase III trial that assessed the efficacy and safety of durvalumab (N= 476) as a consolidation therapy compared with placebo (N=237) in patients with stage III NSCLC who did not have disease progression after two or more cycles of platinum-based chemoradiotherapy up to 12 months.[1] Patients were randomly assigned in a 2:1 ratio to receive durvalumab intravenously or matching placebo every 2 weeks up to 12 months. Randomization was stratified according to age (<65 vs. ⩾65 years), sex, and smoking history (current or former smoker vs. never smoked). The study drug was discontinued if there was confirmed disease progression, unacceptable toxic effects, or withdrawal of consent. Patients could receive the study drug until disease progression (unless they had rapid tumor progression or symptomatic progression requiring urgent intervention) and could receive the drug again (re-treatment) if disease control had been achieved at the end of the 12 months but the disease had progressed during follow-up. The median follow up duration at the February 13, 2017 cut-off date for interim analysis for PFS was 14.5 months (Range: 0.2 -29.9 months).[1] At the updated analysis, the median

follow–up duration at the March 22, 2018 data cut-off was 25.2 months (Range: 0.2 -43.1 months).[2]

Dose modification was allowed due to the toxicity. The median relative dose intensity was 100% in each group (range, 29 to 100 in the durvalumab group and 50 to 100 in the placebo group).[1]

Baseline patient characteristics are listed in Table 6 in Section 6 and were generally well balanced across groups. The median age of patients in the PACIFIC study was 64.0 years (Range: 23 to 90); 70% patients were male. The majority of patients in the study had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 (48.8%) or 1 (50.8%); 99.7% of patients received concurrent chemotherapy with radiation therapy. Molecular phenotype (PD-L1 and EGFR) was generally well balanced between the two treatment groups. The majority of patients were current (16.4%) and past smokers (74.6%).

Efficacy

The co-primary outcomes in the PACIFIC study were overall survival (OS) and progression free survival (PFS). At the February 13, 2017 cut-off (the interim analysis) the median PFS time was 16.8 months (95% CI: 13.0 to 18.1) in durvalumab group and 5.6 months (95% CI: 4.6 to 7.8) in placebo group. The hazard ratio was stratified by randomization strata (i.e., age, sex and smoking history). The stratified hazard ratio for disease progression or death was 0.52; (95% CI, 0.42 to 0.65, p<0.001). This analysis was considered the final analysis for PFS since PFS achieved statistical significance. At the March 22, 2018 data cut –off, the updated median PFS time was 17.2 months (95% CI, 13.1 to 23.9) in the durvalumab group, and 5.6 months (95% CI, 4.6 to 7.7) in the placebo group respectively. The stratified HR was 0.51 (95% CI 0.41 – 0.63). At the first interim analysis for OS, durvalumab showed a statistically significant benefit in OS over placebo, with a 32% reduction in the risk of death (stratified HR: 0.68; 99.73% CI, 0.47 to 0.997; P = 0.0025)[2]. This analysis was considered the final analysis for OS since the OS achieved statistical significance.

At the February 13, 2017 data cut off, the overall response rates were 28.4% and 16% in patients with durvalumab and patients with placebo respectively. At the updated analyses (March 22, 2018), the overall response rates were 30.0% (95% CI, 25.8 to 34.5) and 17.8% (95% CI, 13.0 to 23.6, P<0.001) in patients with durvalumab and the patients with placebo, respectively.

At the February 13, 2017 data cut-off, it was reported that the median duration of response was longer in patients with durvalumab than in patients with placebo (not reached vs. 13.8 months). At the March 22, 2018 data cut-off, similarly, the median duration of response was not reached (95% CI, 27.4 to not reached) in the durvalumab group and was 18.4 months (95% CI, 6.7 to 24.5) in the placebo group).

Quality of life (QoL) was a secondary outcome and were measured with European Organization for Research and Treatment of Cancer (EORTC) QoL Questionnaire C30 (QLQ-C30) including time to symptom deterioration (e.g., fatigue, pain), time to QoL/function deterioration (e.g., physical function; role function; emotional function, global health status/QoL); and EORTC Lung Cancer Module (LC13) including time to symptom deterioration (e.g., dyspnoea, cough, hemoptysis, chest pain). Health related quality of life showed a high level of compliance (>80%) for both groups for up to 48 weeks. Results across all subscales did not indicate any meaningful difference in symptom deterioration, function, and the overall QoL between the durvalumab and placebo groups, despite a longer duration of study therapy for the durvalumab group.

Harms

At the March 22, 2018 data cut-off a total of 138 (29.1%) patients with durvalumab and 54 (23.1%) patients with placebo reported SAEs. Based on the earlier date cut-off, the most frequently reported SAEs were pneumonia (5.7% in durvalumab group and 5.1% in placebo groups, respectively), pneumonitis (3.4% in in durvalumab group and 3.0% in placebo group respectively), and radiation pneumonitis (3.6% in durvalumab group versus 1.3% in placebo group respectively). At the updated analysis, the proportion of SAEs were similar.

A total of 96.8% patients in the durvalumab group and 94.9% patients in the placebo group experienced an adverse event. Grade 3 or 4 adverse events of any cause occurred in 30.5% of the patients in the durvalumab group and in 26.1% of those in the placebo group respectively.

Additionally, 66.7% of the patients in the durvalumab group and 49.1% of the patients in the placebo group reported at least one adverse events of special interest which were defined as immune related adverse events. A total of 60 (12.6%) patients in the durvalumab group and 18 (7.7%) patients in the placebo group experienced pneumonitis.

Table 1: Highlights of Key Outcomes[1,2]

	PACIFIC			
	Cut-off date: February 13, 2017 (median F/U, month (range): 14.5 (0.2 - 29.9)		Cut-off date: March 22, 2018 (median F/U, month (range): 25.2 (0.2 -43.1)	
	Durvalumab (N= 476)	Placebo (N= 237)	Durvalumab (N= 476)	Placebo (N= 237)
OS				
median (95%CI)	NA		NR (34.7, NR)	28.7(22.9, NR)
HR (99.73% CI)			0.68 (0.47, 0.997)	
p-value			0.0025	
PFS				
median (95%CI)	16.8 (13.0, 18.1)	5.6 (4.6, 7.8)	17.2(13.1, 23.9)	5.6 (4.6, 7.7)
HR (95%CI)	0.52 (0.42, 0.65)		0.51 (0.41 - 0.63)	
p-value	<0.001		Not reported	
ORR				
Patients with ORR n(%)	126 (28.4)	34 (16.0)	133 (30.0)	38 (17.8)
95%CI (%)	24.28, 32.89	11.31, 21.59	25.79, 34.53	12.95, 23.65
p-value	<0.001		<0.001	
DOR, months	NR	13.8	NR (27.4 to NR)	18.4 (6.7 to 24.5)
p-value	NR		NR	

OS = overall survival; **PFS** = progression-free survival; **ORR**: objective response rate; **DOR** = duration of response; **CI** = confidence interval, F/U = follow up; **HR** = hazard ratio, NA = not available; **NR** = not reached; Note: HR < 1 favours Durvalumab

1.2.2 Additional Evidence

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

Patient Advocacy Group Input

Patients providing input had direct experience with durvalumab. Patients reported that durvalumab provided a sense of well-being, more independence, less stress, and allowed patients to engage more so with their families and loved ones. Patients also commented on the burden they felt was lifted off of their caregivers. Few side effects related to durvalumab were reported by patients. The most common side effects of durvalumab included fatigue and nausea. Patient input reported that both patients and their physicians felt uncertainty whether side effects were caused by durvalumab, or were residual side effects experienced from previously received treatments. Overall, there were positive sentiments regarding durvalumab, as it is a treatment they felt was beneficial to patients, and innovative as the first treatment that could be made available for patients in this indication.

Provincial Advisory Group (PAG) Input

Clinical factors:

- Treatments after progression on durvalumab
- Duration of treatment

Economic factors:

- Drug wastage
- Additional resources and chemotherapy chair time to prepare and administer durvalumab
- Additional resources required to monitor and manage infusion related reactions and adverse events

Registered Clinician Input

All clinicians agreed that there is a significant unmet need, as the current standard of care for patients following chemoradiation is observation; durvalumab would serve as a new treatment for patients with locally advanced, unresectable NSCLC following curative intent platinum-based chemoradiation therapy for up to one year. Clinicians also commented on the favourable toxicity profile of durvalumab. The clinicians agreed that the patient eligibility criteria in the PACIFIC trial would be applicable to clinical practice. One of the clinician inputs highlighted patients with PD-L1 <1% in the trial, stating that while the benefit of durvalumab among this subpopulation is unclear, it is possible that these patients may still benefit.

Summary of Supplemental Questions

There were no supplemental questions identified for this review.

Comparison with Other Literature

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

1.2.3 Factors Related to Generalizability of the Evidence

Table 2: Assessment of generalizability of evidence for Durvalumab (Imfinzi) for NSCLC

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence (PACIFIC) [1,2]</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td rowspan="3">Population</td><td>Performance Status</td><td>Patients were included if they had a WHO of 0 or 1.

Baseline characteristics<table><tr><th>WHO</th><th>Durvalumab</th><th>Placebo</th></tr><tr><td>0</td><td>234 (49.2)</td><td>114 (48.1)</td></tr><tr><td>1</td><td>240 (50.4)</td><td>122 (51.5)</td></tr></table>Subgroup Analysis for OS (unstratified HR for death)<table><tr><th>WHO</th><th>Durvalumab</th><th>Placebo</th><th>HR (95% CI)</th></tr><tr><td>0</td><td>87/234 (37.2)</td><td>49/114(43.0)</td><td>0.82 (0.57, 1.16)</td></tr><tr><td>1</td><td>96/242(39.7)</td><td>67/123 (54.5)</td><td>0.58 (0.42, 0.79)</td></tr></table></td><td>Does WHO performance status limit the interpretation of the trial results (efficacy or toxicity) with respect to the target population?</td><td>Clinical practice may include more patients with a performance status of 2. Patients must be fit enough to get through combined modality therapy and are a selected group in the first place. This will likely not impact generalizability.</td></tr>
<tr><td>Ethnicity or Demographics</td><td>Details on race, ethnicity and geographic location baseline characteristics were reported in section 6. The majority of patients were Caucasian (69.3%) while a smaller percentage was Asian (26.9%).</td><td>If the trial was conducted outside of Canada, is there a known difference in effect based on ethnicity that might yield a different result in a Canadian setting?</td><td>There is no known difference based on ethnicity, and the 70% Caucasian rate is likely similar to practice.</td></tr>
<tr><td>Stage of the NSCLC</td><td>Patients were eligible to enroll in the PACIFIC study if they had locally advanced, unresectable Stage III NSCLC patients who have not progressed following definitive, platinum-based, concurrent chemoradiation therapy

PAG is requesting clarity regarding the following specific patient populations:
Whether durvalumab is after concurrent chemoradiation therapy only or after radiation and chemotherapy given sequentially
Patients with stage III disease who do not receive chemoradiation therapy
Patients with resectable disease who receive neoadjuvant or adjuvant chemoradiation therapy</td><td>Can durvalumab be administered to other patient populations other than the eligible patient population in the PACIFIC study?</td><td>There is an ongoing study in the sequential space.[3]

In the PACIFIC study, it is patients who had concurrent therapy (although some also had induction therapy pre-chemoradiation)

Patients with stage III who do not receive chemoradiation therapy will not be eligible. Ongoing trials are in this space for surgically treated patients.</td></tr>
</table>

Domain	Factor	Evidence (PACIFIC) [1,2]	Generalizability Question	CGP Assessment of Generalizability
				Patients with stage III disease who have resection as part of their treatment are a heterogenous group. This includes patients with T3N1 disease where resection and peri-operative chemotherapy is standard of care. Durvalumab would not be generalizable to that group, and ongoing studies are happening. Patients with stage III disease that have "partial" operations - i.e. leaving a macroscopic burden of disease (patients with R2 resections or positive nodes not removed) - are often treated with chemoradiation as part of their definitive treatment, and durvalumab would be generalizable to these patients (independent studies will not be done) Patients with stage III disease who have upfront chemoradiation and may have surgery after chemoradiation may receive durvalumab. Many of these patients never get to surgery AND there is no evidence that surgical treatments reduce the effectiveness of immunotherapy. Small phase I/ II studies are ongoing using immune therapy prior to surgery[4 5], but no large phase III trials are currently known

Domain	Factor	Evidence (PACIFIC) [1,2]	Generalizability Question	CGP Assessment of Generalizability
				to be planned. There is noconsensus among the CGP whether durvalumab would be used in this very small subset of patients who have planned trimodality therapy and there is currently no evidence to confirm whether durvalumab would be used in this small subset of patients. Patients with stage I cancer treated with surgery or radiation treatments, who subsequently have mediastinal recurrence are also a subgroup not included in the PACIFIC study but for whom concurrent chemoradiation therapy is standard of care and for whom durvalumab will be considered. There are a number of minor clinical groups for whom this will be generalized: Stage II unresectable, stage IV treated with radical intent chemoradiation, and the aforementioned surgically treated patients. Patients with mixed histology (i.e. any small cell component) are usually excluded from both small cell and non-small cell trials, but clinically may be treated like non-small cell in this setting and durvalumab would be used.

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence (PACIFIC) [1,2]</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td></td><td>Active HIV, Hepatitis B or Hepatitis C infection</td><td>Patients with active HIV, Hepatitis B or hepatitis C were excluded from study.</td><td>Are the results of the study generalizable to patients with active HIV, Hepatitis B or Hepatitis C infection?</td><td>There is no reason these results will not be generalizable to these groups of patients if appropriate.</td></tr>
<tr><td></td><td>Biomarkers</td><td>Although Durvalumab is an anti-PD-L1 inhibitor, PD-L1 expression was not a criterion for eligibility for the trial. However, patients were required to have adequate tissue for biomarker status testing.

Baseline characteristics
<table>
<tr><th></th><th>Durvalumab</th><th>Placebo</th></tr>
<tr><td>PD-L1</td><td></td><td></td></tr>
<tr><td>< 25%</td><td>187 (39.3)</td><td>105 (44.3)</td></tr>
<tr><td>≥ 25%</td><td>115 (24.2)</td><td>44 (18.6)</td></tr>
<tr><td>Unknown</td><td>174 (36.6)</td><td>88 (37.1)</td></tr>
<tr><td>EGRF</td><td></td><td></td></tr>
<tr><td>Positive</td><td>29 (6.1)</td><td>14 (5.9)</td></tr>
<tr><td>Negative</td><td>315 (66.2)</td><td>165 (69.6)</td></tr>
<tr><td>Unknown</td><td>132 (27.7)</td><td>58 (24.5)</td></tr>
</table>
Subgroup Analysis for OS (unstratified HR for death)
<table>
<tr><th></th><th>Durvalumab</th><th>Placebo</th><th>HR (95% CI)</th></tr>
<tr><td>PD-L1</td><td></td><td></td><td></td></tr>
<tr><td>< 25%</td><td>74/187(39.6)</td><td>41/105(39.0)</td><td>0.92(0.63-1.34)</td></tr>
<tr><td>≥ 25%</td><td>37/115(32.2)</td><td>23/44(52.3)</td><td>0.46 (0.27-0.78)</td></tr>
<tr><td>Unknown</td><td>72/174 (41.4)</td><td>52/88(59.1)</td><td>0.77(0.49, 1.20)</td></tr>
<tr><td>EGRF</td><td></td><td></td><td></td></tr>
<tr><td>Positive</td><td>10/29(34.5)</td><td>6/14(42.9)</td><td>-</td></tr>
<tr><td>Negative</td><td>117/317(36.9)</td><td>60/165(48.5)</td><td>0.64(0.48,0.85)</td></tr>
<tr><td>Unknown</td><td>56/130(43.1)</td><td>30/58(51.7)</td><td>0.77(0.49, 1.20)</td></tr>
</table></td><td>Are the biomarkers (PD-L1, EGFR effect modifier (i.e., differences in effect based on biomarker status)? Are the results of the trial applicable to all subgroups equally?</td><td>Currently, based on one study, PD-L1 status is not clearly important. A subsequent non-prespecified analysis of PD-L1 negative patients did not seem to show benefit, but this needs to be confirmed with other ongoing studies in this space, and follow-up. Based on current evidence, there is no clear reason not to apply the benefit equally.

Further, there is no substantial biomarker group for whom the results shouldn't be generalized.</td></tr>
</table>

Domain	Factor	Evidence (PACIFIC) [1,2]	Generalizability Question	CGP Assessment of Generalizability
Intervention	Line of therapy	Durvalumab is indicated for locally advanced, unresectable NSCLC whose disease has not progressed following curative intent platinum-based chemoradiation therapy. Patients who completed 12 months of therapy and had SD, PR, or CR at completion entered follow up period, retreatment was offered with patient's consent if patient had disease progression with or without confirmation. The patient should not enter retreatment if any of the exclusion criteria were fulfilled, such as any unresolved toxicity. It was reported that eighteen (3.8%) patients in the durvalumab group and eight (3.4%) patients in the placebo group were retreated with their original treatment.	Are the results of the trial generalizable to other lines of therapy?	Durvalumab should be used for the treatment of patients with locally advanced, unresectable NSCLC following curative intent platinum-based chemoradiation therapy, for up to a maximum of 12 months.

1.2.4 Interpretation

Burden of Illness in Canada: Approximately 28,000 new cases of lung cancer, and 21,000 deaths from lung cancer occur each year in Canada, of which 85% are non-small cell lung cancer (NSCLC). Approximately 20% of these patients will have cancer that is locally advanced in the chest but not visibly metastatic to areas outside the chest. For these patients, there is over an 85% probability of death within five years.

Stage III NSCLC represents approximately 20% of non-small cell lung cancer patient presentations in Canada, and approximately up to 50% of these patients have historically received concurrent chemotherapy with radiation.

Need: Patients with locally advanced NSCLC have a highly lethal condition and multiple causes of morbidity and mortality, including local cancer progression and respiratory failure, systemic non-brain relapse and progression, a high rate of central nervous system relapse and progression, death and morbidity from toxicities of therapy, and death and morbidity from comorbid illnesses.

The standard of care, established over 20 years ago, for fit appropriate patients has been thoracic radiation therapy and concurrent systemic platinum-based chemotherapy. During that time, no major advances for patients have arisen from clinical trials, including attempts to improve local control with radiation escalation or surgery, attempting to improve local and metastatic control with consolidative systemic therapies, and attempting to reduce CNS relapse with cranial irradiation. Any advances over the last twenty years have come from minor improvements in patient selection (using PET scans), diagnostic pathways (using endobronchial ultrasounds), and radiation techniques (using 3 dimensional planning and intensity modulation). Despite these advances, survival is still rare, with 5 year survival in the 20% range for radically treated patients.

Durvalumab was studied in this highly lethal disease, where there are currently no other effective therapies despite over 20 years of research and clinical trials. It is attempting to fill a significant need.

Intervention of Interest and rationale for its use: Durvalumab is a programmed-death ligand 1 inhibitor (PD-L1) inhibitor. PD-L1 is a ligand expressed by multiple cells including tumour cells and immune cells that interacts primarily with the PD-1 receptor on T-cells. PD-L1 and PD-1 interaction allows tumour cells to evade the body's immune system. While targeting this axis in the metastatic setting has shown effectiveness, particularly when PD-L1 is demonstrably present on tumour cells. This is the first study to demonstrate benefit in the stage III setting. The rationale for combining with chemoradiation is to try to increase immunogenic cell death which may be potentiated by chemoradiation.

Review Methodology and Findings: The pCODR methods team reviewed the literature and performed a systematic review for this submission of Durvalumab as consolidation therapy for patients who had been treated with concurrent chemotherapy and radiation for locally advanced (Stage III) NSCLC. The landmark study that was found looking at the question of consolidation durvalumab was the PACIFIC study. In fact, the only randomized study looking at consolidation PD-1/PD-L1 therapy at the time of the review was the PACIFIC study.

The PACIFIC study randomized patients in a two to one fashion to consolidation durvalumab for one year or placebo after completion of chemoradiation. Eligible patients were started on therapy within 6 weeks of the completion of their chemoradiation, and continued on every two week therapy for up to a full year. The study was performed early in the development of durvalumab, before pharmacokinetic data revealed every four weeks dosing to be feasible and pharmacokinetically equivalent. However, the recommended dosing for durvalumab should be 10 mg/kg body weight every 2 weeks or pharmacologically equivalent dose.

Internal Validity and Face Validity: PACIFIC was a well-designed, well-reported study. The toxicity is consistent from other reported phase III studies examining immunotherapy in similar patient populations. The survival and subsequent treatments in the placebo arm are higher than in other phase III studies with stage III patients, but is accounted for by the randomization time (enrolling patients after chemoradiation), the requirement for patients to be recovered from toxicities and with a good performance status (patient selection), the very aggressive follow-up schedule (every two month imaging), and the high treatment rate in progressing patients.

Effectiveness: The two co-primary endpoints of PACIFIC, OS and PFS, were both statistically and clinically meaningfully superior for patients who received durvalumab compared to placebo. With a median follow-up of 25.2 months, OS was improved by 32% (HR 0.68), and two year OS was improved from 55% to 66%. Progression free survival was improved by 48%, with a median of 6 months in the control arm and 17 months in the durvalumab group, with 18 months PFS improved from 27% to 44%.

All clinically relevant secondary endpoints including time to distant metastases, time to next systemic therapy and response rate favoured durvalumab. Quality of life was not detrimentally affected by durvalumab based on the quality of life analysis performed.

Based on the primary analysis of OS, durvalumab has the potential to significantly improve outcomes for the group of patients recently treated with chemoradiation therapy. Median OS has not been reached. Given the short follow-up (median of 25 months), it is not possible to tell if long term cure rates are being improved, such as what we would hope from an adjuvant treatment – or if death is being delayed, such as what we expect from palliative treatments. There are some uncertainties regarding the duration of benefit from one year of durvalumab, which may be answered with further follow-up. However, even if evaluated solely as a palliative treatment, durvalumab shows benefit with a significant delay of death, without significant increases in toxicity or decreases in quality of life.

When translating the efficacy seen in this clinical trial to the effectiveness in the 'real world', it is expected that patients and practices will differ somewhat from what was done on study. Patients who would have been overtly excluded from the clinical trial would be included in clinical practice. Patients who were followed with every two month scanning on clinical trial will be followed less frequently. Patients who are not overtly excluded, but are underrepresented in clinical trials (such as the elderly, lower socioeconomic status and education level, and those with comorbid illness), will be better represented in real practice.

Lung cancer patients have heterogeneous clinical situations that are not represented in clinical trials, but for who still need to be treated with the best evidence available. Patients who were overtly excluded from the clinical trial include those with HIV, hepatitis C, and hepatitis B. It is likely that as immune therapy safety is established in these patients in other settings, that they will be treated with durvalumab in this setting. Outside of perhaps uncontrolled hepatitis B, most patients with HIV on highly active anti-retroviral therapy with normal CD4 counts, controlled hepatitis B, or with hepatitis C, would receive therapy in this setting. Patients with any small cell component of their histology were excluded from this study, and they are also excluded from small cell studies. In the locally advanced/non-metastatic setting, these patients would be treated with chemoradiation, and durvalumab would be appropriate to administer. Certain stage II patients and current stage IV patients are treated with chemoradiation to the chest in a curative attempt, and these are also patients for whom trials will not be independently conducted, but for whom consolidation durvalumab would be appropriate. Certain stage III patients are treated with attempts at surgery, either prior to or following chemoradiation. Durvalumab may be used for concurrent chemoradiation patients, whether or not additional treatments like surgery are added to the treatment.

In clinical practice, it is likely that the use of durvalumab will not be considered for patients not treated with radical concurrent therapy at this time. Patients who have only radiation (not concurrent chemotherapy) will not be eligible to receive therapy. Patients who have sequential therapy without concurrent therapy will not be eligible to receive immunotherapy. Patients who receive surgery and chemotherapy but not radiation therapy will not be eligible for durvalumab at this time.

Performance status 2 patients, patients with unresolved toxicities after concurrent therapy, and patients who had grade 2 or greater pneumonitis at any time present a challenge in extrapolating this data to the 'real world', given that these were all ineligibility criteria. 25% of patients who signed consent for the study were not eventually randomized, likely as a result of these factors. In clinical practice, this may result in either increased toxicity, if it is mandated that patients are enrolled within 6 weeks of radiation, then patients and physicians may minimize toxicity or be more generous with performance status. If treatment within 6 weeks is not mandated, then physicians may allow the patients to recover longer and begin treatment at a later time period, which will have an unknown impact on efficacy.

Effectiveness will likely be similar amongst all of the subgroups that receive durvalumab therapy after chemoradiation. There is no clear indication that any subgroup does substantially worse with durvalumab than any other subgroup. Benefit from consolidation durvalumab was demonstrated regardless of performance status, age, stage (3A or 3B), PD-L1 status, EGFR status, and type of chemotherapy, although non-significant trends were observed. In terms of PD-L1 status, a post-hoc analysis revealed that patients with very low PD-L1 did not appear to benefit, which is consistent with findings in the metastatic setting that PD-L1 high patients appear to benefit more from anti-PD1/L1 therapy. As this is a post-hoc analysis, it is unlikely that this will change practice until further studies/meta-analysis confirm this hypothesis-generating observation. There was also a statistically non-significant observation that patients who were treated within 14 days of completing radiation appeared to have better hazard ratio (HR 0.42 compared to HR 0.81 for OS), but this difference may be exaggerated by the unexplained higher event rate in the placebo arm of the 14 day group (56.5% vs 46%).

To summarize, for effectiveness and equity, durvalumab appears to provide a significant, clinically meaningful, benefit in terms of overall survival for patients who were enrolled on trial. For patients who were ineligible for trial, but for whom chemoradiation is part of the standard of care, equity would suggest that these patients may also receive benefit from durvalumab in this setting, and the effectiveness is unlikely significantly different.

Safety (Toxicity and Adverse Events): In terms of toxicity, there are several toxicities that occur with chemoradiation therapy, and additional toxicities that may be clinically relevant with the use of durvalumab. For toxicities reported in the frequency table (See Table 13 in Section 6), results are similar with placebo or durvalumab for most grade 1 and 2 toxicities. As patients were enrolled within two to six weeks of ending chemoradiation therapy, it is probable that many of these events (particularly in the placebo group) were sequelae of previous treatment, while others may be secondary to disease progression. The trial did not report the duration of these toxicities in each group, but this would be important in understanding relative impact of durvalumab versus side effects from chemoradiation alone. This may be captured in the quality of life studies.

Pneumonitis was a particular concern for these patients receiving high dose thoracic radiation. Pneumonitis clinically can be difficult to distinguish from other etiologies of shortness of breath or cough, particularly with immune therapy where presentations different from typical drug induced hypersensitivity pneumonitis are common. Patients who had any grade 2 pneumonitis at any time prior to enrollment were excluded from the trial. The adverse event of pneumonitis was only reported in 12.6% of patients in the durvalumab arm (any grade) compared to 7.7% of patients in

the placebo group and there was also a radiation pneumonitis rate of 20.2% in the durvalumab arm and a 15.8% rate in the placebo arm. Grade 3/4 radiation pneumonitis occurred more numerically more frequently in the durvalumab group (3.6% vs 1.3%), but was rare, while Grade 3/4 pneumonitis that wasn't classified as radiation pneumonitis occurred in 1.9% and 1.7% respectively. It is probable that severe radiation pneumonitis is increased with durvalumab therapy, but the absolute increase appears to be small.

Other Grade 3 adverse events were similar between the two arms, indicating that the drug was associated with manageable toxicity – consistent with other single agent studies of durvalumab in lung cancer. Patients who received durvalumab discontinued treatments due to adverse events only 15% of the time, compared to 9.7% of placebo patients. This indicates a relatively well tolerated regimen for one year.

When extrapolating into clinical practice, it is possible that the adverse event rate will increase through less stringent selection of patients, and less rigorous monitoring than in clinical trials. Even taking this into account, this is still a regimen that will likely have a favourable risk:benefit ratio for the majority of patients and population.

The Submitter provided feedback on the pERC Initial Recommendation requesting that pERC reconsider the exclusion of durvalumab for patients receiving sequential chemoradiation therapy. The Submitter requested that pERC reconsider the patient population eligible for durvalumab to allow clinicians to make case-by-case determinations as to whether a patient who received curative-intent sequential chemoradiation therapy could benefit from treatment with durvalumab.

In response to the Submitter's feedback, the CGP re-affirm that the PACIFIC trial evaluated durvalumab in patients who received concurrent chemoradiation therapy. There is insufficient evidence at this time to support the use of durvalumab in settings other than curative intent concurrent chemoradiation therapy. There are ongoing studies evaluating durvalumab in other settings, including patients who receive sequential chemoradiation therapy. The evidence at this time does not support extrapolation to patients not treated with concurrent chemoradiation therapy.

1.3 Conclusions

The CGP concludes that there is a clear, significant, net clinical benefit of durvalumab therapy for consolidation of locally advanced unresectable NSCLC following curative intent platinum-based chemoradiation therapy, for up to a maximum of 12 months, compared to placebo (watch and wait). In making this conclusion, the CGP considered:

- The burden of illness for stage III non-small cell lung cancer is significant. Approximately 4,500 to 5,000 new cases of stage III NSCLC occur each year in Canada per year, of which approximately 2,500 will receive concurrent chemoradiation. Of those who receive chemoradiation, approximately 1,250 will be alive two years after the completion of chemoradiation, and 500 will be alive at 5 years. There is a clear clinical need to improve the likelihood of having prolonged survival for stage III NSCLC.

- The sole phase III study that addressed the use of consolidation durvalumab in this population was the PACIFIC study referenced in this review. As of the last update, it revealed a significant, clinically meaningful, benefit in OS, with 2 year survival improved by an absolute amount of 11%. This came at the expense of some toxicity, most notably grade 3 or 4 radiation pneumonitis increasing from 1.3 to 3.6%. This toxicity may be manageable with intervention such as high dose steroid medicines, but impacts negatively on quality of life for these patients and can be life threatening.

- Of those 2,500 patients who were treated with chemoradiation, approximately 60-70% (1,500) of patients would be eligible to receive durvalumab. In the absence of durvalumab, approximately 300 will survive 5 years and 750 will survive 2 years. If durvalumab therapy were available and given to those patients, 2 year survival would increase from 750 to approximately 900. It's too soon to know what the impact would be on 5 year survival, but an increase of over 150 people living two years is significant. With patient selection, of those 1,500 patients who receive durvalumab, an additional ~15 to 30 appear to experience significant grade 3 or 4 radiation pneumonitis.

- In translating to real world utilization, safety and toxicity will be concern, and will rely on adapting processes currently in place for managing immune toxicity in the palliative setting, to managing immune toxicity and overlapping radiation toxicity in the 'curative' setting. Stage III NSCLC patients are complex patients, treatment with radiation therapy and chemotherapy is complex treatment, and adding immunotherapy adds another layer of complexity and it is uncertain how these various levels of complexity will work in the 'real world' setting. Ideally, post-approval or post-marketing surveillance of real-world outcomes, particularly toxicity, in such a complex disease/treatment space will add additional information to address this uncertainty that exists.

- There is currently no evidence to inform optimal sequencing of therapies after treatment with durvalumab, when patients progress to metastatic disease. In the absence of such evidence, it is expected that physicians will wish to use first principles for therapy. Namely, that the treatment will depend on the tumour characteristics (PD-L1 status, EGFR status), patient characteristics (performance status, tolerance for chemotherapy, and tolerance for other therapies), and disease course characteristics (time and burden of recurrence). For patients who recur after having completed 12 months of durvalumab therapy and an appropriate interval, treatment will be likely what is given for first line non-small cell lung cancer in the advanced/metastatic setting. For patients who recur while on durvalumab therapy, treatment will be dependent on what previous systemic therapy was received, but will likely not include immunotherapy at this time. For patients who recur a short interval after receiving durvalumab therapy, optimal treatment and treatment patterns are unknown.

- Currently, there is no evidence to inform when or whether retreatment durvalumab on progression would be appropriate, but as only a small number of patients in the clinical trial were retreated with durvalumab at this time upon progression in comparison to treatment with other PD-1 or PD-L1 inhibitors, it is likely that physicians would treat with medications of proven benefit in the metastatic/advanced setting.

2 BACKGROUND CLINICAL INFORMATION

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

2.1 Description of the Condition

Lung cancer represents the second most common cause of cancer among both men and women in Canada, but the largest cause of death from cancer. In 2016, there were approximately 28,400 new cases of lung cancer and 20,800 deaths from lung cancer.[6] Roughly 85% of these cases would be classified as NSCLC. Approximately 20% of NSCLC patients have stage III disease at the time of presentation.[7] For stage III disease, 5 year survival ranges from 13% in stage IIIC disease to 35% in stage IIIA disease. Radical intent therapy is delivered where appropriate, and approximately 50% of patients receive combined chemotherapy with radiation therapy with radical/curative intent. The balance receiving typically palliative radiotherapy, trimodality therapy, systemic chemotherapy, or palliative care alone. For patients treated with chemotherapy and radiation (bimodality therapy), the median survival is approximately 24 months, with approximately 20% of patients surviving 5 years.[8] The incidence of NSCLC rises with age and the median age at diagnosis is 70 years.

For most patients with stage III disease, primary surgery is not feasible or recommended [9]. Stage III disease itself represents patients with a variety of clinical presentations including T4 N0/N1 disease and T3 N1 disease, where surgery is often recommended - but the majority of stage III lung cancer patients have N2 or N3 disease. This is disease in the mediastinum or supraclavicular areas. No major advances from clinical trials have occurred over the past two decades – with higher doses of radiation[10], prophylactic cranial radiation[11], altered chemotherapy regimens[12], and consolidation chemotherapy[13] all failing to improve overall survival. In stage III disease, death can occur from multiple causes, including local progression and relapse; distant non-brain metastases, brain metastases, and assorted other causes such as cardiac events and cardiorespiratory comorbid conditions.[8,14]

Unlike stage IV lung cancer, stage III non-small cell lung cancer, when treated curatively, is not treated differently by histology or molecular subtype. Squamous cell and non-squamous cell patients are treated essentially the same, although some patients with non-squamous histology may receive pemetrexed as part of concurrent therapy. Patients are also treated the same regardless of ALK or EGFR status. Advances in treating stage III disease group of patients have come from changes in practice outside of clinical trials such as the incorporation of smoking cessation into clinics, the incorporation of Positon Emission Tomography staging (PET), and most importantly, advances in radiation techniques that allow more patients to be safely treated.

2.2 Accepted Clinical Practice

For stage III non-small cell lung cancer, treatment requires a coordinated multidisciplinary approach that may include radiology, thoracic medicine, thoracic surgery, radiation and medical oncology. For patients with the N2 or N3 disease – mediastinal lymph nodes, supraclavicular lymph nodes etc., and for many patients with either T4 N0/1 or T3N1 disease, primary surgery is not feasible or recommended. For patients who fall into these categories, combined modality chemotherapy and radiation therapy is delivered when acceptable.

Considerations in deciding on who to treat with radical therapy include: Whether 60 Gray (Gy) or radiation can be delivered safely to the tumour bulk over an approximate 6 week period, taking into account the patients baseline pulmonary function, radiation tolerance, and the anatomic distribution of the tumour; whether the patients performance status, comorbidity, baseline

symptoms, and weight loss would allow radical chemoradiation to be given; and patient tolerance for a treatment with more short term toxicity and longer expected survival. For patients where a decision is made to proceed with radical therapy, typical treatments would include daily radiation therapy concurrent with chemotherapy administered during the radiation. Concurrent chemotherapy regimens vary, with uncertainty regarding the optimal regimen, but typically patients who are fit would receive cisplatinum-based chemotherapy – such as cisplatin-pemetrexed, cisplatin-etoposide or cisplatin-vinca alkaloid, while older or less fit patients may receive carboplatin-etoposide or carboplatin-paclitaxel. Consolidation chemotherapy – or chemotherapy after the completion of radiation – is rarely used as it has not been shown to be effective in randomized studies. Induction chemotherapy – or chemotherapy delivered prior to definitive radiation – is less effective than concurrent therapy, but may be used in certain clinical situations where radiation cannot be safely given immediately.

After the completion of chemoradiation, there is no routine therapy (other than smoking cessation if applicable) recommended. Patients are generally followed, and may receive further treatment if they progress or develop metastatic disease and remain fit enough for treatment. Death and debility occur due to several factors, including local progression, new thoracic disease, distant non-brain metastases, brain metastases, cardiac complications of therapy, and a variety of other causes from comorbid conditions and respiratory complications. In the past, the most common patients subsequently receive was radiation therapy, and approximately 25% will receive subsequent systemic therapy, and a small percentage will have subsequent surgery for an isolated metastases or local progression only[14-16]. In the current era of more aggressive follow-up, biomarker driven treatments, and immunotherapy for advanced disease, it is expected that this number would be substantially higher – approximately 70% - 80% of patients will have recurrence of progression of disease prior to death, and systemic therapy likely received by ~50-60% of those patients, or approximately 35-40% of the initial group. The actual numbers of patients in the population who subsequently receive systemic therapy in the modern era with immunotherapy and molecular therapy is unknown.

If further systemic treatment is considered, the type of systemic treatment will depend on the tolerance of the patient for previous therapy, and the time elapsed from previous treatments. Depending on these factors, and the patients biomarker status, physicians may treat a patient with a 'first-line' systemic therapy regimen for metastatic disease or second line therapy for advanced disease. For patients with biomarker negative disease (EGFR/ALK/PD-L1 negative), they may be treated with a first line doublet chemotherapy regimen (carboplatin/cisplatin with pemetrexed, gemcitabine, or paclitaxel largely), or a second line regimen either immunotherapy (nivolumab, atezolizumab, or pembrolizumab) or chemotherapy (pemetrexed or docetaxel). For patients with biomarker positive disease, they will typically receive first line targeted or immunotherapy treatment – with gefitinib, afatinib, erlotinib, or osimertinib for EGFR positive patients, alectinib or crizotinib for ALK positive patients, and pembrolizumab for EGFR negative, ALK negative, PD-L1 positive patients.

Immunotherapy in lung cancer, particularly the use of anti-programmed death 1 or anti-programmed death ligand 1 therapy – has been used in cases of advanced cancer for the last several years, and is in a state of evolution. After first line chemotherapy for advanced disease has failed, single agent nivolumab, pembrolizumab, or atezolizumab provides significant benefit for a portion of patients, with approximately 50% of patients surviving one year and 20-30% surviving for two years in clinical trials[17-19]. Currently, pembrolizumab is given for a maximum of 24 months and retreatment may be initiated after progression, while nivolumab and atezolizumab are given until disease progression. For patients with a high PD-L1 staining score on their tumour (>50%), two year survival in the first line setting is significantly improved with pembrolizumab compared to chemotherapy, with a 24 month survival of 40-50%[20]. Recently, the addition of immune therapy with pembrolizumab to standard chemotherapy was shown to significantly

improve survival in both the squamous and non-squamous settings in patients.[20,21] For patients with driver mutations (EGFR and ALK), immunotherapy monotherapy in the advanced setting has not been successful thus far, however the combination of chemotherapy, atezolizumab, and bevacizumab shows some promise in this area.[22]

Durvalumab has been studied in the advanced setting in lung cancer, but is not a part of routine treatment for patients with metastatic or incurable disease currently. It is the first PD1 or PD-L1 inhibitor however to be studied in the context of stage III disease being used for consolidation therapy.

In the PACIFIC study[2,23], patients who had completed chemotherapy and radical radiation were randomized within 6 weeks of the completion of radiation to receive either placebo or durvalumab for up to 12 months. As this study began prior to the full understanding of the pharmacokinetics of durvalumab, patients received 10 mg/kg intravenously every two weeks for one year in total. Today, every four week dosing is generally used in durvalumab studies given the equivalent pharmacokinetics.[24]

Patients in the PACIFIC study had a multitude of chemotherapy regimens prior to enrolment, but had to have recovered from side effects of the therapy such that toxicity was less than grade 2. The exception to this was pneumonitis, whereby patients were excluded if they had grade 2 pneumonitis previously – even if it had resolved. Patients were enrolled throughout the world, with characteristics representative of those who typically receive combined modality therapy. Patients were followed aggressively with routine CT imaging every eight weeks, which is anywhere from two to six times as aggressive as standard.

In 2017, results were presented that showed a benefit in terms of progression free survival in this population, with an improvement in median progression free survival of 11 months. In 2018, results were presented that showed a benefit in overall survival, with a reduction in the risk of death by 32% in the durvalumab arm, and a two year survival that improved from 56% to 66%. This improvement was statistically significant and clinically meaningful.

2.3 Evidence-Based Considerations for a Funding Population

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

- Proportion of NSCLC (85%) 24,480
- Proportion with stage III disease (20%) 4,896
- Proportion treated with radical chemoradiation (50-60%) 2,080-2,497
- Proportion likely eligible for immunotherapy (60-70%) 1,248-1,750
- Estimate of other patients treated with radical chemoradiation (stage II patients not suitable for surgery; stage IV oligometastatic patients receiving chemoradiaton) 300

Based on the above assumptions, there are between 1,548 and 2,050 patients with advanced NSCLC treated with radical chemoradiation as part of therapy.

2.4 Other Patient Populations in Whom the Drug May Be Used

Durvalumab was studied in patients with NSCLC who have received chemotherapy and radiation as combined bimodality therapy, and the study included patients who received either concurrent chemotherapy and radiation. While only stage III patients who completed chemotherapy and radiation were included in the clinical trial, patients with lung cancer may have a multitude of rare other presentations where they receive high dose thoracic radiation concurrent with

chemotherapy. These include Stage II inoperable patients who may receive combined modality chemoradiation[25,26], and Stage IV disease with a solitary extrathoracic metastases (such as a brain metastases) who may also combined modality chemotherapy and radiation as part of radical intent therapy.[27-29]

In addition to certain stage II and stage IV patients, a certain percentage of patients will have stage III disease treated with surgery as part of their care path. This includes patients who have more extensive disease at the time of primary resection and have stage III incompletely resected disease subsequently treated with chemoradiation, and patients for whom surgery may be considered sometime after their chemoradiation treatment.

In terms of the stage III patients treated with chemotherapy and radiation, it is possible that many would have been ineligible or uninterested in further therapy within 6 weeks of completing radiation therapy. Twenty-five percent of patients who signed consent for the PACIFIC study did not move on to randomization. Patients were required to have a very good performance status (ECOG 0 or 1) within 6 weeks of the completion of radiation in order to enrol. It is probable that clinicians will try to extrapolate out a few weeks further, and treat patients up to 8-12 weeks from completion of radiation therapy. Although there is a greater degree of uncertainty in these patients, the negative consequences of a strict timing criteria (i.e. patients must begin within 6 weeks of completion of radiation therapy) must be considered. If clinicians are forced to treat in a certain time period for funding, then patients with more borderline performance status or relative contra-indications will be treated in order to not lose eligibility.

While the slight majority of patients are treated radically with chemotherapy and radiation, there are still a substantial number of patients who receive palliative doses of radiation therapy for stage III disease, including those with poor lung function, poor performance status/emergent presentations, excessive radiation volumes, excessive weight loss, extensive comorbidity, or patient choice. These are not patients for whom it's expected consolidation immunotherapy will be considered.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

Two patient advocacy groups, Lung Cancer Canada (LCC) and the Ontario Lung Association (OLA), provided input on the use of durvalumab for the treatment of patients with locally advanced, unresectable NSCLC following curative intent platinum-based chemotherapy, for up to a maximum of 12 months. LCC gathered information from patients via a survey and an environmental scan which included information from patient forums and interviews. LCC gathered information from a survey of patients and caregivers from 2015 called the Faces of Lung Cancer Survey. A total of 91 patients, all of whom have or have had lung cancer, and 72 caregivers completed this survey. All caregivers were currently caring for, or had previously cared for a patient living with lung cancer. Information from 21 respondents was obtained from an environmental scan; information from ten respondents, seven patients and three caregivers, was obtained from searching patient forums and 11 respondents, ten patients and one caregiver, were interviewed for this submission. LCC reported that these data were gathered between August to October of 2018. LCC did not provide demographic information regarding the Faces of Lung Cancer Survey, however 13 of 21 respondents (62%) identified through the environmental scan and patient interviews were female. Information regarding age was available from 19 of 21 respondents obtained via the environmental scan and interviews; the mean age was 61 years of age (range, 37-77).

OLA obtained feedback from a Toronto based lung health support group comprising of six members, including a patient with lung cancer, a patient with idiopathic pulmonary fibrosis (IPF), and four patients with chronic obstructive pulmonary disease (COPD). OLA also conducted one phone interview with a patient with lung cancer. OLA also noted referencing feedback from previous submissions to pCODR over the past three years throughout this submission for durvalumab. Input from a certified respiratory educator (CRE) was also incorporated by OLA, as a way to enhance their patient input submission. OLA stated that the CRE was used as a *"review check,"* where they reviewed the submission and offered feedback and suggestions as appropriate. All information was obtained during September 2018, and all respondents were Canadian.

From a patient's perspective, feelings of stress and frustration were reported by patients as the only treatment option available to them was observation. Many patients reported experiencing fatigue leading to loss of independence as a result of their lung cancer. Side effects from chemoradiation were reported to be debilitating. In addition to reporting physical symptoms, such as fatigue, nausea and vomiting, patients reported impacts on their daily lives, as some patients reported having had to quit their jobs as a result of having to receive their treatments. Extremely sore throats were reported as a side effect from radiation therapy, and was reported to significantly impede patient's ability to swallow.

All patient experiences related to durvalumab for this summary were reported from LCC, who confirmed in follow-up that all patients part of their submission had experience with durvalumab. Durvalumab provided patients with a sense of well-being, more independence, less stress, and allowed patients to engage more so with their families and loved ones. Patients also commented on the burden they felt was lifted off of their caregivers. Few side effects related to durvalumab were reported by patients. The most common side effects of durvalumab included fatigue and nausea. However, there were reports of confusion related to the cause of some side effects, such as fatigue or pneumonitis. LCC reported that both patients and their physicians felt uncertainty whether side effects were caused by durvalumab, or were residual side effects experienced from previously received treatments. LCC suggested creating educational materials to resolve the confusion resultant from durvalumab and its associated side effects. Overall, there were positive sentiments regarding durvalumab from LCC, as it is a treatment they felt was beneficial to patients, and innovative as the first treatment that could be made available for patients in this indication.

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

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

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with NSCLC

LCC reported that after patients are treated with chemoradiation there are currently no other therapies available leaving them only with the option to *"watch and wait,"* a process some patients refer to as *"active surveillance"* or *"expectant management."* Having to *"watch and wait"* LCC mentioned that patients feel a lack of control over their circumstances resulting in greater stress and worry. Without clear treatment options patients feel that *"Watching and waiting is nerve racking*," they *"never know what is going on,"* and are left hoping for better results every time they check in with their physician. One patient indicated feeling afraid that her lung cancer would return, and, if it did, whether there would be available treatment options for her. Some patients remain hopeful for a longer and healthier life saying *"You never give up,"* while others recognize they *"don't' have much of a choice."*

Pain, which can be very intense at times, shortness of breath, cough, which can be a chronic symptom, coughing up blood, weakness and extreme fatigue are some symptoms and challenges OLA indicated patients experience as a result of lung cancer. Fatigue was reported multiple times by OLA as being difficult to manage by patients, as they reported having to plan their days around managing it. Adding to the difficulty of managing symptoms due to lung cancer, is the constant variability in experienced symptoms as OLA indicated a lack of consistency in what patients experience throughout their disease. OLA indicated that patient's ability to work, travel, socialize and participate in leisure and physical activities are aspects of daily life that are affected for those with lung cancer. The following quotes provided by OLA illustrate patients' struggles with disease symptoms, particularly fatigue, and a loss of independence:

- *"It robbed me of my ability to do anything on my own."*
- *"This disease makes it hard to do day to day activities such as house cleaning, shopping and cooking. It has affected all parts of my life."*
- *"I have lost a significant amount of weight and am tired, weak and without energy. I am no longer able to do the activities I enjoy. It is very hard to be positive and hopeful."*
- *"Physical exertion of any kind causes my breathing to get worse."*

OLA also indicated the difficulty patients experience navigating through their diagnosis; patients indicate needing more information to help them understand what they are going through and what decisions and next steps they need to take. Several patients reported feeling rushed during appointments with their doctors, and expressed a greater need for information to be communicated in *"easy to understand"* language with clear descriptions of their treatment options. Interviewed individuals also mentioned the lack of timeliness experienced waiting for results or to be diagnosed, resulting in heightened anxiety. One female patient said, *"I waited many months to see a specialist not knowing what exactly was wrong with me or what the prognosis might be,"* while another female patient said, *"It took a year to finally make the diagnosis."* The daughter of another lung cancer patient said, *"The most frustrating thing for me was how long it took to get her diagnosed."* OLA indicated that nearly all respondents reported feelings of anxiety and depression associated with a diagnosis of lung cancer.

LCC indicated that a patient's diagnosis may be hard on family and friends in addition to the patient as one respondent said, "The diagnosis was tough on the family and her son thought she would die." LCC felt it was important to highlight that as durvalumab is currently being reviewed for treatment in stage 3B non-resectable lung cancer after chemoradiation, this space has a curative intent, and are hopeful that durvalumab will increase patient's chances of a cure.

3.1.2 Patients' Experiences with Current Therapy for NSCLC

LCC stated that there is currently no available therapy to prescribe lung cancer patients in this setting. Following chemoradiation, patients are asked to watch and wait. All patients included in the LCC's submission indicated that they had been treated with chemoradiation therapy. Nearly all patients indicated having experienced side effects that interfered with daily living, with most patients reporting side effects such as nausea (n=6), vomiting (n=4), and extreme fatigue (n=12) which LCC indicated was consistent with other reports of side effects to do with chemotherapy. Only one patient indicated having experienced no side effects, and was reported by LCC to have *"even put on weight following chemo radiation therapy."* Other patients reported having difficulty engaging in activities that they enjoyed or taking part in daily chores; for example, one patient reported being unable to mow her lawn, while others had to quit sports such as golfing or endurance training and running. One patient reported being unable to play with her grandchildren like she used to. Loss of hair (n=1), sunburn (n=1), diarrhea (n=1), and pain in the throat (n=1) were other reported side effects. Pain in the throat made it difficult for patients to swallow liquid pills, which is a side effect also mentioned by patients interviewed by OLA.

LCC also reported that one patient experienced a drop in their white blood cell count due to chemoradiation therapy so severe they had to stop treatment and also could not see any visitors. Some patients also reported having to quit their jobs. One patient commented on the consuming effect his treatments had on his life, as, even though he was retired, he mentioned his life seeming to revolve around his treatments.

Spiriva, Seebri, Advai, Symbicort, Daxas, Prednisone, Ventolin, Atrovent, Serevent, Onbrez, Tudorza and Ventolin (as needed) were previously received treatments reported by patients interviewed by OLA. One patient indicated currently undergoing radiation and chemotherapy. Another patient indicated having received a double lung transplant earlier in 2018. OLA mentioned that while current treatments do provide some relief for symptoms such as, fatigue, shortness of breath, cough, appetite loss and low energy, their management can be improved, and that other symptoms, such as palpitations, dry mouth, mouth sores, vision and urinary problems still require better management. Radiation therapy was reported by patients to leave them with extremely sore and painful throats, impeding their ability to swallow food.

While both LCC and OLA highlighted that side effects could be very debilitating for some patients, LCC noted that chemoradiation therapy is an effective therapy. The majority (89%) of the patients interviewed by LCC reported significant shrinkage in tumour size.

In addition to describing experiences with current therapies, the respondents also expressed a desire to have fewer medical appointments and decreased costs. Secondary costs related to the disease and treatments were also reported as causing burden to patients. For example, one patient noted having to pay for a driving service to take her to treatment appointments and then back home out of pocket. In addition to travel costs, due to weight loss patients must make sure to maintain good nutrition; one patient was advised to buy Ensure. For patients with fixed incomes or who receive pension, buying certain foods, such as Ensure, can be quite costly and result in additional burden.

OLA also reported the following as being aspects of the disease experience they would like improved: greater independence, more energy, improved training for general practitioners to be

better educated about lung diseases, clearer communication with their physician, and overall reduction in unnecessary delays in diagnosis and treatment.

OLA noted that the idea of foregoing treatment was not considered by any of the respondents interviewed regardless of stage of disease. Respondents indicated a need for communication with their physician to improve their understanding of their available treatment options and the intent of these treatment options. Patients indicated that with greater communication would lead to better decision-making and coping.

3.1.3 Impact of NSCLC and Current Therapy on Caregivers

OLA reported that caregivers of patients with lung cancer also indicated that their work, finances, relationships with friends and family, their ability to travel and socialize, and their physical and leisure activities were all impacted by their loved one's condition. Both patients and caregivers reported having their independence impacted due to the condition. OLA also highlighted the emotional toll of caregivers having to watch their loved ones suffer from their condition, while being able to do very little to aid with the pain and discomfort they are experiencing.

As mentioned previously by LCC, some patients resorted to having to quit their jobs due to having lung cancer. Caregivers were also reported by LCC to have had to take time off work to help manage their loved ones who are receiving chemotherapy. One caregiver noted that his son needed to take leaves of absence from work for six weeks to help his son with his appointments. Based on the FOLCR survey, 59% of caregivers reported reduced number of hours worked and 8% reported quitting their jobs.

According to LCC many caregivers worry that the diagnosis of lung cancer implies a death sentence, and that caregivers feel great anxiety and burden from their loved one's diagnosis. Based on data from the FOLCR survey, LCC reported that caregivers can experience the weight of lung cancer more acutely than patients, as they experience greater emotional burden due to the negative implications and subconscious attitudes associated with lung cancer, which can lead to feeling so isolation. LCC indicated that caregivers can feel anxiety, worry, depression and psychological distress from feeling the need to take "ownership for protecting their loved ones," which can lead to decreased quality of life for both the caregiver and patient. One patient responded to her husband's diagnosis by stating *"It's absolutely terrible, it's traumatic, it truly is traumatic." "The worry, the stress, the fear and the grief."*

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for and Experiences To Date with NSCLC

No patients within the patient input provided by OLA reported having experience with durvalumab. All patient experiences related to durvalumab are based on input provided by LCC. Ten patients and one caregiver were interviewed by LCC, and information was obtained from seven patients and three caregivers via an online scan; all of these respondents were confirmed by LCC to have experience with durvalumab. LCC stated that, compared to chemotherapy, all information received from forums and interviews indicated patients felt better on durvalumab. Overall, patients had a better sense of well-being, improved treatment experience, more manageable side effects, and better functionality while on durvalumab.

Compared to chemotherapy, LCC mentioned patients feel a general sense of well-being that allowed them to eventually take on more activities. One patient who required help with housework during her chemotherapy treatment stated, "I still have a cleaning late but my goal is to not need one soon!" during visits to the hospital for infusions of durvalumab, patients mentioned feeling less stressed, tired and experiencing fewer side effects leading to improved

quality of life. Two patients mentioned being able to go to their appointments alone, and even when caregivers attended their visits with them their purpose was geared more toward emotional support rather than because of physical need. LCC highlighted that the experience receiving durvalumab helped to provide relief to both patients and caregivers of some of the burden related to lung cancer. Previously, it was mentioned that patients felt burdened by the loss their ability to engage in activities of daily living. While receiving durvalumab, patients experienced less fatigue and felt more functional, allowing them to engage in activities they could not while receiving chemoradiation. Patients reported having more energy, being able to conduct household chores, such as yard work or general work around the house, engage with family, such as taking children to school or to the playground or playing with grandchildren, and partake in sports, such as golfing, swimming, yoga and strength training. One patient reported that while she is now able to walk her children to the park and school, she is still unable to go for long bicycle rides or play tag. In addition to taking up swimming, one patient also began walking her daughter's dog, shopping, going out for breakfast with her daughter more often, and having an overall positive attitude; this patient mentioned feeling lucky and recognizing that not all lung cancer patients may be as fortunate as her.

Side effects experienced while receiving durvalumab were few, including one patient who did not experience any side effects. Though the most common reported side effects reported were fatigue and nausea, it was reported by all seven patients from the online scan that there was an overall better sense of wellbeing while receiving durvalumab compared to chemotherapy; nausea, reported by five patients, and fatigue, reported by two patients, due to durvalumab were reportedly less severe than fatigue and nausea experienced while receiving chemotherapy. Of interviewed patients, six patients reported experiencing fatigue and two patients reported nausea while being treated with durvalumab; these patients also agreed that nausea and fatigue experienced on durvalumab were less severe compared to chemotherapy. One patient reported that fatigue was persistent throughout their chemotherapy treatment, however this was not the case while they were treated with durvalumab. For example, one patient was unable to play golf during chemotherapy treatments due to fatigue, however they were able to continue to golf while receiving durvalumab and reported they felt stronger every day even though sometimes they were tired.

Other side effects included irregular kidney function requiring hydration and steroids reported by one patient, increased fatigue, shortness of breath, and erratic temperature changes reported by another patient, lung inflammation which developed after a patient's third infusion of durvalumab, and another patient who developed thyroiditis. Many patients mentioned uncertainty about whether experienced side effects were due to durvalumab, or whether they were residual side effects from chemoradiation. Some patients continued to experience improvements in fatigue and the amount of energy they had, adding to the confusion about whether the fatigue experienced was a subsiding side effect from chemoradiation or whether patients were adjusting to durvalumab. LCC stated that even clinicians felt uncertainty regarding the cause of the fatigue. One patient reported experiencing no serious side effects, but then suddenly developed a hacking cough, the source of which her doctors had a difference of opinion on; this patient was then taken off durvalumab treatment. Two patients developed pneumonitis, where the causes were also questioned by their oncologists and radiologists as pneumonitis was stated to be a known side effect of immunotherapy and radiation therapy. Both of the patients who experienced pneumonitis, were treated with prednisone. LCC suggested the creation of educational materials to help better manage side effects, and combat some confusion related to side effects of durvalumab.

While OLA's input did not include information regarding direct experience with durvalumab, they provided a list of key treatment outcomes patients and their caregivers wanted addressed in regard to lung cancer: stopping or slowing progression of disease, reducing of pain, fatigue, cough

and shortness of breath, and improvement of appetite and energy. In addition, pain, fatigue, nausea, shortness of breath, appetite loss, low energy, the inability to battle infection, burning of the skin and impact on mood were side effects patients and caregivers wanted to see improvements for, or eliminated. The burden of cost was also mentioned, as both patients and caregivers mentioned either a reduction or elimination of costs associated with new treatments. Patients mentioned preferring treatment options that tallow them to stay at home; patients reported that more practical treatments may prevent both the patients and their caregivers from taking time off work, prevent disruptions in daily routines, and maintain quality of life. One female lung cancer patient commented on her desire to spend her time with the people she cares about rather than at hospitals, *"if I have less than three years to live, I would like to be able to enjoy that time with my family."*

3.3 Additional Information

Information obtained from OLA indicated a greater desire to be well-informed regarding their treatment options, and possible side effects from them by patients. Patients prefer to know more regarding their treatment options up front, to make better decisions with their preferences in mind, and to help determine what side effects they are willing to tolerate.

LCC provided input stating that durvalumab is the first innovative treatment in stage 3B non-resectable cancer; LCC highlighted that this stage of cancer has a curative intent, and completely aligns with patient values due to its potential for providing patients with a cure. With the great burden lung cancer places on patients, families and public healthcare funds, LCC stated that as a society we are obligated to provide patients with this potential for cure. The World Conference on Lung Cancer in Toronto was where data for the PACIFIC Trial was presented, where LCC stated social media responses from physicians were positive with Twitter tweets declaring in regards to durvalumab, *"It's a new standard of care!"*

4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

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

Overall Summary

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

Clinical factors:

- Treatments after progression on durvalumab
- Duration of treatment

Economic factors:

- Drug wastage
- Additional resources and chemotherapy chair time to prepare and administer durvalumab
- Additional resources required to monitor and manage infusion related reactions and adverse events

Please see below for more details.

4.1 Currently Funded Treatments

PAG noted that there is currently no consolidation treatment for stage III locally advanced, unresectable NSCLC whose disease has not progressed following platinum-based chemoradiation therapy. The standard of care following platinum-based chemoradiation therapy is close observation, although some patients may be treated with two further cycles of platinum-based chemotherapy as consolidation at the discretion of the physician.

4.2 Eligible Patient Population

PAG noted the trial enrolled patients with both squamous and non-squamous Stage III NSCLC. There is potential indication creep for patients that either receive thoracic radiotherapy alone, or followed by sequential chemotherapy (i.e. not concurrent). These patients were not included in the PACIFIC clinical trial. In addition, PAG noted that patients with Stage IIIb disease are usually not treated with chemoradiation, as they are treated similarly to Stage IV disease with the same treatments.

PAG is seeking clarity on the patients who would be eligible and those who would not be eligible for treatment with durvalumab such as:

- Disease stage
- Whether durvalumab is after concurrent chemoradiation therapy only or after radiation and chemotherapy given sequentially
- Patients with stage III disease who do not receive chemoradiation therapy
- Patients with resectable disease who receive neoadjuvant or adjuvant chemoradiation therapy

4.3 Implementation Factors

As the current standard of care is observation, incremental resources would be required to prepare, administer and monitor durvalumab infusions. Durvalumab is an immunotherapy that is administered intravenously over 60 minutes, once every two weeks requiring chemotherapy chair time. There are adverse events associated with durvalumab that need to be monitored and treated. The costs of additional physician clinic visits, diagnostic imaging tests and management of adverse events would need to be considered.

PAG also noted that durvalumab infusion requires inline filters and must be administered immediately after preparation as there is no information on stability of the infusion mixture at room temperature.

PAG noted that there is the potential for drug wastage due to small number of patients, although there are two vial sizes to minimize drug wastage.

PAG is seeking clarity on the duration of treatment, whether treatment should be stopped at 12 months or if options to continue beyond 12 months or re-starting at time of disease progression if stopped at 12 months should be recommended, as these are options described in the PACIFIC trial.

It will be helpful for pERC to specify that treatment should start up to 6 weeks (1-42 days) following completion of concurrent chemoradiation as per the PACIFIC study.

4.4 Sequencing and Priority of Treatments

Durvalumab is an immunotherapy that is a PD-L1 inhibitor. Durvalumab is indicated for stage III locally advanced, unresectable disease until disease progression. PAG is seeking advice on treatments after durvalumab, when patients progress and have metastatic disease. For metastatic disease, currently funded treatments include other PD-1 inhibitors (nivolumab, pembrolizumab), chemotherapy, and targeted oral therapies. PAG is seeking data on the use of other PD-1 inhibitors and PD-L1 inhibitors in the treatment of metastatic disease after progression on durvalumab. What are the benefits and cost effectiveness of treatment with PD-1 inhibitors in metastatic disease after treatment with a PD-L1 inhibitor (i.e. durvalumab) in locally advanced disease?

4.5 Companion Diagnostic Testing

PAG noted that PD-L1 testing was conducted in the trial but the trial concluded that benefit with durvalumab was observed irrespective of PD-L1 expression.

4.6 Additional Information

None.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

Four clinician inputs were provided for durvalumab for the treatment of patients with locally advanced, unresectable NSCLC following curative intent platinum-based chemoradiation therapy. Input was provided as two joint clinician submissions and two individual clinician submissions. In total, there were nine clinicians who provided input. Their input is summarised below.

All clinicians agreed that there is a significant unmet need, as the current standard of care for patients following chemoradiation is observation; durvalumab would serve as a new treatment for patients with locally advanced, unresectable NSCLC following curative intent platinum-based chemoradiation therapy for up to one year. Clinicians also commented on the favourable toxicity profile of durvalumab. The clinicians agreed that the patient eligibility criteria in the PACIFIC trial would be applicable to clinical practice. One of the clinician inputs highlighted patients with PD-L1 <1% in the trial, stating that while the benefit of durvalumab among this subpopulation is unclear, it is possible that these patients may still benefit.

Clinicians providing input noted that when treating with durvalumab in clinical practice, there should be consideration for a patient's performance status, status of autoimmune disease, or contraindications to immunotherapy. Some clinicians recommended that patients not be considered candidates for durvalumab if their disease grows immediately throughout chemoradiation, they require systemic corticosteroids for radiation pneumonitis, they have an organ transplant or immunosuppressing disease, and if there is presence of an autoimmune comorbidity requiring systemic corticosteroids or immunosuppressants.

Varying clinician opinions were present regarding extending the use of durvalumab to patient populations beyond the trial, specifically patients who received chemotherapy and radiation therapy sequentially or radiation therapy alone or chemotherapy alone.

When asked whether clinicians would consider use of PD-1 inhibitors, such as nivolumab or pembrolizumab, for metastatic disease in patients previously treated with durvalumab for stage 3 disease, there were varying opinions among the clinicians. Three of the clinician inputs suggested that consideration of PD-1 inhibitors following durvalumab was appropriate given certain considerations. One of the clinician inputs did not support the use of PD-1 inhibitors following durvalumab.

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

5.1 Current Treatment(s) for NSCLC

All clinicians indicated there are no active treatments currently available for patients with locally advanced, unresectable NSCLC following curative intent platinum-based chemoradiation therapy. Observation is the current standard of care in this setting.

5.2 Eligible Patient Population

All clinicians agreed that the eligible patient population was reflected in the funding request, and that these patients faced a high unmet need. In addition, the eligibility criteria for patients in the PACIFIC trial would be applicable to clinical practice. Two of the clinician inputs suggested extending the criteria of eligible patients to those who received chemotherapy and radiation therapy sequentially, in addition to having received them concurrently. Supporting this expansion of eligibility to sequential chemotherapy and radiation therapy, one of the clinician inputs mentioned that while the majority of patients are treated with concurrent chemotherapy and radiation, a small number of patients are treated sequentially. The most common reason was

stated to be an absence of a radiation facility at the institution where the patient is receiving chemotherapy, other reasons include but are not limited to, concerns for a patient's performance status at the time of their diagnosis, presence of comorbidities, and potential toxicity related to concurrent chemotherapy and radiation. The clinician input suggested that patients who underwent chemotherapy followed by a curative dose of radiation could benefit from receiving durvalumab if treated within six weeks (42 days) from their last dose. Further, the clinician input indicated that extending the pool of eligible patients to those who underwent sequential chemotherapy and radiation is in line with the Health Canada label for durvalumab.

One of the clinician inputs mentioned the status of patients with PD-L1 <1%, and suggested that durvalumab still be considered a potential treatment option for these patients. In an exploratory analysis in the PACIFIC trial, there was no improvement in overall survival for patients with PD-L1 <1%, however there was an improvement in progression-free survival. The clinician input highlighted the following limitations to the post-hoc analysis involving patients with PD-L1 <1%:

- the analysis was unplanned and trial arms were subject to unbalance in baseline characteristics
- patients who progress after chemoradiation, especially within the first two years, have a high likelihood of being resistant to systemic therapy, have systemic recurrence, poor performance status leading to overall clinically poor outcomes
- the sample of patients in this subgroup for analysis was small.

The clinician input also mentioned that PD-L1 expression can be upregulated by chemotherapy and radiation, impacting PD-L1 expression post-chemotherapy and radiation. Therefore, the clinician input suggested that, while the benefit among patients with PD-L1 <1% may be uncertain, it is still possible, and suggest caution in over-interpreting subgroup analyses. Parallels were also drawn by clinician input to the inclusion of subgroups of patients for other treatments, including EGFR/ALK+ patients with metastatic NSCLC for treatment with second-line nivolumab as well as pembrolizumab based on the CHECKMATE 057 and KEYNOTE 042 trials, respectively.

5.3 Relevance to Clinical Practice

The clinicians stated that durvalumab would become standard of care, replacing observation, for patients following chemoradiation. All clinicians agreed that consideration of autoimmune disease would be needed prior to treating patients with durvalumab. Clinicians may also need to consider whether patients have existing contraindications with immunotherapy; one of the clinicians suggested that patients with an active pre-existing autoimmune condition may still be considered for immunotherapy after consultation with relevant specialists.

One of the clinicians suggested, patients with poor performance status who are likely not to complete chemoradiation and whose disease grows immediately following chemoradiation should not be eligible for durvalumab. Another clinician input suggested that the following patients would also not be considered candidates for durvalumab: 1) patients with clinically significant radiation pneumonitis requiring systemic corticosteroid, 2) patients with autoimmune comorbidity requiring systemic corticosteroid and/or immunosuppressants, except for those with autoimmune endocrinopathies who are on adequate replacement and those with vitiligo and psoriasis not requiring systemic therapy, and 3) patients with an organ transplant or immunosuppression disease. The clinician input noted that durvalumab could be used as maintenance therapy to prevent the occurrence of a second lung cancer, which lung cancer patients who have survived prior curative chemotherapy, radiation or surgical therapy, regardless of histology, are at high risk of developing; specifically, patients with a second primary lung tumour treated with chemoradiation should be allowed to receive durvalumab maintenance therapy. It was noted that

currently patients with at least stable disease post-curative intent chemoradiation do not receive any maintenance therapy.

Two of the clinician inputs commented on the favourable toxicity profile of durvalumab; one of the clinicians mentioned that durvalumab is well tolerated, and that few patients discontinued due to toxicities. Overall, one of the clinician inputs stated that the decrease in recurrence rates from treatment with durvalumab are expected to translate to benefits in overall survival.

5.4 Sequencing and Priority of Treatments with Durvalumab

The clinicians agreed that durvalumab would be given to patients following chemoradiation, specifically within six weeks of their final dose of chemoradiation. The clinicians highlighted that currently patients are observed and are not treated with anything following chemoradiation, therefore durvalumab would become standard of care.

One of the clinician inputs stated that patients could be retreated with durvalumab (re-treatment was allowed in the pivotal trial) after having experienced a benefit from the one-year durvalumab maintenance therapy. Retreatment with durvalumab for patients upon progression is not included within the Health Canada approved indication "for patients with locally advanced, unresectable NSCLC whose disease has not progressed following platinum-based chemoradiation therapy". Using evidence from the KEYNOTE 024, 042, 189 and 407 trials, the clinicians emphasized that patients experienced survival benefit with the use of platinum-based chemotherapy and pembrolizumab for all PD-L1 subgroups, and pembrolizumab for those with PD-L1 of at least 50%. As patients may benefit from PD-L1 therapy, the clinician input suggested that patients could be retreated with PD-L1 therapy with or without platinum-based chemotherapy upon recurrence or metastatic disease after durvalumab maintenance, if patients fulfilled the eligibility criteria for PD-L1 therapy with or without platinum-based chemotherapy and did not progress while receiving durvalumab.

5.5 Companion Diagnostic Testing

Three of the four clinician inputs indicated that durvalumab treatment in this setting does not required companion diagnosis testing. The other clinician input also agreed that no testing would be required as patient subgroups in the PACIFIC Trial related to PD-L1 expression (≥25%, <25%, and unknown) showed benefit with durvalumab. Testing for PD-L1 expression using the 22C3 antibody was mentioned to occur more frequently and reported at the time of initial diagnosis; therefore, the clinician input suggested that patients with adequate diagnostic tissue will have their PD-L1 status known at the time of treatment with durvalumab maintenance. The clinician input noted that based on the results of the BLUEPRINT Trial, there was good concordance between SP263 and 22C3 diagnostic PD-L1 testing.

5.6 Additional Information

1. In the PACIFIC trial, patients received concurrent chemotherapy and radiation therapy. In your opinion, can the results of this trial be generalized to patients who received chemotherapy and radiation therapy sequentially? To patients who only received chemotherapy? To patients who only received radiation therapy?

Based on the input already mentioned above, some clinicians agree with generalizing treatment with durvalumab to patients who received chemotherapy and radiation therapy sequentially. All but one of the clinician inputs agreed use of durvalumab could be generalized to patients who received chemotherapy and radiation sequentially.

In regards to generalizing treatment with durvalumab to patients who received only radiation therapy or only chemotherapy, there were varying opinions among the clinicians. One of the clinician inputs suggested that generalizing to patients who received high dose radiation therapy was possible. However, the input stated that use of durvalumab to patients with Stage 3 NSCLC who received only chemotherapy was not appropriate, as chemotherapy is not provided with the intention to cure. Another clinician input mentioned that there is currently no evidence to allow for generalization of durvalumab to patients who receive chemotherapy or radiation therapy alone; currently there are trials underway that address this concern. This clinician input mentioned that they expected pCODR to comment on this generalization when the data becomes available, and that reimbursement criteria will be revised appropriately when the occurs. Two of the clinician inputs did not comment on this matter.

2. Durvalumab is a PD-L1 inhibitor, would you consider PD-1 inhibitors (e.g. pembrolizumab, nivolumab) for metastatic disease in patients previously treated with durvalumab for Stage III disease?

One of the clinician inputs did not support the use of PD-1 inhibitors for patients with Stage 3 metastatic disease who had previously been treated with durvalumab, due to higher risk of lung toxicity with an anti-PD-1. One of the clinician inputs thought that using PD-1 inhibitors following durvalumab would be appropriate if they did not experience progression on durvalumab. Another clinician input mentioned that use of PD-1 inhibitors following durvalumab would depend on the amount of time that elapsed between the end of durvalumab treatment and occurrence of relapse; if the patient relapsed on durvalumab or within three months of stopping durvalumab, the clinician input did not recommend use of PD-1 inhibitors. Based on evidence from the PACIFIC trial, one of the clinician inputs stated that patients who had at least stable disease during durvalumab maintenance for one year could be retreated at the time of progression. The clinician cited supporting data from the KEYNOTE 024, 042, 189, and 407 trials of patients with PD-L1 <1% and PD-L1 1-49%. The clinician input stated there should be the option of being retreated with pembrolizumab in combination with platinum-based chemotherapy. For patients with PD-L1 expression of 50% or greater, the clinician input recommended they be retreated with either pembrolizumab or durvalumab alone, or pembrolizumab in combination with platinum-based chemotherapy.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the efficacy and safety of durvalumab in the treatment of patients with locally advanced, unresectable non-small cell lung cancer (NSCLC) whose disease has not progressed following platinum-based chemoradiation therapy (CRT) for up to a maximum of 12 months.

6.2 Methods

The systematic review protocol was developed jointly by the CGP and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in Table 3 below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold. The literature search strategy and detailed methodology used by the pCODR Methods Team are provided in Appendix A.

Table 3: Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators[a]	Outcomes
Published or unpublished RCTs In the absence of RCT data, fully published clinical trials investigating the safety and efficacy of Durvalumab should be included.	Patients with locally advanced, unresectable NSCLC whose disease has not progressed following curative intent platinum-based CRT for up to a maximum of 12 months Subgroups: • Age (<65 vs. ≥ 65 years) • Sex (Female vs. male) • Smoking status (Smoker vs. non-smoker) • Histologic type (Squamous histology vs. all other type) • Stage IIIA vs. Stage IIIB • WHO performance status at baseline ("0" vs. "1") • PD-L1 status (<25% vs. ≥25% vs. unknown) • EGFR positive vs. EGFR negative vs. unknown • Response to CRT (Complete response vs. partial response vs. stable disease)	Durvalumab	• Placebo • Standard of care (i.e., active observation, active surveillance, watch and wait • Two further cycles of platinum based chemotherapy following platinum based CRT[b]	Primary • **OS** • **PFS** • **HRQoL** Secondary • OS24 • ORR • DOR • APF12 • APF18 • PFS2 • TTDM Safety • AEs (especially, immune-related AEs, e.g., pneumonitis • SAEs • WDAEs
Abbreviations: AE=adverse events; APF12 = proportion of patients alive and progression-free at 12 months from randomization; APF18 = proportion of patients alive and progression-free at 18 months from randomization; CRT = chemoradiation therapy; DOR=duration of response; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EGFR = Epidermal growth factor receptor; HRQoL= Health related quality of life; NSCLC = non-small cell lung cancer; ORR=objective response rate; OS = overall survival; OS24 = proportion of patients alive at 24 months from randomization; PD-L1 = Programmed death-ligand ; PFS2 = time from randomization to second progression; RCT=randomized controlled trial; SAE=serious adverse events; TTDM = time to death or distant metastasis; WDAE=withdrawals due to adverse events; vs. = versus; yrs = years;				
Notes:				

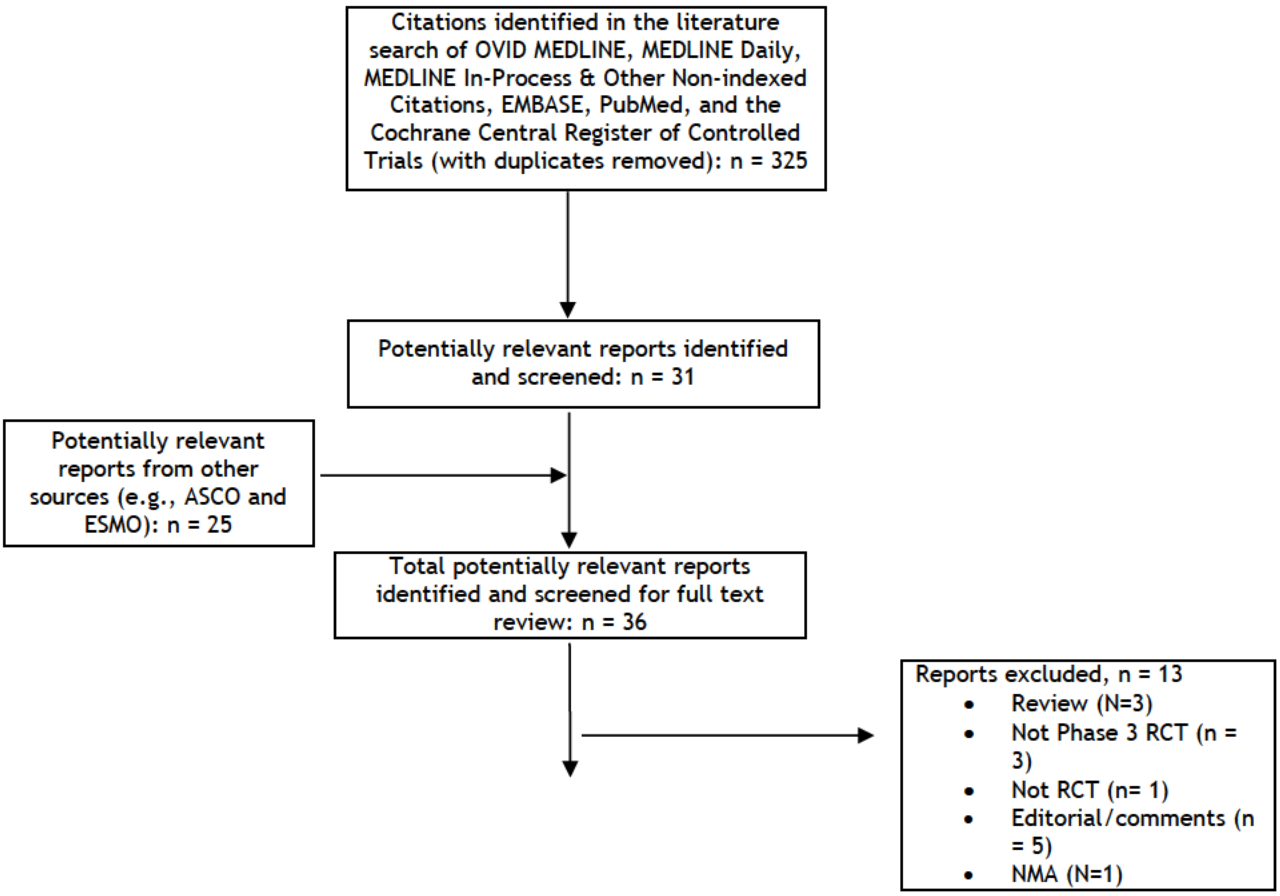
[a] Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions).
[b] Based on PAG input and clinical experts input, two further cycles of platinum based chemotherapy following platinum based CRT have been used in some institutions in Canada (institution based), although it is not a standard of care for all patients in all institutions)

6.3 Results

6.3.1 Literature Search Results

Of the 36 potentially relevant reports identified, one study (Study PACIFIC) in 23 citations was included in the pCODR systematic review. [1,2,23,30-49] Thirteen studies were excluded.[50-62] Studies were excluded because one was not RCT,[56] three were not phase 3 RCT,[50,51,53] three were reviews, [54,59,60] five were editorial or comments [52,54,58,61,62] and one was network meta-analysis (NMA).[57]

Figure 1: QUOROM Flow Diagram for Inclusion and Exclusion of studies



23 reports presenting data from 1 clinical trial (PACIFIC) included

Study (18 publications /conference abstracts)

- DE WIT et al. (2018);[38]
- HUI et al. (2017, 2017, 2018);[39-41]
- ANTONIA et al.(2014, 2016, 2017, 2017, 2018, 2018);[1,2,23,30-32]
- ISAAC (2018);[43]
- MURAKAMI et al. (2017);[45]
- CHO et al (2015);[36]
- Creelan et al. (2015);[37]
- PACIFIC Study Protocol ;[46]
- LAACK et al, (2018);[44]
- Clinicaltrials.gov; [34]
- EMA report [48]

5 Reports identified from other sources:

- Clinical study report ;[33]
- Clinical study report Addendum;[35]
- PACIFIC Protocol Amendments;[47]
- Product Monograph;[42]
- Health Canada reviewer report[49]

6.3.2 Summary of Included Studies

The pCODR systematic review included one phase III RCT (the PACIFIC trial) that assessed the safety and efficacy of durvalumab as consolidation therapy compared with placebo in patients with locally, advanced, unresectable stage III NSCLC who did not have disease progression after two or more cycles of platinum-based chemoradiotherapy.[1,2] A total of 713 patients were randomly assigned to receive durvalumab at a dose of 10 mg/kg of body weight, IV infusion, every 2 weeks (n = 476) or to matching placebo, IV infusion (n = 237) for up to 12 months. The study drug was discontinued if there was confirmed disease progression, unacceptable toxic effects, or withdrawal of consent. Patients could receive the study drug until disease progression (unless they had rapid tumor progression or symptomatic progression requiring urgent intervention) and could receive the drug again (re-treatment) if disease control had been achieved at the end of the 12 months but the disease had progressed during follow-up.[33,35,46,47]

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6.3.2.1 Detailed Trial Characteristics

The summary of the trial and select quality characteristics are presented in Table 4 and Table 5

Table 4: Summary of Trial Characteristics of the Included Study

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Study PACIFIC (NCT02125461) Characteristics International, randomized (2:1 ratio), placebo controlled, double-blind, phase 3 trial Sample size Randomized N= 713 ; Treated n=709 Number of centres and number of countries[a]: 235 centers in 26 countries Patient Enrolment Dates: 09 May 2014 to 22 April 2016 Two data cut-off dates reported: - February 13, 2017 for interim analysis for PFS. Median F/U time: 14.5 months; range: 0.2 -29.9 months). However, the analysis was considered as the final analysis for PFS since PFS achieved statistical significance. [b] -March 22, 2018: Median F/U time: 25.2 months;	Key inclusion criteria: • Patients with locally advanced, unresectable (Stage III) NSCLC; • Patients received at least 2 cycles of platinum-based chemotherapy concurrent with radiation therapy, which must be completed within 1 to 42 days prior to randomization in the study; • Patients must have not progressed following definitive, platinum-based, concurrent chemoradiation therapy; • Life expectancy ≥12 weeks; • WHO Performance Status of 0 or 1 • Adequate organ and marrow function Key exclusion criteria: • Mixed small cell and non-small cell lung cancer histology • Patients who receive sequential chemoradiation therapy for locally advanced NSCLC • Patients with locally advanced NSCLC who have progressed whilst definitive platinum based, concurrent chemoradiation therapy • Prior exposure to any anti-PD-1 or anti-PD-L1 antibody • Patients with ≥ Grade 2 pneumonitis from prior chemoradiation therapy • Any prior Grade ≥3 immune-related adverse event (irAE) while receiving any previous immunotherapy agent;	Intervention Durvalumab 10 mg / kg, IV infusion, once every 2 weeks as consolidation therapy for up to 12 months[d] Comparator: Matching placebo	Co-primary outcomes: OS PFS Secondary • OS24 • ORR • DOR • APF12 • APF18 • PFS2 • TTSSD • TTDM Secondary PRO: • EORTC QLQ-C30 • EORTC QLQ-LC13 • EQ-5D-5L Safety • AEs • SAEs • WDAEs • AEs of special interest: Pneumonitis, etc.

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
range: 0.2 -43.1 mos. This cut-off was planned for primary analysis for PFS and the first interim analysis for OS. However, the analysis was considered as the final analysis for OS since OS achieved statistical significance.[c] <u>Final Analysis Date:</u> For OS, since the trial reached statistical significance on the basis of this interim analysis for OS, the results presented herein are considered final for overall survival. Patients will continue to be followed for long-term survival and updated OS analyses will be presented in future reports, as needed. <u>Ongoing study:</u> PACIFIC is still an ongoing study. The estimated study completion date :July 9, 2019 <u>Funding:</u> AstraZeneca	• Active or prior documented autoimmune disease within the past 2 years. • Active or prior documented inflammatory bowel disease (e.g, Crohn's disease, ulcerative colitis) • History of primary immunodeficiency, organ transplant that requires therapeutic immunosuppression, tuberculosis • History of hypersensitivity to durvalumab or any excipient. • Active HIV, HBV or HCV.		

Abbreviations: AE=adverse events; APF12 = proportion of patients alive and progression-free at 12 months from randomization; APF18 = proportion of patients alive and progression-free at 18 months from randomization; CRT = chemoradiation therapy; DOR=duration of response; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EGFR = Epidermal growth factor receptor; F/U = follow up; HRQoL= Health related quality of life; mons = months; NSCLC = non-small cell lung cancer; ORR=objective response rate; OS = overall survival; OS24 = proportion of patients alive at 24 months from randomization; PD-L1 = Programmed death-ligand ; PFS2 = time from randomization to second progression; RCT=randomized controlled trial; SAE=serious adverse events; TTDM = time to death or distant metastasis; TTSSD =Time to second subsequent therapy or death; WDAE=withdrawals due to adverse events; vs. = versus; yrs = years; PRO questionnaires will be assessed using the EORTC-QLQ-C30 with the EORTC-QLQ-LC-13 module (HRQoL with lung cancer specific additional concerns) and EQ-5D-5L. All items/questionnaires will be scored according to published scoring guidelines or the

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
developer's guidelines, if published guidelines are not available. All PRO analyses will be based on the Intent-to-Treat (ITT) population, unless stated otherwise; WHO PS = World Health Organization Performance Status.			

[a] This ongoing study is being conducted at study centers in North and Latin America, Europe, and Asia Pacific. A total of 308 study centers in 28 countries were selected for this study, of which 235 study centers in 26 countries enrolled patients.

[b] February 13, 2017 data cut-off was a planned first interim analysis for PFS. This data cut-off for the interim PFS analysis was done when approximately 367 PFS events have occurred (52% maturity). Since PFS achieved statistical significance based on this analysis, this was considered as the final PFS analysis. [33]

[c] The March 22, 2018 data cut-off was a planned primary analysis for PFS and the interim analysis for OS. The data cut-off for the primary PFS analysis and first interim OS analysis was done when at least 458 PFS events have occurred (65% maturity). For OS, the final analysis was planned to be conducted when approximately 491 deaths had occurred (69% maturity). Since the OS reached statistical significance based on this interim analysis, the analysis was considered the final for OS.[2]

[d] For patients who completed 12 months of therapy and had SD, PR, or CR at completion continued to be followed up for progression. Per the protocol, patients had the option to re-start study treatment (the treatment they were originally randomized to for the first 12 months) upon evidence of disease progression if they were eligible to do so, and it was considered the best treatment option for the patient.[33]

Data source: CSR-PFS, CSR-OS, Protocols [33,35,46,47]

Table 5: Select quality characteristics of included studies of durvalumab in patients with locally advanced, unresectable NSCLC whose disease has not progressed following curative intent platinum-based CRT for up to a maximum of 12 months

Study	Treatment vs. Comparator	Primary outcome	Required sample size	Sample size	Randomization method	Allocation concealment	Blinding	ITT Analysis	Final analysis	Early termination	Ethics Approval
PACIFIC	Durvalumab vs. placebo	OS PFS	702	713	IVRS/IWRS	Yes	DB	Yes	No	No	Yes

Abbreviations: DB = double blind; ITT = intention to treat; IVRS = Interactive Voice Response System; IWRS = interactive web response service; PFS = progression free survival; OS = overall survival

Notes:
a: Sample size calculation and analysis: the study was considered positive if either PFS or OS was significantly longer with durvalumab than with placebo. Approximately 702 patients were needed for 2:1 randomization to obtain 458 PFS events for the analysis of PFS and 491 OS events for the analysis of OS. It was estimated that the study would have a ≥95% power to detect a hazard ratio for disease progression or death of 0.67 and a ≥85% power to detect a hazard ratio for death of 0.73, on the basis of a log-rank test with a two-sided significance level of 2.5% for PFS or OS. Between-group comparisons were performed with the use of the log-rank test, stratified according to age, sex, and smoking history. Sensitivity analyses included assessment of evaluation bias, evaluation-time bias, and attrition bias in the determination of disease progression and adjustment for various covariates in the estimation of the hazard ratio for disease progression or death.[1]
b: Randomization: randomization was stratified by age at randomization (<65 versus ≥65 years of age), sex (male versus female), and smoking history (smoker versus non-smoker).[1]
c: Blind and allocation concealment: patients, investigators and study centers were blinded to treatment assignment. PFS and ORR were confirmed by a blinded independent review committee (BIRC).[1]
d: Two data cut-off dates reported in this review: The first data cut-off was on February 13, 2017 for the interim PFS analysis as planned . The second cut-off date was on March 22, 2018 for the interim OS analysis and the primary PFS analysis.
e: Safety data was summarised descriptively and was not formally analysed.[46]

a) Trial

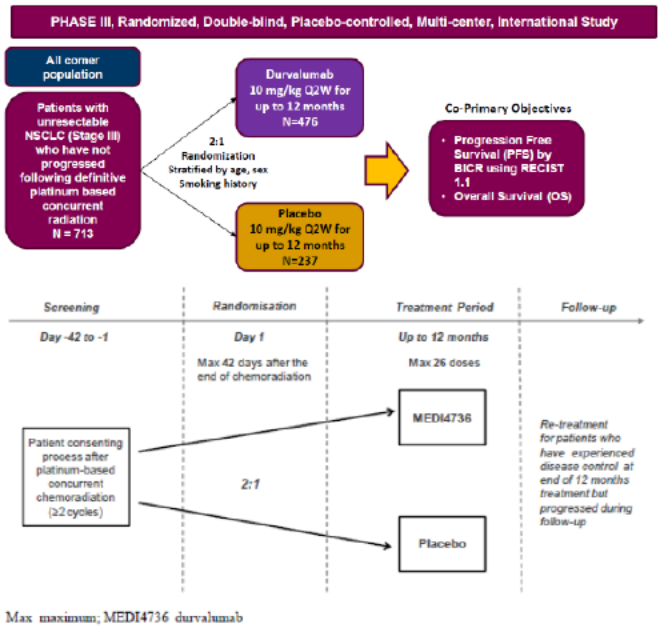
The PACIFIC trial was a randomized, double blind, placebo controlled, international phase III trial that assessed the efficacy and safety of durvalumab as a consolidation therapy compared with placebo in patients with stage III NSCLC who did not have disease progression after two or more cycles of platinum-based chemoradiotherapy up to 12 months. The trial was conducted in 235 centers in 26 countries including Australia, Asia, Europe, South America, South Africa and North America (i.e., USA, Canada and Mexico).[46,47] The trial was sponsored by AstraZeneca.

The key inclusion criteria were presented in Table 4 and Table 5. Briefly, 18 years of age or older; locally advanced, unresectable stage III NSCLC; no disease progression after two or more cycles of platinum-based chemotherapy concurrently with definitive radiation therapy; a WHO performance status of 0 or 1 (on a 5-point scale, in which higher numbers indicate greater disability), an estimated life expectancy of ≥ 12 weeks, and completion of the last radiation dose within 1 to 42 days.[47] The key exclusion criteria included: mixed small cell and non-small cell lung cancer histology; patients who receive sequential chemoradiation therapy for locally advanced NSCLC; patients with locally advanced NSCLC who have progressed while definitive platinum based, concurrent chemoradiation therapy; prior exposure to any anti-PD-1 or anti-PD-L1 antibody; Patients with any grade pneumonitis from prior chemoradiation therapy; any prior Grade ≥3 immune-related adverse event while receiving any previous immunotherapy agent; active or prior documented autoimmune disease within the past 2 years; active or prior documented inflammatory bowel disease; active HIV, HBV or HCV; and history of primary

immunodeficiency, organ transplant that requires therapeutic immunosuppression, tuberculosis, hypersensitivity to durvalumab; and.[47] The study design of PACIFIC is presented in

Figure 2 below.

Figure 2: Study flow chart



Date source: EMA report[48]

The study PACIFIC consisted of the treatment phase and the follow-up phase.[46]

Treatment Phase [46]

- Eligible patients were randomized using a centralized interactive web response system (IWRS)/ interactive voice response system (IVRS);
- Patients were randomized on a 2:1 ratio to receive either durvalumab or matching placebo. Randomization was stratified by age at randomization (<65 versus ≥65 years of age), sex (male versus female), and smoking history (smoker versus non-smoker);
- Efficacy was assessed by objective tumour assessments every 8 weeks for the first 12 months, then every 12 weeks thereafter, until confirmed objective disease progression as defined by Response Evaluation Criteria In Solid Tumours (RECIST) 1.1 (irrespective of the reason for stopping study drug and/or subsequent post discontinuation anticancer therapy).
- Progression were considered as confirmed if the following criteria were met: ≥20% increase in the sum diameters of target lesions compared with the nadir at 2 consecutive visits with an absolute increase of at least 5 mm; and/or worsening of non-target lesions or new lesions; and/or additional new unequivocal lesions. If a patient discontinued study drug (and/or received a subsequent cancer therapy) prior to progression then the patient should still continue to be followed until confirmed objective disease progression.

Follow-up phase[46]

- Patients who have completed the treatment period and achieved disease control and patients who have discontinued study drug due to toxicity or a reason other than confirmed progression of disease entered follow-up phase.

- Retreatment during follow-phase: Patients who achieved and maintained disease control (i.e., CR, PR, no evidence of disease, or SD) through to the end of the 12-month treatment period, may restart study drug upon evidence of confirmed Progression of disease during follow-up period. To restart study drug the patient must not have received an intervening cancer therapy post study drug discontinuation. Patients may restart study drug for up to 12 months with the same treatment criteria as the initial 12-month treatment period. Patients will only be able to restart study drug once; thus a maximum of two 12-month periods will be allowed.[47]
- Post-discontinuation anticancer therapy during follow-phase: A total of 241(50.6%) patients with durvalumab and 154 (65%) with placebo discontinued the study treatment at the March 22, 2018 cut-off.[2] A total of 195 (41.0%) patients with durvalumab and 128 (54.0%) patients with placebo received post-discontinuation anticancer therapy. Most patients received cytotoxic chemotherapy (26.9% patients in the durvalumab group versus 30.0% patients in the placebo group); 9.9% patients in durvalumab and 13.1% patients in placebo received targeted therapy; 8.0% patients with durvalumab and 22.4% patients with placebo received immunotherapy; 17.2% patients with durvalumab and 23.6% patients with placebo received radiotherapy.[2]

The co-primary outcomes were overall survival (OS) and progression-free survival (PFS). Secondary endpoints included overall survival at month 24 (OS24), objective response rate (ORR), duration of confirmed response (DOR), proportion of patients alive and progression-free at 12 months from randomization (APF12), proportion of patients alive and progression-free at 18 months from randomization (APF18), time from randomization to second progression (PFS2), time to death or distant metastasis (TTDM), Time to second subsequent therapy or death (TTSSD) and safety. Health-Related Quality of Life (HRQoL) was also measured as secondary endpoint using the European Organization for Research and Treatment of Cancer core 30 quality of life Questionnaire (EORTC QLQ-C30) with the EORTC-QLQ-LC-13 module (HRQoL with lung cancer specific additional concerns) and EQ-5D-5L and EuroQol EQ-5D.[46,47]

The primary analysis for the co-primary outcomes (OS, PFS) were based on the intention-to-treat (ITT), Patients who were randomised but did not subsequently go on to receive study drug are included in the ITT population. Based on the protocol amendments, the Type I error was split between the 2 co-primary outcomes, OS and PFS. The alpha level for OS and PFS was changed from 4.5% and 0.5%, respectively, to 2.5% equally. So that the statistical test can detect a smaller yet clinical meaningful treatment effect on PFS.[47]

The first analysis data cut-off occurred when it was expected that 458 PFS events have occurred (65% maturity). If the true PFS HR is 0.67, the study would provide 95% power to demonstrate a statistically significant difference for PFS with a 2-sided significance level of 2.5% in the ITT population; The smallest treatment difference that would be statistically significant is HR 0.8. The second analysis data cut-off occurred when it was expected that 491 OS events have occurred (70% maturity). If the true OS HR is 0.73, this number of death events would provide approximately 85% power to demonstrate a statistically significant difference for OS. The smallest treatment difference that would be statistically significant is HR 0.81.

Protocol Amendments [33,47]

All protocol amendments were approved by the Sponsor. For the purpose of this review, the key protocol amendments and rational for the protocol amendments are presented below:

- Amendment #2 (August 8, 2014): Addition of a data cut-off date to occur when it was expected that 275 PFS events have occurred.

- Amendment #3 (February 18, 2015: The protocol was updated to allow patients who had completed radiation therapy from within 14 days from their last dose to within 42 days.
- Amendment # 4 (February, 11, 2016):
  -The EORTC QLQ-LC13 change in baseline score was revised from "≥5" to "≥10". The 10-point was considered as the clinically meaningful change of the EORTC QLQ-C30, and was generally more accepted by regulators and payers.
  -The Type I error was split between the 2 co-primary endpoints, OS and PFS. The alpha level for OS and PFS was changed from 4.5% and 0.5%, respectively, to 2.5% equally. So that the statistical test can detect a smaller yet clinical meaningful treatment effect on PFS. This changes were made based on two observations as follows: 1) From recently published immune-oncology agents' data, a smaller treatment effect had been observed in the NSCLC patients with EGFR mutations; and 2) Recent approvals of other immune-oncology agents in NSCLC patients who were eligible to receive second-line and above treatment make the collection of OS data in this patient population more challenging. Hence, greater alpha had been assigned to PFS outcome to protect the probability of success of PFS (and OS still remains as the co-primary outcomes in this study).

b) Populations

Table 6 outlines the baseline characteristics of the patients in study PACIFIC. A total of 713 patients were randomized in the PACIFIC trial. Baseline and demographic characteristics were generally balanced between the two groups, including age, gender, WHO PS, disease stage (IIIa versus IIIb). The median age of patients in the PACIFIC study was 64.0 years (range: 23 to 90 years); 70% patients were male and 99.6% of patients had a WHO PS of 0 or 1; 69.3% were white; the majority of patients were current (16.4%) and past smokers (74.6%); 99.7% of patients received concurrent chemotherapy with radiation therapy. Molecular phenotype (PD-L1 and EGFR) was generally well balanced between the two treatment groups.

Table 6: Baseline Characteristics, Stratification Factors, and Prior Therapy (ITT Population*)

	Durvalumab (N=476)	Placebo (N=237)	Total (N=713)
Age - years			
Median (range)	64 (31-84)	64 (23-90)	64 (23-90)
Sex - no. (%)			
Male	334 (70.2)	166 (70.0)	500 (70.1)
Female	142 (29.8)	71 (30.0)	213 (29.9)
Race - no. (%)†			
White	337 (70.8)	157 (66.2)	494 (69.3)
Black or African-American	12 (2.5)	2 (0.8)	14 (2.0)
Asian	120 (25.2)	72 (30.4)	192 (26.9)
Other	6 (1.3)	6 (1.3)	12 (1.68)
Not reported	1 (0.2)	0	1 (0.1)
Disease stage			
IIIA	252 (52.9)	125 (52.7)	377 (52.9)
IIIB	212 (44.5)	107 (45.1)	319 (44.7)
Other‡	12 (2.5)	5 (2.1)	17 (2.4)
WHO performance status score — no. (%)¶			
0	234 (49.2)	114 (48.1)	348 (48.8)
1	240 (50.4)	122 (51.5)	362 (50.8)
Not reported	2 (0.4)	1 (0.4)	3 (0.4)
EGFR mutation status — no. (%)			

	Durvalumab (N=476)	Placebo (N=237)	Total (N=713)
Negative	317 (66.6)	165 (69.6)	482 (67.6)
Positive	29 (6.1)	14 (5.9)	43 (6.0)
Unknown	130 (27.3)	58 (24.5)	188 (26.4)
PD-L1 expression level — no. (%)			
<25%	187 (39.3)	105 (44.3)	292 (41.0)
≥25%	115 (24.2)	44 (18.6)	159 (22.3)
Unknown	174 (36.6)	88 (37.1)	262 (36.7)
Histology - no. (%)			
Squamous	224 (47.1)	102 (43.0)	326 (45.7)
Non-squamous	252 (52.9)	135 (57.0)	387 (54.3)
Smoking status - no. (%)			
Current smoker	79 (16.6)	38 (16.0)	117 (16.4)
Former smoker	354 (74.4)	178 (75.1)	532 (74.6)
Never smoked	43 (9.0)	21 (8.9)	64 (9.0)
Prior radiotherapy - no. (%)§			
<54 Gy	3 (0.6)	0	3 (0.6)
>54- ≤66 Gy	442 (92.9)	217 (91.6)	659 (92.4)
>66-≤74 Gy	30 (6.3)	19 (8.0)	49 (6.9)
Prior chemotherapy - no. (%)‖			
Induction chemotherapy	123 (25.8)	68 (28.7)	191 (26.8)
Concurrent with radiation therapy	475 (99.8)	236 (99.6)	711 (99.7)
Best response to previous CRT - no. (%)			
Complete response	9 (1.9)	7 (3.0)	16 (2.2)
Partial response	237 (49.8)	112 (47.3)	349 (48.9)
Stable disease	223 (46.8)	115 (48.5)	338 (47.4)
Progression	2 (0.4)	0	2 (0.3)
Non-evaluable	5 (1.1)	2 (0.8)	7 (1.0)
Not applicable	0	1 (0.4)	1 (0.1)

*The intention-to-treat (ITT) population included all patients who were randomized. Percentages may not total 100 because of rounding.
†Race was reported by the patients.
‡As reported previously, patients with other disease stages included 12 patients in the durvalumab group (4 with Stage IV, 4 with Stage IIB, 3 with Stage IIA, and 1 with Stage IA) and 5 patients in the placebo group (2 with Stage IIB, 1 with Stage IIA, and 2 with Stage IB).
¶World Health Organization (WHO) performance status (PS) scores range from 0 to 5, with 0 indicating no symptoms and higher scores indicating increased disability.
§The decision regarding the actual dose was based on investigator or radiologist assessment of each individual patient, resulting in doses that differed from the inclusion criteria. All radiation therapy was administered concurrently with chemotherapy.
‖Patients may have received prior chemotherapy in more than one context.

Data source: From the New England Journal of Medicine, Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC, Volume no: 379, Page no:2342-50, Supplementary Appendix. Copyright © 2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[2]

c) Interventions

Patients in PACIFIC were randomized to receive either durvalumab (N = 476) or placebo (N = 237).[1] A total of 473 patients received durvalumab and 236 received placebo. The study drug was administrated after randomization on day 1 for up to 12 months. The study drug was discontinued if there was disease progression, receiving alternative anticancer therapy, unacceptable adverse events, or withdrawal of consent.

Treatment dosing schedule[33,46,47]

The dosing schedule for the two treatment groups in PACIFIC are presented below:
•Durvalumab: 10 mg / kg body weight, IV infusion every two weeks for up to 12 months.
•Placebo: matching placebo

Re-treatment with study drug during the follow up-period: Patients who completed 12 months of therapy and had SD, PR, or CR at completion entered follow up period, retreatment was offered with patient's consent if patient had disease progression. The patient should not enter retreatment if any of the exclusion criteria were fulfilled, such as any unresolved toxicity. It was reported that eighteen (3.8%) patients in the durvalumab group and eight (3.4%) patients in the placebo group were retreated with their original treatment (see Table 7 below).[2,35]

Dose modification was allowed due to the toxicity. The median relative dose intensity was 100% in each group (range, 29 to 100 in the durvalumab group and 50 to 100 in the placebo group).[1]

Table 7: Patients with re-treatment (cut-off: March 22, 2018)

	Durvalumab	Placebo
Patients randomised, n	476 (48.4)	237 (24.1)
Patients completed 12-month study drug treatment, n (%)	232 (48.7)	82 (34.6)
Patients received re-treatment, n (%)	18 (3.8)	8 (3.4)
Patients ongoing re-treatment at data cut off, n (%)	8 (44.4)	0
Patients completed 12 months of re-treatment, n (% of retreatment)	2 (11.1)	0
Patients discontinued re-treatment , n (% of retreatment)	8 (44.4)	8 (100.0)

Data source: CSR addendum-OS, [35] Antonia for OS[2]

d) Patient Disposition

The patient disposition for PACIFIC is presented in

Figure 3. In total, 983 patients were eligible for enrollment in the trial, and 713 (99.4%) were randomized to receive durvalumab (N = 476) or placebo (N = 237). Three patients (0.6%) in the durvalumab group and one patient (0.4%) in the placebo group, did not receive assigned treatment. [23]

Two cut-off dates were reported for this review. The first cut-off (For PFS) occurred on February 13, 2017. 371 patients had disease progression (214 in the durvalumab group and 157 in the placebo group). The overall median follow-up was 14.5 months (range, 0.2 to 29.9).[23] The second cut-off date (for the first interim OS and the primary PFS) occurred on March 22, 2018, after 299 deaths had occurred (61% of the expected 491 events)[2].

As of the data cut-off on March 22, 2018, 232 (48.7%) patients in durvalumab and 82 (34.6%) patients in placebo group completed 12- month trial. A total of 183 (38.4) patients in durvalumab and 116 (48.9) patients in placebo had died. The rate of discontinuation from the study drug were 50.6% in the durvalumab and 65% in placebo group respectively, with disease progression being the most common reason for discontinuation in both treatment groups (31.1% vs. 49.4% in durvalumab and placebo group respectively). As seen in

Figure 3, the overall number of patients discontinuing treatment were relatively similar between two treatment groups; although discontinuations due to adverse events were numerically lower in

patients who received placebo (23 out of 237, 9.7%) compared to those who received durvalumab (73 out of 476, 15.3%).

Figure 3: Patient disposition at final analysis of overall survival (Data cut-off date: 22 March 2018 [study ongoing])

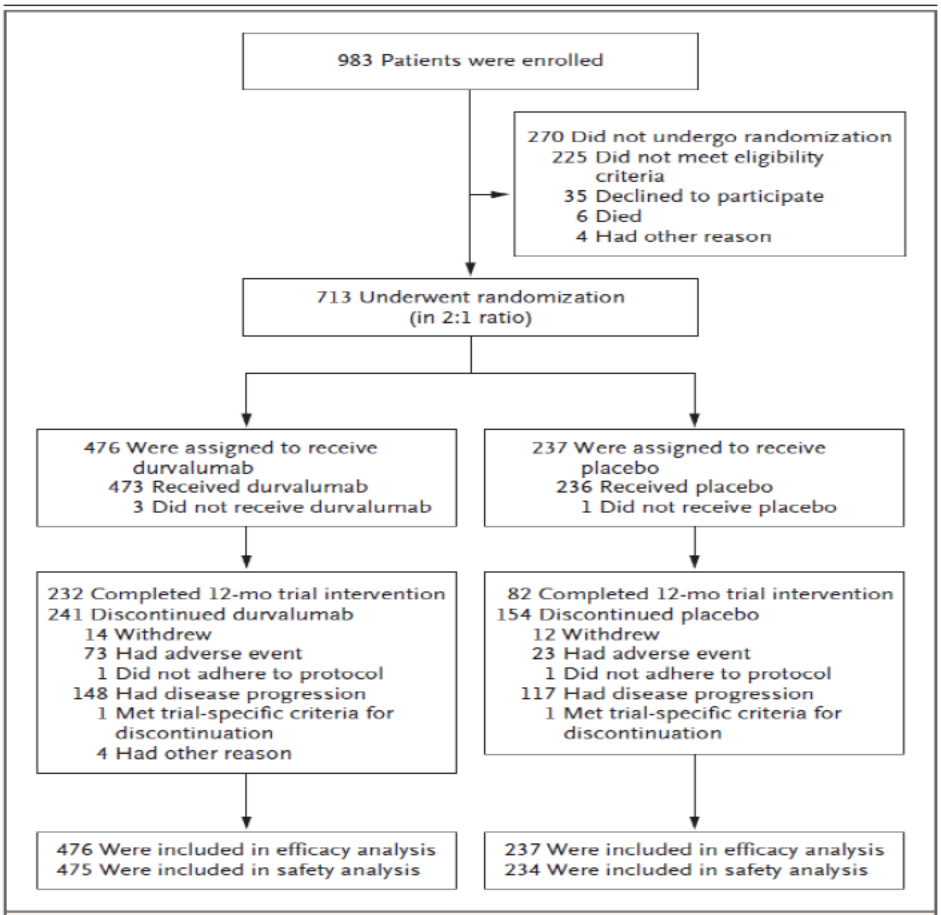


Figure 1. Trial Enrollment and Outcomes of the Patients.

Shown are data until the data-cutoff date of March 22, 2018. Enrolled patients were those who provided written informed consent. Four patients (three in the durvalumab group and one in the placebo group) underwent randomization but did not receive the assigned intervention because of the patient's decision (in two), neutropenia (in one), and worsening chronic obstructive pulmonary disease (in one). Patients who completed 12 months of the trial intervention were those for whom the electronic case-report form showed that they had received the maximum cycles of immunotherapy. Two patients who had been assigned to the placebo group received one dose of durvalumab in error and were included in the safety analysis set for durvalumab.

Data source: From the New England Journal of Medicine, Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC, Volume no: 379, page no: 2342-50. Copyright © 2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. [2]

e) Limitations/Sources of Bias

• Immature OS: OS data in the PACIFIC trial were immature at the time of the data analysis. The median OS in the durvalumab group was not reached. With sufficient follow-up, OS could be evaluated by any benefit may be confounded by subsequent post trial treatments.

• No statistical analysis for between group differences (durvalumab vs. placebo) was performed in terms of the median PFS time and median OS times (i.e., mean between group difference, 95% CI and p value), which may limit the interpretation of the clinical significance of the PFS and OS findings. However, the submitter responded that based on recently published oncology value frameworks by ESMO, the OS benefit from PACIFIC trial meet the maximum benefit score for clinical benefit either with curative or non-curative intent (i.e., increase in 3-year survival alone ≥ 5% for curative intent, or HR ≤ 0.70 and gain ≥ 5 months for control >12 months in non-curative setting).[63]

• There was no adjustment for multiplicity for all secondary outcomes and subgroup analysis. The chance of obtaining a statistically significant result (false positive) increases as the number of tests performed increased. On the other hand, reported no statistical significance also could be due to underpowered small sample size for any specific subgroup. In addition, subgroup interaction was not tested. The manufacturers' Checkpoint meeting response indicated that as pre-specified in the SAP, statistical tests using the approach of Gail and Simon 1985 were performed for OS and PFS to assess the presence of qualitative interaction between treatment and the stratification factors (i.e. if the direction of treatment effect varies by age at randomization, sex or smoking history).[64] No statistical test was performed to assess if the magnitude of OS or PFS benefit with durvalumab varies by the stratification factors or any of the pre-specified subgroups. Therefore, the findings from the subgroup analyses should be interpreted with caution.

• Health related quality of life (assessed with EORTC QLQC30, EORTC QLQLC13 and EQ-5D-5L) is a clinically important outcome for cancer patients. Quality of life was designed as a secondary outcome in the PACIFC trial and was considered exploratory. Results across all QoL subscales did not indicate any clinically meaningful difference in symptom deterioration, function, and the overall QoL between the durvalumab and placebo groups, despite a longer duration of study therapy for the durvalumab group. Overall, compliance was high (>80%) for both groups up to 48 weeks, but decreased substantially over time.[40,41] At week 180, no patient in the durvalumab group and only one patient in the placebo group responded to the quality of life questionnaires.[35] Given these limitations, it is difficult to interpret the findings of EORTC QLQC30, EORTC QLQLC13 and EQ-5D-5L reported in the trial.

• Among all of the patients who were assigned a therapy at randomization, three (0.6%) patients did not receive durvalumab and one (0.4%) patient did not receive placebo.[2] Reasons for patients failing to receive their assigned therapy were not provided. However, due to the small percentage of the patients did not receive the study treatment, the impact of included those patients in the ITT population was considered minimal.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

Efficacy analyses were performed in ITT population (N = 713). Two data cut-offs are presented in this pCODR review. The first data cut-off occurred on February 13, 2017 for the interim analysis for PFS. This analysis cut-off data represents a median follow-up of 14.5 months (range: 0.2 to 29.9).[1] The second data cut-off was on March 22, 2018 for the interim analysis for OS and represents a median follow-up of 25.2 months (0.2 to 43.1).[2]

Overall survival

One of the co-primary outcomes in PACIFC trial was OS. It was defined as the time from the date of randomization until death due to any cause.[33] The results of OS are presented in Figure 4, and Table 8 below. The OS curves were obtained using the Kaplan-Meier method and treatment differences were assessed using a stratified log-rank test. In addition, the hazard ratio was stratified by randomization strata (i.e., age, sex, and smoking history). The Kaplan-Meier method was used to calculate medians and 95% confidence intervals. The Lan-DeMets spending function that approximates an O'Brien−Fleming approach was used to account for multiple comparisons, which were introduced by including interim analyses for superiority.[2] Sensitivity analyses for overall survival included the assessment of attrition bias. No adjustment for multiple comparisons was planned for these subgroup analyses.

At the March 22, 2018 data cut-off, it was reported that 183 (38.4%) patients died in the durvalumab group and 116 (48.9%) patients died in the placebo group.[2] The 12-month overall survival rate was 83.1% (95% CI, 79.4 to 86.2) in the durvalumab group, as compared with 75.3% (95% CI, 69.2 to 80.4) in the placebo group (see Table 8). The 24-month overall survival rate was 66.3% (95% CI, 61.7 to 70.4) in patients with durvalumab while 55.6% (95% CI, 48.9 to 61.8) in patients with placebo (Two sided P = 0.005). (Table 8) The median survival time was not reached (NR, [95%CI, 34.7, NR] in the durvalumab group and was 28.7 (95%CI, 22.9, NR) in placebo group. Durvalumab significantly prolonged overall survival compared to placebo (HR: 0.68; 99.73% CI, 0.47 to 0.997; two sided P = 0.0025) (Figure 4, and Table 8). Durvalumab showed a statistically significant benefit in OS over placebo, with a 32% reduction in the risk of death.

Subgroup analysis for OS: For analyses of OS in pre-specified subgroups, an unstratified Cox regression model was used to calculate hazard ratios and 95% confidence intervals. It was reported that the improvements (numerically or statistically significant improvement) in OS favoring durvalumab over placebo were observed across all subgroups based on demography, geographical region, prior chemoradiation, and baseline disease characteristics (Figure 5). Furthermore, statistically significant differences were observed in subgroups of age < 65 years, female patients , NSCLC stage IIIA, PD-L1 ≥25% and unknown patients, EGFR mutation negative, and in WHO performance status "1"; but not in subgroups of ≥ 65 years, male; stage IIIB ; PD-L1 < 25%, EGFR mutation positive or unknown and WHO PS "0". However, the results from subgroup analysis should be interpreted with caution due to underpowered small sample sizes in each subgroup and no adjustment for multiplicity control as well as no subgroup interaction analysis was performed. (See Figure 5)

Sensitivity analysis: A sensitivity analysis was performed using stratification factors as determined by the baseline case report form variables instead of the IVRS values in the stratified log-rank test. Two multivariate Cox regression models were used to adjust for the pre-specified covariates. Covariates for model 1 included: sex, age at randomization, and smoking history. Covariates for model 2 included: sex, age at randomization, smoking history, stage of disease at study entry (Stage IIIA vs Stage IIIB), histology (squamous vs all other), best response to prior anticancer therapy (CR vs PR vs SD), WHO performance status (normal vs restricted activity), region (Asia vs Europe vs North America and South America), and race (White vs Black/African-American vs Asian vs Other). [35] It was reported that the sensitivity analysis results (HR: 0.67; 95% CI: 0.53, 0.86) were generally consistent with the primary analysis of OS.

Figure 4: Overall Survival in the Intention-to-Treat Population (Cut-off date: March 22, 2018, median follow up time: 25.2 months (range: 0.2 to 43.1 months)

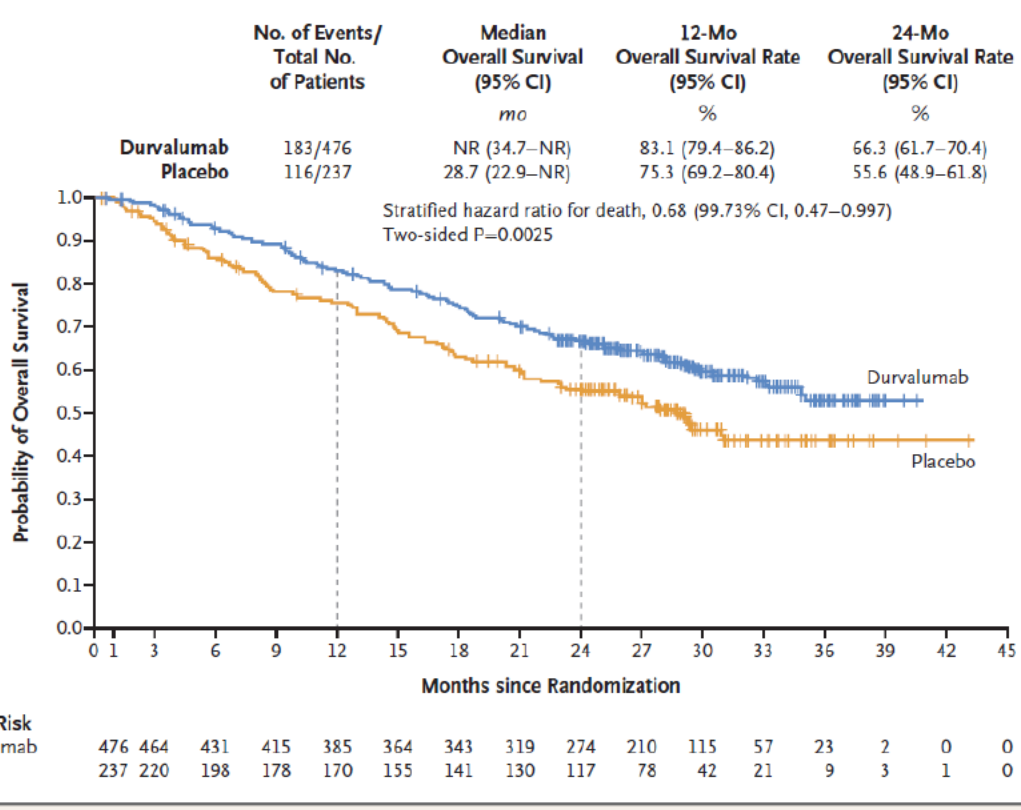


Figure 2. Overall Survival in the Intention-to-Treat Population.

Shown are Kaplan–Meier curves for overall survival. Tick marks indicate censored data, and the dashed vertical lines indicate the times of landmark analyses of overall survival. The intention-to-treat population included all the patients who underwent randomization. In this analysis of overall survival, the hazard ratio and its corresponding confidence interval of 100[1−α]%, with adjustment for the interim analysis, are presented. NR denotes not reached.

Data source: From the New England Journal of Medicine, Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC, Volume no: 379, Page no: 2342-50. Copyright © 2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. [2]

Table 8: Overall survival (Cut-off: March 22, 2018)

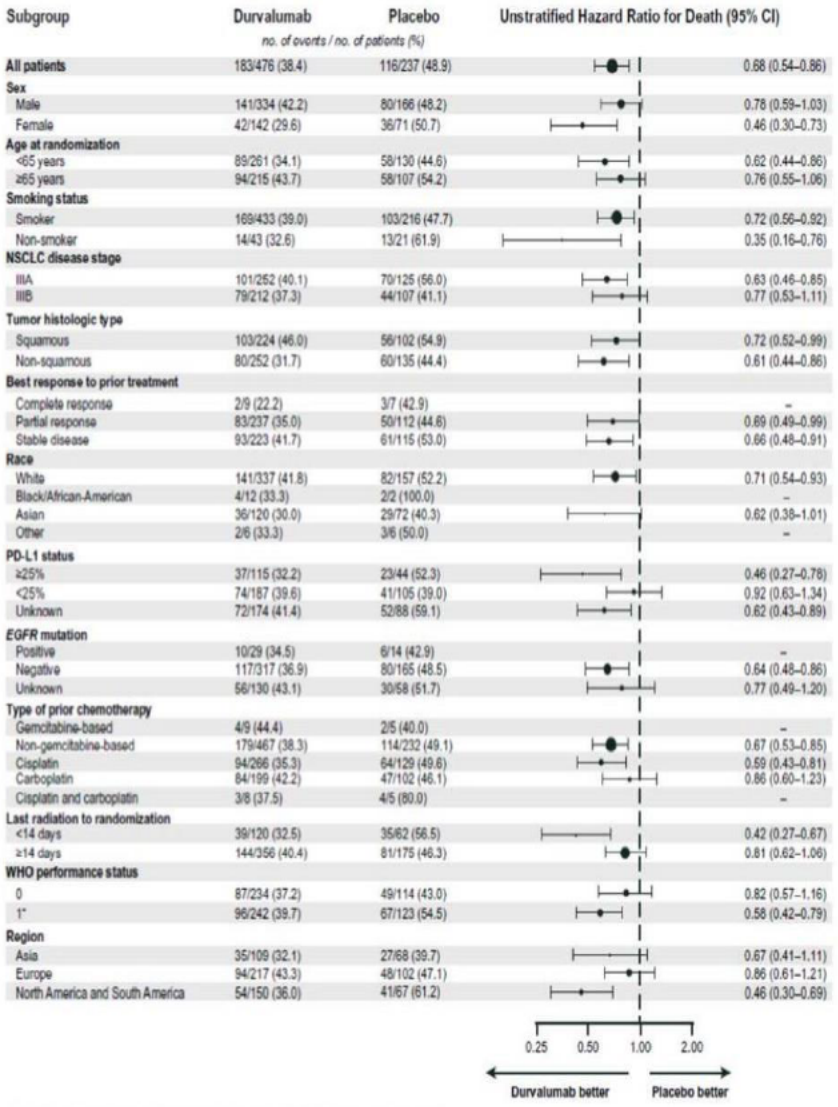
Survival status	Durvalumab (N=476)	Placebo(N=237)
Death, n (%)	183 (38.4)	116 (48.9)
Median OS, months (95% CI)	NR (34.7, NR)	28.7 (22.9, NR)
OS rate at 12 months, %(95% CI)	83.1(79.4, 86.2)	75.3 (69.2, 80.4)
OS rate at 24 months, % (95%CI)	66.3 (61.7, 70.4)	55.6 (48.9, 61.8)
p-value for OS rate at 24 months	0.005	
HR(durvalumab vs. placebo) (99.73%CI)	0.68 (00.47, 0.997)	

Survival status	Durvalumab (N=476)	Placebo(N=237)
p-value	0.00251	

CI = Confidence interval, HR = hazard ratio; mos = months; NR = Not reached; OS = overall survival
Data source: Antonia - OS [2]

Figure 5: Analysis of Overall Survival for Prespecified Subgroups (ITT Population).

The hazard ratio and 95% confidence interval are not calculated for subgroups with less than 20 events. EGFR denotes epidermal growth factor receptor, NSCLC non-small-cell lung cancer; PD-L1 programmed death ligand-1, and WHO World Health Organization.



Data source: From the New England Journal of Medicine, Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC, Volume no: 379, Page no:2342-50, Supplementary Appendix. Copyright © 2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[2]

Progression-Free-Survival

The other co-primary outcome in the PACIFIC trial was progression-free-survival (PFS). PFS was defined as the time from randomization to objective disease progression or death from any cause regardless of whether the patient withdrew from durvalumab or placebo or received another anticancer therapy prior to progression. PFS was assessed by both blinded independent central review (BIRC) using RECIST 1.1 criteria and investigators. [47,33] PFS curves were obtained using the Kaplan-Meier method. The treatment group differences were calculated using a stratified log-rank test, stratified by age, sex, and smoking history.[1] The findings of PFS are presented in

Figure 6, and Table 9 below. At the February 13, 2017 cut-off, the median follow-up time was 14.5 months; range: 0.2 -29.9 months. In the durvalumab group, 214 (45%) patients had disease progression and the median PFS time was 16.8 months (95% CI: 13.0 to 18.1).[1] In placebo group, 157 (66.2%) patients had progressive disease and the median PFS time was 5.6 months (95% CI: 4.6 to 7.8) (

Figure 6).[1] The HR for disease progression or death was 0.52, 95% CI 0.42 to 0.65, p<0.001. The results of PFS assessed by investigators were consistent with that by BICR in favor of durvalumab over placebo. (See Table 9) At the March 22, 2018 data cut -off, the updated (the primary analysis) median PFS time was 17.2 months (95% CI, 13.1 to 23.9) in the durvalumab group, and 5.6 months (95% CI,4.6 to 7.7) in the placebo group respectively. The stratified hazard ratio for disease progression or death was 0.51; 95% CI, 0.41 to 0.63.

Subgroup analysis: Based on the February 13, 2017 data cut-off, the subgroup analysis of PFS was performed, in which hazard ratios and 95% confidence intervals were calculated using an unstratified Cox regression model. A PFS benefit with durvalumab was consistently observed across all subgroups. It was reported that the unstratified hazard ratio of disease progression were 0.56 (0.41 - 0.75) and 0.53 (0.40-0.71) in normal WHO performance status and restricted WHO performance status respectively.[1] The PFS benefit with durvalumab was observed irrespective of PD-L1 expression (HR, 0.59 [95% CI, 0.43 to 0.82] for a PD-L1 expression level of <25%, 0.41 [95% CI, 0.26 to 0.65] for a PD-L1 expression level of ≥25%), and 0.59 (0.42, 0.83) for unknown PD-L1 expression level.[1] A PFS benefit was observed in both smoker and non-smoker, but, more evident benefit were observed in patients who had never smoked. However, the absence of adjustment for multiple comparisons limits the extrapolations to any subgroups.

Sensitivity analyses: Based on the February 13, 2017 data cut-off, the sensitivity analyses included assessment of evaluation bias, evaluation-time bias, and attrition bias in the determination of disease progression and adjustment for various covariates in the estimation of the hazard ratio for disease progression or death. The manufacturer reported that the PFS results were consistent across all sensitivity analyses.[33]

APF12 and APF 18

Based on the data at the cut-off date of February 13, 2017[1] reported that the 12-month progression-free survival rate (APF12) was 55.9% (95% CI, 51.0 to 60.4) in patients with durvalumab and 35.3% (95%CI, 29.0 to 41.7) in patients with placebo respectively. The 18-month progression-free survival rates were 44.2% (95% CI, 37.7 to 50.5) and 27.0% (95% CI, 19.9 to 34.5) in patients with durvalumab and patients with placebo respectively.

Figure 6: Progression-free Survival (Cut-off: February 13, 2017)

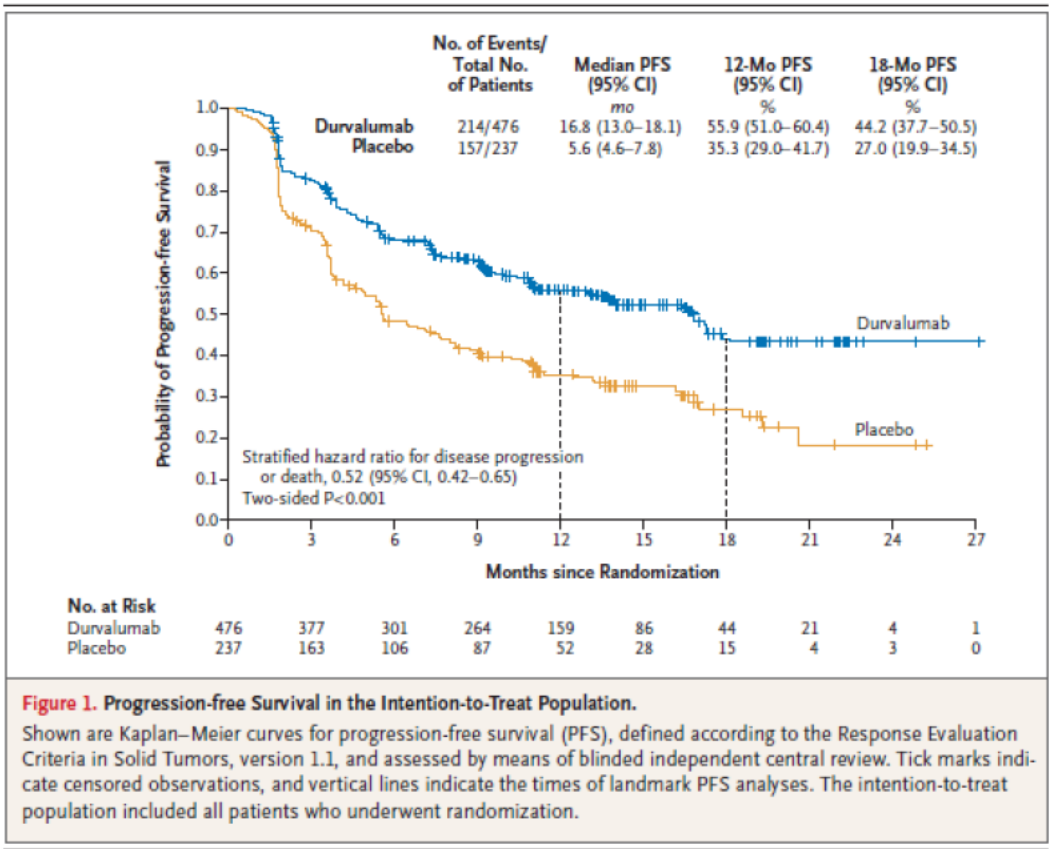


Figure 1. Progression-free Survival in the Intention-to-Treat Population.

Shown are Kaplan–Meier curves for progression-free survival (PFS), defined according to the Response Evaluation Criteria in Solid Tumors, version 1.1, and assessed by means of blinded independent central review. Tick marks indicate censored observations, and vertical lines indicate the times of landmark PFS analyses. The intention-to-treat population included all patients who underwent randomization.

Data source: From the New England Journal of Medicine, Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer, volume: 377, page: 1919-29. Copyright © 2017 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[33]

Table 9: Progression-free survival (Cut-off: Feb 13, 2017))

	BICR assessments		Investigator's assessments	
Progression status	Dur(N=476)	Pla(N=237)	Dur(N=476)	Pla(N=237)
Total events, n (%)	214 (45.0)	157 (66.2)	252 (52.9)	167 (70.5)
Progression, n (%)	189 (39.7)	140 (59.1)	226 (47.5)	154(65)
Death in the absence of progression, n(%)	25 (5.3)	17 (7.2)	26(5.5)	13(5.5)
Censored patients, n (%)	262 (55.0)	80 (33.8)	224 (47.1)	70 (29.5)
Censored RECIST 1.1 progression	0	0	0	0
Censored death	10 (2.1)	1 (0.4)	3(0.6)	1(0.4)
Progression-free at time of analysis	235 (49.4)	73 (30.8)	203 (42.6)	64 (27)
Lost to follow-up	0	0	0	0
Withdrawn consent	12 (2.5)	4 (1.7)	11(2.3)	3 (1.3)
Discontinued study	5 (1.1)	2 (0.8)	7 (1.5)	2 (0.8)
Median PFS, mos((%%CI)	16.8 (13.0, 18.1)	5.6 (4.6, 7.8)	13.6 (11.0, 14.0)	7.4 (5.6, 9.0)
PFS rate at 12 months (%)	55.9 (51.0, 60.4)	35.3 (29.0, 41.7)	52.6(47.8, 57.1)	34.8(28.7, 41.1)
PFS rate at 18 months (%)	44.2 (37.7, 50.5)	27.0(19.9, 34.5)	37.4 (37.1, 43.1)	23.5 (17.2, 30.3)
HR (95%CI)	0.52 (0.42, 0.65)		0.61 (0.51, 0.76)	

	BICR assessments		Investigator's assessments	
Progression status	Dur(N=476)	Pla(N=237)	Dur(N=476)	Pla(N=237)
p-value	<0.0001		<0.0001	

BICR = blinded independent central review; CI = confidence interval; Dur = Durvalumab; HR = Hazard ratio; PFS = progression free survival; Pla = placebo; RECIST 1.1 = Response Evaluation Criteria In Solid Tumors version 1.1
Source: CSR-PFS p.76-77/2273(Table 15)[33] Antonia-PFS,[1] EMA report.[48]

Health-related quality of life

As secondary outcomes, Quality of life were measured with European Organization for Research and Treatment of Cancer (EORTC) QoL Questionnaire C30 (QLQ-C30) including time to symptom deterioration (e.g., fatigue, pain), time to QoL/function deterioration (e.g., physical function; role function; emotional function, global health status/QoL); and EORTC Lung Cancer Module (LC13) including time to symptom deterioration (e.g., dyspnoea, cough, hemoptysis, chest pain).

The EORTC QLQ - C30 and EORTC QLQ- LC13 were assessed at baseline, every 4 weeks for the first 8 weeks, followed by every 8 weeks until completion of study treatment or discontinuation of study treatment due to adverse events or disease progression. The assessment for the EORTC QLQ -C30 and EORTC QLQ-LC13 was up to week 180 plus 30 days during the follow-up period. Change from baseline at each assessment point were reported in clinical study report. [35]

The EORTC QLQ-C30 ≥ 10 points change was considered clinically meaningful change. In addition, the impact of treatment and disease state on health state utility using the EQ-5D-5L health state utility index (EQ-5D-5L) based on patient reported data was assessed as exploratory outcome.(protocol OS PFS).[46]

It was reported that the results from the March 22, 2018 data cut-off were generally consistent with those from the February 13, 2017 data cut-off.[35] Health related quality of life (patient-reported-outcome data) showed a high level of compliance (>80%) for both groups for up to 48 weeks.[2,48] At week 60 compliance decreased to less than 65%. At the week 180, no patient in durvalumab group and only one patient in the placebo group reported EORTC QLQ-C30, L13 and EQ-5D-5L. Results across all subscales did not indicate any meaningful difference in symptom deterioration, function, and the overall QoL between the durvalumab and placebo groups, despite a longer duration of study therapy for the durvalumab group.[35,48] Based on the February 13, 2017 data cut-off, Hui et al.,[40,41] reported that there was no difference between durvalumab and placebo groups in time to deterioration except for "other pains", which favoured durvalumab compared to placebo (HR 0.72; 95% CI 0.58-0.89).[40,41] The post-hoc analysis showed delays in deterioration of overall pain (HR 0.75; 95% CI 0.60-0.93), chest pain (HR 0.74; 95% CI 0.57-0.97), arm/shoulder pain (HR 0.74; 95% CI 0.58-0.95), nausea/vomiting (HR 0.72; 95% CI 0.54-0.97), insomnia (HR 0.75; 95% CI 0.58-0.97) and hemoptysis (HR 0.70; 95% CI 0.50-0.99) in favour of durvalumab. The author concluded that primary analysis showed that no deterioration in terms of EORTC30 and LC13.[40,41]

OS24

See Table 8 and Figure 4 in the section of overall survival.

Objective Response Rate

As a secondary outcome reported in the trial, objective response rate (ORR, RECIST 1.1 as assessed by the BICR) was defined as the number (%) of patients who had at least one visit response (a complete response or partial response) and was based on all randomized patients who have measurable disease.[33,35] Response rates were estimated with the use of the Clopper-Pearson method and compared with the use of Fisher's exact test.[46,47] At the cut-off date of February 13, 2017, the overall response rates were 28.4% and 16% in patients with durvalumab and patients with placebo respectively. In the updated analyses (March 22, 2018), the overall response rates were 30.0% (95% CI, 25.8 to 34.5) and 17.8% (95% CI, 13.0 to 23.6) in in patients with durvalumab and the patients with placebo respectively (P<0.001).

Table 10: Results for ORR, DOR, TTFSTD and TTSSTD

	PACIFIC			
	Cut-off date: February 13, 2017 (median F/U, months (range): 14.5 (0.2 - 29.9)		Cut-off date: March 22, 2018 (median F/U, months (range): 25.2 (0.2 -43.1)	
	Durvalumab (N= 476)	Placebo (N= 237)	Durvalumab (N= 476)	Placebo (N= 237)
ORR				
Patients with ORR n(%)	126 (28.4)	34 (16.0)	133 (30.0)	38 (17.8)
95%CI (%)	24.3, 32.9	11.3, 21.6	25.79, 34.53	12.95, 23.65
p-value	<0.001		<0.001	
DOR				
median (95%CI)	NR	13.8 (6.0, NR)	NR (27.4, NR)	18.4 (6.7, 24.5)
p-value	Not reported		Not reported	
PFS2				
median (95%CI)	Not reported		28.3 (25.1, 34.7)	17.1 (14.5 to 20.7)
HR (95%CI)	Not reported		0.58 (0.46 to 0.73)	
TTDM				
median (95%CI)	23.2 (23.2 to NR)	14.6 (10.6 to 18.6)	28.3 (24.0 to 34.9)	16.2 (12.5 to 21.1)
HR (95%CI)	0.52 (0.39, 0.69)		0.53 (0.41 to 0.68)	
TTFSTD				
median (95%CI)	Not reported		21.0 (16.6, 25.5)	10.4 (8.3, 12.5)
HR (95%CI)	Not reported		0.58 (0.47, 0.72)	
TTSSTD				
median (95%CI)	Not reported		29.3 (26.0, 34.9)	18.6 (14.8, 23.9)
HR (95%CI)	Not reported		0.63 (0.50, 0.79)	

ORR = Objective Response Rate; DOR = duration of response; NR = not reached; PFS2 = Time from randomization to second progression or death; TTDM = Time to Death or metastasis; TTFSTD = time to the first subsequent therapy or death; TTSSTD = time to the second subsequent therapy or death.

Data source: Antonia -PFS,[1] Antonia-OS[2]

Duration of Response

Duration of response (DOR, RECIST 1.1 as assessed by the BICR) was defined as the time from the date of first documented response until the first date of documented progression or death in the absence of disease progression. [35] At the February 13, 2017 data cut-off, it was reported that the median duration of response was longer in patients with durvalumab than in patients with placebo (NR vs. 13.8 months).[1] The median duration of response was not reached (NR) in the durvalumab

group, while the median duration of response was 13.8 months (95% CI, 6.0 to NR) in the placebo group. At the March 22, 2018 data cut-off, similarly, the median duration of response was not reached (95% CI, 27.4 to NR) in the durvalumab group and was 18.4 months (95% CI, 6.7 to 24.5) in the placebo group (see Table 10) .[2]

Time from randomization to second progression or death (PFS2)

Patients was assessed every 12 weeks for a second progression following first progression. PFS2 status was defined according to local standard clinical practice (not based on RECIST measurements) and may include any of: objective radiological, symptomatic progression or death. At the March 22, 2018 data cut-off, the second progression event or death occurred in 361 (50.6%) patients (217 [45.6%] in patients with durvalumab and 144 [60.8%] in patients with placebo respectively). It was reported that the time to second progression or death was longer in patients with durvalumab than patients with placebo (median PFS2 time, 28.3 months [95% CI, 25.1 to 34.7] in durvalumab group versus 17.1 months [95% CI, 14.5 to 20.7] in placebo group; HR 0.58 [95% CI, 0.46 to 0.73]) (see Table 10).[2,48]

Time to Death or metastasis (TTDM)

At the February 13, 2017 data cut-off, [1] it was reported that the median time to death or distant metastasis (TTDM) was 23.2 months (95% CI, 23.2 to NR) in patients with durvalumab compared to14.6 months (95% CI,10.6 to 18.6) in patients with placebo (HR, 0.52; 95% CI, 0.39 to 0.69; P<0.001). At the March 22, 2018 data cut-off, the updated analysis showed that the median TTDM was 28.3 months [95% CI, 24.0 to 34.9] in the patients with durvalumab compared to 16.2 months [95% CI, 12.5 to 21.1] in patients with placebo group. Both cut-off data showed a longer TTDM in durvalumab group than that in placebo group (**Table 10**).

Time to first and second subsequent therapy or death

The time to the first subsequent therapy or death as well as the time to the second subsequent therapy or death were longer in the durvalumab group than that in the placebo group[2] (**Table 10**).

Harms Outcomes

Study Exposure
The safety analyses were performed based on the safety analysis set, which included 475 patients in the durvalumab group and 234 patients in the placebo group.

At the March 22, 2018 data cut-off, the median duration of therapy for patients in the durvalumab group was 40.1 weeks (range, 1 to 54) and 28 weeks (range, 1 to 53) in the placebo group.[2] The median number of IV infusions were 20 (range, 1 to 27) in patients with durvalumab and 14 (1 - 26) in patients with placebo (Table 11).[48]

Table 11: Duration of exposure (safety analysis set) (Cut-off date: Feb 13, 2017)

Table 47 Duration of exposure (safety analysis set)

Treatment duration	Durvalumab (N=475)	Placebo (N=234)	Total (N=709)
Number of infusions			
n	475	234	709
Mean	16.5	14.8	16.0
Std Dev	9.01	8.83	8.98
Median	20.0	14.0	18.0
Min	1	1	1
Max	27	26	27
≥20 Infusions (% of population)	239 (50.3)	94 (40.2)	333 (47.0)
≥26 Infusions (% of population)	90 (18.9)	35 (15.0)	125 (17.6)
Total treatment duration (weeks) [a]			
n	475	234	709
Mean	35.1	31.0	33.7
Std Dev	18.66	18.29	18.63
Median	44.0	31.7	40.1
Min	1	1	1
Max	55	54	55
Total treatment duration (patient years)	319.8	138.8	458.6
Actual treatment duration (weeks) [b]			
n	475	234	709
Mean	33.0	29.6	31.8
Std Dev	18.01	17.66	17.95
Median	38.7	28.0	36.1
Min	1	1	1
Max	54	53	54
Total treatment duration (patient years)	300.0	132.7	432.7

a Total treatment duration is defined as (last dose date + 13 days or death date or data cut off, whichever occurs earlier - first dose date + 1) / 7.
b Actual treatment duration = total treatment duration, excluding total duration of dose delays.
Max maximum; Min minimum; Std Dev standard deviation.
Source: Table 11.3.1.1

Data source: EMA report [48]

Post Discontinuation disease related anticancer therapies[2]

Overall, 241 (50.6%) patients discontinued treatment with durvalumab and 154 (64.6%) discontinued treatment with placebo. Among the patients who discontinued study treatment, 195 (41.0%) patients in durvalumab group and 128 (54.0%) patients received post-discontinuation disease-related anticancer therapies. The most common post-discontinuation anti-cancer therapies included:

- chemotherapy (26.9% in the durvalumab group versus 30% in the placebo group)
- radiotherapy (17.2% in the durvalumab group versus 23.6% in the placebo group)
- immunotherapy (8% in the durvalumab group versus 22.4% in the placebo group)
- targeted therapy (9.9% in the durvalumab group versus 13.1% in the placebo group)
- other therapies (0.2% in the durvalumab group versus 0.4% in the placebo group)

The key harm outcomes are summarized in Table below.

Deaths

At the March 22, 2018 data cut-off, 183 (38.4%) in patients with durvalumab and 116 (48.9%) patients with placebo died (See Figure 4).[2] The majority of deaths were related to NSCLC only (147/183 [80.3%] and 86/116 [74.1%], respectively). A total of 4.4% patients with durvalumab and 6.4%) patients with placebo died due to an AE or due to both the NSCLC and an AE, which is consistent with the results reported at the earlier data cut-off. [2]

Adverse Events

The adverse events are presented in Table . A total of 96.8% patients in the durvalumab and 94.9% patients in the placebo experienced adverse event. Grade 3 or 4 adverse events of any cause occurred in 30.5% of the patients in the durvalumab group and in 26.1% of those in the placebo group respectively. The safety profiles of durvalumab and placebo reported at March 22, 2018 cut-off were consistent with those reported at the earlier cut-off.[1,2]

Table 12: Adverse Events of Any Cause Reported in ≥10% of Patients in Either Treatment Group (As treated population: March 22, 2018)

	Durvalumab (N=475)		Placebo (N=234)	
	Any Grade*	Grade 3 or 4	Any Grade*	Grade 3 or 4
Number of patients with event (percent)				
Any event	460 (96.8)	145 (30.5)	222 (94.9)	61 (26.1)
Cough	167 (35.2)	2 (0.4)	59 (25.2)	1 (0.4)
Fatigue	114 (24.0)	1 (0.2)	48 (20.5)	3 (1.3)
Dyspnea	106 (22.3)	7 (1.5)	56 (23.9)	6 (2.6)
Radiation pneumonitis	96 (20.2)	7 (1.5)	37 (15.8)	1 (0.4)
Diarrhea	88 (18.5)	3 (0.6)	46 (19.7)	3 (1.3)
Pyrexia	72 (15.2)	1 (0.2)	22 (9.4)	0
Nausea	68 (14.3)	0	31 (13.2)	0
Decreased appetite	68 (14.3)	1 (0.2)	30 (12.8)	2 (0.9)
Pneumonia	63 (13.3)	21 (4.4)	18 (7.7)	9 (3.8)
Pneumonitis	60 (12.6)	9 (1.9)	18 (7.7)	4 (1.7)
Arthralgia	59 (12.4)	0	26 (11.1)	0
Upper respiratory tract infection	59 (12.4)	1 (0.2)	24 (10.3)	0
Pruritus	59 (12.4)	0	12 (5.1)	0
Rash	58 (12.2)	1 (0.2)	18 (7.7)	0
Constipation	56 (11.8)	1 (0.2)	20 (8.5)	0
Hypothyroidism	55 (11.6)	1 (0.2)	4 (1.7)	0
Headache	52 (10.9)	1 (0.2)	21 (9.0)	2 (0.9)
Asthenia	51 (10.7)	3 (0.6)	31 (13.2)	1 (0.4)
Back pain	50 (10.5)	1 (0.2)	27 (11.5)	1 (0.4)
Musculoskeletal pain	39 (8.2)	3 (0.6)	24 (10.3)	1 (0.4)
Anemia	36 (7.6)	14 (2.9)	26 (11.1)	8 (3.4)

Note: Adverse events are included in the summary tables of AEs if they started after the first dose of study treatment (or for pre-existing AEs the severity worsened after the first dose) up to 90 days after the last dose of study treatment received or up to the start date of any subsequent systemic anticancer therapy, whichever occurred first.

Data source: From the New England Journal of Medicine, Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC, Volume no: 379, Page no:2342-50, Supplementary Appendix. Copyright © 2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[2]

Serious adverse events

At the March 22, 2018 data cut-off: A total of 138 (29.1%) patients with durvalumab and 54 (23.1%) patients with placebo reported SAEs,[2] which is consistent with that reported at the February 13, 2017 data cut-off. Based on the earlier date cut-off, the most frequently reported SAEs were pneumonia (5.7% in durvalumab group and 5.1% in placebo groups, respectively), pneumonitis (3.4% in in durvalumab group and 3.0% in placebo group respectively), and radiation pneumonitis (3.6% in durvalumab group versus 1.3% in placebo group respectively).[1] A similar updated findings of the most frequents SAE were also reported at the March 22, 2018 data cut-off.[35]

WDAE

Discontinuation of the trial due to adverse events occurred in 15.3% (73 out of 476) patients with durvalumab and 9.7% (23 out of 237) patients with placebo. The most frequent adverse events leading to the discontinuation of the trial were pneumonitis (4.8% patients with durvalumab versus 2.6% patients with placebo), radiation pneumonitis (1.3% versus 1.3%), and pneumonia (1.1% versus 1.3%).[2]

Adverse Events of Special Interest

Adverse events of special interest identified in the protocol are immune related adverse events such as pneumonitis. Based on the March 22, 2018 data cut-off, 66.7% of the patients with durvalumab and 49.1% of the patients with placebo reported at least one adverse events of special interest,[2] which is consistent with that reported in the earlier data cut-off.[48] A total of 60 (12.6%) patients in the durvalumab group and 18 (7.7%) patients in the placebo group experienced pneumonitis. [2]

6.4 Ongoing Trials

No ongoing trials were identified.

7 SUPPLEMENTAL QUESTIONS

There were no supplemental questions identified for this review.

8 COMPARISON WITH OTHER LITERATURE

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

9 ABOUT THIS DOCUMENT

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

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. 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 will supersede this Initial Clinical Guidance Report.

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

APPENDIX A: LITERATURE SEARCH STRATEGY AND DETAILED METHODOLOGY

1. Literature search via OVID platform

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** August 2018, **Embase** 1974 to 2018 September 28, **Ovid MEDLINE(R) ALL** 1946 to September 28, 2018

#	Searches	Results
1	(durvalumab* or imfinzi* or MEDI4736 or MEDI-4736 or 28X28X9OKV or L01XC28).ti,ab,ot,kf,kw,hw,rn,nm.	2017
2	Carcinoma, Non-Small-Cell Lung/	53150
3	(NSCLC or NSCLCs).ti,ab,ot,kf,kw,hw.	106769
4	((lung cancer* or lung carcinoma* or lung neoplasm*) adj2 (nonsmall cell or non-small cell)).ti,ab,ot,kf,kw,hw.	154622
5	(lung adj2 (adenocarcinoma* or adeno-carcinoma*)).ti,ab,ot,kf,kw,hw.	50194
6	((bronchial cancer* or bronchial carcinoma* or bronchial neoplasm*) adj2 (nonsmall cell or non-small cell)).ti,ab,ot,kf,kw,hw.	486
7	(bronchial adj2 (adenocarcinoma* or adeno-carcinoma*)).ti,ab,ot,kf,kw,hw.	252
8	((pulmonary cancer* or pulmonary carcinoma* or pulmonary neoplasm*) adj2 (nonsmall cell or non-small cell)).ti,ab,ot,kf,kw,hw.	54
9	(pulmonary adj2 (adenocarcinoma* or adeno-carcinoma*)).ti,ab,ot,kf,kw,hw.	5020
10	((lung cancer* or lung carcinoma* or lung neoplasm*) adj2 (large cell or squamous cell)).ti,ab,ot,kf,kw,hw.	8535
11	((bronchial cancer* or bronchial carcinoma* or bronchial neoplasm*) adj2 (large cell or squamous cell)).ti,ab,ot,kf,kw,hw.	111
12	((pulmonary cancer* or pulmonary carcinoma* or pulmonary neoplasm*) adj2 (large cell or squamous cell)).ti,ab,ot,kf,kw,hw.	34
13	or/2-12	216217
14	1 and 13	906
15	14 use medall	91
16	14 use cctr	87
17	15 or 16	178
18	*durvalumab/	307
19	(durvalumab* or imfinzi* or MEDI4736 or MEDI-4736 or 28X28X9OKV or L01XC28).ti,ab,kw,dq.	950
20	18 or 19	995

21	exp Non Small Cell Lung Cancer/	116788
22	(NSCLC or NSCLCs).ti,ab,kw,dq.	106453
23	((lung cancer* or lung carcinoma* or lung neoplasm*) adj2 (nonsmall cell or non-small cell)).ti,ab,kw,dq.	144446
24	(lung adj2 (adenocarcinoma* or adeno-carcinoma*)).ti,ab,kw,dq.	34507
25	((bronchial cancer* or bronchial carcinoma* or bronchial neoplasm*) adj2 (nonsmall cell or non-small cell)).ti,ab,kw,dq.	486
26	(bronchial adj2 (adenocarcinoma* or adeno-carcinoma*)).ti,ab,kw,dq.	250
27	((pulmonary cancer* or pulmonary carcinoma* or pulmonary neoplasm*) adj2 (nonsmall cell or non-small cell)).ti,ab,kw,dq.	54
28	(pulmonary adj2 (adenocarcinoma* or adeno-carcinoma*)).ti,ab,kw,dq.	5000
29	((lung cancer* or lung carcinoma* or lung neoplasm*) adj2 (large cell or squamous cell)).ti,ab,kw,dq.	5002
30	((bronchial cancer* or bronchial carcinoma* or bronchial neoplasm*) adj2 (large cell or squamous cell)).ti,ab,kw,dq.	111
31	((pulmonary cancer* or pulmonary carcinoma* or pulmonary neoplasm*) adj2 (large cell or squamous cell)).ti,ab,kw,dq.	34
32	or/21-31	215406
33	20 and 32	469
34	33 use oemezd	304
35	conference abstract.pt.	3201858
36	conference review.pt.	10463
37	35 or 36	3212321
38	34 and 37	155
39	limit 38 to yr="2013 -Current"	155
40	34 not 37	149
41	39 or 40	304
42	17 or 41	482
43	limit 42 to english language	449
44	remove duplicates from 43	331

2. **Literature search via PubMed**

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

Search	Query	Items found
#15	Search **#13 AND #14**	6
#14	Search **publisher[sb]**	530390
#13	Search **#1 AND #12**	88
#12	Search **#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11**	92715
#11	Search **(pulmonary cancer*[tiab] OR pulmonary carcinoma*[tiab] OR pulmonary neoplasm*[tiab]) AND (large cell[tiab] OR squamous cell[tiab])**	277
#10	Search **(bronchial cancer*[tiab] OR bronchial carcinoma*[tiab] OR bronchial neoplasm*[tiab]) AND (large cell[tiab] OR squamous cell[tiab])**	242
#9	Search **(lung cancer*[tiab] OR lung carcinoma*[tiab] OR lung neoplasm*[tiab]) AND (large cell[tiab] OR squamous cell[tiab])**	11393
#8	Search **pulmonary[tiab] AND (adenocarcinoma*[tiab] OR adeno-carcinoma*[tiab])**	6224
#7	Search **(pulmonary cancer*[tiab] OR pulmonary carcinoma*[tiab] OR pulmonary neoplasm*[tiab]) AND (nonsmall cell[tiab] OR non-small cell[tiab])**	146
#6	Search **bronchial AND (adenocarcinoma*[tiab] OR adeno-carcinoma*[tiab])**	1618
#5	Search **(bronchial cancer*[tiab] OR bronchial carcinoma*[tiab] OR bronchial neoplasm*) AND (nonsmall cell[tiab] OR non-small cell[tiab])**	494
#4	Search **lung AND (adenocarcinoma*[tiab] OR adeno-carcinoma*)**	32499
#3	Search **(lung cancer*[tiab] OR lung carcinoma*[tiab] OR lung neoplasm*) AND (nonsmall cell[tiab] OR non-small cell[tiab])**	55205
#2	Search **Carcinoma, Non-Small-Cell Lung[MH] OR NSCLC[tiab] OR NSCLCs[tiab]**	55592
#1	Search **durvalumab[tiab] OR MEDI4736[tiab] OR MEDI-4736[tiab] OR 1428935-60-7[tiab] OR 1428935-60-7[rn] OR 28X28X9OKV[tiab]**	187

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: Imfinzi/durvalumab), nonsmall cell lung cancer (NSCLC)

Select international agencies including:

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

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

Search: Imfinzi/durvalumab), nonsmall cell lung cancer (NSCLC)

Conference abstracts:

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

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

Search: Imfinzi/durvalumab), nonsmall cell lung cancer (NSCLC) - last 5 years

Detailed Methododolgy

The literature search was performed by the pCODR Methods Team using the search strategy above.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates via Ovid; Embase (1974-) via Ovid; The Cochrane Central Register of Controlled Trials (August 2018) via OVID; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were imfinzi/durvalumab) and nonsmall cell lung cancer (NSCLC).

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents, but not limited by publication year.

The search is considered up to date as of January 31, 2019.

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

Study Selection

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

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

Quality Assessment

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

Data Analysis

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

Writing of the Review Report

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

The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.

The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net clinical benefit of the drug.

The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups, by the Provincial Advisory Group (PAG), and by Registered Clinicians.

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