CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Atezolizumab (Tecentriq) for Non-Small Cell Lung Cancer

June 20, 2018

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1 GUIDANCE IN BRIEF

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

This Clinical Guidance is based on: a systematic review of the literature atezolizumab (Tecentriq) for non-small cell lung cancer (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 atezolizumab (Tecentriq) for non-small cell lung cancer (NSCLC), a summary of submitted Provincial Advisory Group Input on atezolizumab (Tecentriq) for non-small cell lung cancer (NSCLC), and a summary of submitted Registered Clinician Input on atezolizumab (Tecentriq) for non-small cell lung cancer (NSCLC), and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

The objective of this review is to evaluate the effectiveness and safety of atezolizumab (Tecentriq) for the treatment of patients with locally advanced or metastatic non-small cell lung cancer who have progressed on or after systemic chemotherapy until loss of clinical benefit. The Health Canada regulatory approval is for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy.

Atezolizumab is the first immune checkpoint inhibitor evaluated in NSCLC targeting the PD-L1 ligand. Notably, prior immune checkpoint inhibitors evaluated in this setting (nivolumab and pembrolizumab) target the PD1 receptor. The recommended dose of atezolizumab is 1200 mg (fixed dose) every 3 weeks as an intravenous infusion.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included two randomized trials. The results of OAK (N = 1225) and POPLAR (N = 287) will be presented below:

OAK

OAK was a phase III international, multi-centre, open-label randomized controlled trial (RCT) that included adult patients with locally advanced or metastatic NSCLC who had progressed during or after prior platinum-containing chemotherapy regimens. To be eligible the patients had to have a measurable disease based on the Response Evaluation Criteria in Solid Tumours (RECIST; version 1.1) criteria, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, a life expectancy of 12 weeks or longer , and adequate hematologic and end-organ function.

Patients were randomly assigned to receive atezolizumab (1200 mg every 3 weeks) or docetaxel (75 mg/m^2 every 3 weeks) using a 1:1 randomization stratified by PD-L1 expression on tumour-infiltrating immune cell (IC levels; more details in Table 6.4), number of previous chemotherapy regimens (one versus two), and histology (non-squamous versus squamous cell tumours).

The primary outcome of the study was overall survival (OS) compared between treatment groups within the intention-to-treat (ITT) population, and in the PD-L1 expression population (PD-L1 expression on ≥1% of tumour cells [TC] or tumour-infiltrating immune cells [IC]). Secondary endpoints included investigator-assessed progression-free survival (PFS), objective response rate (ORR), duration of response (DOR), and safety.[1] The results of the primary efficacy analysis, which was performed on the first 850 patients (425 in each study arm) according to the trials statistical analysis plan, are published and will be presented in this report. The results of the secondary efficacy analysis for the 1225 randomized ITT patients (613 in the atezolizumab and 612 in the docetaxel arm) have not been published to date. Safety analysis included 609 of 613 of patients assigned to the atezolizumab group, and 578 of 612 of those assigned to the docetaxel group.[1]

Demographic and baseline characteristics were well balanced between the study groups. The median age in the primary population was 64 years (range 33-85), 61% of the patients were males, 70% were White, and 37% and 63% had an ECOG performance status of 0 and 1, respectively. EGFR and ALK mutations positive patients comprised a small proportion of patients on the trial (10% and <1%, respectively). Notably, 16% and 50% of patients respectively had an unknown EGFR and ALK mutation status.

Efficacy

The key efficacy outcomes of the OAK trial are presented in Table 1.1. As of the 07-Jul-2016 primary data cut-off date, after a median follow-up of 21 months:

- The median OS was 13.8 months (95% CI 11.8, 15.7) in the atezolizumab group and 9.6 months (95% CI 8.6, 11.2) in the docetaxel group (stratified HR= 0.73; 95% CI 0.62, 0.87; p=0·0003). [1]
- The median PFS rate was 2.8 months (95% CI 2.6, 3.0) with atezolizumab and 4.0 months (95% CI 3.3, 4.2) with docetaxel (HR = 0.95; 95% CI 0.82, 1.10; p=0.49).[1]
- ORR was reported to be similar between the two treatment groups (14% in the atezolizumab group and 13% in the docetaxel group). However, a higher proportion of patients in the docetaxel arm had stable disease (42%) than in the atezolizumab arm (35%). [1] The median DOR in the primary ITT population was longer with atezolizumab (16·3 months) than with docetaxel (6·2 months; HR = 0.34; 95% CI 0.21, 0.55; p<0.0001).[1]

Quality of Life

Health-related quality of life (HRQoL) was assessed by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaires (EORTC QLQ-C30 and QLQ-LC13), with a response rate higher than 80% for all cycles up to Cycle 27 in the atezolizumab group and Cycle 23 in the docetaxel group, respectively.[2] At baseline, patients in both atezolizumab and docetaxel groups reported moderate-to high functioning and global health scores (>60). Based on the EORTC QLQ-C30 data, atezolizumab delayed time to deterioration in physical functioning (HR=0.75; 95% CI 0.58, 0.98; p=0.0329) and role functioning (HR=0.79; 95% CI 0.62, 1.00; p=0.0544). However, there was no statistically significant differences between the atezolizumab and docetaxel arms in terms of time to deterioration in global QoL (HR= 0.94; 95% CI 0.72, 1.24).[2]

Patients in the atezolizumab group reported numerically improved HRQoL from baseline starting around Cycle 3 and continuing until Cycle 13 (the point at which fewer than 25% of patients who were evaluable for patient-reported outcomes had remained in the study). More details are provided in section 6.3.2.2.

Harms

As of the 07-Jul-2016 data cut-off, adverse events (AEs) of any cause were reported in 94% of patients in the atezolizumab group and in 96% of those in the docetaxel group. The proportion of patients with treatment-related grade 3 or 4 AEs was 15% in the atezolizumab group and 43% in the docetaxel group (Table 1.1). One grade 5 AE was reported in the docetaxel group.[1]

Mortality due to AEs was reported in 2% of patients in each group, and non-fatal serious AEs in 32% and 31% of patients in the atezolizumab docetaxel groups, respectively. One treatment-related death occurred in the docetaxel group due to a respiratory tract infection. AEs leading to dose modifications, delay or interruption were reported in 25% (of patients who received atezolizumab and 34% of patients who received docetaxel. Eight percent of patients in the atezolizumab group and 19% of those in the docetaxel group discontinued treatment due to AEs (Table 1.1).[1] Immune-related AEs (irAEs) were comparable between the atezolizumab (31%) and docetaxel (31%) groups. Grade 3 or 4 irAEs occurred in 6% of 609 patients in the atezolizumab group.[3]

Table 1.1: Highlights of Key Outcomes in OAK Trial

	Primary ITT population	
Efficacy outcomes	**Atezolizumab (N=425)**	**Docetaxel (N=425)**
Primary Outcome: OS		
Deaths, n (%)	271 (64)	298 (70)
Median OS, months (95% CI)	13.8 (11.8,15.7)	9.6 (8.6,11.2)
HR (95%CI)	0.73 (0.62, 0.87)	
p-value	0·0003	
Key Secondary outcomes		
Median PFS, months (95% CI)	2.8 (2.6, 3.0)	4.0 (3.3, 4.2)
HR (95%CI)	0.95 (0.82, 1.10)	
p-value	0.49	
ORR, n (%)	58 (14)	57 (13)
Median duration of response, months (95% CI)	16.3 (10.0, NE)	6.2 (4.9, 7.6)
HR (95%CI)	0.34 (0.21, 0.55)	
p-value	<0.0001	
HrQoL		
TTD - Physical Function months (95%CI)	NE (13.2, NE)	6.7 (5.1, NE)
HR (95%CI)	0.75 (0.58, 0.98)	
p-value	0.0329	
TTD - Role Function months (95%CI)	11.4 (7.1, 18.2)	5.1 (4.2, 7.7)
HR (95%CI)	0.79 (0.62, 1.0)	
p-value	0.0544	
TTD – HrQoL months (95%CI)	16.2 (10.8, NE)	NE (5.7, NE)

	Primary ITT population	
Efficacy outcomes	**Atezolizumab (N=425)**	**Docetaxel (N=425)**
HR (95%CI)	0.94 (0.72, 1.24)	
p-value	0.6634	
	Safety Population	
Harms	**Atezolizumab (N=609)**	**Docetaxel (N=578)**
Grade 3-4 AEs, n(%)	227 (37)	310 (54)
AE (any grade), n(%)	573 (94)	555 (96)
TRAE Grade 3-4, n(%)	90 (15)	247 (43)
WDAE, n(%)	46 (8)	108 (19)
Treatment-related death, n(%)	0 (0)	1 (<1)

AE = adverse event, **CI** = confidence interval, **HR** = hazard ratio, **HRQoL** = health-related quality of life, **NE** = not estimated; **NR** = not reported; **ORR** = objective response rate; **OS** = overall survival; **PFS** = progression-free survival; **SD** = standard deviation, **TRAE** = treatment-related adverse event; **TTD** = time to deterioration, measured by the EORTC QLQ-C30 questionnaire; **WDAE** = withdrawal due to adverse event

HR < 1 favours atezolizumab

POPLAR

POPLAR was a phase II international, multicenter, open-label RCT of atezolizumab versus docetaxel in adult patients with locally advanced or metastatic NSCLC who had progressed during or after prior platinum-containing chemotherapy regimens. To be eligible the patients had to have a measurable disease based on the RECIST (version 1.1) criteria, an ECOG performance status of 0 or 1, an adequate hematologic and end-organ function, and provided tumour specimens for central PD-L1 testing before enrolment.[4]

Patients were randomly assigned to receive atezolizumab (1200 mg every 3 weeks) or docetaxel (75 mg/m^2 every 3 weeks) using a 1:1 randomization stratified by tumour-infiltrating immune cell PD-L1 expression (IC levels), number of previous chemotherapy regimens (one versus two), and histology (non-squamous versus squamous cell tumours).

The primary outcome of the study was overall survival (OS) compared between treatment groups within the intention-to-treat (ITT) population, and in the PD-L1 expression population (PD-L1 expression on ≥1% of tumour cells or tumour-infiltrating immune cells). Secondary endpoints included investigator-assessed PFS, ORR, DOR, and safety Other exploratory endpoints included atezolizumab pharmacokinetics, patient-reported outcomes, biomarkers, and pharmacodynamics.[4]

Demographic and baseline characteristics were well balanced between the study groups, except for a 12% greater proportion of female patients in the docetaxel group (35% in the atezolizumab group versus 47% in the docetaxel group). Overall, the median age of the study participants was 62 years old (range 36-84 years); 61% of the randomized patients were males; 79% percent were white; and 32% and 68% had a ECOG performance score of 0 and 1, respectively.[5]

Efficacy

The key efficacy outcomes of POPLAR trial are presented in Table 1.2.

As of 08-May-2015 data cut-off date, after a median follow-up of 14·8 months:

- The median OS was 12.6 months (95% CI 9.7, 16.4) in the atezolizumab group and 9.7 months (95% CI 8.6, 12.0) in the docetaxel group (stratified HR 0.73; 95% CI 0.54, 0.99; p=0·040).[4]

- The median PFS rate was 3.0 months (95% CI 2.8, 4.1) w atezolizumab and 2.7 months (95% CI 3.3, 4.2) for docetaxel, with the PFS curves crossing at about 4 months (HR = 0.94; 95% CI 0.72, 1.23; p=0.65).[4]
- ORR was reported to be similar between the two treatment groups (14.6% in the atezolizumab group and 14.7% in the docetaxel group). At the data cut-off date, 57% of responders in the atezolizumab group and 24% of those in the docetaxel group had an ongoing response.[4] The median DOR was 14.3 months (95% CI 11.6, non-estimable) in the atezolizumab group and 7.2 months (95% CI 5.6, 12.5) in the docetaxel group (HR=0.41; 95% CI 0.18, 0.96; p=0.034).[4]

As of 01-Dec-2015 data cut-off, after a median follow up of 22 months:

- The median OS was statistically higher in the atezolizumab group (12·6 months) than in the docetaxel group (9·7 months; HR 0·69, 95% CI 0·52–0·92).[5]
- ORR was 15.3% (95% CI 9.8, 22.2) in the atezolizumab group and 14.7% (95% CI 9.3, 21.6) in the docetaxel group; with the median DOR being 18.6 months among the responders in the atezolizumab group and 7.2 months among the responders in the docetaxel group.[6]

Quality of Life

No clinically meaningful change (improvement or decline) from baseline was observed for patients in the atezolizumab arm during the study period in global health status, functioning (physical, role, emotional, cognitive, and social) or any of the symptom subscales, indicating that atezolizumab did not have a detrimental impact on health related quality of life (HRQoL).[7] Deterioration of lung cancer symptoms was defined as a 10-point or higher increase above the baseline. Deterioration of at least one lung cancer symptoms was reported in 211 patients (114 in the atezolizumab group and 97 in the docetaxel group).[6]

Harms

As of 08-May-2015 data cut-off, the incidence of AEs of any cause was 96% with either or docetaxel. Grade 3 or 4 AEs occurred in 40.0% of patients in the atezolizumab group and 53.0% of those in the docetaxel group. The proportion of patients with treatment-related grade 3 or 4 AEs was 11% in the atezolizumab group and 39% in the docetaxel group. Grade 5 AEs was reported in 4% of patients in each treatment group.[4] The incidence of non-fatal serious AEs was comparable between the two study groups AEs of any grade leading to treatment withdrawal were observed in 8% of patients in the atezolizumab group and 22% of those in the docetaxel group.[4]

Table 1.2: Highlights of Key Outcomes in POPLAR Trial

	ITT population	
Efficacy outcomes	**Atezolizumab (N=144)**	**Docetaxel (N=143)**
Primary Outcome: OS		
08-May-2015 data cut-off[4]		
Deaths, n (%)	78 (54)	95 (66)
Median OS, months (95% CI)	12.6 (9.7,16.4)	9.7 (8.6,12.0)
HR (95%CI)	0.73 (0.53, 0.99)	
p-value	p=0.040	

	ITT population	
Efficacy outcomes	**Atezolizumab (N=144)**	**Docetaxel (N=143)**
01-Dec-2015 data cut-off[5]		
Deaths, n (%)	90 (63)	110 (77)
Median OS, months (95% CI)	12.6 (9.7,15.8)	9.7 (8.6,12.0)
HR (95%CI)	0.69 (0.52, 0.92)	
p-value	NR	
Key Secondary outcomes		
08-May-2015 data cut-off[4]		
Median PFS, months (95% CI)	2.7 (2.82.0, 4.1)	3.0 (2,8, 4.1)
HR (95%CI)	0.94 (0.72, 1.23)	
p-value	0.645	
ORR, n (%)	21 (14.6)	21 (14.7)
Median duration of response, months (95% CI)	14.3 (11.6, NE)	7.2 (5.6, 12.5)
HR (95%CI)	0.41 (0.18, 0.96)	
p-value	0.034	
	Safety Population	
Harms Outcomes	**Atezolizumab (N=142)**	**Docetaxel (N=135)**
Grade 3-4 AEs, n(%)	57 (40)	71 (53)
AE (any grade), n(%)	136 (96)	130 (96)
TRAE Grade 3-4, n(%)	16 (11)	52 (39)
WDAE, n(%)	11 (8)	30 (22)
Treatment-related death, n(%)	NR	NR

AE = adverse event, **CI** = confidence interval, **HR** = hazard ratio, **HRQoL** = health-related quality of life, **NE** = not estimated; **NR** = not reported; **ORR** = objective response rate; **OS** = overall survival; **PFS** = progression-free survival; **SD** = standard deviation, **TRAE** = treatment-related adverse event; **TTD** = time to deterioration, measured by the EORTC QLQ-C30 questionnaire; **WDAE** = withdrawal due to adverse event

HR < 1 favours atezolizumab

Limitations

Overall, both the OAK and POLAR trials were well-designed RCTs with clearly-defined study questions, appropriate randomization methods, and clearly defined study outcomes. However, the following study limitations should be taken into account when interpreting the results:

- OAK and POPLAR were open-label phase III and phase II trials, respectively. The open label nature of the trials might introduce the risk of reporting and performance biases, as the study participants and the investigators were aware of the treatment assignments. Given the similar routes (i.e., intravenous injection) and intervals (i.e., every three weeks) of drug administration for atezolizumab and docetaxel, blinding both patients and investigators through the use of matching placebos could have prevented potential bias associated with their knowledge about treatment allocation.
- In both trials, the assessments of tumor response and disease progression (ORR and PFS) were conducted by the investigators. The lack of independent assessment may

expose the trials to detection bias (i.e., systematic difference between the groups in assessment, diagnosis, or verification of study outcomes).

- According to the OAK and POPLAR statistical analysis plans, there was no type-I error adjustments for any of the secondary endpoint (i.e, PFS, ORR, and safety) analyses. Therefore, results of these analyses should be considered exploratory.
- In the OAK trial, a statistically significant OS benefit was observed in patients who were treated with atezolizumab. However, no difference in PFS was demonstrated. Although PFS has been used as a proxy for OS in trials of cancer treatments, the Clinical Guidance Panel noted that the discrepancy between PFS and OS had been reported with the use of other immune-checkpoint inhibitors that target the PD-1 or PD-L1; and that this discrepancy might be explained by a potentially delayed immune response to this class of cancer treatments.
- The incidence of grade 3 or 4 immune-related AEs (irAEs) was reported for patients on the atezolizumab arm only. This might be due to the fact that irAEs are mechanism based inflammatory toxicity events that occur after immunotherapy regimens, while they are not frequently observed with chemotherapy agents (including docetaxel).
- The current pCODR submission and its related publications focused on the primary efficacy results of the OAK trial (data from the first 850 out of 1225 enrolled patients, according to the trials statistical analysis plan).

1.2.2 Additional Evidence

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

Patient Advocacy Group Input

From a patient's perspective, lack of timeliness regarding testing and diagnosis, difficulty managing symptoms, especially fatigue and exhaustion, the effect of lung cancer on day-to-day lives, a lack of information making navigation of lung cancer and next steps about care are all concerns regarding the experience of lung cancer. Chemotherapy is regarded with fear and immunotherapies are considered much more positively by patients who express a need for more effective and tolerable treatment options. Patients mention that drugs used to manage symptoms of lung cancer are only effective for some symptoms, while problems such as, palpitations, dry mouth, mouth sores, vision and urinary problems and impacts on mood are still in need of better management. Inconvenient treatment scheduling and distant locations of treatment centres can take up valuable time and may result in large financial expenses due to travel.

Please see Section 3 for a summary of input received from the patient advocacy groups.

Provincial Advisory Group (PAG) Input

Clinical factors:

- Comparison to other immunotherapies
- Sequencing with chemotherapy, other immunotherapies and with oral targeted therapies
- Patient group eligible for treatment

Economic factors:

- Treatment duration

Please see Section 4 for summary of input received from the PAG.

Registered Clinician Input

The clinicians identified that atezolizumab provides another immunotherapy option for the treatment of NSCLC, after failure on chemotherapy, in patients who have no mutations. They noted that atezolizumab could be used, regardless of PD-L1 status, in patients not previously treated with immunotherapy. They noted that atezolizumab has similar benefits and toxicity profile as other immunotherapies available for NSCLC, although there are no direct comparative studies with other immunotherapies.

Summary of Supplemental Questions

Critical appraisal of the Manufacturer-submitted indirect treatment comparison of pharmacological interventions used as second or higher lines of treatment for locally advanced/metastatic NSCLC

The submitted ITC used a standard Bayesian approach to assess the relative efficacy and safety of pharmacological interventions of second or greater lines of treatment for patients with advanced/metastatic NSCLC (including targeted therapies, chemotherapy regimens, PD1/PD-L1 inhibitors, placebo, and combined therapies).[8]

Based on the results of network meta-analyses, the overall survival HRs were similar for atezolizumab, nivolumab and pembrolizumab. These three PD-1/PD-L1 inhibitors seemed to perform better than other treatments of interest.[8]

See section 7.1 for more information.

Comparison with Other Literature

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

1.2.3 Factors Related to Generalizability of the Evidence

Table 2 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

[Table 2]: Assessment of generalizability of evidence for atezolizumab (Tecentriq) for NSCLC

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td rowspan="2">Population</td><td>Performance status</td><td>The included trials limited eligibility to patients with an ECOG performance status of 0 or 1.
<u>OAK</u>
<table><tr><td>ECOG</td><td colspan="2">Study Cohorts</td></tr><tr><td></td><td>A</td><td>B</td></tr><tr><td>0</td><td>155 (36%)</td><td>160 (38%)</td></tr><tr><td>1</td><td>270 (64%)</td><td>265 (62%)</td></tr></table>
<u>POPLAR</u>
<table><tr><td>ECOG</td><td colspan="2">Study Cohorts</td></tr><tr><td></td><td>A</td><td>B</td></tr><tr><td>0</td><td>90 (37%)</td><td>85 (38%)</td></tr><tr><td>1</td><td>151 (63%)</td><td>137 (62%)</td></tr></table></td><td>Does performance status limit the interpretation of the trial results (efficacy or toxicity) with respect to the target population (e.g., Canadian clinical practice, patients without the factor, etc.)?</td><td>The CGP agree that patients with a good performance (ECOG PS 0-2) should qualify for treatment with atezolizumab. The CGP agree there is, no reason to think treatment would be less tolerated in these patients.

Prior decisions for pembrolizumab and nivolumab have generalized the trial evidence into patients with ECOG PS 2. Additionally, there is Canadian experience with using nivolumab in patients with PS 2 supporting the tolerability concerns in sicker patients.</td></tr>
<tr><td>Line of therapy</td><td>The trials assessed 2nd or 3rd lines of therapy:

Both trials required that patients have disease progression during or following treatment with one or two prior platinum-containing regimens.</td><td>Are the results of the trial generalizable to other lines of therapy?</td><td>The CGP agree that the available evidence only supports the use of atezolizumab in the second line setting.

In patients that have a driver mutation, treatment with atezolizumab should be subsequent to targeted agents and a platinum doublet.</td></tr>
<tr><td rowspan="2">Intervention</td><td>None</td><td></td><td></td><td></td></tr>
<tr><td>Duration of treatments</td><td>In the included trials, patients in the atezolizumab group continued to receive the study treatment until loss of clinical benefit or unacceptable toxicity.</td><td>Is the duration of treatment allowed in the trial applicable in the Canadian setting?</td><td>Treatment with atezolizumab should be until disease progression with patients being allowed to continue treatment beyond progression if there is evidence of benefit. This aligns with the design of the trial.</td></tr>
<tr><td>Comparator</td><td>Standard of care</td><td>In the included trials, docetaxel was used as a comparator (75 mg/m2 every 3 weeks, until disease progression or unacceptable toxicity)</td><td>If the comparator is non-standard, are the results of the trial applicable in the Canadian setting?</td><td>Both trials were designed prior to results from the Checkmate 017/057 or Keynote 10 studies, when docetaxel remained the appropriate standard of care for the control arm.

A network meta-analysis provided with this report, indicate that atezolizumab, nivolumab and pembrolizumab are all superior to docetaxel in this setting. The efficacy of each immunotherapy agent appears similar based on this analysis.</td></tr>
</table>

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
Outcomes	Appropriateness of primary and Secondary Outcomes	The included trials measured the following clinical outcomes: Primary- OS Secondary- PFS (by investigator), ORR, safety, quality of life	Were the primary and secondary outcomes appropriate for the trial design?	The CGP agree that OS is an important outcome with trials evaluating immunotherapies. However PFS is more difficult to evaluate with immunotherapies.
Setting	None			

1.2.4 Interpretation

Improved understanding of the inhibitory and stimulatory signals important in regulation of T cell activation and the subsequent immune response has resulted in the development of multiple therapeutic agents targeting immune activation. This represents the most significant therapeutic change in cancer therapy in recent years. Monoclonal antibodies targeting CTLA-4, or Programmed Cell Death-1 (PD-1) receptor and its ligand (PD-L1) have become standard therapies in a number of cancers already and are being evaluated across the spectrum of malignancies with great expectations. In patients with metastatic melanoma, long term disease control has been observed in approximately 20% of patients following therapy with the CTLA-4 inhibitor, ipilimumab.[9]

Immunotherapy agents have already established a therapeutic role for patients with advanced NSCLC. Studies evaluating the PD-1 inhibitors, nivolumab[10,11] and pembrolizumab,[12] have demonstrated improved overall survival in comparison to docetaxel, among patients previously treated with platinum-based chemotherapy. Longer follow up of an early phase study of nivolumab demonstrated survival of 20% at three years and beyond.[13] The CGP noted input from the registered clinician indicating that nivolumab many have greater efficacy in squamous NSCLC compared to non-squamous. The CGP do not support this and agree that there is no evidence to support a differential effect among the different histological types. In response to these data, nivolumab is an approved and funded therapy in patients who progressed after platinum-based chemotherapy, regardless of tumor expression of PD-L1. Pembrolizumab is also approved and funded therapy in the same patient population with tumors expressing any level PD-L1 (TPS ≥ 1%). Additionally, pembrolizumab has demonstrated improved overall survival in comparison to platinum-based chemotherapy in patients with tumors expressing high levels of PD-L1 (TPS ≥ 50%)[14] and is now approved and funded in Canada for this indication as well.

Atezolizumab represents another immunotherapy agent for the treatment of advanced NSCLC that acts on the PD-1/PD-L1 pathway. However, atezolizumab is a PD-L1 inhibitor, unlike nivolumab and pembrolizumab, which inhibit the receptor (PD-1). Two randomized trials have evaluated atezolizumab in comparison to docetaxel, in patients who received one, or two prior platinum-based therapies. Both trials were designed prior to results from the Checkmate 017/057 (investigating nivolumab) or Keynote 10 (investigating pembrolizumab) studies, when docetaxel remained the appropriate standard of care for the control arm. Both the OAK and the POPLAR trials are methodologically well conducted trials, without major concerns. Neither was placebo controlled. The trials were similar in design, with the same eligibility criteria, interventions and outcomes. The OAK trial enrolled 1225 patients to either atezolizumab 1200mg iv every three weeks, or docetaxel. The initial analysis, on the first 850 patients, demonstrated an improvement in overall survival from 9.6 months to 13.8 months (HR 0.73, 95% CI 0.62-0.87) for patients randomized to atezolizumab versus docetaxel. These benefits were seen both in patients with tumors expressing PD-L1 and those without PD-L1 expression and the magnitude of effect was similar in all histologies. The improvement in overall survival favoured patients randomized to atezolizumab in all subgroups, other than patients with tumors containing an *EGFR* mutation, where the HR was greater than 1 (HR 1.24, 95%CI 0.71 – 2.18). There were insufficient patients with *ALK* translocations to make any meaningful recommendation about this subgroup. Interestingly, there were no significant improvements in either ORR (14% vs 13%), or PFS (2.8 months vs 4.0 months, HR 0.95, 95% CI 0.82-1.10). However, the duration of response was significantly greater for patients randomized to atezolizumab versus docetaxel (16.3 months vs 6.2 months, HR 0.34, 95% CI 0.21-0.55). Similar findings were observed in the randomized phase II trial – POPLAR. There were 287 patients randomized. Overall survival was higher among patients randomized to

atezolizumab than docetaxel (12.6 months vs 9.7 months, HR 0.77, 95% CI 0.56-1.06). With longer follow up this result became statistically significant (HR 0.73, 95% CI 0.54 – 0.99). In the POPLAR study, there did appear to be an association between PD-L1 status and efficacy, although this trial was substantially smaller than the OAK trial. Patients who were PD-L1 negative for both tumor cells (TC) and immune cells (IC) did not appear to have any improvement in overall survival in comparison to docetaxel.

It is clear that therapy with atezolizumab is associated with improved overall survival in comparison to docetaxel in patients who have received prior platinum-based chemotherapy. Patient reported outcomes were also improved in the phase III OAK trial. Quality of life was assessed using the EORTC-QLQ 30 and QLQ LC13. Completion rates were high. Given the exploratory nature of this analysis, the results on QoL should be interpreted with caution. Patients randomized to atezolizumab demonstrated longer time to deterioration in physical and role functioning, as well as patient reported chest pain. There were no differences observed in global quality of life, or other lung cancer related symptoms. More patients randomized to docetaxel experienced worsening health related quality of life scores between baseline and cycle 5 and 6, including physical functioning, role functioning and symptoms including diarrhea, sore mouth, dyspnea, peripheral neuropathy and alopecia. In addition, patients randomized to atezolizumab experienced fewer overall adverse effects (AEs) and fewer grade 3 and 4 AEs (15% vs 43%). The incidence of immune related AE (irAE) was 31%, but only 6% of patients experienced grade 3 and 4 irAEs. These numbers are similar to the incidence of AEs and irAEs observed in trials of nivolumab and pembrolizumab.

There is a significant burden of illness from NSCLC in Canada. It represents the largest cause of death from cancer. There are approximately 28,600 new cases and 21,800 deaths from lung cancer annually in Canada. While there are already funded immunotherapy treatments available to lung cancer patients who have progressed following platinum-based therapies, atezolizumab would represent an alternate treatment choice for patients and physicians. Atezolizumab was identified as a desirable treatment among patient advocacy groups. Interviews with Canadian and US patients who have received therapy with atezolizumab identified positive experiences from treatment with atezolizumab. Many patients reported shrinkage of their cancer and improvement in well-being. Additionally, treatment every three weeks was identified as reducing the burden of treatment, including financial burden. Registered clinician input also identified three weekly administration of atezolizumab as representing an advantage over nivolumab. At present nivolumab is the preferred immunotherapy agent in patients with PD-L1 negative tumors (approximately 50-55%). Therefore, the option to treat every three weeks has potential to impact as many as half of the patients receiving immunotherapy after progression of platinum-based chemotherapy.

At present, there are no trials directly comparing atezolizumab with either nivolumab, or pembrolizumab. The only comparisons are indirect. The HRs for each trial demonstrated similar magnitudes of benefit for each agent in comparison to docetaxel: Checkmate 017 (HR 0.59, 95% CI 0.44-0.79); Checkmate 057 (HR 0.73, 95%CI 0.59 – 0.89); Keynote 10 (2mg/kg HR 0.71, 95%CI 0.58-0.88, 10mg/kg HR 0.61, 95%CI 0.49-0.75). The Submitter's network meta-analysis, which was critically appraised and summarized in this report (see Section 7), represents a more detailed and systematic approach to examine these indirect comparisons. Atezolizumab, nivolumab and pembrolizumab are all superior to docetaxel in that analysis. The efficacy of each immunotherapy agent appears similar based on this analysis.

Both the OAK and POPLAR trials treated patients until disease progression and allowed treatment beyond progression in patients demonstrating clinical benefit. While the optimal duration of immunotherapy remains unclear, evidence from a trial of one year of nivolumab versus nivolumab until disease progression suggested improved efficacy for patients continuing treatment until progression. [15]This provides indirect support for the strategy employed in OAK and POPLAR. Based on the results of the OAK trial, PD-L1 testing is not recommended to identify patients for atezolizumab therapy. Nevertheless it should be noted that there are some issues regarding the SP142 test for PD-L1 expression. The Blueprint 1 trial, supported by the International Association for the Study of Lung Cancer (IASLC), compared PD-L1 expression between four antibody tests: 28-8, 22C3, SP142 and SP 263.[16] Agreement between the 28-8, 22C3 and SP263 antibodies was high, whereas SP142 exhibited fewer stained tumor cells overall. Blueprint 2 demonstrated poor inter-rater reliability between pathologists in the evaluation of PD-L1 expression on immune cells.[17]

In summary, atezolizumab has demonstrated superior efficacy to docetaxel in randomized trials of NSCLC patients who progressed following platinum-based chemotherapy. These improvements are associated with fewer adverse events and may also be associated with improvement in some aspects of quality of life. NSCLC represents a substantial burden of illness in Canada. While treatment alternatives already exist for atezolizumab, it does offer some advantages to both patients and physicians, in regards the frequency of administration and fewer clinic visits. Atezolizumab should be considered as an alternative immunotherapy agent in NSCLC patients with good performance status (ECOG 0-2) progressing after platinum-based therapy, with no prior immunotherapy and no history of autoimmune diseases that represent a contraindication to immune checkpoint inhibitor therapy.

1.3 Conclusions

The Clinical Guidance Panel concludes that there is a net overall clinical benefit from atezolizumab in the treatment of advanced NSCLC following progression on platinum-based chemotherapy. This was based on two randomized trials both demonstrating similar evidence of improved overall survival for patients randomized to atezolizumab 1200mg IV every three weeks, versus docetaxel chemotherapy. Patients receiving atezolizumab experienced fewer grade 3 and 4 adverse events overall and fewer treatment related adverse events than patients receiving docetaxel.

The Clinical Guidance Panel also considered a number of caveats to this conclusion:

- NSCLC represents the most common cause of death from cancer in Canada. Monoclonal antibodies directed against the PD-1/ PD-L1 axis represent a significant advance in the treatment options for patients with advanced non-small cell lung cancer.
- To date, the anti PD-1 therapies, nivolumab and pembrolizumab, have demonstrated superior efficacy (ORR, PFS and OS) in comparison to docetaxel, as second-line therapy in advanced NSCLC. Additionally, pembrolizumab has demonstrated superior efficacy in comparison to platinum-based doublets, as first-line therapy in patients with tumors expressing PD-L1 in greater than 50% of tumor cells (TPS ≥ 50%).
- The current submission for atezolizumab represents a third option for immunotherapy treatment among patients who have progressed following platinum-doublet chemotherapy. In the OAK trial, median overall survival was improved from 9.6 months to 13.8 months (HR 0.73, 95% CI 0.62-0.87) for patients

randomized to atezolizumab versus docetaxel. Similarly, in the POPLAR trial, median overall survival was improved from 9.5 months to 11.4 months (HR 0.77, 95% CI 0.56 – 1.06). With longer follow up this result became statistically significant (HR 0.73, 95% CI 0.54 – 0.99).

- The incidence of immune related adverse events among patients receiving atezolizumab was 31%, and the incidence of grade 3 and 4 adverse events was only 6%. In the larger OAK trial patients randomized to atezolizumab experienced longer time to deterioration for physical functioning and role functioning. Longer time to deterioration for patient reported chest pain was also observed.
- There are no direct comparisons between atezolizumab and other PD-1/PD-L1 inhibitors. However, indirect comparisons suggest that the efficacy of atezolizumab is similar to that of nivolumab, or pembrolizumab.
- Patients with activating mutations (EGFR or ALK mutations) should first be treated with targeted agents followed by a platinum containing regiment before qualifying for atezolizumab.
- The therapy is valued by patients and clinicians who identify that the three weekly administration represents an advantage over two weekly administration of nivolumab.
- Atezolizumab would insert into the NSCLC treatment algorithm as a subsequent line of therapy for patients who have failed platinum-based chemotherapy, for patients with good ECOG performance status (0-2), with no specific contraindications to immune checkpoint inhibitor therapy and with no prior immunotherapy.
- Treatment with atezolizumab should be until disease progression with patients being allowed to continue treatment beyond progression if there is evidence of benefit.

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 third most commonly diagnosed cancer among men and second most in women in Canada, and the largest cause of death from cancer. In 2017 there were approximately 28,600 new cases of lung cancer and 21,100 deaths from lung cancer.[18] About 85% of these cases would be classified as Non-Small Cell Lung Cancer (NSCLC). Approximately 50% of NSCLC patients have stage IV disease at the time of presentation, with another 25-30% presenting with locally advanced stage III disease.[19] Only 20-25% of patients present with early stage disease amenable to surgical resection. The incidence of NSCLC rises with age and the median age at diagnosis is 70 years. Given the high proportion of patients presenting with advanced stage, it is not surprising that the expected five year survival is only 18%.[18]

2.2 Accepted Clinical Practice

Multiple treatment options exist for patients with advanced NSCLC. Nevertheless, available data would suggest that in adults (<70 years) only one in three patients receive systemic therapy and the rate of treatment declines with advancing age.[19,20] Significant changes in the management of advanced NSCLC have taken place over the last decade. We have moved from a simple algorithm applicable to all patients,[21] to an algorithm in which histology and molecular profile are used to individualize treatment decisions.[22]

Historically, platinum-based therapy was offered as first-line treatment of advanced NSCLC with cisplatin or carboplatin in combination with gemcitabine, vinorelbine, paclitaxel, or docetaxel.[21] Treatment beyond disease progression, for patients well enough to consider further therapy, might include docetaxel,[23] pemetrexed[24] and/ or erlotinib.[25] Histology has now become an important factor in defining algorithms for squamous and non-squamous cancers.[26] A platinum-agent plus pemetrexed has emerged as the preferred chemotherapy option for patients with non-squamous cancers, whereas a platinum-agent plus gemcitabine, or carboplatin plus paclitaxel would be preferred for patients with squamous cancers. Maintenance therapy with pemetrexed is routinely recommended for patients with non-squamous NSCLC.[27]

More recently, data from multiple studies have emerged demonstrating the importance of molecular profiling of lung adenocarcinomas. One representative study from the Lung Cancer Mutation Consortium (LCMC) undertook molecular profiling of 1007 lung adenocarcinomas.[28] Among evaluable tissue, oncogenic drivers were found in 64% of cases. Commonly observed gene mutations included *KRAS* (25%), *EGFR* (17%) and *ALK* (8%). Mutations occurring in <1-2% of patients included *ERBB2*, *BRAF*, *MET*, *NRAS*, *MEK* and *ROS1*.[28] Therapeutic options for several of these oncogenic driver mutations have demonstrated superior efficacy to standard chemotherapies and have dramatically changed the treatment paradigms for advanced NSCLC. Oral targeted therapies directed at the tyrosine kinase domain of the *EGFR*, *ALK* and *ROS1* genes have all shown high objective response rates and improved progression free survival (PFS) than standard chemotherapy options and have been incorporated into treatment algorithms. Molecular profiling of lung adenocarcinomas for *EGFR* mutations and *ALK* translocations is now routinely performed at the time of initial lung cancer diagnosis. Molecularly targeted therapies such as gefitinib,[29,30] afatanib,[31,32] crizotinib[33] and alectinib[34] are now the preferred initial therapy in patients with these molecular abnormalities.

The development of immune checkpoint inhibitors represent the most significant recent change in the treatment algorithm for advanced NSCLC. The interaction between the Programmed Cell

Death–1 (PD-1) receptor and its ligand (PD-L1) represents an inhibitory signal to T-cell activation. It is one of the mechanisms by which cancers are thought to escape immune surveillance. Monoclonal antibodies directed against the PD-1 receptor are now approved therapy in the treatment of advanced NSCLC. Nivolumab and pembrolizumab, both anti PD-1 antibodies, have shown higher overall response rates (ORR) and improved overall survival (OS) in comparison to second-line chemotherapy with docetaxel.[10-12]

Checkmate 017 and 057 studies established nivolumab as a second-line therapy in advanced NSCLC.[10,11] In patients with squamous histology, the ORR observed for patients treated with nivolumab (3mg/kg every 2 weeks) was double that observed with docetaxel chemotherapy (20% vs 9%, p=0.008).[11] OS was also significantly longer for nivolumab than docetaxel (9.2 months vs 6.0 months, HR 0.59, 95%CI 0.44 – 0.79). In patients with non-squamous histology, similar findings were observed.[10] ORR was significantly higher in patients randomized to nivolumab compared with docetaxel (19% vs 12%, p=0.02), as was OS (12.2 months vs 9.4 months, HR 0.73, 95%CI 0.59 – 0.89). The Keynote 10 trial observed similar findings for second-line pembrolizumab in patients with tumors expressing PD-L1.[12] Pembrolizumab 2mg/kg, or 10mg/kg both showed significantly greater ORR than docetaxel (2mg/kg 18% vs 9%, p=0.0005, 10mg/kg 18% vs 9%, p=0.0002). OS was also significantly greater among patients receiving pembrolizumab (2mg/kg 10.4 months vs 8.5 months, HR 0.71, 95%CI 0.58-0.88, 10mg/kg 12.7 months vs 8.5 months, HR 0.61, 95%CI 0.49-0.75).

There is mixed information regarding the predictive value of tumor PD-L1 expression. Patients were not selected according to PD-L1 status in both the Checkmate 017 and 057 trials. In Checkmate 017, conducted in patients with squamous NSCLC, PD-L1 status was neither prognostic, nor predictive for OS.[11] However, in the Checkmate 057 trial, conducted in patients with non-squamous NSCLC, PD-L1 status appeared to be predictive of improved OS in patients receiving nivolumab. PD-L1 expression ≥ 1%, ≥5%, or ≥10% was associated with higher OS in patients randomized to nivolumab. The Keynote 10 trial did not include NSCLC patients with tumors not expressing PD-L1. Higher ORR and improved OS were observed in patients with tumors expressing PD-L1 in 50% or greater of cells. [12]

In the first-line setting, therapy with pembrolizumab was shown to be superior to platinum-based chemotherapy in NSCLC patients with tumors expressing PD-L1 in 50% or greater of cells (Keynote 24).[14] The ORR was 44.8% vs 27.8% in the pembrolizumab compared to chemotherapy groups, respectively and OS was significantly greater with pembrolizumab (6 month survival 80.2% vs 72.4%, respectively HR 0.60, CI=0.41-0.89, p=0.005).[14] Interestingly a similarly designed trial of nivolumab versus platinum-based chemotherapy failed to demonstrate any improvement in OS in NSCLC patients with tumors expressing PD-L1 in 5% or greater of cells.[35] Lastly, a randomized phase II trial demonstrated significant improvement in ORR from the addition of pembrolizumab to carboplatin and pemetrexed chemotherapy.[36] These data have already modified practice in the US and will likely change practice in Canada over the next year. The current treatment algorithm for advanced NSCLC is summarized in Figure 1 below.

Atezolizumab is the first PD-L1 inhibitor evaluated in NSCLC. The POPLAR[4] and OAK[1] trials are randomized phase II and phase III trials evaluating atezolizumab versus docetaxel as second-line therapy in advanced NSCLC. Improved OS was observed in both the POPLAR trial (12.6 months vs 9.7 months, HR 0.73, 95%CI 0.53-0.99)[4] and the OAK trial (13.8 months versus 9.6 months, HR 0.73, 95%CI 0.62-0.87).[1] While OS were very similar, differing results were observed between the two trials, concerning the predictive value of PD-L1 expression. No improvement in OS was observed in PD-L1 negative patients in the POPLAR trial, whereas improved OS was observed in PD-L1 positive and negative patients in the larger OAK trial.

The efficacy of atezolizumab appears similar to both nivolumab and pembrolizumab (both PD1 inhibitors). All three agents demonstrate improved OS in comparison to docetaxel as second-line therapy for advanced NSCLC. No direct comparisons exist between the three agents. The

magnitude of benefit of all three agents in comparison to docetaxel appears similar. Therefore atezolizumab represents an alternative second-line treatment option for patients with advanced NSCLC that has progressed following platinum-based chemotherapy.

Patients with advanced NSCLC		
Line of Therapy	[Subgroup by mutation positive]	[Subgroup by mutation negative]
1st-Line	EGFR or ALK TKI	Platinum-agent plus pemetrexed, gemcitabine, paclitaxel, or vinorelbine
Maintenance	EGFR or ALK TKI	Pemetrexed in non-squamous NSCLC only
2nd-Line	Osimertinib, ceritinib, alectinib, or platinum-agent plus pemetrexed. Maintenance pemetrexed in non-squamous NSCLC.	Nivolumab, or pembrolizumab (in PD-L1 ≥ 1%)
3rd Line	Platinum-agent plus pemetrexed (if not previously received), or docetaxel)	Docetaxel
4th Line	Nivolumab or pembrolizumab (in PD-L1 ≥ 1%)	Erlotinib

2.3 Evidence-Based Considerations for a Funding Population

	Proportion	Number of Patients
Lung cancer in Canada annually	100%	28,600[18]
Diagnosed with NSCLC	85%	24,310
Locally advanced or metastatic disease	75%	18,233
Receiving any first-line therapy Received immunotherapy in first-line Receive first line chemotherapy	30-35% 30% 70%	5,470-6,382 1641-1915 3829-4467
Receiving any second-line therapy	50%	2735-3192
Received immunotherapy in second-line	70%	1915-2234

Based on the above assumptions, there are between 2735 and 3192 patients annually with advanced NSCLC who receive second line therapy. Assuming one third were PD-L1 positive and received first-line pembrolizumab, and who would subsequently not be eligible for second line treatment with an immunotherapy, there are between 1915 and 2234 patients who may be candidates for second-line immunotherapy. These would be good performance status patients (ECOG 0-2) who had advanced NSCLC that progressed on or after platinum-based chemotherapy, with good organ function. Patients with asymptomatic or treated brain metastases would be considered for treatment. Patients with a known history of autoimmune disorders would generally not be considered for treatment with an immune checkpoint inhibitor. PD-L1 status would generally not be used in the selection of patients for second line immunotherapy.

These patients are already candidates for nivolumab or pembrolizumab. These agents are both publically funded. The same population of patients would be candidates for therapy with atezolizumab as an alternative to nivolumab or pembrolizumab.

2.4 Other Patient Populations in Whom the Drug May Be Used

The population of patients eligible for therapy with atezolizumab should be easily identified. NSCLC patients with tumors strongly positive for PD-L1 (expression ≥ 50%) would likely receive first-line pembrolizumab based on the Keynote 24 trial. The population of patients eligible for second-line therapy with atezolizumab, will be the same population currently considered for second-line therapy with nivolumab or pembrolizumab. This population includes patients with tumors that are both PD-L1 positive and negative.

There is some potential for use in patients with poor performance status (ECOG 3) and for patients with relative contraindications to immunotherapy agents such as autoimmune disorders. However, this also exists for currently funded therapies of nivolumab and pembrolizumab.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

Patient and caregiver input regarding lung cancer was gathered through two patient advisory groups: Lung Cancer Canada (LCC) and The Lung Association – Ontario (OLA). The OLA provided information on patients' experiences with advanced/metastatic NSCLC and current therapies. LCC provided information on patients' experiences with current therapies including atezolizumab for the treatment of advanced or metastatic NSCLC that progressed on or after systemic chemotherapy.

OLA captured information through a total of 14 phone interviews that had previously been conducted. Patients were asked open-ended questions about lung cancer symptoms and their impact, experience with current and new treatments, as well as expectations for new therapies. Two phone interviews were completed approximately one year ago in two patients living with COPD and lung cancer; and 12 interviews were completed 18 months ago among eight lung cancer patients/survivors and four family members. All interview respondents resided within Canada.

LCC captured information through phone interviews and environmental scans of online forums, which were created by LCC for lung cancer patients and their families. Individual phone interviews were conducted with five patients; demographic information on the five interview respondents in summarized in Table 1. The phone interviews were conducted using a semi-structured guide, which asked patients to discuss their thoughts, feelings and hopes related to their lung cancer journey including (but not limited to) diagnosis, treatments received, side effects, burden on family, and functionality on new treatment. Through online forums, LCC also obtained input from 17 patients and eight caregivers. Demographic information on the 25 online forum respondents was limited; there were at least six females and at least six males in the sample, and the gender of the other respondents is unknown. In addition, patient input was also obtained by LCC from two patients who contributed to a previous pCODR submission.

Table 1: Demographic information on patient respondents interviewed by LCC

Patient	Geographical location	Sex	Age (years)
1	Canada	Male	61
2	Canada	Male	69
3	US	Female	54
4	US	Female	68
5	US	Male	65

All five LCC patient interview respondents are currently receiving treatment with atezolizumab. LCC indicated that four patients accessed the drug through a clinical trial and one patient accessed it through private insurance. Two patients are receiving first-line atezolizumab therapy; one receiving atezolizumab alone, and the other receiving it in combination with chemotherapy. One patient is receiving second-line atezolizumab therapy following progression on chemotherapy. Another patient is on atezolizumab alone, following intolerance to chemotherapy and atezolizumab combination. The final interviewed patient is on their fifth-line treatment, taking atezolizumab following chemotherapy, bevacizumab, erlotinib and nivolumab. Through the LCC online forums it was determined that two patient respondents are currently receiving chemotherapy plus atezolizumab combination therapy, and the remaining 23 patients are on atezolizumab as single-agent therapy, however, the specific line of therapy could not be determined.

Considering both LCC and OLA, input was obtained from a total of 45 respondents, which included 32 patients, 12 caregivers, and one respiratory educator.

From a patient's perspective, lack of timeliness regarding testing and diagnosis, difficulty managing symptoms, especially fatigue and exhaustion, the effect of lung cancer on day-to-day lives, and a lack of information about lung cancer and treatment options making navigation of the disease and next steps about care difficult, are all concerns regarding the experience of lung cancer. Chemotherapy is regarded with fear and immunotherapies are considered much more positively by patients who express a need for more effective and tolerable treatment options. Patients mention that drugs used to manage symptoms of lung cancer are only effective for some symptoms, while problems such as, palpitations, dry mouth, mouth sores, vision and urinary problems and impacts on mood are still in need of better management. Inconvenient treatment scheduling and distant locations of treatment centres can take up valuable time and may result in large financial expenses due to travel.

As stated by LCC, atezolizumab is offered as a second-line treatment for NSCLC, independent of PD-L1 expression, among patients who have progressed after receiving chemotherapy and pembrolizumab. The only other second-line immunotherapy currently available to patients is nivolumab. Atezolizumab may serve as another option for patients to consider as a second-line immunotherapy after progression or if they are unresponsive to nivolumab.

OLA telephone interview respondents identified the following key issues patients and caregivers felt needed to be addressed by a new treatment: slowing or complete halt of disease progression, reduction of pain, fatigue, cough and shortness of breath, nausea, inability to fight infection, and burning of skin and impact on mood, improvement of appetite and energy, and reduced or eliminated cost burden associated with new treatments. The option of conducting treatments at home was also expressed by patients; this would reduce the burden on patient's caregivers as well as reduce disruptions to daily routines. LCC noted that out of 30 patient and caregiver respondents, atezolizumab resulted in a 50% to 60% reduction in tumour size among 18 patients, in some cases even resulting in no evidence of disease. Patients reported they responded to atezolizumab quickly, and survived longer than the average survival for patients on chemotherapy and atezolizumab. Patients experienced relatively minimal side effects, with 13 out of 22 patient respondents reporting low or no side effects, versus nine patients who had medium or high/severe side effects. Fatigue was the side effect reported by most patient respondents. Less frequently reported side effects included low appetite, rash, shortness of breath, itchiness, nausea and autoimmune difficulties. Regardless of experiencing side effects, patients showed favourable outcomes (i.e., being cancer free for one to two years, having greater quality of life and having enough energy to work and spend time with family), and expressed that they would still recommend trying atezolizumab if facing side effects. There was an expressed need for better patient monitoring in order to better respond to, and help patients understand their side effects.

Below is a summary of the specific input received from OLN and LCC. Quotes are reproduced as they appeared in interviews 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.

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with NSCLC

For patients, fear and anxiety are strongly associated with the experience of NSCLC due to the unknown responses and outcomes on treatment, and wait times for appointments and treatments. One OLA patient respondent stated that she *"waited six months to see the specialist and by then he said he couldn't do anything. It was too late"*. OLA patient respondents expressed their frustration for how long it took to make a diagnosis, with one patient mentioning that "*it took a*

year to finally make the diagnosis", and another saying, *"It's a really horrific time, and you are filled with fear about your survival."*

Symptoms and problems experienced by patients can be very burdensome due to the variable nature of them, as symptoms change frequently making them hard to manage. Some symptoms include pain, which can be very intense at times, shortness of breath, cough, weakness and extreme fatigue. Extreme fatigue and exhaustion, in particular, were symptoms that many patients in the OLA sample reported were difficult to manage, and patients had to plan their days around managing these symptoms.

OLA patient respondents expressed the impact lung cancer had on their day-to-day lives, affecting work, travel, social life, their ability to participate in leisure and physical activities, relationships with friends and family, independence, emotional well-being, and their financial situation. One patient with lung cancer expressed distress regarding their loss of independence:

"This disease has affected all parts of my life. I am not able to go outside on cold days, I am no longer able to drive, and must volunteer drivers to get to my appointments, I am dependent on my neighbours to get my mail each day and take my weekly trash out. I have lost a significant amount of weight and am tired, weak and without energy. I am no longer able to do the activities I enjoy. It is very hard to be positive and hopeful."

Patients also mentioned a lack of information regarding the disease, treatment options, and an eventual prognosis communicated in a way that would apply to them. Many found it difficult to obtain the information they felt they needed to help them navigate the condition of lung cancer and understanding the next steps they should take.

3.1.2 Patients' Experiences with Current Therapy for NSCLC

According to LCC, current treatment options for patients with NSCLC are either chemotherapy or, for the few who qualify, pembrolizumab in the first-line. Upon progression with pembrolizumab, the next step is likely to be chemotherapy. For those that received chemotherapy first, the only second-line immunotherapy after progression would be nivolumab. If a patient is unresponsive or intolerant to nivolumab, patients are left without any other treatment option and must return to chemotherapy.

Chemotherapy is currently a necessary treatment for patients, however it is a treatment that is often faced with fear by patients. One patient in the LCC sampled noted that *"chemo wasn't worth it with only a 5% chance of working,"* and that should they have to go back to receiving chemotherapy they *"would rather die"*. Chemotherapy is seen as undesirable by patients, and patients expressed a need for a treatment that is both more effective and tolerable.

LCC did not obtain information on the specific treatments received by patients in their sample (for both phone interview and online forum patients); however, they indicated that all patients had received chemotherapy, and some patients also had experience with targeted therapies and immunotherapies after chemotherapy. Similarly, OLA also did not capture information on patient experiences with currently available treatments; but they did report on other drug treatments used by patients for symptoms of breathlessness and other breathing issues, which included Spiriva, Seebri, Advair, Symbicort, Daxas, Prednisone, Ventolin, Atrvent, Serevent, Onbrez, Tudorza and Ventolin (as needed). Within this sample there were also two patients undergoing treatment: radiation and chemotherapy, and radiation only. Side effects experienced by patients included fatigue, shortness of breath, cough, appetite loss, low energy, palpitations, dry mouth, mouth sores, vision and urinary problems, and impact on mood. However, not all symptoms are easily managed; patients note that symptoms including palpitations, dry mouth, mouth sores, vision and urinary problems and impacts on mood still require better management. Both patients

undergoing treatment within the LCC sample reported feelings of extremely sore and painful throats; another patient mentioned how treatment affected their ability to handle bills and loose change due to a loss of feeling in their fingers. There was also a desire for treatments to provide greater independence and increased energy.

Many patients in the OLA sample expressed an inconvenience related to schedules of treatment and the abundance of medical appointments, especially those who live far distances away from treatment centres. One patient in the OLA sample mentioned that it takes her a ten-hour drive or an airplane flight to receive treatment; regular treatments result in pricey travel bills and a heavy investment of time for patients. Medical appointments also result in out-of-pocket expenses for individuals, as one patient had to pay for a driving service to and from appointments, and another had to pay for specific food products as a result of their weight loss. The financial burden can be quite severe, especially for patients who are on a fixed income/pension. Frequent visits to hospitals and clinics are also expensive and resource-intensive for the healthcare system.

In addition to difficulties with treatment, patients make note that diagnosis of their condition is not always clear or smooth. To avoid delays in diagnosis and treatment patients felt that their general practitioners required greater training and knowledge about lung diseases. Also, biopsies used to confirm a diagnosis of lung cancer were described as *"incredibly painful"* by a patient in the OLA sample. Another patient had to undergo the procedure for the biopsy three times due to a lack of experience from the technician who had difficulty reaching the tumour. All of the participants within the OLA sample stated that they would like greater understanding of treatment options and how these options impact them. Even patients with advanced disease did not consider the option of not being treated. A need for greater communication regarding treatment options and their disease was expressed as being key to helping in decision-making and coping processes.

3.1.3 Impact of NSCLC and Current Therapy on Caregivers

Caregivers within the OLA sample reported that caring for loved ones with lung cancer affected their work, finances, relationships with friends and family, their physical and leisure activities, independence and ability to travel and socialize. OLA made note of the overarching theme of the distress among caregivers watching those with lung cancer suffer in pain with the knowledge that there is little that can be done to alleviate the pain and discomfort.

Similarly to patient experiences reported by OLA, caregivers within the LCC sample mentioned feelings of anxiety and fear associated with lung cancer, wanting to spend more time with their loved ones, and wanting to return to regular day-to-day living. In the 2015 Faces of Lung Cancer Report (FoLCR), more caregivers than patients reported feelings of anxiety associated with the lung cancer experience (61% versus 42%, respectively). These feelings of fear and anxiety regarding the disease can be compounded when combined with stress associated with long wait times and unclear prognoses. A caregiver whose husband had lung cancer stated, *"He was really sick, we just about lost him. I was really scared, I didn't know what would happen"*. Caregivers expressed that quality of life and spending time with loved ones were important to helping reduce feelings of anxiety associated with lung cancer.

Caregivers in the LCC sample also mentioned feelings of stigma and shame with their experiences of lung cancer. *"The stigma experienced by patients with lung cancer is undeniable. The majority of patients with lung cancer report experiencing stigma, often related to guilt, regret, perceived blame and other negative beliefs about smoking history"* (FoLCR 2017). However, caregivers also experience these negative feelings; a caregiver stated, *"My mother died last year of lung cancer as a result of a lifetime of smoking and I often wonder what role the feeling of having imposed this illness son herself played throughout her illness. It pained me to have to watch her go*

through the agony of being diagnosed with the illness, receiving chemotherapy and radiation while also having to bear the weight of this uncompassionate/unwarranted stigma".

3.1.4 Patient Expectations of future lung cancer treatments

As reported by OLA telephone interview respondents, the key issues patients and caregivers felt needed to be addressed by a new treatment were the slowing or complete halt of disease progression, reduction of pain, fatigue, cough and shortness of breath, nausea, inability to fight infection, and burning of skin and impact on mood, improvement of appetite and energy, and reduced or eliminated cost burden associated with new treatments. The option of conducting treatments at home was also expressed by patients; this would reduce the burden on patient's caregivers as well as reduce disruptions to daily routines.

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for and Experiences To Date with atezolizumab

Experience with atezolizumab is based on the input received from the 22 patients and 8 caregivers obtained through phone interviews and environmental scans of online forums conducted by LCC.

As stated by LCC, atezolizumab is offered as a second-line treatment for NSCLC among patients who have progressed after receiving chemotherapy and pembrolizumab. The only other second line immunotherapy currently available to patients is nivolumab; atezolizumab may serve as another option for patients to consider as a second-line immunotherapy after progression or if they are unresponsive to nivolumab. LCC noted that atezolizumab provides patients with much needed choice of treatment both versus chemotherapy and other immunotherapy. According to LCC, chemotherapy is not very well tolerated or effective, and often faced with fear by patients, atezolizumab provided patients with a much more effective and less taxing treatment option.

As atezolizumab is not dependent on PD-L1 expression, LCC noted that atezolizumab may allow for patients to receive quicker access to care; biopsies to determine if patients qualify as candidates for targeted immunotherapies take time, result in worry for patients and caregivers waiting on results and patients conditions may worsen in the process. Atezolizumab may provide a quicker treatment option, as well as a treatment option for patients who cannot be given pembrolizumab or nivolumab. Atezolizumab was shown to be effective, as 18 of 30 patients and caregiver respondents noted a reduction of tumour size from 50% to 60%, in some cases actually resulting in no evidence of disease.

LCC remarked that patients respond to atezolizumab quickly; one patient said she felt *"back to normal"*, and that within three months of treatment with atezolizumab she felt almost like she did before her diagnosis. Many patients reported that they had beat the average survival mark; 10 patients had reached or exceeded the 10 month mark, which is the average overall survival on chemotherapy, and eight reached or exceeded the 14 month mark, which is the average overall survival for atezolizumab. Of the eight patients who reached or exceeded the 14 month mark, lengths of overall survival included 18 months, two years, three years, and even four years. In addition to living longer, the patients were living well with few side effects.

The common side effects associated with atezolizumab are reported in Table 2. Fatigue was the side effect reported by most patient respondents.

Table 2: Common side effects of atezolizumab

Side effect	Number of patients reporting side effect (n=22)
Fatigue	10
Low appetite	4
Rash	3
Shortness of breath	2
Itchiness	2
Diarrhea	2
Nausea and auto-immune difficulties	2
Weakness	1
Flu-like symptoms	1
Sore mouth	1
Other	4

In terms of the severity of side effects associated with atezolizumab, the majority of patient respondents reported less severe side effects; 13 out of 22 patients reported either no or low side effects, versus nine patients who reported medium or high/severe side effects in response to atezolizumab (Table 3). The majority of patients tolerated atezolizumab relatively well.

Table 3: Severity of side effects in response to atezolizumab

Severity of side effects	Number of patients reporting on severity (n=22)
No side effects	5
Low	8
Medium	2
High/severe	7

Even in response to side effects, patient input highlighted effective outcomes after atezolizumab therapy. Among two patients who had to halt treatment due to side effects, both reported beneficial results, including being cancer free for one and a half to two years. One patient mentioned that even though they had side effects, they would still *"recommend giving atezolizumab a shot"*. The number and severity of side effects greatly impact a patient's quality of life, therefore fewer and less severe side effects allow the patients to return to their lives and spend their time meaningfully. A patient on her fifth infusion of atezolizumab stated, *"I'm going to be 80 this year but would love to see my middle school granddaughter graduate from high school"*. Another patient said that she was able to spend quality time travelling with her grandchildren to Italy, Australia, London and Paris. On treatments with two week infusion schedules, such as chemotherapy, planning trips would be much more difficult, compared to atezolizumab which has a more comfortable three week schedule. Less time spent at hospitals and clinics also allows patients to spend that quality time with their friends and family, while also reducing costs associated with travel and time spent away from work by their caregivers. One patient who was taking atezolizumab reported that they could still work while on this treatment, and that *"a three week (infusion) schedule offers a lot more flexibility to do good work"*. With a low five-year survival rate of lung cancer (17%), atezolizumab gives patients hope for effective and long lasting treatments. *"There's hope that (atezolizumab) has permanently changed the relationship between cancer and immune system*", was stated by a patient who stopped taking atezolizumab two years ago and continues to live cancer free today.

LCC raised the issue of follow-up programs that will allow for better monitoring of patient side effects and responses to them as they develop. In one case, side effects reported may not have been due to atezolizumab, but from the washout of a previous treatment. *"I had some dry skin*

and mild diarrhea but nothing that would make me go off (atezolizumab). Unsure if it was due to (atezolizumab) or radiation though. I am in no pain. I'm not tired. I walk about five miles per day and play with my grandkids". LCC remarked that if patients are educated about side effects, more accurate information will be reported, and highlighted the need for more quality data regarding new therapies.

3.2.2 Caregiver Experiences with Atezolizumab

Among caregivers, fear, anxiety and stigma were common feelings. Caregivers worry about the wellbeing of their loved ones with lung cancer, and this worry is compounded by wait times for testing. A patient made a statement of his wife saying, *"At first there was a lot of fear and anxiety, as it is for most. This (atezolizumab) alleviated my wife's worry even more than mine. We are very grateful"*. Caregivers also shared thoughts of being grateful toward atezolizumab for allowing family members to spend more quality time with their loved ones affected by lung cancer; a caregiver mentioned that they were *"very grateful and appreciative of the extra time this new treatment has given [them] to be able to share with him (their loved one)"*.

3.3 Additional Information

No additional information was provided by the OLA.

Additional information provided by LCC noted that, before 2009, the treatment options available for lung cancer patients was limited. Between 2012 to currently, there have been 20 new reviews for lung cancer related therapies, including this current review. The goal is that there will be better treatments and improved patient outcomes. A three week dosing schedule will allow patients to spend more quality time with friends and family as they choose, reduce overall travel time for patients and free up limited and expensive healthcare resources. The addition of atezolizumab into the health care system will not place a burden, as there are already two immunotherapies included, and the addition of atezolizumab will not result in an increase in the population that will qualify for immunotherapy. Also, the inclusion of atezolizumab into the market will result in beneficial competition and result in price reductions that will benefit patients and the healthcare system. The addition of atezolizumab into the list of available treatment options for patients with lung cancer will increase the number of treatment options a patient has, and hopefully lead to better patient outcomes.

4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

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

Overall Summary

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

Clinical factors:

- Comparison to other immunotherapies
- Sequencing with chemotherapy, other immunotherapies and with oral targeted therapies
- Patient group eligible for treatment

Economic factors:

- Treatment duration

Please see below for more details.

4.1 Factors Related to Comparators

Treatments now available in the second line treatment of NSCLC include immunotherapy (nivolumab, pembrolizumab), pemetrexed, docetaxel and oral targeted therapies. Since atezolizumab is an immunotherapy targeting the same pathway as nivolumab and pembrolizumab, other immunotherapies would be the appropriate comparator and PAG is seeking information comparing atezolizumab to nivolumab or pembrolizumab, noting that atezolizumab is a PD-L1 inhibitor (i.e. ligand) with a different mechanism of action although same pathway as nivolumab and pembrolizumab which are PD-1 inhibitors (receptor).

4.2 Factors Related to Patient Population

PAG is seeking clarity on the eligible patient population. The funding request is for patients previously treated with chemotherapy. However, it does not specify histology, number of previous lines of therapy, PD-L1 expression, or presence or absence of mutations.

PAG noted that the POPLAR and OAK trials included patients with EGFR mutations. PAG is seeking information on the place in the treatment pathway for atezolizumab and whether it is an option to oral EGFR targeted therapies or a replacement of oral EGFR targeted therapies in patients previously treated with chemotherapy, oral targeted therapy or both chemotherapy and oral targeted therapy.

In addition, PAG noted that the POPLAR trial did not have patients with ALK translocation and in the OAK trial, only 1% of patients had ALK translocation. PAG is seeking clarity on whether patients with ALK translocation would benefit or not benefit from treatment with atezolizumab.

4.3 Factors Related to Dosing

Atezolizumab is administered every three weeks and at the same dose (1200mg) for all patients. PAG noted that there would be no drug wastage as atezolizumab is supplied as 1200mg vials.

PAG noted that additional resources may be required to monitor infusion related reactions and immune related adverse events. However, this is similar to monitoring for reactions with other immunotherapies.

PAG is seeking clarity on treatment duration and treatment until lack of benefit with a definition of disease progression.

4.4 Factors Related to Implementation Costs

Atezolizumab is indicated for patients previously treated with chemotherapy. PAG noted that pembrolizumab and nivolumab are available treatment options after chemotherapy and that pembrolizumab is available in first-line treatment for patients with PD-L1 expression equal to or greater than 50%. PAG indicated that chemotherapy would be treatment option for patients previously treated with immunotherapy. If recommended for funding, PAG noted that patients previously treated with other immunotherapies would not be eligible for subsequent treatment with atezolizumab.

4.5 Factors Related to Health System

PAG noted that the OAK trial concluded that atezolizumab is effective regardless of PD-L1 expression but that the POPLAR trial showed improvement in overall survival was associated with PD-L1 expression. PAG would like confirmation that PD-1 testing is not required.

4.6 Factors Related to Manufacturer

None.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

Two joint clinician inputs were received, one from Lung Cancer Canada Medical Advisory Board and one from Cancer Care Ontario Lung Drug Advisory Group, with a total of ten clinicians providing input.

The clinicians identified that atezolizumab provides another immunotherapy option for the treatment of NSCLC, after failure on chemotherapy, in patients who have no mutations. They noted that atezolizumab could be used, regardless of PD-L1 status, in patients not previously treated with immunotherapy. They noted that atezolizumab has similar benefits and toxicity profile as other immunotherapies available for NSCLC, although there are no direct comparative studies with other immunotherapies.

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

5.1 Current Treatment(s) for NSCLC

For patients who have failed platinum doublet chemotherapy, docetaxel or nivolumab, regardless of PD-L1 status, are treatments available. If patients are PD-L1 >50%, pembrolizumab is another treatment choice.

5.2 Eligible Patient Population

The clinicians providing input believe that oncologists would use atezolizumab in NSCLC patients who have progressed beyond first line treatment and who were not treated with immunotherapy first line. Those who are EGFR or ALK positive would also receive a targeted therapy second line and not receive atezolizumab until after failure of platinum doublet.

The clinicians providing input estimate that approximately 3,191 Canadian NSCLC patients per year may qualify for an immunotherapy in second line. This number was arrived at by a series of assumptions based on literature and clinical experience. These assumptions are:

- Estimate 28,600 Canadians were diagnosed with lung cancer in 2017.
- 80 - 85% are diagnosed with NSCLC. 85% was used for the purposes of this calculation.
- 75% of all NSCLC patients diagnosed are in the Stage III and IV.
- Approximately 50% of all those patients at may receive treatment. Please note that this is a high estimate. Many physicians feel that 50% represents a “best case scenario” and the actual number of patients treated are much lower.
- 30% of patients treated may be PD-L1>50% (these will receive pembrolizumab first line).
- 50% of patients who are treated are able to move onto a second line of treatment.

The clinicians providing input noted that there may be some uptake in the use of atezolizumab in favour of nivolumab, as per the favourable results of overall survival benefit in patients with metastatic adenocarcinoma of the lung who do not have a PD-L1 status or are less than 50% positive, and are EGFR and ALK wildtype. (They also noted that nivolumab seems to have a more prominent efficacy profile for squamous lung cancers in clinical trial data compared to non-squamous pathologies.) Since this is around 40% of metastatic NSCLC, it does represent a sizable patient population if clinicians favour the use of atezolizumab over nivolumab in that specific indication.

Atezolizumab may or may not be favoured over nivolumab in being used for adenocarcinomas, given that there is a 4 month OS benefit with atezolizumab on docetaxel compared to nivolumab

with 3 month OS benefit with crossover in the Kaplan-Meier curves. It should not be in ALK+ (none were recruited in the study) or EGFR+ patients (crossed over in subgroup analyses).

5.3 Identify Key Benefits and Harms with atezolizumab

[One group of clinicians providing input noted that in clinical practice, physicians have observed a similar side effect profile between atezolizumab, pembrolizumab and nivolumab. The side effects experienced are consistent with the clinical trials. Their patients on immunotherapy generally experience significantly lower side effects over those on chemotherapy. Some patients even have no side effects. The benefit of treatment is the durability of the response in patients in whom a response is seen. Over 20% of patients are multi-year survivors which is not the norm in stage IV lung cancer.

Another group of clinicians providing input identified that atezolizumab is a relatively well tolerated systemic agent that provides another therapeutic option for EGFR and ALK-negative metastatic NSCLC who have failed doublet platinum chemotherapy. Most toxicities are mild, aside from the immune mediated reactions affecting primarily the thyroid, lung, and gut.

5.4 Advantages of atezolizumab Over Current Treatments

[Clinicians feel that immunotherapy is superior to chemotherapy in terms of efficacy, and patient quality of life. However, the clinicians providing input noted that no direct comparison in efficacy among immunotherapies (pembrolizumab, nivolumab and atezolizumab) is made. The toxicity profiles of these immunotherapy agents are similar, but are all collectively less toxic and myelosuppressive than docetaxel.

Currently nivolumab (PDL-1 inhibitor) is the standard of care for NSCLC patients who are not 1) PD-L1 positive, 2) EGFR or ALK-positive and 3) have progressed on first line treatment. Patients who are PD-L1 positive would be given pembrolizumab (either first or second line).

Atezolizumab has demonstrated advantages over nivolumab. Like pembrolizumab, atezolizumab is infused every three weeks. Nivolumab is infused every two weeks. They both also have a shorter infusion time than nivolumab. Physicians felt that these advantages could be significant on patient time and hospital resource utilization as about 25% of their immunotherapy patients could be on treatment for more than a year.

Although non-comparative, the median overall survival data for atezolizumab was higher for atezolizumab versus nivolumab. In the phase 3 OAK trial, patients treated with atezolizumab had an overall survival of 13.8 months compared with 9.6 months for docetaxel. In the CheckMate 057 trial, patients treated with nivolumab had a median overall survival of 12.2 months versus 9.4 months for docetaxel. In addition, both OAK/POPLAR suggest that atezolizumab is effective in all subgroups of PDL-1 expression, whereas the results of CheckMate suggests that nivolumab may not be as effective in the low (PDL-1 <10% subgroup.

The clinicians providing input indicated that a positive funding recommendation for atezolizumab would give patients a chance at an efficacious treatment that has the potential to reduce healthcare resource usage due to its three week infusion schedule and one that has the potential to deliver a higher overall survival benefit than the current standard of care. Atezolizumab has certain advantages over nivolumab: Its three week dosing schedule can potentially save time and resources. Nivolumab is administered every other week. Although non-comparative, the trial

results suggest additional survival benefit with atezolizumab. Access to this medication will lead to improve patient outcomes.

5.5 Sequencing and Priority of Treatments with atezolizumab

The clinicians would consider atezolizumab as a second or third line option, upon progression on platinum doublet chemotherapy or pemetrexed, in patients who are EGFR negative and ALK negative. It was noted that PD-L1 status is not required for this medication. The clinicians providing input indicated that physicians would not use atezolizumab in patients who have been treated with pembrolizumab first line.

Atezolizumab would join nivolumab and pembrolizumab as immunotherapy options for the treatment of NSCLC. The clinicians providing input noted that there is a place for all three immunotherapy options. Pembrolizumab has approval as a first line option for PD-L1 ≥ 50% and can is expected to be established as a standard of care in these patients (with the exception of patients for whom targeted therapy is an option).

In patients who are EGFR or ALK positive, it was noted that physicians prefer to use another targeted therapy upon progression after front line targeted therapy. For patients who do not have another targeted therapy option or are unable to tolerate the targeted therapy, after progression on platinum-doublet chemotherapy, physicians would require PD-L1 testing to help aid in their decision as to whether to use immunotherapy and the type of immunotherapy that would be used.

Atezolizumab is also a PD-L1 inhibitor. Both nivolumab and pembrolizumab are PD-1 inhibitors. Comparisons between the two are difficult to make due to limited published studies in this area. However as patients use these treatments, there is the opportunity to collect real-world data to better understand the impact of these therapies on patient outcomes.

The clinicians providing input feel that adding atezolizumab to funded products does not increase the number of patients that will be given access to immunotherapy. Funding atezolizumab means patients and physicians will have a choice of nivolumab, atezolizumab or pembrolizumab in the second line setting. If atezolizumab is priced similarly to nivolumab, usage will result in a cost savings to the system due to its three week dosing schedule as opposed to nivolumab's two week schedule. Negotiation and competitive pressures may also lower prices.

5.6 Companion Diagnostic Testing

PD-L1 testing may be used to determine which immunotherapy agent could be used, but will not affect use of atezolizumab as it seems to have efficacy regardless of what PD-L1 status. Thus, unlike pembrolizumab, diagnostic testing is not necessary for atezolizumab.

5.7 Additional Information

None.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the effect of Atezolizumab, as monotherapy, in the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who have progressed on or after platinum chemotherapy.

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

Summary and critical appraisal of the Manufacturer-submitted indirect treatment comparison of pharmacological interventions used as second or higher lines of treatment for locally advanced/metastatic NSCLC.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the CGP and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in Table 6.1. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold. The literature search strategy and detailed methodology used by the pCODR Methods Team are provided in Appendix A.

[Table 6.1]. Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published and unpublished RCTs In the absence of RCT data, fully published clinical trials investigating the safety and efficacy of Atezolizumab for NSCLC will be included.	Adult patients with advanced or metastatic NSCLC who have progressed on or after previous platinum-based chemotherapy <u>Subgroups:</u> – Sex – Age – ECOG performance score – Number of previous treatments – Smoking status – Histology (squamous vs non-squamous cell carcinoma) – CNS metastasis – PD-L1 expression – Presence of ALK and EGFR mutations	Atezolizumab 1200 mg (IV) every three weeks	Docetaxel Nivolumab Pembrolizumab	Efficacy • OS • PFS • ORR • CR • PR Safety • AEs • Immune-related AEs • SAEs • WDAE QoL

AE=adverse events; **ALK** = anaplastic lymphoma kinase; **CNS** = central nervous system; **CR**=complete response; **ECOG** = Eastern Cooperative Oncology Group; **EGFR** = Epidermal growth factor receptor; **IV** = intravenous infusion; **mg** = milligram; **NSCLC** = non-small cell lung cancer; **ORR**=objective response rate; **OS**= overall survival; **PD-L1** = programmed death-ligand1; **PFS**= progression-free survival; **PR**=partial response; **QoL**=quality of life; **RCT**=randomized controlled trial; **SAE**=serious adverse events**; WDAE**=withdrawal due to adverse events

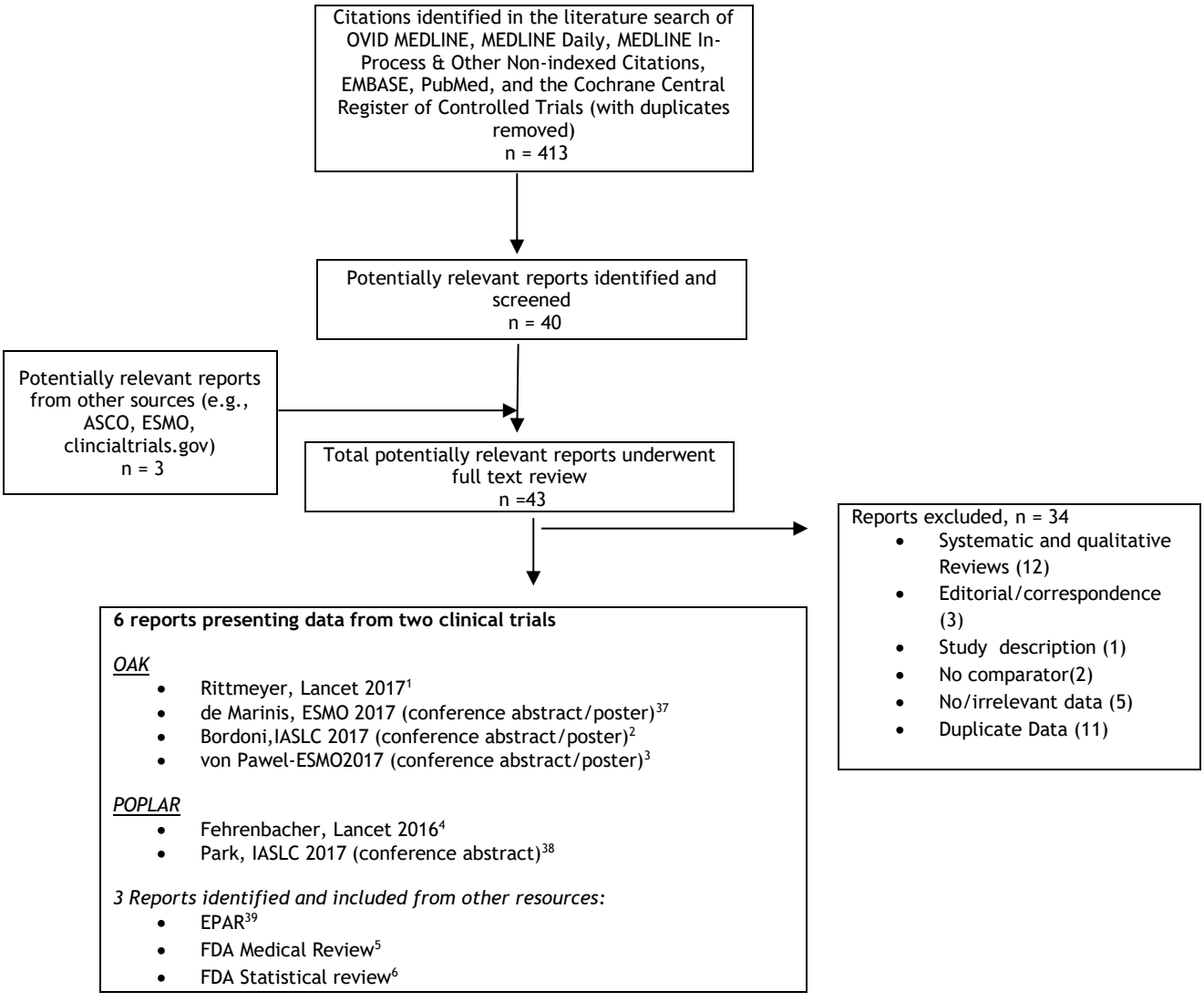
** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*

6.3 Results

6.3.1 Literature Search Results

Of the 43 potentially relevant citations identified, nine citations reporting data from two clinical trials were included in the pCODR systematic review,[1-6,37-39] and 34 studies were excluded. Studies were excluded because they did not report the results of a clinical trial design,[40-55] used no comparators,[56,57] or did not report data on outcomes and/or subgroups of interest,[58-62] Conference abstracts and journal articles which reported duplicate data from the included full articles were excluded.[60,63-72] If data from the single data-cut-off point was reported in more than one citation, the citation which included more detailed or more recent data was included. Figure 6.1 illustrates the PRISMA flow Diagram for the study selection process.

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



Note: Additional reports were obtained from the Submitter: Manufacturer's report on the indirect treatment comparisons,[8,73] Hoffmann-La Roche Checkpoint Response(13-Feb-2018)[7]

6.3.2 Summary of Included Studies

Two randomized controlled trials (RCTs) met the selection criteria of this review:

OAK (n=1225) was a phase III international, multi-centre, open-label RCT of atezolizumab versus docetaxel in patients with locally advanced or metastatic NSCLC who had progressed during or after prior platinum-containing chemotherapy regimens.[1-3,37] The results of the primary efficacy analysis, which was performed on the first 850 patients (425 in each study arm) according to the trials statistical analysis plan, are published and will be reported in this report. A secondary analysis for the 1225 randomized patients has been conducted by the Manufacturer. The rational for the enrollment of additional patients and this secondary analysis is described further in section 6.3.2.1a.

POPLAR (n=287) was Phase II, international, multicenter, open-label RCT of atezolizumab versus docetaxel in patients with locally advanced or metastatic NSCLC who had progressed during or after prior platinum-containing chemotherapy regimens.[4]

6.3.2.1 Detailed Trial Characteristics

The trials included in this systematic review are compared and contrasted in Table 6.2. Relevant summary information on trial characteristics is also provided in section 2.1.3.

Table 6.2: Summary of Trial Characteristics of the Included Studies

Trial Design	Inclusion Criteria	Intervention and Comparator (Sample Size)	Trial Outcomes
Study: OAK[1,2,3,#1,37] GO28915 NCT02008227[74] Phase III international, multicenter, open-label randomized controlled trial with active control Number randomized: primary population: (n=850) Total randomized: (n=1225) Total number of patients enrolled in Canada: 15[75] Number treated: (n = 1187) Number of centres and number of countries: 194 academic or community centres in 31 countries . Patient Enrolment Dates: 11-Mar-2014 to 29-Apr-2015 Data cut-off date:	Key Inclusion Criteria: • Aged 18 years or older • Histologically or cytologically documented locally advanced or metastatic NSCLC • measurable disease per RECIST criteria(version 1.1) • ECOG performance status of 0 or 1 • Any PD-L1 status • Disease progression during or following treatment with one or two prior platinum-containing regimens Key Exclusion Criteria: • History of autoimmune disease • Prior treatments with docetaxel, CD137 agonists, anti-CTLA4, or therapies targeting the PD-L1 and PD-1 pathway • Active or untreated CNS metastases	Arm 1: Atezolizumab 1200 mg IV Q3W, until loss of clinical benefit or unacceptable toxicity (n=425 Primary Population) (n=613 Total Randomized) Arm 2: Docetaxel 75 mg/m2 Q3W, until disease progression or unacceptable toxicity (n=425 Primary Population) (n=612 Total Randomized)	Primary OS Secondary: PFS (by investigator) ORR Safety • AEs • SAEs • irAEs • WDAE

Trial Design	Inclusion Criteria	Intervention and Comparator (Sample Size)	Trial Outcomes
Primary analysis: 07-Jul-2016 Secondary analysis:[7] 15-Dec-2017 Final Analysis Date: Planned for 2019 (third quarter)[7] Funding: Hoffmann-La Roche Limited			
Study: POPLAR[4,38] NCT01903993 GO28753[76] Phase II, international, multicenter, open- label, randomized controlled trial with active control Number randomized: (n = 287) Total number of patients enrolled in Canada: 5[75] Number treated: (n = 277) Number of centres and number of countries: 61 academic or community centres in 13 countries (including 2 Canadian centres) Patient Enrolment Dates: 05-Aug-2013 to 31-Mar-2014 Data cut-off dates: Primary analysis 15-Jan-2015 Interim: 8-May-2015 Final Analysis Date: December 1, 2015 Funding: Hoffmann-La Roche Limited	Key Inclusion Criteria: • Aged 18 years or older • Histologically or cytologically documented locally advanced or metastatic NSCLC • measurable disease per RECIST criteria(version 1.1) • ECOG performance status of 0 or 1 • Any PD-L1 status • Disease progression during or following treatment with one or two prior platinum-containing regimens Key Exclusion Criteria: • History of autoimmune disease • Prior treatments with docetaxel, CD137 agonists, anti-CTLA4, or therapies targeting the PD-L1 and PD-1 pathway • Active or untreated CNS metastases	Arm 1: Atezolizumab 1200 mg IV Q3W (n=144) Arm 2: Docetaxel 75 mg/m2 Q3W (n=143)	Primary OS Secondary: PFS (by investigator) ORR Safety • AEs • SAEs • irAEs • WDAE
AE = adverse events; **CNS** = central nervous system; **ECOG** = Eastern Cooperative Oncology Group; **irAEs** = immune-related adverse events; **IV** = intravenous; **mg =** milligram**; mg/m^2** = milligram per square meter of body surface; **ORR** = objective response rate; **OS**= overall survival; **PD-L1** = programmed death-ligand1; **PFS** = progression-free survival;			

Trial Design	Inclusion Criteria	Intervention and Comparator (Sample Size)	Trial Outcomes

Q3W = once every three weeks; **RECIST**: Response Evaluation Criteria in Solid Tumours, version 1.1; **SAE** = serious adverse events; **WDAE** = withdrawal due to adverse events

Table 6.3: Select quality characteristics of included studies of Atezolizumab in patients with non-small cell lung cancer (NSCLC)

Study	Treatment vs. Comparator	Primary outcome	Required sample size	Sample size	Randomization method	Allocation concealment	Blinding	ITT Analysis	Final analysis	Early termination	Ethics Approval
OAK[1]	Atezolizumab vs Docetaxel	OS	1100 up to 1300	850 (primary population) 1225 (total randomized)	Permuted block randomization (block of 8)	None	None	Yes	No	No	Yes
POPLAR[4]	Atezolizumab vs Docetaxel	OS	285	287	Permuted block randomization (block of 4)	None	None	Yes	Yes	No	Yes

ITT = intention-to-treat; **OS** = overall survival

a) Trials

Two trials met the inclusion criteria for this review:

OAK

OAK was an international, multi-centre, open-label RCT with the primary objective of evaluating the effect of atezolizumab on overall survival in patients with locally advanced or metastatic NSCLC who had progressed during or after prior platinum-containing chemotherapy regimens. The trial was conducted in 194 academic or community oncology centres in 31 countries.[1]

To be eligible in the study patients were required to be 18 years or older, and have measurable disease based on the Response Evaluation Criteria in Solid Tumours (RECIST; version 1.1) criteria, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, a life expectancy of 12 weeks or longer, and adequate hematologic and end-organ function based on defined laboratory results. Patients also had to have received one or two previous platinum based chemotherapy regimens for stage IIIB or IV NSCLC. Patients with EGFR or ALK mutations were further required to have failed on an EGFR tyrosine kinase inhibitor (TKI; e.g., erlotinib, gefitinib), or ALK inhibitor (e.g., crizotinib), respectively.[1] Patients were excluded if they had active or untreated central nervous system (CNS) metastases (those with treated asymptomatic supratentorial CNS metastases were eligible); had a history of autoimmune disease; or had received previous treatments with docetaxel, CD137 agonists, anti-CTLA4, or therapies targeting the programmed death-ligand 1 (PD-L1) and programmed cell death protein 1 (PD-1) pathway. Patients were also excluded if they were not able to understand the local language(s) by which the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaires, i.e., QLQ-C30 and QLQ-LC13, were available.[1]

Patients were randomly assigned (in a 1:1 ratio) by computer-generated permuted blocks of eight, using an interactive voice or web response system (bracket), to receive atezolizumab or docetaxel. Randomization was stratified by tumour-infiltrating immune cell PD-L1 expression (IC0,

IC1, IC2, IC3 levels), number of previous chemotherapy regimens (one versus two), and histology (non-squamous versus squamous cell tumours). PD-L1 expression was assessed prospectively, according to the scoring criteria that are shown in Table 6.4, using the SP142 immuno-histochemical assay (Ventana Medical Systems, Inc., Tucson, AZ, USA).[1] The study was open-label and treatment allocation was not masked.[1]

Tumour assessments were performed at the baseline, then every 6 weeks until week 36 and every 9 weeks thereafter. The assessments continued until disease progression, regardless of treatment discontinuation. However, for patients receiving atezolizumab after disease progression, tumour assessments continued until treatment discontinuation. Patients were followed up for survival status during the study period while receiving treatment and every three months after treatment discontinuation.[1]

Table 6.4: PD-L1 scoring criteria and subsets in OAK and POPLAR trials

Description of IHC Scoring Algorithm	PD-L1 Expression Level
Absence of any discernible PD-L1 staining OR presence of discernible PD-L1 staining of any intensity in ICs covering **< 1%** of tumor area occupied by tumor cells, associated intratumoral, and contiguous peri-tumoral desmoplastic stroma	IC0
Presence of discernible PD-L1 staining of any intensity in ICs covering between **≥ 1% and < 5%** of tumor area occupied by tumor cells, associated intratumoral, and contiguous peri-tumoral desmoplastic stroma	IC1
Presence of discernible PD-L1 staining of any intensity in ICs covering between **≥ 5% and < 10%** of tumor area occupied by tumor cells, associated intratumoral, and contiguous peri-tumoral desmoplastic stroma	IC2
Presence of discernible PD-L1 staining of any intensity in ICs covering **≥ 10%** of tumor area occupied by tumor cells, associated intratumoral, and contiguous peri-tumoral desmoplastic stroma	IC3
Absence of any discernible PD-L1 staining OR presence of discernible PD-L1 staining of any intensity in **< 1%** TCs	TC0
Presence of discernible PD-L1 staining of any intensity in **≥ 1% and < 5%** TCs	TC1
Presence of discernible PD-L1 staining of any intensity in **≥ 5% and < 50%** TCs	TC2
Presence of discernible PD-L1 staining of any intensity in **≥ 50%** TCs	TC3

IC = tumor-infiltrating immune cell; NSCLC = non–small cell lung cancer; PD-L1 = programmed death–ligand 1; TC = tumor cell.

PD-L1 subsets were constructed from the combination of PD-L1 expression on tumour-infiltrating immune cells (ICs) and tumour cells (TCs) and included the following subsets:

- TC3 or IC3 and complementary group TC0/1/2 and IC0/1/2
- TC3 or IC2/3 and complementary group TC0/1/2 and IC0/1
- TC2/3 or IC2/3 and complementary group TC0/1 and IC0/1
- TC1/2/3 or IC1/2/3 and complementary group TC0 and IC0

The PD-L1 subsets were determined based on IC levels from stratification and TC levels derived from raw percentage staining scores at enrollment.

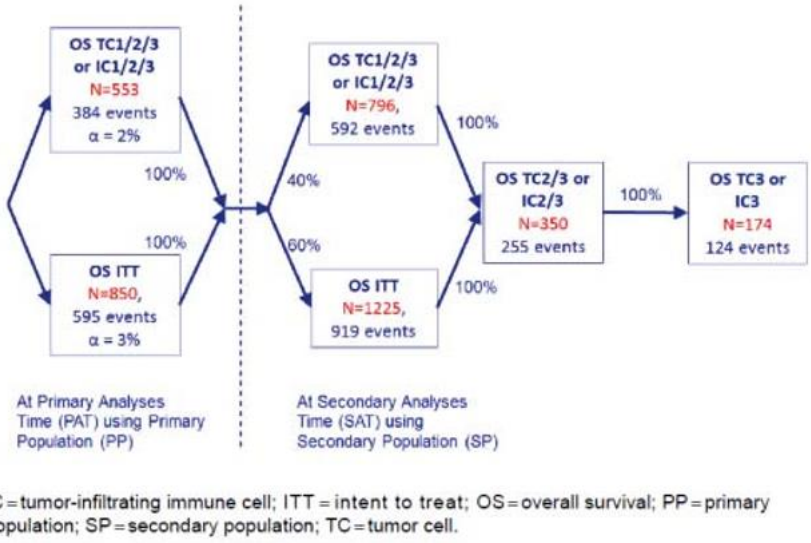
Source: [FDA Statistical Review, page 23-24][6]

The primary outcome of the study was overall survival (OS) compared between treatment groups within the intention-to-treat (ITT) population, and in the PD-L1 expression population (Tumour Cells [TC]1/2/3 or Tumour-Infiltrating Immune Cells [IC]1/2/3 subgroups; PD-L1 expression on ≥1% of tumour cells or tumour-infiltrating immune cells; Table 6.4). Secondary endpoints included investigator-assessed progression-free survival (PFS), objective response rate (ORR), duration of response (DOR), and safety.[1]

The OAK trial was initially planned to enroll 850 patients, with an estimated enrollment of 255 PD-L1 IC2/3 patients and 425 PD-L1 IC1/2/3 patients. In light of emerging data from other studies, the sample size was increased to 1100 patients (up to 1300; Amendment #3), to provide sufficient power for an OS comparison in patients with high PD-L1 expression (TC3 or IC3), assuming a 20% prevalence of the TC3 or IC3 subgroup.[6,39] The final enrollment in the trial was 1225 patients.[1] During the course of the OAK trial, data from the phase II, randomized POPLAR trial showed an OS benefit that was extended to lower PD-L1 expression levels. Results from POPLAR trial also revealed a late separation of survival curves, suggesting that the assessment of OS required a relatively long follow-up.[4] Based on these results, the statistical design of the OAK trial was modified back to test OS, as a co-primary outcome, in the ITT population and in the TC1/2/3 or IC1/2/3 population, for which the initial 850 randomized patients were deemed to provide sufficient power (95·3% in the ITT population and 98·6% in the TC1/2/3 or IC1/2/3 population) and follow-up time (Amendment #5). Therefore, the primary efficacy analysis was performed on the first 850 patients who were randomly assigned to a treatment group.[1] A secondary analyses for the 1225 randomized ITT patients would be considered, if the null hypothesis in the primary OS analysis was rejected.[5]

For the primary analysis of the first 850 patients enrolled, type I error rate (α) was split between the ITT population (α = 3%) and the TC1/2/3 or IC1/2/3 subgroup (α = 2%). Depending on the outcome of the primary OS comparisons, alpha would be hierarchically passed to the 1225 ITT patients and the related PD-L1 expression subgroups (Figure 6.2).[6]

Figure 6.2: Type I error control in OAK trial



IC = tumor-infiltrating immune cell; ITT = intent to treat; OS = overall survival; PP = primary population; SP = secondary population; TC = tumor cell.

Source: [FDA Statistical report, page 12][6]

Data cut-off date for the primary analysis of the efficacy and safety data was 07-Jul-2016, when 569 patients (approximately 70% of patients in the primary efficacy analysis population) had died. At the time of the analysis, the median follow-up time was around 21 months in both arms.[1,6] There was no pre-planned interim analyses for the efficacy outcomes.[5]

There were five amendments to the protocol, which are summarised below:[6]

- Amendment #1(10-Feb-2014) provided revisions for European Union countries.
- Amendment #2 (5-Aug-2014) modified the treatment duration for atezolizumab to allow patients to be receive atezolizumab until loss of clinical benefit (i.e., the 16-cycle or 12-month initial treatment, follow-up, and re-treatment periods would no longer apply). This amendment also added an exclusion criterion (i.e., known tumour PD-L1 expression status from other clinical trials) to ensure a natural distribution of the prevalence of PD-L1 expression levels.
- Amendment #3 (02-Dec-2014) expanded planned PD-L1 expression subgroups to include PD-L1 expression on TCs in addition to ICs. This amendment also increased the sample size from 850 to 1100 patients (up to 1300 patients) to allow for testing patients with TC3 or IC3 as first step in the hierarchy.
- Amendment #4 (06-Oct-2015) updated the implementation of approaches for the management of gastrointestinal, dermatologic, endocrine, pulmonary toxicity, hepatotoxicity, potential pancreatic or eye toxicity and other immune-mediated adverse events (AEs).
- Amendment #5 (28-Jan-2016) changed back the statistical analysis plan to the first 850 randomized patients in the ITT population in addition to the TC1/2/3 or IC1/2/3 subgroup among these 850 patients.

Further changes to the Statistical Analyses Plan included: revision in type I error control plan, inclusion of all randomized patients in the ORR analysis (regardless of whether they had measureable disease at baseline), and additional exploratory analyses to summarize the efficacy and safety efficacy outcomes after disease progression in patients who received at least one dose of atezolizumab after their first event.[5,39]

POPLAR

POPLAR was a multi-centre, open-label, phase II randomized controlled trial (RCT) with the primary objective of comparing the efficacy and safety of atezolizumab with those of docetaxel on overall survival in patients with locally advanced or metastatic NSCLC who had progressed during or after prior platinum-containing chemotherapy regimens. The trial was conducted in 61 academic or community oncology centres in 13 countries in Europe and North America.[4]

To be eligible in the study patients were required to be 18 years or older, and have measurable disease based on the Response Evaluation Criteria in Solid Tumours (RECIST; version 1.1) criteria, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, an adequate hematologic and end-organ function, and provided tumour specimens for central PD-L1 testing on formalin-fixed paraffin-embedded sections before enrolment. Patients were excluded if they had active or untreated CNS metastases, history of pneumonitis, autoimmune disease; or had received previous treatments with docetaxel, CD137 agonists, anti-CTLA4, anti-PD-L1, or anti-PD-1 therapeutic antibodies, or PD-L1–PD-1 pathway-targeting agents.[4]

Patients were randomly assigned (in a 1:1 ratio) by computer-generated permuted blocks of four, using an interactive voice or web response system (bracket), to receive atezolizumab or docetaxel. Randomization was stratified by tumour-infiltrating immune cell PD-L1 expression (IC levels), number of previous chemotherapy regimens (one versus two), and histology (non-

squamous versus squamous cell tumours). PD-L1 expression was assessed by immuno-histochemistry according to the scoring criteria that are shown in Table 6.4.[4] The study was open-label and treatment allocation was not masked.[4]

Tumour assessments were performed by imaging at baseline, then every 6 weeks until week 36 and every 9 weeks (range 8-10 weeks) thereafter. The assessments continued until disease progression, regardless of treatment discontinuation. However, for patients receiving atezolizumab after disease progression, tumour assessments continued until treatment discontinuation.[4]

The primary outcome of the study was overall survival (OS) compared between treatment groups within the intention-to-treat (ITT) population, and in the PD-L1 expression subgroups. Secondary endpoints included investigator-assessed (per RECIST version1.1) PFS, ORR, DOR, and safety. Other exploratory endpoints included atezolizumab pharmacokinetics, patient-reported outcomes, biomarkers, and pharmacodynamics.[4]

The trial was designed to enrol 285 total patients, with a minimum of 55 patients in the PD-L1 IC2 or IC3 subgroup, that would provide an 82·3% power to detect target HRs of 0.65 in the ITT population (assuming 180 deaths), 0.35 in TC3 or IC3 PD-L1 expression subgroup, 0.50 in C2/3 or IC2/3 subgroup, and 0.60 in TC1/2/3 or IC1/2/3 subgroup, at a two-sided α level of 0.5.[4] Determination of the study power for the ITT and TC1/2/3 or IC1/2/3 populations was based on the following assumptions: event times are exponentially distributed, median overall survival in the control group would be 8 months, and patients would be enrolled over 8 months.[4]

Three interim analyses were to be performed when approximately 30, and 100 events in the overall population occurred. Type I error (α) values specified for the first, second, and third planned interim analyses were 0.0001, 0.0001, and 0.001, respectively. The primary OS analyses were to be performed when approximately 150 events occurred, using a two-sided α level of 4.88%. However, the protocol was later amended (see the details below) to increase the total number of death events for the final OS analysis from the original 150 to 180, and the analysis based on approximately 150 deaths was changed from the pre-specified final analysis to the third interim analysis, with associated alpha allocation of 0.0001.[5]

The primary analysis data cut-off date was 08-May-2015, after a median follow-up of 14.8 months (range 0.2+ to 19.6) in the atezolizumab group and 15.7 months (range 0.1–18.7) in the docetaxel group.[4]

The first version of the study protocol was issued on 30-Apr-201 and the protocol was amended five time, as summarized below:[5,39]

- Amendment #1 (29-Jul-2013) made minor corrections and modifications to the inclusion/exclusion criteria, laboratory assessments, and concomitant medications sections of the protocol.
- Amendment #2 (30 Jan-2014) revised the protocol to reflect the continuation of enrollment of patients until a minimum of approximately 54 patients PD-L1–positive were accrued. In the case that the prevalence of PD-L1–positive patients was lower than 18%, up to a maximum of approximately 300 total patients could be enrolled. Additionally, the description of the primary efficacy endpoint was amended to state that the treatment effect would be expressed as hazard ratios obtained using a Cox regression model stratified by histology subtype (squamous versus non-squamous), PD-L1 expression category (IHC 0, IHC 1, IHC 2, and IHC 3), and number of prior chemotherapy regimens (1 versus 2), including 95% CIs.
- Amendment #3 (21-May-2014) modified treatment duration for atezolizumab to allow patients to be treated until clinical benefit was no longer being experienced. The amendment also changed the frequency of tumour assessments (after 36 weeks) from

every 12 weeks to every 9 weeks to be more consistent with clinical practice. The timing of the interim safety and efficacy data evaluation by the Internal Monitoring Committee was also changed from when 30 and 60 deaths were observed to when approximately 30 and 100 deaths had occurred. The amendment changed the AE/safety follow-up period from 90 to 30 days due to the low frequency of significant drug-related AEs following treatment discontinuation across studies.

- Amendment #4 (25-Jul-2014) changed the safety follow-up period back to the original 90 days to allow further evaluation of safety after treatment discontinuation.
- Amendment #5 (24-Feb-2015) adjusted the event threshold for the primary analysis to approximately 180 death events and converted the originally planned analysis at approximately 150 death events to an interim analysis. The amendment clarified that stratification by PD-L1 IHC status was based on PD-L1 expression on tumour-infiltrating immune cells (ICs). This protocol amendment allowed for subgroup analyses based on other categories of PD-L1 expression including expression on tumour cells (TCs).

b) Populations

OAK

Between 11-Mar-2014 and 29-Apr-2015, 1225 patients were enrolled in the OAK trial, and were randomized to receive either atezolizumab (n=613) or docetaxel (n=612).[1]

- Primary population: the first 850 of 1225 enrolled patients were included in the primary efficacy analysis (425 patients in each arm enrolled between 11-Mar-2014 and 28-Nov-2014).
- Intention-to-treat (ITT) population: all randomized patients formed the ITT population.
- Safety population: 609/613 of patients assigned to the atezolizumab group, and 578/612 of those assigned to the docetaxel group received treatment and were included in the safety analysis population.[1]

The baseline characteristics of the primary ITT population are summarized in Table 6.5. As the table shows, demographic and baseline characteristics were well balanced between the study groups in the ITT population. The median age in the primary ITT population was 64 years (range 33-85), 61% of the patients were males, 70% were White, and 63% of had an ECOG performance score of 1. Of the 850 patients in the primary ITT population, 222 (26%) patients had squamous cell, and 628 (74%) had non-squamous cell carcinoma histology. Overall, 436 (54%) patients were classified in the PD-L1 TC1/2/3 (≥1%) or IC1/2/3 (≥1%) category (57% in the atezolizumab group versus 52% in the docetaxel group), and 137 (16%) patients in the PD-L1 TC3 (≥50%) or IC3 (≥10%) category (17% in the atezolizumab group versus 15% in the docetaxel group).

At the baseline, 75% of the patients in both study groups had received one and the remaining 25% had received two prior treatment(s) for locally advanced or metastatic NSCLC. Previous anti-cancer therapies were balanced between the treatment groups. The types and frequencies of prior cancer therapies reported by at least 10% of the primary ITT population are summarized in Table 6.6. As shown, at the study enrollment, the most common previous anti-cancer treatments included carboplatin (53%), pemetrexed (48%), and cisplatin (38%); followed by paclitaxel, gemcitabine, bevacizumab, and erlotinib.[39]

Table 6.5: Baseline characteristics of the primary ITT population in OAK trial

	Atezolizumab (n=425)	Docetaxel (n=425)	Overall (N=850)
Age (years)			
Median (range)	63·0 (33·0–82·0)	64·0 (34·0–85·0)	64·0 (33·0–85·0)
Age ≥ 65 years	190 (45%)	207 (49%)	397 (47%)
Sex			
Male	261 (61%)	259 (61%)	520 (61%)
Female	164 (39%)	166 (39%)	330 (39%)
Race			
White	302 (71%)	296 (70%)	598 (70%)
Asian	85 (20%)	95 (22%)	180 (21%)
Black	5 (1%)	11 (3%)	16 (2%)
Other*	13 (3%)	9 (2%)	22 (3%)
Unknown	20 (5%)	14 (3%)	34 (4%)
ECOG performance status			
0	155 (36%)	160 (38%)	315 (37%)
1	270 (64%)	265 (62%)	535 (63%)
Tobacco use history			
Never	84 (20%)	72 (17%)	156 (18%)
Current	59 (14%)	67 (16%)	126 (15%)
Previous	282 (66%)	286 (67%)	568 (67%)
***EGFR* mutation**			
Positive	42 (10%)	43 (10%)	85 (10%)
Negative	318 (75%)	310 (73%)	628 (74%)
Unknown	65 (15%)	72 (17%)	137 (16%)
***EML4-ALK* translocation**			
Positive	2 (<1%)	0	2 (<1%)
Negative	223 (52%)	201 (47%)	424 (50%)
Unknown	200 (47%)	224 (53%)	424 (50%)
***KRAS* mutation**			
Positive	26 (6%)	33 (8%)	59 (7%)
Negative	99 (23%)	104 (24%)	203 (24%)
Unknown	300 (71%)	288 (68%)	588 (69%)
Histology			
Non-squamous	313 (74%)	315 (74%)	628 (74%)
Squamous	112 (26%)	110 (26%)	222 (26%)
PD-L1 subgroups			
TC3 or IC3	72 (17%)	65 (15%)	137 (16%)
TC2/3 or IC2/3	129 (30%)	136 (32%)	265 (31%)
TC1/2/3 or IC1/2/3†	241 (57%)	222 (52%)	463 (54%)
TC0 and IC0	180 (42%)	199 (47%)	379 (45%)
Number of previous therapies in the locally advanced or metastatic setting			
1	320 (75%)	320 (75%)	640 (75%)
2	105 (25%)	105 (25%)	210 (25%)

Data are median (range) and n (%), unless otherwise indicated. ECOG=Eastern Cooperative Oncology Group. IC=tumour-infiltrating immune cell. PD-L1=programmed death-ligand 1. TC=tumour cell. * Other includes American Indian, Alaska native, Hawaiian native, other Pacific Islander, other, and multiple. †Tumour tissue for eight patients was not evaluable for TC1/2/3 or IC1/2/3.

Data are median (range) and n (%), unless otherwise indicated
ECOG = Eastern Cooperative Oncology Group; **IC** = tumour-infiltrating immune cell; **PD-L1** = programmed death-ligand ; **TC** = tumour cell

Source: [Rittmeyer, Lancet 2017; Table 1][1]

Table 6.6: Prior cancer therapies reported by ≥10% of the primary ITT population in OAK trial

Therapy Setting Regiment/Agent	Docetaxel (Randomized) (N=425)	Atezolizumab (Randomized) (N=425)	All Patients (N=850)
Total number of patients with at least one treatment	424 (99.8%)	425 (100.0%)	849 (99.9%)
Overall total number of treatments	1355	1419	2774
METASTATIC			
Total number of patients with at least one treatment	370 (87.1%)	385 (90.6%)	755 (88.8%)
Total number of treatments	1019	1091	2110
CARBOPLATIN	224 (52.7%)	229 (53.9%)	453 (53.3%)
PEMETREXED	195 (45.9%)	210 (49.4%)	405 (47.6%)
CISPLATIN	153 (36.0%)	167 (39.3%)	320 (37.6%)
PACLITAXEL	85 (20.0%)	110 (25.9%)	195 (22.9%)
GEMCITABINE	90 (21.2%)	77 (18.1%)	167 (19.6%)
BEVACIZUMAB	56 (13.2%)	69 (16.2%)	125 (14.7%)
ERLOTINIB	44 (10.4%)	41 (9.6%)	85 (10.0%)
ADJUVANT/NEO-ADJUVANT			
Total number of patients with at least one treatment	103 (24.2%)	97 (22.8%)	200 (23.5%)
Total number of treatments	248	226	474
CISPLATIN	72 (16.9%)	67 (15.8%)	139 (16.4%)
MAINTENANCE			
Total number of patients with at least one treatment	67 (15.8%)	80 (18.8%)	147 (17.3%)
Total number of treatments	86	100	186
PEMETREXED	51 (12.0%)	49 (11.5%)	100 (11.8%)

Multiple uses of a specific medication for a patient were counted once in frequency for the medication. Likewise, multiple uses within a specific medication class for a patient were counted once in frequency for the medication class.
Data Cut-off: 7 Jul 2016; RAVE Data Extracted: 19 Aug 2016.

Source: [EPAR, page 70][39]

Table 6.7 summarizes the baseline characteristics of the PD-L1 expression subgroups. In the TC1/2/3 or IC1/2/3 sub-population, the demographic and baseline characteristics were generally comparable between the study groups except imbalances (>5%) in age groups, sex and race. In the atezolizumab arm, there were smaller proportion of patients aged ≥ 65 years (43% versus 55% in the docetaxel arm); a greater proportions of male participants (65% versus 57% in the docetaxel arm); and a smaller proportion of Asian patients (14% versus 21% in the docetaxel arm).

Table 6.7: Baseline characteristics of the primary TC1/2/3 or IC1/2/3 subpopulation in OAK trial

	TC1/2/3 or IC1/2/3	
	Atezolizumab (N=241)	Docetaxel (N=222)
Age (years)		
Median	63	64
Range	35, 82	39, 85
Age category, n (%)		
<65	138 (57)	101 (46)
≥65	103 (43)	121 (55)
Sex, n (%)		
Male	157 (65)	126 (57)
Female	84 (35)	96 (43)
Race, n (%)		
White	184 (76)	159 (72)
Asian	33 (14)	46 (21)
Black or African American	4 (2)	4 (2)
Others	20 (18)	13 (5)
Region, n (%)		
US	79 (33)	83 (37)
Non-US	162 (67)	139 (63)
Histology, n (%)		
Squamous	112 (26)	110 (26)
Non-Squamous	313 (74)	315 (74)
Baseline ECOG PS, n (%)		
0	90 (37)	85 (38)
1	151 (63)	137 (62)
Smoking History, n (%)		
Current	37 (15)	33 (15)
Never	39 (16)	38 (17)
Previous	165 (69)	151 (68)
Number of prior therapies (IxRS)		
1	174 (72)	164 (74)
2	67 (28)	58 (26)
IC score (IxRS)		
0	34 (14)	21 (10)
1	113 (47)	108 (49)
2	48 (20)	49 (22)
3	46 (19)	44 (20)

Source:[FDA Medical report; Table 25, page 72][5]

POPLAR

Between 05-Aug-2013 and 31-Mar-2014, 287 patients were enrolled in the POPLAR trial, and were randomized to receive either atezolizumab (n=144) or docetaxel (n=143).[4]

- Intention-to-treat (ITT) population: all randomized patients formed the ITT population.
- Safety population: 142 of 144 of patients assigned to the atezolizumab group, and 135 of 143 patients assigned to the docetaxel group received treatment and were included in the safety analysis.[4]

The baseline characteristics of the ITT population are summarized in Table 6.8.

As the table shows, demographic and baseline characteristics were balanced between the study groups, except for a 12% greater proportion of female patients in the docetaxel group (35% in the atezolizumab group versus 47% in the docetaxel group). Overall, the median age of the study participants was 62 years old (range 36-84 years); 61% of the randomized patients were males; 79% percent were white; and 68% had a ECOG performance score of 1.[5] Of the 287 enrolled patients, 97 patients (34%) had squamous cell, and 190 (66%) had non-squamous cell carcinoma histology; 189 (66%) patients had one previous line of chemotherapy, and 98 (34%) had two previous lines of chemotherapy. Overall, 68% of patients were classified in the PD-L1 TC1/2/3 (≥1%) or IC1/2/3 (≥1%) category, and 16% in the PD-L1 TC3 (≥50%) or IC3 (≥10%) category.[4]

Table 6.8: Baseline characteristics of the ITT population in POPLAR trial

	Atezolizumab (n=144)	Docetaxel (n=143)
Age (years)	62 (42–82)	62 (36–84)
Sex		
Male	93 (65%)	76 (53%)
Female	51 (35%)	67 (47%)
Tobacco use history		
Never	27 (19%)	29 (20%)
Current	25 (17%)	21 (15%)
Previous	92 (64%)	93 (65%)
Pathology or histology		
Non-squamous	95 (66%)	95 (66%)
Squamous	49 (34%)	48 (34%)
ECOG performance status*		
0	46 (32%)	45 (32%)
1	96 (68%)	97 (68%)
PD-L1 tumour-infiltrating immune cell expression level		
0	62 (43%)	63 (44%)
1	53 (37%)	54 (38%)
2	19 (13%)	18 (13%)
3	10 (7%)	8 (6%)
PD-L1 tumour cell expression level		
0	96 (67%)	82 (57%)
1	19 (13%)	21 (15%)
2	14 (10%)	25 (18%)
3	15 (10%)	15 (11%)
Number of previous therapies in the locally advanced or metastatic setting		
1	93 (65%)	96 (67%)
2	51 (35%)	47 (33%)
EGFR mutation†		
Thr790Met	1 (1%)	0
Positive	10 (12%)	8 (10%)
Negative	72 (87%)	75 (90%)
EMLA-ALK translocation‡		
Yes	0	3 (5%)
No	61 (100%)	55 (95%)
KRAS mutation§		
Yes	14 (33%)	13 (43%)
No	28 (67%)	17 (57%)

Data are median (range) or n (%). ECOG=Eastern Cooperative Oncology Group. PD-L1=programmed death ligand 1.*Of 142 patients in each group. †Of 83 patients in each group with known *EGFR* mutation status. ‡Of 61 patients in the atezolizumab group and 58 in the docetaxel group with known *EMLA-ALK* translocation status. §Of 42 patients in the atezolizumab group and 30 in the docetaxel group with known *KRAS* mutation status.

Data cut-off date: 08-May-2015

Source: .[Fehrenbacher, Lancet 2016; Table 1][4]

Interventions

OAK

Treatment Dosing Schedule

Atezolizumab was administered as an intravenous 1200 mg fixed dose (equivalent to 15 mg/kg for a patient with a body weight of 80 kg) every 3 weeks (21 ±3 days) until loss of clinical benefit or unacceptable toxicity. Docetaxel was administered intravenously at 75 mg/m^2 every 3 weeks, until unacceptable toxicity or disease progression, as assessed by the investigator. No docetaxel to atezolizumab cross-over was allowed.[1,39]

Overall, treatment duration was longer than 12 months in 125 (21%) of 609 patients in the atezolizumab group and 14 (2%) of 578 patients in the docetaxel group. Median treatment duration was 3.4 months (range 0–26) in the atezolizumab group and 2.1 months (range 0–23) in the docetaxel group. Patients in the atezolizumab group were allowed to continue treatment beyond the disease progression. Forty percent of patients in the atezolizumab group received the study treatment beyond progression, with a median treatment duration of three cycles (range 1–34) beyond progression.[1] In the OAK trial, patients were able to continue treatment beyond RECIST defined disease progression if the investigator deemed the patient to be receiving clinical benefit. Tumour assessments were done at baseline, then every 6 weeks until week 36 and every 9 weeks thereafter until patients discontinue treatment.

Dose delays, reductions or modifications

Although dose reductions for atezolizumab were not allowed in this study, one atezolizumab-treated patient was reported by the investigator to have asthenia leading to dose reduction. There was no record of dose reduction found for this patient. Asthenia from this patient was included in the summary of AEs leading to dose modification.[7] Docetaxel dose modifications were performed according to the locally approved label.[39]

Concomitant and subsequent interventions

During the study, 92% of patients in the atezolizumab group and 96% of those in the docetaxel group were taking a concomitant or subsequent medication.[7]

Table 6.9 summarizes the types and frequencies of anti-cancer treatments received by the primary ITT population after discontinuation of study treatments. As the table shows, the proportion of the patients who received subsequent chemotherapy was higher in the atezolizumab group (41.0%) than in the docetaxel group (31.0%). Docetaxel was the most commonly used post-study chemotherapy agent, with 25.9% of patients treated in the atezolizumab group and 2.4% of those in the docetaxel group. The proportion of the patients who received subsequent immunotherapy was higher in the docetaxel group (17.2%) than in the atezolizumab group (4.5%). Nivolumab was the most common immunotherapy agent (13.8% and 3.8% of patients in the atezolizumab and docetaxel groups, respectively). The proportion of patients who received subsequent targeted therapy was similar between the two groups (14.8% and 15.5% of patients in the atezolizumab and docetaxel groups, respectively).The most commonly used targeted therapy agents included erlotinib hydrochloride, erlotinib, and bevacizumab.[1]

Table 6.9: Post-study anti-cancer treatments in OAK trial (Primary ITT population)

Treatment	Atezolizumab n=425	Docetaxel n=425
Total patients with at least one treatment	206 (48·5)	192 (45·2)
Chemotherapy	176 (41·4)	131 (30·8)
Docetaxel	110 (25·9)	10 (2·4)
Carboplatin	35 (8·2)	29 (6·8)
Gemcitabine	24 (5·6)	38 (8·9)
Vinorelbine	18 (4·2)	22 (5·2)
Gemcitabine hydrochloride	17 (4·0)	20 (4·7)
Pemetrexed	15 (3·5)	22 (5·2)
Vinorelbine tartrate	15 (3·5)	22 (5·2)
Paclitaxel	20 (4·7)	12 (2·8)
Cisplatin	7 (1·6)	11 (2·6)
Pemetrexed disodium	7 (1·6)	8 (1·9)
Paclitaxel albumin	7 (1·6)	6 (1·4)
Gimeracil/oteracil potassium/tegafur	7 (1·6)	5 (1·2)
Irinotecan	6 (1·4)	6 (1·4)
Etoposide	3 (0·7)	2 (0·5)
Amrubicin	1 (0·2)	2 (0·5)
Irinotecan hydrochloride	2 (0·5)	1 (0·2)
Methotrexate	0	2 (0·5)
Mitomycin	0	2 (0·5)
Amrubicin hydrochloride	1 (0·2)	0
Cytarabine	0	1 (0·2)
Oxaliplatin	0	1 (0·2)
Targeted therapy	63 (14·8)	66 (15·5)
Erlotinib hydrochloride	14 (3·3)	27 (6·4)
Erlotinib	18 (4·2)	20 (4·7)
Bevacizumab	9 (2·1)	9 (2·1)
Afatinib	5 (1·2)	6 (1·4)
Ramucirumab	6 (1·4)	1 (0·2)
Osimertinib mesylate	1 (0·2)	5 (1·2)
Gefitinib	3 (0·7)	2 (0·5)
Crizotinib	2 (0·5)	2 (0·5)
Abemaciclib	2 (0·5)	1 (0·2)
Osimertinib	2 (0·5)	1 (0·2)
AUY922 (HSP90 inhibitor)	0	2 (0·5)
Blinded patritumab	1 (0·2)	1 (0·2)
Ceritinib	2 (0·5)	0
Trastuzumab emtansine	2 (0·5)	0
Aflibercept	1 (0·2)	0
BBI608 (cancer stem cell inhibitor)	1 (0·2)	0
BVD-523 (ERK inhibitor)	1 (0·2)	0
Cabozantinib	1 (0·2)	0
Cetuximab	0	1 (0·2)
Lurbinectedin	1 (0·2)	0
Ranibizumab	1 (0·2)	0
Vemurafenib	1 (0·2)	0
Vorinostat	1 (0·2)	0
Immunotherapy	19 (4·5)	73 (17·2)
Nivolumab	16 (3·8)	58 (13·6)
MEDI4736 (anti-PD-L1 monoclonal antibody)	0	7 (1·6)
L-DOS47 (anti-CEACAM6 AFAIKL2 immunoconjugate)	2 (0·5)	3 (0·7)
Lambrolizumab	0	4 (0·9)
Ipilimumab	0	2 (0·5)
Durvalumab	0	1 (0·2)
RO6958688 (T-cell bispecific monoclonal antibody)	1 (0·2)	0
Tremelimumab	0	1 (0·2)

Data are n (%), unless otherwise indicated. Patients were only counted once if they received more than one nonprotocol therapy of the same type. Patients were counted more than once if they received more than one type of the nonprotocol therapy. CEACAM6=carcinoembryonic antigen related cell adhesion molecule 6. ERK=extracellular signal–regulated kinase. HSP90=heat shock protein 90. PD-L1=programmed death-ligand 1.

Source: [Rittmeyer, Lancet 2017, appendix; Table S3][1]

POPLAR

Treatment Dosing Schedule

Atezolizumab was administered as an intravenous 1200 mg fixed dose (equivalent to 15 mg/kg for a patient with a body weight of 80 kg) every 3 weeks (21 ±2 days) until loss of clinical benefit or unacceptable toxicity. Docetaxel was administered intravenously at 75 mg/m^2 every 3 weeks, until unacceptable toxicity or disease progression, as assessed by the investigator. Forty-two percent of the patients randomized to the atezolizumab arm were treated beyond progression. No

docetaxel to atezolizumab cross-over was allowed.[1,5,39] In the POPLAR trial, patients were able to continue treatment beyond RECIST defined disease progression if the investigator deemed the patient to be receiving clinical benefit. Tumour assessments were done at baseline, then every 6 weeks until week 36 and every 9 weeks thereafter until patients discontinue treatment.

As of the 08-May-2015 data cut-off, 142 patients in the atezolizumab arm and 135 patients in the docetaxel arm received at least one dose of the study treatment. The median number of doses received in the atezolizumab group was 6 (range 1-28) and the median duration of treatment was 3.7 months (range 0-19). In the docetaxel group, the median number of doses was 4 (range 1-26) and the median duration of therapy was 2.1 months (range 0-17). Treatment duration was longer than 12 months in 30 (21.1%) patients in the atezolizumab group and 5 (3.7%) patients in the docetaxel group.[5]

Dose delays, reductions or modifications

No dose reductions for atezolizumab were reported in the POPLAR study.[7] Docetaxel dose modifications were performed according to the locally approved label. [39]

Concomitant and subsequent interventions

During the study, 92% of patients in the atezolizumab group and 96% of those in the docetaxel group were taking a concomitant or subsequent medication.[7]

Table 6.10 summarizes the types and frequencies of anti-cancer treatments received by the ITT population after discontinuation of study treatments. As the table shows, the proportion of the patients who received subsequent chemotherapy was higher in the atezolizumab group (37.5%) of patients) than in the docetaxel group (32.2%). Docetaxel was the most commonly used post-study chemotherapy agent, with 27.1% of patients treated in the atezolizumab group and 1.4% of those in the docetaxel group. None of the patients in the atezolizumab group received immunotherapy after disease progression. The proportion of the patients who received subsequent immunotherapy in the docetaxel group was 4.9%, with nivolumab being the most commonly used immunotherapy agent in this group. In addition, higher proportion of patients in the docetaxel group received at least one subsequent targeted therapy agent; Erlotinib was the most commonly used targeted therapy.[4]

Table 6.10: Post-study anti-cancer treatments in POPLAR trial (ITT population)

	Atezolizumab (n=144)	Docetaxel (n=143)
Total patients with at least one treatment	58 (40.3%)	59 (41.3%)
Overall total number of treatments	107	111
Chemotherapy: total patients with at least one treatment	54 (37.5%)	46 (32.2%)
Overall total number of treatments	87	76
Docetaxel	39 (27.1%)	2 (1.4%)
Gemcitabine*	12 (8.3%)	24 (16.8%)
Vinorelbine	4 (2.8%)	16 (11.2%)
Carboplatin	8 (5.6%)	9 (6.3%)
Pemetrexed‡	6 (4.2%)	9 (6.3%)
Paclitaxel	4 (2.8%)	5 (3.5%)
Cisplatin	4 (2.8%)	3 (2.1%)
Irinotecan§	3 (2.1%)	1 (0.7%)
Etoposide	1 (0.7%)	1 (0.7%)
Paclitaxel albumin	2 (1.4%)	0
Investigational drug BBI608	0	1 (0.7%)
Mitomycin	0	1 (0.7%)
NUC-1031 (gemcitabine protide)	0	1 (0.7%)
Immunotherapy: total patients with at least one treatment	0	7 (4.9%)
Overall total number of treatments	0	8
Nivolumab — no. (%)	0	3 (2.1%)
Atezolizumab — no. (%)	0	2 (1.4%)
AM0010 (pegylated recombinant human IL-10) — no. (%)	0	1 (0.7%)
Lambrolizumab — no. (%)	0	1 (0.7%)
MEDI4736 (anti-PD-L1 monoclonal antibody) — no. (%)	0	1 (0.7%)
Targeted therapy: total patients with at least one treatment	17 (11.8%)	21 (14.7%)
Overall total number of treatments	19	23
Erlotinib¶	8 (5.6%)	13 (9.1%)

Gefitinib	3 (2.1%)	1 (0.7%)
Afatinib	1 (0.7%)	2 (1.4%)
Ceritinib	1 (0.7%)	1 (0.7%)
Ramucirumab	2 (1.4%)	0
BB1608 (cancer stem cell inhibitor)	0	1 (0.7%)
Bevacizumab	1 (0.7%)	0
BGJ398 (FGFR inhibitor)	0	1 (0.7%)
Cetuximab	0	1 (0.7%)
Crizotinib	0	1 (0.7%)
Denosumab	1 (0.7%)	0
Dovitinib — no. (%)	0	1 (0.7%)
Panitumumab	1 (0.7%)	0
Poziotinib	0	1 (0.7%)
Unknown: total patients with at least one treatment	0	4 (2.8%)
Overall total number of treatments	0	4
Generic component(s) not known	0	2 (1.4%)
Investigational drug	0	2 (1.4%)

* Includes gemcitabine and gemcitabine hydrochloride.
† Includes vinorelbine and vinorelbine tartrate.
‡ Includes pemetrexed and pemetrexed disodium.
§ Includes irinotecan and irinotecan hydrochloride.
‖ Includes erlotinib and erlotinib hydrochloride.
Patients were only counted once if they received more than one nonprotocol therapy of the same type.
Patients were counted more than once if they received more than one type of the nonprotocol therapy.

Source: [Fehrenbacher, 2016, Appendix; Table S1][4]

c) Patient Disposition

OAK

Patient disposition for the OAK trial is presented in Figure 6.3. A total of 1225 patients with previously treated locally advanced or metastatic NSCLC were enrolled in the trial, and randomized to receive atezolizumab (n=613) or docetaxel (n=612). A total of 609 out of 613 patients in the atezolizumab group, and 578 out of 612 patients in the docetaxel group received their assigned study treatments and were included in the safety analysis. Four patients in the atezolizumab arm and 34 in the docetaxel arm did not receive the study treatment. Of the 1225 enrolled patients the first 850 patients (425 in the atezolizumab group and 425 in the docetaxel group) were included in the primary ITT efficacy analysis.[1]

As of 07-Jul-2016 data cut-off date (primary analysis), 58 (14%) patients in the atezolizumab group arm were continuing with the study treatments, compared to 3 (0.7%) in the docetaxel group. Sixty nine (16%) of the patients in the atezolizumab group and 75 (17.6%) of those in the docetaxel group had discontinued treatment and were in the survival follow up period. A total of 298 (70.1%) patients atezolizumab group and 374 (88.0%) in the docetaxel group had withdrawn from the study due to death; two patients in each group were lost to follow up; and 26 (6.1%) patients in the atezolizumab group and 48 (11.3%) patients in the docetaxel group had discontinued study due to a reason other than death.[1]

Protocol violations were reported in 16.5% of patients in the docetaxel arm and 19.8% of patients in the atezolizumab arm. The most common on-study protocol deviation was related to the category of “other procedural deviation significant for safety and/or efficacy”, with similar

frequency between the two study arms. This category included: missing lab or tumour assessment, tumour assessment performed out of window, failure to report a serious AE within 24 hours, delay in obtaining signature for informed consent form amendment or to allow continuation of treatment after disease progression. Additionally, three patients (0.7%) in the docetaxel arm versus 19 patients (4.5%) in the atezolizumab arm received "treatment beyond discontinuation criteria"; two patients in the docetaxel arm and one patient in the atezolizumab arm received a prohibited concomitant medication; two patients in the docetaxel arm had deviations in the category of "incorrect study treatment or wrong dose", of which one patient who was randomized to the docetaxel arm received atezolizumab.[39]

Figure.6.3: Disposition diagram of participants in OAK trial (Primary Population)

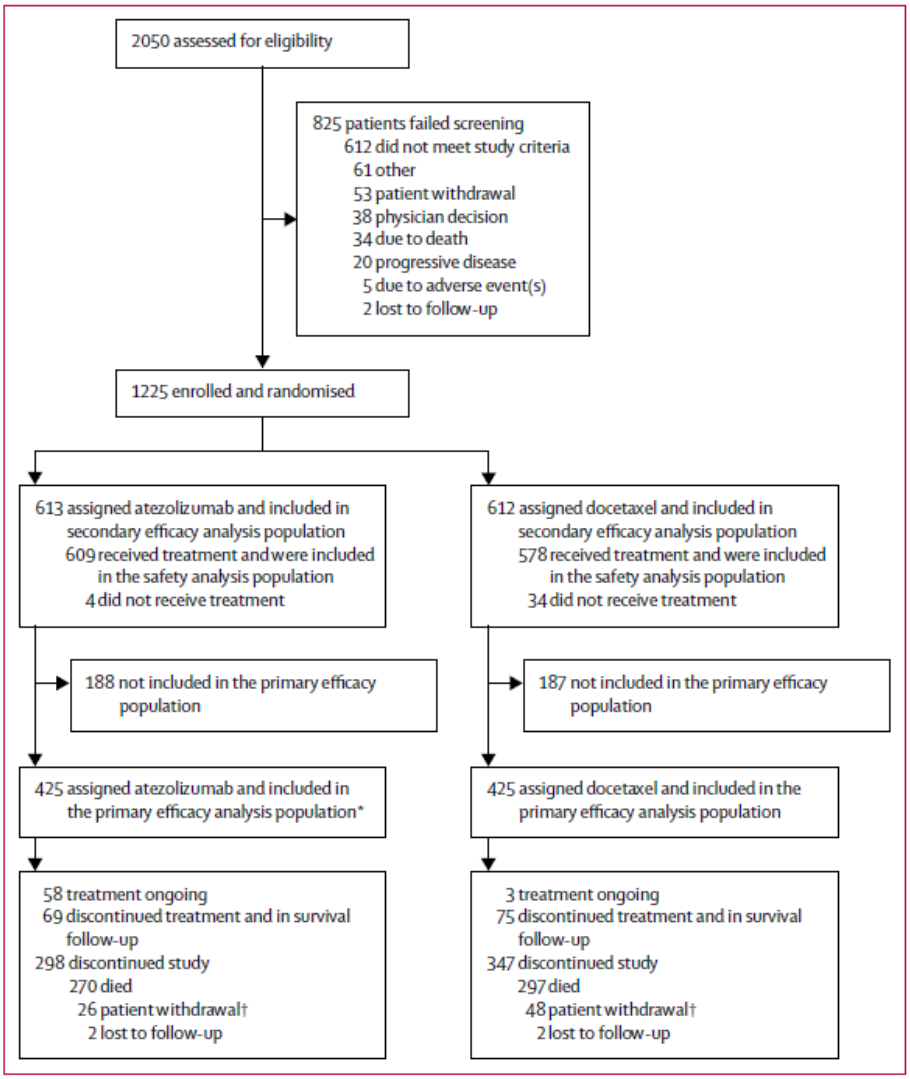


Figure 1: **Trial profile**
*One patient randomly assigned to docetaxel received atezolizumab. †The deaths of one patient in the atezolizumab group and of one patient in the docetaxel group were collected via public records. This is why the number of deaths for the overall survival analysis is 271 in the atezolizumab group and 298 in the docetaxel group and not 270 *vs* 297 as shown. These two patients are shown as patient withdrawal.

* **Source**: .[Rittmeyer, Lancet 2017; Figure 1][1]

POPLAR

Patient disposition for the POPLAR trial is presented in Figure 6.4. A total of 287 patients with previously treated with NSCLC were enrolled in the trial, and randomized to receive atezolizumab (n=144) or docetaxel (n=143).All randomized patients were included in the ITT analysis. A total of 142 out of 144 patients in the atezolizumab group, and 135 out of 142 patients in the docetaxel group received their assigned study treatments and were included in the safety analysis. Two patients in the atezolizumab arm and eight in the docetaxel arm did not receive the study treatment.[4]

As of the 08-May-2015 data cut-off, 24 (17%) patients in the atezolizumab group arm were continuing with the study treatments, compared to one (0.7%) in the docetaxel group. At the data cut-off date, 118 (83%) of 144 patients in the atezolizumab group had discontinued treatment; of which, 36 patients were in the survival follow up period, and 84 had dropped out of the study due to death (78 patients), patient withdrawal (5 patients), and lost to follow-up (one patient). Of the 143 patients in the docetaxel group, 134 (99%) patients had discontinued treatment; of which, 36 patients were in the survival follow up period, and 106 had dropped out of the study due to death (93 patients), patient withdrawal (12 patients), and lost to follow-up (one patient).[4]

Table6.4: Disposition diagram of participants in POPLAR trial

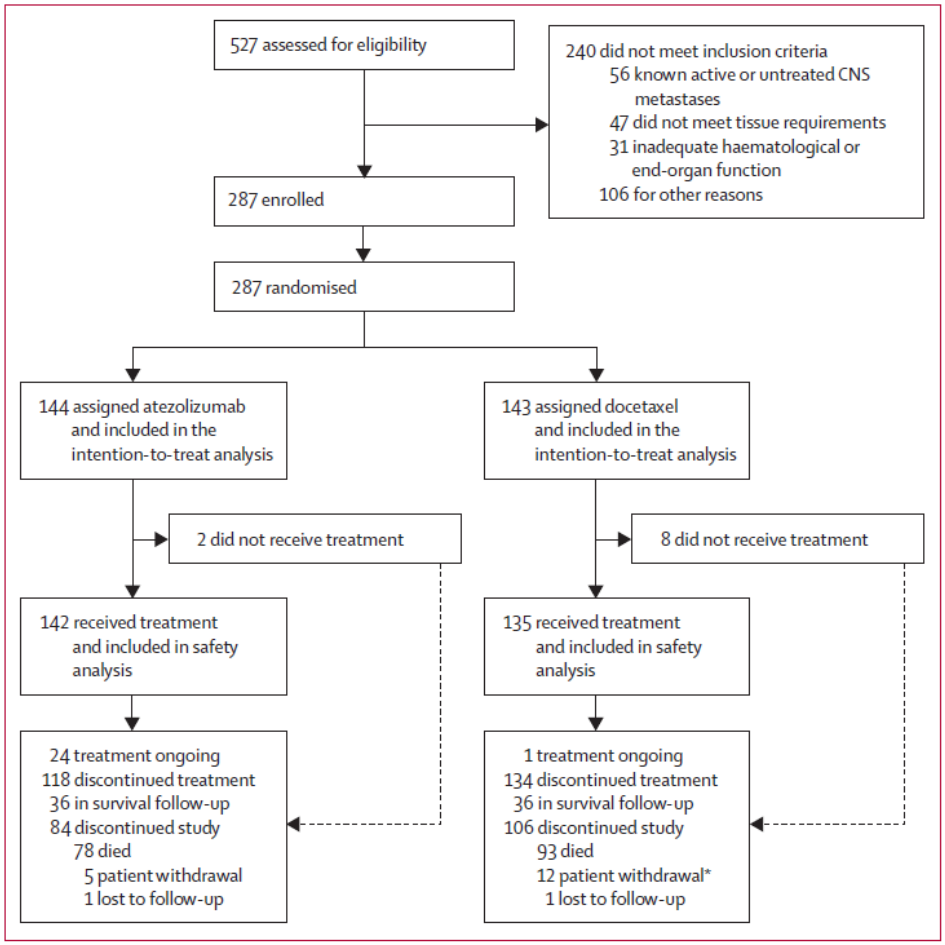


Figure 2: **Trial profile**
*Deaths determined from public records for two patients who withdrew from the docetaxel group.

*Deaths determined from public records for two patients who withdrew from the docetaxel group.

Source: [Fehrenbacher, Lancet 2016; Figure 3][4]

As the 08-May-2015 data cut-off date, major protocol deviations were reported in 37 (12.9%) patients (17 in the atezolizumab arm and 20 in the docetaxel arm). Fourteen patients (7 in the atezolizumab and 7 in the docetaxel arm) had at least one eligibility violation; and 24 patients (11 in the atezolizumab and 13 in the docetaxel arm) had at least one study procedure violation. More details are shown in Table 6.11.[39]

Table 6.11: Summary of major protocol deviations or violations in POPLAR trial

Summary of Major Protocol Deviations and Violations
Intent-to-Treat Patients
Protocol: GO28753 (Data Cut: 8May2015)

Deviation Category Types of Deviations	Docetaxel (N=143)	Atezolizumab (N=144)	All Patients (N=287)
Total number of patients with at least one deviation	20 (14.0%)	17 (11.8%)	37 (12.9%)
Overall total number of deviations	22	20	42
Eligibility Violations			
Total number of patients with at least one deviation	7 (4.9%)	7 (4.9%)	14 (4.9%)
Total number of events	8	8	16
Untreated and/or excluded CNS metastases	3 (2.1%)	1 (0.7%)	4 (1.4%)
Did not meet Laboratory requirements	1 (0.7%)	2 (1.4%)	3 (1.0%)
Excluded concurrent illness	2 (1.4%)	1 (0.7%)	3 (1.0%)
Treatment with prohibited medication within excluded window relative to randomization	0	3 (2.1%)	3 (1.0%)
Did not meet Prior NSCLC treatment requirements	1 (0.7%)	1 (0.7%)	2 (0.7%)
Prior excluded immunotherapy	1 (0.7%)	0	1 (0.3%)
Study Procedures Violations			
Total number of patients with at least one deviation	13 (9.1%)	11 (7.6%)	24 (8.4%)
Total number of events	14	12	26
Other procedural deviation significant for safety and/or efficacy	12 (8.4%)	10 (6.9%)	22 (7.7%)
Prohibited medication	0	2 (1.4%)	2 (0.7%)
Incorrect treatment or wrong dose	1 (0.7%)	0	1 (0.3%)

A patient will be only counted once if received more than one deviation of the same type.
A patient will be counted more than once if received more than one type of the deviation.
Atezolizumab patient 200005 reported receiving prohibited concomitant therapy/medication and this is reported as a Eligibility Violation and a Study Prodeccured Violation.
Data Cut-off: 8 May 2015; SDTM Data Extracted: 16 Jul 2015.

Source: [EPAR, page 84][39]

d) Limitations/Sources of Bias

Overall, both the OAK and POLAR trials were well-designed RCTs with clearly-defined study questions, appropriate randomization methods, and clearly defined study outcomes. However, the following study limitations should be taken into account when interpreting the results:

- OAK and POPLAR were open-label phase III and phase II trials, respectively. The open label nature of the trials might introduce the risk of reporting and performance biases, as the study participants and the investigators were aware of the treatment assignments. This could particularly be important in reporting of subjective outcomes by the patients (e.g., patient-reported HRQoL) and care providers (e.g., selective reporting of treatment-related AEs). The investigators and assessors may measure and report the AEs of the new drug more frequently and consider the AEs of the comparators as normal or acceptable, or vice versa. The observed differences in patient-reported outcomes demonstrated between arms in the OAK trial should also be interpreted with caution.

- Given the similar routes (i.e., intravenous injection) and intervals (i.e., every three weeks) of drug administration for atezolizumab and docetaxel, blinding both patients and investigators through the use of matching placebos could have prevented potential bias associated with their knowledge about treatment allocation.

- In the OAK trial, the open-label nature of the study could explain the difference in the rate of discontinuation of the study treatment by patient's request (dropout), which was 11% [48/425] of patients in the docetaxel arm compared to 6% [26/425] of those in the atezolizumab arm. Similarly, in the POPLAR trial, the higher percentage of drop-outs in the docetaxel arm (8% [12/143] versus 3% [5/144] in the atezolizumab arm) could be attributed to the lack of blinding. Differing dropout rates between the treatment arms could have led to biased results, especially if the distribution of potential covariates (e.g., characteristics of patients who discontinued treatment and/or the timing of dropouts) differed substantially between the study groups (missing not at random).

- In both trials, the assessments of tumor response and disease progression (ORR and PFS) were conducted by the investigators. The lack of independent assessment may expose the

trials to detection bias (i.e., systematic difference between the groups in assessment, diagnosis, or verification of study outcomes).

- According to the OAK and POPLAR statistical analysis plans, there was no type-I error adjustments for any of the secondary endpoint (i.e, PFS, ORR, and safety) analyses. Therefore, results of these analyses should be considered exploratory.

- In the OAK trial, a statistically significant OS benefit was observed in patients who were treated with atezolizumab. However, no difference in PFS was demonstrated. Although PFS has been used as a proxy for OS in trials of cancer treatments, the Clinical Guidance Panel noted that the discrepancy between PFS and OS had been reported with the use of other immune-checkpoint inhibitors that target the PD-1 or PD-L1; and that this discrepancy might be explained by a potentially delayed immune response to this class of cancer treatments.

- The incidence of grade 3 or 4 immune-related AEs (irAEs) was reported for patients on the atezolizumab arm only. This might be due to the fact that irAEs are mechanism based inflammatory toxicity events that occur after immunotherapy regimens, while they are not frequently observed with chemotherapy agents (including docetaxel).

- The current pCODR submission and its related publications focused on the primary efficacy results of the OAK trial (data from the first 850 out of 1225 enrolled patients, according to the trials statistical analysis plan). The manufacturer confirmed that the OAK secondary analysis (1225 ITT population) had been conducted, but a publication on the final efficacy analysis is not yet confirmed.[7]

External validity

- The included trials included advanced or metastatic NSCLS patients with good performance status (i.e., ECOG performance score 0 or 1). This inclusion criterion may reduce the generalizability of the trial results. However, the Clinical Guidance Panel felt that the trial results were generalizable to patients with ECOG performance score 2. They based their opinion based on similar previous decisions that generalized trial evidence for pembrolizumab and nivolumab into patients with a ECOG performance score 2, as well as a Canadian study using nivolumab in sicker patients (i.e., ECOG performance score 2).

- To assess the efficacy and safety of atezolizumab in locally advanced or metastatic NSCLCT, both OAK and PPOPLAR trials used docetaxel as comparator. Other potentially relevant, and clinically important, comparators (i.e., immunotherapy agents such as nivolumab and pembrolizumab) were not assessed in the included trials. Notably, the CGP indicated that the trials used to determine the efficacy and safety of these other immunotherapies were conducted during the same time as the OAK and POPLAR trials. The Manufacturer has submitted a network meta-analysis (NMA) report that indirectly compares atezolizumab to other pharmacological interventions used as second or higher lines of treatment for locally advanced/metastatic NSCLC. A summary and critical appraisal of the Manufacturer's NMA can be found in Section 7 of this report.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

OAK

Efficacy Outcomes

Overall Survival

OS was the primary outcome in the OAK trial, defined as the time from randomization to death from any cause.[6] OS was compared between the treatment groups using a stratified log-rank test at the two-sided significance level. The Kaplan-Meier approach was used to estimate the median overall survival; the Brookmeyer-Crowley methodology was used to estimate 95% confidence intervals (CIs). The hazard ratio (HR) was estimated with a stratified Cox regression analysis. Stratification factors were the same used for randomization (i.e., PD-L1 expression levels, number of previous chemotherapy regimens, and histology). Patients not reported as having died at the time of analysis were censored at the date they were last known to be alive. Patients without post-baseline information were censored at the randomization date plus one day.[1]

The results of primary OS analysis are summarized in Table 6.12.

At the 07-Jul-2016 primary data cut-off date, after a median follow-up of 21 months, 569 deaths had occurred in the primary ITT population (271 of 425 patients in the atezolizumab group and 298 of 425 patients in the docetaxel group). The median OS was estimated to be statistically greater in the atezolizumab group (13.8 months; 95% CI 11.8, 15.7), when compared with that in the docetaxel group (9.6 months; 95% CI 8.6, 11.2), and the stratified HR was 0.73 (95% CI 0.62, 0.87; p=0·0003). In the TC1/2/3 or IC1/2/3 sub-population, 300 patients had died at the primary data cut-off date (151 of 241 patients in the atezolizumab group and 149 of 222 patients in the docetaxel group). There was a statistically significant improvement in median OS for patients in the atezolizumab group (15.7 months; 95% CI 12.6, 18.0), when compared with that in the docetaxel group (10.3 months; 95% CI 8.8, 12.0). The stratified HR was 0.74 (95% CI 0.59, 0.94; p=0·0102).[1]

Table 6.12: Primary analyses of overall survival in the OAK trial (ITT population and PD-L1 subgroups)

Study groups	ITT population		TC1/2/3 or IC1/2/3 subgroup	
	Atezolizumab (N=425)	Docetaxel (N=425)	Atezolizumab (N=241)	Docetaxel (N=222)
Deaths, n (%)	271 (64)	298 (70)	151 (63)	149 (67)
12-month OS (%)	55	41	58	43
18-month OS (%)	40	27	44	29
Median OS, months (95% CI)	13.8 (11.8,15.7)	9.6 (8.6,11.2)	15.7 (12.6, 18.0)	10.3 (8.8, 12.0)
HR (95% CI) p-value	0.73 (0.62, 0.87) p=0·0003		0.74 (0.59, 0.94) p=0.0102	

CI = confidence interval; **HR** = hazard ratio; **IC** = PD-L1 expression on tumour-infiltrating immune cells; **ITT** = intention-to-treat; **N** = number randomized; **n**= number of events; **OS**= overall survival; **TC** = PD-L1 expression on tumour cells

Data cut-off date: 07-Jul-2016

Source: [Rittmeyer, Lancet 2017][1]

Overall survival subgroup analyses

Subgroup analyses of OS were performed to determine the consistency of the treatment effect according to the PD-L1 expression levels and other key baseline characteristics of the study population. The HRs from these analyses were estimated with an un-stratified Cox regression analysis, due to the exploratory nature of subgroup analyses and small sample sizes in specific subgroups.[1] The results of primary subgroup analyses are summarized in Figure 6.6.

The OS benefit of atezolizumab was consistent across the pre-defined PD-L1 expression subgroups. OS improvement was observed in all PD-L1 expression subgroups, including the PD-L1 low or undetectable (TC0 and IC0) subgroup. Patients with high PD-L1 expression (TC3 or IC3 subgroup) gained the greatest benefit from atezolizumab (median OS= 20.5 months; 95% CI 17·5, not evaluable) compared to docetaxel (median OS=8.9 months; 95% CI 5.6, 11.6). However, the interaction terms used for assessing subgroup and treatment effect interactions, in the Cox proportional hazard model, indicated that PD-L1 expression might be an effect modifier of treatment effect on OS (p=0.0086).[1] Therefore, the investigators performed an analysis of mutually exclusive subgroups to assess the independent contribution of PD-L1 expression on the treatment effect. In the TC1/2/3 and IC0 subgroup, the median overall survival was 13.2 months (95% CI 7.8, 20.5) with atezolizumab and 12.0 months (3.7–14.7) with docetaxel (HR= 0.72; 95% CI 0.36,1.45). In the TC0 and IC1/2/3 subgroup, the median OS was 14.3 months (95% CI 10.6, 18.4) with atezolizumab and 9.8 months (7.3, 13.7) with docetaxel (HR=0.73; 95% CI 0.52, 1.02). The estimates of HR in both subgroups were similar to those in the ITT analysis. However, the 95% CIs included the null hypothesis value of 1 (possibly due to smaller sample sizes); thus the observed benefit was considered to be inconclusive.[1] .

Additional subgroup analyses were performed based on the key baseline variables (Figure 6.5). As the figure shows, OS HRs favoured atezolizumab across predefined subgroups, except the subgroup of patients with EGFR mutations for which the HR was greater than 1 (HR = 1.24; 95% CI 0.71, 2.18); However, the point estimate was inconclusive as its 95% CI included 1.[1]

A supplementary report of the OAK data, which was presented in the European Society for Medical Oncology (ESMO) 2017 Congress, presented the results of subgroup analyses based on the patients' response status per RECIST v1.1.[37] According to this report, atezolizumab was associated with a greater OS benefit, when compared to docetaxel, regardless of patients' overall response status. Patients in the atezolizumab group with and objective (complete or partial) response derived the greatest survival benefit when compared with docetaxel-treated patients with an objective response (HR = 0.32; 95% CI 0.16, 0.63). The OS benefit was also observed with atezolizumab in the subgroups of patients with stable disease (HR = 0.70; 95% CI 0.53, 0.92) and progressive disease (HR = 0.72; 95% CI 0.56, 0.93).[37]

Figure 6.5: Forest Plots of overall survival in OAK subgroups

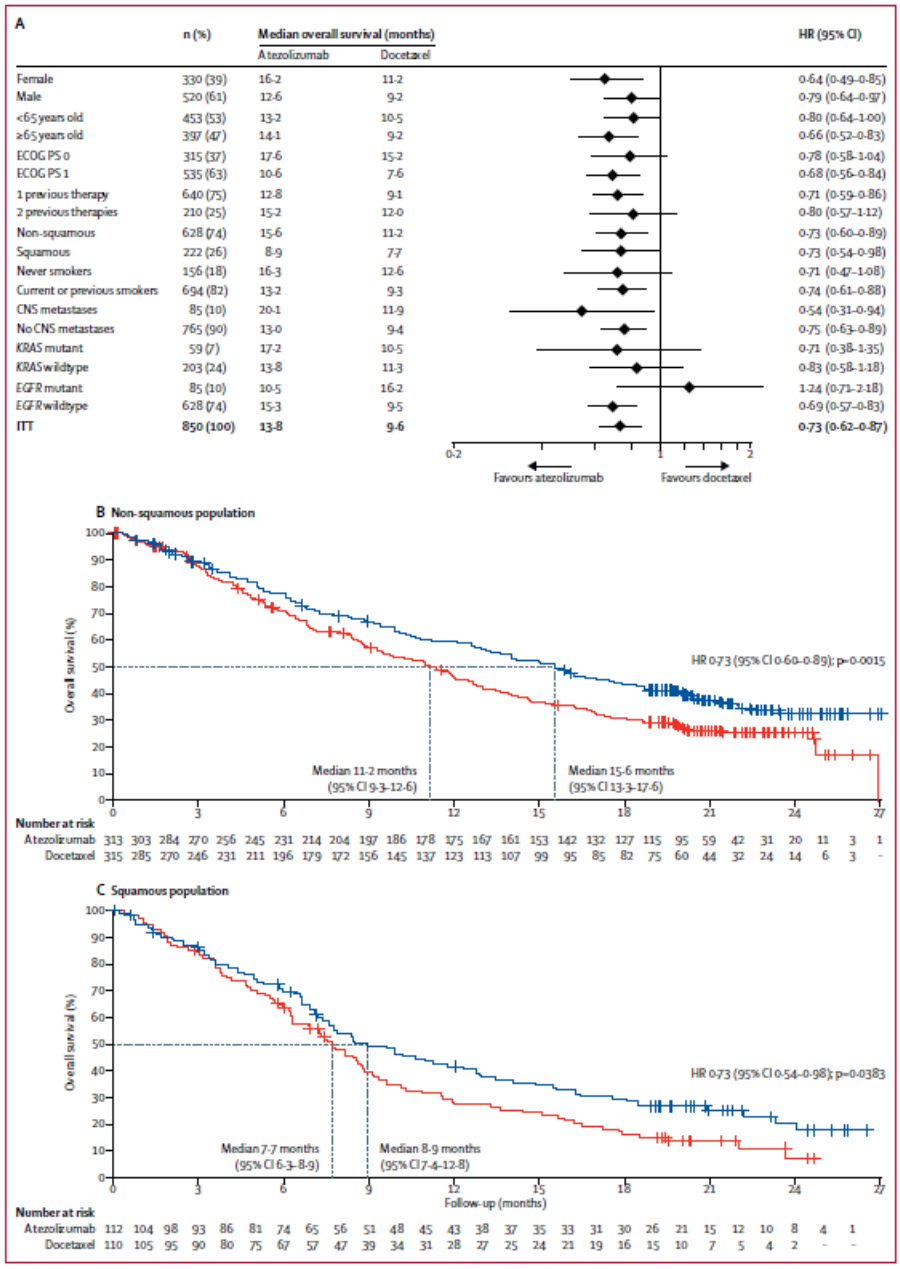


Figure 3: Overall survival in prespecified subgroups
(A) Median overall survival was estimated by Kaplan-Meier analysis. Stratified for ITT and unstratified for subgroups. (B) Kaplan-Meier estimates in the non-squamous histology subgroup (unstratified). (C) Kaplan-Meier estimates in the squamous histology subgroup (unstratified). ECOG PS=Eastern Cooperative Oncology Group performance status. HR=hazard ratio. ITT=intention-to-treat.

CI = confidence interval; **CNS** = central nervous system; ECOG = Eastern Cooperative Oncology Group; **HR** = hazard ratio; **IC** = PD-L1 expression on tumour-infiltrating immune cells; **ITT** = intention-to-treat; **N** = number randomized; **n**= number of events; **OS**= overall survival; **TC** = PD-L1 expression on tumour cells

Median overall survival was estimated by Kaplan-Meier analysis. Stratified for ITT and unstratified for subgroups

Source: [Rittmeyer, Lancet 2017; Figure 3][1]

Progression-free Survival

PFS was a secondary outcome in the OAK trial, defined as the time from randomization to investigator-assessed disease progression or death from any cause, whichever occurred first.[6] Disease progression was determined based on the investigator's assessment using the Response Evaluation Criteria in Solid Tumours (RECIST; version 1.1). PFS curves for the two treatment groups were generated using the Kaplan-Meier method, and PFS was compared between the two study arms using a stratified log-rank test. Patients who were alive and have not experienced disease progression at the time of analysis were censored at the time of the last tumour assessment. Patients with no post-baseline tumour assessment were censored at the randomization date plus one day.[6]

As of 07-Jul-2016 data cut-off date, the median PFS rate was 2.8 months (95% CI 2.6, 3.0) for atezolizumab and 4.0 months (95% CI 3.3, 4.2) for docetaxel (Table 6.13); with the PFS curves crossing at about 6 months. However, the stratified HR indicated that PFS was not statistically different between the treatment groups (HR = 0.95; 95% CI 0.82, 1.10; p=0.49).[1] Similar results were observed in the TC1/2/3 and IC1/2/3 sub-population. The median PFS rate was 2.8 months (95% CI 2.6, 4.0) for atezolizumab and 4.1 months (95% CI 2.9, 4.3) for docetaxel (HR= 0.91; 95% CI 0.74, 1.12; p=0.38).[1]

Objective Response Rate

Objective response rate (ORR) was defined as the percentage of patients who achieved either a confirmed complete response (CR) or partial response (PR) by investigators according to RECIST 1.1 criteria as their best confirmed response, relative to all randomized patients. For each study arm, estimates of ORR and its 95% CI were calculated (for the ITT population and PD-L1 subpopulations) using the Clopper-Pearson method. ORR was compared between the two arms using the stratified Mantel-Haenszel test, with the same stratification factors as used in the primary analysis of OS (i.e., PD-L1 expression levels, number of previous chemotherapy regimens, and histology). Normal approximation to the binomial distribution was used to estimate the 95% CIs for the difference in ORRs between the two study groups.[6]

At the 07-Jul-2016 data cut-off date, the proportion of patients with an objective response in the ITT population was similar between the two treatment groups. ORR was reported to be 14% (58/425 patients) and 13% (57/425 patients) in the atezolizumab and docetaxel arms, respectively (Table 6.13).However, a higher proportion of patients in the docetaxel arm had stable disease (42%) than in the atezolizumab arm (35%). In the TC1/2/3 and IC1/2/3 sub-population, ORR was 18% (43/241 patients) with atezolizumab and 16 % (36/222 patients) with docetaxel. Similar to the ITT population, the proportion of patients who had a stable disease was higher in the docetaxel arm (38% versus 33% in the atezolizumab arm).[1]

Duration of response

DOR was defined as the time from the first occurrence of a confirmed objective response to the time of disease progression, as determined by the investigator using RECIST v1.1 criteria, or death, whichever occurred first. Kaplan-Meier method was used to estimate duration of response among patients with an objective response.[6]

The median DOR in the ITT population was longer with atezolizumab (16·3 months; 95% CI 10.0, not evaluable) than with docetaxel (6·2 months; 95% CI 4.9, 7.6). The stratified HR was statistically significant (HR = 0.34; 95% CI 0.21, 0.55; p<0.0001). Similarly, in the TC1/2/3 and IC1/2/3 sub-population, the median DOR was 16.0 months (95% CI 9.7, not evaluable) with

atezolizumab and 6.2 months (95% CI 4.9, 9.2) with docetaxel (HR = 0.38; 95% CI 0.22, 0.65; p=0.0003)(Table 6.13).[1]

Table 6.13: Primary Analyses of secondary efficacy outcomes in OAK trial, ITT and PD-L1 selected groups

	Atezolizumab (n=425)	Docetaxel (n=425)	HR (95% CI)	p value
Progression-free survival (ITT population)				
Patients with event (%)	380 (89%)	375 (88%)	0·95 (0·82–1·10)	0·49
Median (months; 95% CI)	2·8 (2·6–3·0)	4·0 (3·3–4·2)	..	..
Objective response rate (ITT population)				
Objective response (%)	58 (14%)	57 (13%)	..	..
Complete response (%)	6 (1%)	1 (<1%)	..	..
Partial response (%)	52 (12%)	56 (13%)	..	..
Stable disease (%)	150 (35%)	177 (42%)	..	..
Progressive disease (%)	187 (44%)	117 (28%)	..	..
Missing or unevaluable (%)	30 (7%)	74 (17%)	..	..
Duration of response (ITT population)*				
Median (months; 95% CI)	16·3 (10·0–NE)	6·2 (4·9–7·6)	0·34 (0·21–0·55)	<0·0001
Progression-free survival (TC1/2/3 or IC1/2/3)				
Patients with event (%)	216/241 (90%)	193/222 (87%)	0·91 (0·74–1·12)	0·38
Median (months; 95% CI)	2·8 (2·6–4·0)	4·1 (2·9–4·3)	..	..
Objective response (TC1/2/3 or IC1/2/3)				
Objective response	43/241 (18%)	36/222 (16%)	..	..
Complete response	5/241 (2%)	1/222 (<1%)	..	..
Partial response	38/241 (16%)	35/222 (16%)	..	..
Stable disease	79/241 (33%)	85/222 (38%)	..	..
Progressive disease	102/241 (42%)	59/222 (27%)	..	..
Missing or unevaluable	17/241 (7%)	42/222 (19%)	..	..
Duration of response (TC1/2/3 or IC1/2/3)†				
Median (months; 95% CI)	16·0 (9·7–NE)	6·2 (4·9–9·2)	0·38 (0·22–0·65)	0·0003

HR was stratified for progression-free survival in the ITT and TC1/2/3 or IC1/2/3 populations; unstratified for other subgroups and duration of response. *n=58 for the atezolizumab group and n=57 for the docetaxel group. †n=43 for the atezolizumab group and n=36 for the docetaxel group. HR=hazard ratio. IC=tumour infiltrating immune cells. ITT=intention-to-treat. NE=not evaluable. TC=tumour cell.

Table 2: **Summary of key efficacy results**

Source: .[Rittmeyer, Lancet 2017; Table 2][1]

Quality of Life

Health-related quality of life (HRQoL) was assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaires (EORTC QLQ-C30 and QLQ-LC13).[1] The questionnaires were used to determine time to deterioration (TTD), which was defined as the time from baseline to the first time the patient's score shows a 10 points or higher increase above baseline in any of the EORTC transformed scores for the following patient-reported outcomes: cough, dyspnea, chest pain, or arm/shoulder pain, whichever occurred first.[6] A 10-point or higher score change within a patient group was considered to be the threshold for clinically meaningful change from the baseline.[2,6] Only patients with a baseline assessment and at least one on-treatment post-baseline QoL assessment were included in the analysis.[5]

A recent presentation at the International Association for the Study of Lung Cancer (IASLC)'s 18th World Conference on Lung Cancer (October 2017) reported on the HRQoL and post-hoc analyses of patient reported outcomes from the Oak trial.[2] Based on this report, at the baseline, 98.1% of

patients in the atezolizumab group and 96.5% of those in the docetaxel group completed the EORTC QLQ-C30 questionnaire. The completion rate was reported to be higher than 80% for all cycles through Cycles 27 and 23 in the atezolizumab and docetaxel arms, respectively.[2]

Baseline quality of life scores

Baseline HRQoL scores from Day 1 of Cycle 1 are shown in Table 6.14; As the table shows, the baseline scores were similar between the two arms for all patient-reported outcomes, and patients in both atezolizumab and docetaxel groups reported moderate-to high functioning and global health scores (>60).[2]

Table 6.14: Baseline quality of life scores in the OAK trial

	Docetaxel		Atezolizumab	
	n	Mean (SD)	n	Mean (SD)
EORTC QLQ-C30 patient functioning scales *Higher scores indicate greater functioning (scale 0–100)*				
Global health status	387	60.55 (22.25)	410	61.24 (22.31)
Physical functioning	390	73.27 (22.58)	413	74.46 (20.66)
Emotional functioning	390	75.83 (22.59)	411	76.55 (21.77)
Role functioning	388	70.92 (30.68)	413	73.61 (29.13)
Cognitive functioning	390	83.38 (20.68)	411	85.16 (19.16)
Social functioning	389	74.16 (26.92)	411	77.41 (26.13)
EORTC QLQ-C30 Symptom Scales *Lower scores indicate milder symptoms (scale 0–100)*				
Fatigue	390	37.59 (25.69)	413	36.21 (23.92)
Nausea/vomiting	389	8.01 (16.34)	413	7.59 (16.35)
Pain	390	29.70 (29.45)	413	29.98 (29.72)
Dyspnea	389	33.50 (31.11)	412	32.04 (28.73)
Insomnia	388	28.87 (30.55)	413	26.15 (28.72)
Appetite loss	390	26.58 (31.57)	413	22.92 (29.41)
Constipation	388	19.93 (27.39)	410	16.50 (26.81)
Diarrhea	388	5.84 (13.77)	411	7.22 (17.86)
Financial impact	387	20.76 (27.61)	411	18.09 (28.32)
EORTC QLQ-LC13 symptom scales *Lower scores indicate milder symptoms (scale 0–100)*				
Dyspnea	386	28.55 (23.21)	407	26.78 (22.43)
Coughing	383	38.73 (29.64)	406	37.27 (27.23)
Haemoptysis	386	4.32 (13.32)	406	3.86 (12.12)
Sore mouth	387	5.68 (16.34)	404	4.95 (15.32)
Dysphagia	387	6.20 (17.52)	406	5.09 (15.05)
Peripheral neuropathy	386	19.26 (28.94)	406	19.21 (27.77)
Alopecia	384	13.89 (27.95)	405	14.32 (29.07)
Chest pain	385	17.92 (25.33)	403	19.52 (26.49)
Arm/shoulder pain	384	20.49 (28.85)	405	20.16 (27.09)
Pain in other parts	373	27.52 (30.41)	402	27.94 (31.52)

EORTC = European Organization for Research and Treatment of Cancer; **QLQ** = Quality of Life Questionnaire
Source: Full-text conference poster provided by Hoffmann-La Roche Limited [Bordoni, IASLC 2017][2]

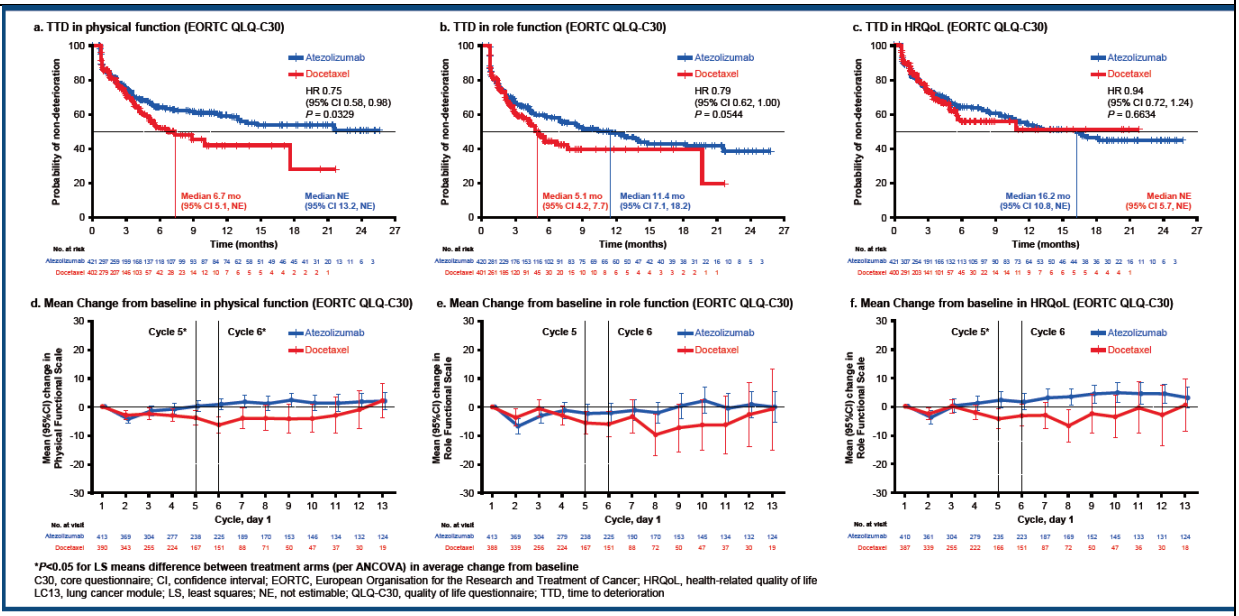
Time to deterioration

Figure 6.6 illustrates the time to deterioration in patient-reported function and global QoL, as measured by the EORTC QLQ-C30. As can be seen in the figure, atezolizumab delayed time to

deterioration in physical functioning (HR=0.75; 95% CI 0.58, 0.98; p=0.0329) and role functioning (HR=0.79; 95% CI 0.62, 1.00; p=0.0544). However, there was no statistically significant differences between the atezolizumab and docetaxel arms in terms of time to deterioration in global QoL (HR= 0.94; 95% CI 0.72, 1.24).[2]

A prolonged time to deterioration in patient-reported chest pain, as measured by the EORTC QLQ-LC13, was reported in the atezolizumab group, when compared to the docetaxel group(HR=0.71; 95% CI 0.49, 1.05; median not reached in either group). Time to deterioration of other lung cancer symptoms (i.e., cough, dyspnoea, and arm or shoulder pain) was reported to be similar between the atezolizumab and docetaxel arms.[2,39]

Figure 6.6: Time to deterioration of patient-reported functioning and health-related quality of life in the OAK trial



*P<0.05 for LS means difference between treatment arms (per ANCOVA) in average change from baseline
C30, core questionnaire; CI, confidence interval; EORTC, European Organisation for the Research and Treatment of Cancer; HRQoL, health-related quality of life
LC13, lung cancer module; LS, least squares; NE, not estimable; QLQ-C30, quality of life questionnaire; TTD, time to deterioration

Source: : Full-text conference poster provided by Hoffmann-La Roche Limited [Bordoni, IASLC 2017][2]

Mean change from the baseline

The mean differences between the study groups, in terms of average changes in HRQoL scores, from the baseline, are presented in Table 6.15 and Figure 6.6. Patients in the atezolizumab group reported numerically improved HRQoL from the baseline starting around Cycle 3 and continuing until Cycle 13 (the point at which fewer than 25% of patients who were evaluable for patient-reported outcomes had remained in the study).[2]

Numerical benefits, favouring atezolizumab, were also observed in physical function and role function as early as Cycle 4 (Figure 6.6). The post-hoc analysis at Cycle 5 and 6 (one cycle=21 days) demonstrated that the average changes from baseline were statistically greater in the atezolizumab arm for HRQoL (Cycle 5, p=0.015), physical functioning (Cycle 5, p=0.029; Cycle 6, p<0.0001) and social functioning (Cycle 6, p=0.032).(Table 6.15) When comparing the average change from baseline between the atezolizumab and docetaxel groups, significantly fewer atezolizumab-treated patients experienced clinically meaningful worsening in diarrhea (Cycle 5, p=0.048), sore mouth (Cycles 5 and 6, p<0.0001 for both cycles), dyspnea (Cycle 5, p=0.032; Cycle

6, p= 0.014), peripheral neuropathy (Cycles 5 and 6, p<0.0001 for both cycles), and alopecia (Cycles 5 and 6, p<0.0001 for both cycles) during treatment (Table 6.15).[2]

Table 6.15: Changes from the baseline in health-related quality of life and patient-reported function in the OAK trial

	By Cycle 5		By Cycle 6	
	LS means difference between treatment arms (average change from baseline)	P value	LS means difference between treatment arms (average change from baseline)	P value
EORTC QLQ-C30 Global Health Status and Function Scales (positive values indicate greater improvement with atezolizumab over docetaxel)				
Global Health Status	4.32*	p=0.0151	3.08	p=0.1257
Physical Function	3.33*	p=0.0290	6.64*	p<0.0001
Role Function	2.93	p=0.1959	4.72	p=0.0542
Emotional Function	2.66	p=0.1110	1.92	p=0.2868
Cognitive Function	-0.67	p=0.6790	-1.08	p=0.5309
Social Function	3.25	p=0.1159	4.68*	p=0.0319
EORTC QLQ-C30 Symptom Scales (negative values indicate greater improvement with atezolizumab over docetaxel)				
Fatigue	-6.27*	p=0.0015	-7.66*	p=0.0003
Nausea/Vomiting	-0.37	p=0.7824	-0.18	p=0.9040
Pain	1.44	p=0.5132	-1.67	p=0.4727
Dyspnea	-4.70*	p=0.0317	-5.92*	p=0.0138
Insomnia	3.50	p=0.1675	0.83	p=0.7564
Appetite Loss	-2.94	p=0.1994	-4.49	p=0.0586
Constipation	-0.31	p=0.8772	-0.33	p=0.8816
Diarrhea	-3.14*	p=0.0482	-2.05	p=0.1748
EORTC QLQ-LC13 Symptom Scales (negative values indicate greater improvement with atezolizumab over docetaxel)				
Dyspnea	-1.66	p=0.3146	-4.80*	p=0.0140
Coughing	-2.60	p=0.2572	-1.38	p=0.5772
Sore Mouth	-7.29*	p<0.0001	-9.23*	p<0.0001
Dysphagia	-0.08	p=0.9595	-2.01	p=0.1575
Peripheral Neuropathy	-12.98*	p<0.0001	-15.71*	p<0.0001
Hemoptysis	-0.24	p=0.7365	-0.91	p=0.2080
Alopecia	-50.59*	p<0.0001	-47.04*	p<0.0001
Chest Pain	-0.91	p=0.6064	-0.58	p=0.7779
Arm/Shoulder Pain	-2.27	p=0.3177	-0.58	p=0.8109
Pain in Other Parts	0.94	p=0.7197	-1.05	p=0.7034

*Values that are significantly in favor of atezolizumab versus docetaxel

EORTC = European Organization for Research and Treatment of Cancer; **LS = least square; QLQ** = Quality of Life Questionnaire

Source: [Bordoni, IASLC 2017(published abstract)][2]

Harms

Safety was a secondary outcome in the OAK trial. The incidence and severity of AEs and laboratory abnormalities were assessed based on the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. AEs that occurred within 30 days from the last study treatment were included in the analysis.[1] Immune-related AEs (irAEs) were defined using Medical Dictionary for Regulatory Activities Terminology (MedDRA) Preferred Terms that included both diagnosed immune conditions and signs and symptoms potentially representative of irAEs, regardless of investigator-assessed causality.[3]

Of the 1225 patients randomized in the OAK trial, 609 patients in the atezolizumab group and 578 patients in the docetaxel group received at least one dose of protocol-specified treatment and were included in the safety analysis. Table 6.16 summarizes safety outcomes and AEs that was reported in at least 10% of treated patients.

As of 07-Jul-2016 data cut-off, AEs of any cause were reported in 573/609 (94%) patients in the atezolizumab group and 555/578 (96%) patients in the docetaxel group. The most common AEs of any grade included fatigue (26.8% with atezolizumab versus 35.5% with docetaxel), decreased appetite (23.5% in each group), cough (23.2% with atezolizumab versus 18.2% with docetaxel), dyspnea (19.4% in each group), and asthenia (19.0% with atezolizumab versus 19.7% with docetaxel). The proportion of patients with treatment-related grade 3 or 4 AEs was 15% (90/609 patients) in the atezolizumab group and 43% (247/578 patients) in the docetaxel group (Table 6.16). One grade 5 AE was reported in the docetaxel group.[1]

The incidence rates for death due to AEs (2% in each group) and non-fatal serious AEs 32% with atezolizumab and 31% with docetaxel) were comparable between the two study groups. One treatment-related death occurred in the docetaxel group due to a respiratory tract infection. AEs leading to dose modifications, delay or interruption were reported in 25% (152/609) of patients who received atezolizumab and 34% (210/5787) of patients who received docetaxel. Eight percent (46/609) of patients in the atezolizumab group and 19% (108/578) of those in the docetaxel group discontinued treatment due to AEs (Table 6.16).[1]

The irAEs observed in the safety population are presented in Table 6.17. As the table shows, the rates of irAEs were comparable between the atezolizumab (31%; 190/609 patients) and docetaxel (31%; 178/578 patients) groups. Grade 1-2 irAEs occurred in 25%, and grade 3 or 4 occurred in 6% of 609 patients in the atezolizumab group. No grade 5 irAEs were reported.[3]

Table6.16: Adverse events in OAK trial (Safety Population)

	Atezolizumab (n=609)	Docetaxel (n=578)
All adverse events	573 (94%)	555 (96%)
Treatment-related adverse events	390 (64%)	496 (86%)
Grade 3 or 4 adverse events	227 (37%)	310 (54%)
Treatment-related grade 3 or 4 adverse events	90 (15%)	247 (43%)
All deaths	10 (2%)	14 (2%)
Treatment-related death	0	1 (<1%)*
Serious adverse events	194 (32%)	181 (31%)
Adverse events leading to withdrawal from treatment	46 (8%)	108 (19%)
Adverse events leading to dose modification, delay, or interruption	152 (25%)	210 (36%)

*One death due to a respiratory tract infection.

Adverse events in at least 10% of patients

Adverse event	Atezolizumab n=609		Docetaxel n=578	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Fatigue	163 (26·8)	17 (2·8)	205 (35·5)	23 (4·0)
Decreased appetite	143 (23·5)	2 (0·3)	136 (23·5)	9 (1·6)
Cough	141 (23·2)	2 (0·3)	105 (18·2)	1 (0·2)
Nausea	108 (17·7)	4 (0·7)	131 (22·7)	2 (0·3)
Diarrhoea	94 (15·4)	4 (0·7)	141 (24·4)	11 (1·9)
Asthenia	116 (19·0)	8 (1·3)	114 (19·7)	13 (2·2)
Dyspnoea	118 (19·4)	15 (2·5)	112 (19·4)	14 (2·4)
Anaemia	70 (11·5)	14 (2·3)	136 (23·5)	33 (5·7)
Alopecia	3 (0·5)	0	202 (34·9)	1 (0·2)
Constipation	107 (17·6)	2 (0·3)	82 (14·2)	1 (0·2)
Pyrexia	108 (17·7)	1 (0·2)	76 (13·1)	1 (0·2)
Peripheral oedema	54 (8·9)	1 (0·2)	82 (14·2)	3 (0·5)
Vomiting	74 (12·2)	2 (0·3)	62 (10·7)	4 (0·7)
Arthralgia	73 (12·0)	3 (0·5)	58 (10·0)	1 (0·2)
Myalgia	39 (6·4)	1 (0·2)	91 (15·7)	4 (0·7)
Back pain	67 (11·0)	7 (1·1)	42 (7·3)	4 (0·7)
Neutropenia	10 (1·6)	3 (0·5)	90 (15·6)	75 (13·0)
Peripheral neuropathy	24 (3·9)	0	65 (11·2)	7 (1·2)
Musculoskeletal pain	64 (10·5)	4 (0·7)	25 (4·3)	1 (0·2)
Stomatitis	19 (3·1)	1 (0·2)	63 (10·9)	11 (1·9)
Dysgeusia	18 (3·0)	0	58 (10·0)	0
Febrile neutropenia	1 (0·2)	1 (0·2)	62 (10·7)	62 (10·7)

Data are n (%), unless otherwise indicated.

Source:[Rittmeyer, Lancet 2016; Table 3 and Table S5 (appendix)][1] Reprinted from The Lancet, 389(10066), Rittmeyer A et al., Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial, 255-265, Copyright (2017), with permission from Elsevier.

Table6.17: Immune-related adverse events in OAK trial (Safety Populations)

irAE	OAK irAE efficacy analysis population (N = 823)[a]		OAK safety population (N = 1187)[a]	
	Atezolizumab (n = 422) n (%)	Docetaxel (n = 401) n (%)	Atezolizumab (n = 609) n (%)	Docetaxel (n = 578) n (%)
Any irAE	130 (31%)	122 (30%)	190 (31%)	178 (31%)
Diarrhea/colitis	72 (17%)	101 (25%)	97 (16%)	141 (24%)
Diarrhea	70 (17%)	97 (24%)	94 (15%)	141 (24%)
Colitis	1 (< 1%)	1 (< 1%)	2 (< 1%)	2 (< 1%)
Gastroenteritis	3 (1%)	5 (1%)	3 (1%)	5 (1%)
Hepatitis	30 (7%)	10 (3%)	57 (9%)	18 (3%)
Hypothyroidism	19 (5%)	2 (1%)	24 (4%)	2 (< 1%)
Diabetes mellitus	15 (4%)	20 (5%)	19 (3%)	28 (5%)
Hyperthyroidism	10 (2%)	1 (< 1%)	17 (3%)	1 (< 1%)
Pneumonitis	5 (1%)	2 (1%)	9 (2%)	4 (1%)
Meningoencephalitis	4 (1%)	0	5 (1%)	0
Guillain-Barre syndrome	2 (1%)	0	4 (1%)	0
Adrenal insufficiency	3 (1%)	0	3 (1%)	0
Ocular inflammatory toxicity	2 (1%)	0	3 (1%)	0
Hypophysitis	1 (< 1%)	0	1 (< 1%)	0
Pancreatitis	1 (< 1%)	0	1 (< 1%)	0

[a] Actual number of patients from the primary efficacy population (N = 850) and from the study safety population (N = 1225) who received ≥ 1 dose of study treatment.

irAE = immune-related adverse event; **N** = number randomized; **n** = number of events

Source:Full-text conference poster provided by Hoffmann-La Roche Limited [von Pawel, ESMO 2017][3]

POPLAR

Efficacy Outcomes

Overall Survival

OS was the primary outcome in the POPLAR trial, defined as the time from randomization to death from any cause.[4] OS was compared between the treatment groups using a stratified log-rank (stratified by histology, number of previous chemotherapy regimens, and tumour-infiltrating immune cell PD-L1 level). The Kaplan-Meier approach was used to estimate the median overall survival; the Brookmeyer-Crowley methodology was used to estimate 95% CIs. The HRs were estimated using a stratified Cox regression analysis. Stratification factors were the same used for randomization (see the factors above). Patients not reported as having died at the time of analysis were censored at the date they were last known to be alive. Patients without post-baseline information were censored at the randomization date plus one day.[4]

The results of primary OS analysis are summarized in Table 6.18.

At the 30-Jan-2015 data cut-off date, after a median follow-up time of approximately 12 months in both arms, 153 death events had occurred in the ITT population (71/144 patients in the atezolizumab group and 82/143 patients in the docetaxel group). The median OS improved by 1.9

months in the atezolizumab group (11.4 months versus 9.5 months in the docetaxel group); however, this improvement in the median survival was not statistically significant (HR = 0.77; 95% CI 0.55, 1.07; p-value =0.11).[5]

At the 08-May-2015 data cut-off date, after a median follow-up of 14·8 months (range 0.2 - 19.6) in the atezolizumab group and 15.7 months (range 0.1–18.7) in the docetaxel group, 173 deaths had occurred in the ITT population (78/144 patients in the atezolizumab group and 95/143 patients in the docetaxel group). The median OS was estimated to be statistically greater in the atezolizumab group (12.6 months; 95% CI 9.7, 16.4), when compared with that in the docetaxel group (9.7 months; 95% CI 8.6, 12.0), and the stratified HR was 0.73 (95% CI 0.54, 0.99; p=0·040). In the TC1/2/3 or IC1/2/3 population, there was a statistically significant improvement in median OS for patients in the atezolizumab group (15.5 months; 95% CI 11.0, not evaluable), when compared with that in the docetaxel group (9.2 months; 95% CI 7.3, 12.8). The stratified HR was 0.59 (95% CI 0.40, 0.85; p=0·0005).[4]

As of 01-Dec-2015 data cut-off, after a median follow up of 22 months, 90/144 (63%) patients in the atezolizumab group and 110/143 (77%) patients in the docetaxel group had died. The comparison of the median OS between the two study groups showed that atezolizumab significantly improved OS compared with docetaxel (12·6 versus 9·7 months; HR 0·69, 95% CI 0·52–0·92).[5]

Table 6.18: Primary analyses of overall survival in the POPLAR trial (ITT population and PD-L1 subgroups)

Study groups	ITT Population		TC1/2/3 or IC1/2/3 Subgroup	
	Atezolizumab (N=144)	Docetaxel (N=143)	Atezolizumab (N=93)	Docetaxel (N=102)
30-Jan-2015 data cut-off[5]				
Deaths, n (%)	71 (49)	82 (57)	NR	NR
Median OS, months (95% CI)	11.4 (9.7,NE)	9.5 (8.6,11.9)	NR	NR
HR (95% CI) p-value	0.77 (0.55, 1.07) p=0.11		NR	
08-May-2015 data cut-off[4]				
Deaths, n (%)	78 (54)	95 (66)		
Median OS, months (95% CI)	12.6 (9.7,16.4)	9.7 (8.6,12.0)	15.5 (11.0,NE)	9.2 (7.3,12.8)
HR (95% CI) p-value	0.73 (0.53, 0.99)† p=0.040		0.59 (0.40, 0.85) p=0.005	
01-Dec-2015 data cut-off[5]				
Deaths, n (%)	90 (63)	110 (77)	NR	NR
Median OS, months (95% CI)	12.6 (9.7,15.8)	9.7 (8.6,12.0)	NR	NR
HR (95% CI) p-value	0.69 (0.52, 0.92) p=NR		NR	

CI = confidence interval; **HR** = hazard ratio; **ITT** = intention-to-treat; **N** = number randomized; **n**= number of events; **OS**= overall survival

† There were discrepancies in reporting confidence intervals for HR (upper limit) between Fehrenbacher 2016 (reported above),[4] FDA Medical Reviews (0.73 ;95% 0.54, 1.00),[5] and the EPAR report (0.73; 95%CI 0.56, 0.80)[39]

Source: [FDA Medical Reviews; Fehrenbacher, Lancet 2016][4,5]

The results of the 3-year OS analysis (07-Apr-2017 data-cut-off) of the POPLAR trial was presented in IASLC's 18th World Conference on Lung Cancer (October 2017). Based on this report the 3-year survival in the atezolizumab group (n=144) was 18.7% compared with 10.0% (p=0.0419) in the docetaxel group (n=143).[38]

Overall survival subgroup analyses

The median OS was estimated by Kaplan-Meier analysis. An unstratified log-rank test was not performed in PD-L1 subgroups due to the small sample sizes. The HRs from these analyses were also estimated with an un-stratified Cox regression analysis.[4]

The OS benefit of atezolizumab increased with increasing PD-L1 IC levels, TC levels, or both. There was a statistically significant OS improvement, favoring atezolizumab, in the TC2/3 or IC2/3 (HR=0.54; 95% CI 0.33, 0.89; p=0·014) and TC1/2/3 or IC1/2/3 (HR=0.59; 95% CI 0.40, 0.85; p=0·005) subgroups. In the TC0 and IC0 subgroup, no statistically significant difference was observed between the atezolizumab and docetaxel groups (HR=1.04; 95% CI 0.62, 1.75; p=0·871).[4]

To assess the independent contribution of each level of PD-L1 expression, the investigators performed an analysis of mutually exclusive subgroups**.** The results of these subgroup analyses showed a numerical improvement in OS rates in the atezolizumab group in patients with PD-L1 expression on tumour cells only (TC1/2/3 and IC0 subgroup; HR= 0.37; 95% CI 0.12, 1.13) and those with PD-L1 expression tumour infiltrating immune cells only (IC1/2/3 and TC0 subgroup; HR= 0.63; 95% CI 0.36, 1.12).[4]

In the TC1/2/3 and IC0 subgroup, the median overall survival was 15 months (95% CI 7.8, 20.5) with atezolizumab and 12.0 months (3.7–14.7) with docetaxel (HR= 0.72; 95% CI 0.36,1.45). In the TC0 and IC1/2/3 subgroup, the median overall survival was 14.3 months (95% CI 10.6, 18.4) with atezolizumab and 9.8 months (7.3, 13.7) with docetaxel (HR=0.73; 95% CI 0.52, 1.02). The estimates of HR in both subgroups were similar to those in the ITT analysis. However, the 95% CIs included the null hypothesis value of 1; and the observed benefit is inconclusive.[4]

Additional subgroup analyses were performed based on the patients' best overall response status. In the subgroup of patients with a complete or partial response, the median OS was not reached in the atezolizumab group, and 16.6 months in the docetaxel group. The OS benefit in this subgroup was statistically significant (HR= 0.14; 95% CI 0.03, 0.66); while in the subgroup of patients with a stable disease, OS rates were comparable (HR= 0.79; 95% CI 0.54, 1.14).[4]

Progression-free Survival

PFS was a secondary outcome in the OAK trial, defined as the time from randomization to investigator-assessed disease progression (the first occurrence of RECIST v1.1) or death from any cause. PFS curves for the two treatment groups were generated using the Kaplan-Meier method, and the 95% CIs were generated using the Brookmeyer-Crowley method. PFS was compared between the two study arms using a stratified log-rank test. Patients who were alive without disease progression at the time of analysis were censored at the time of the last tumour assessment. Patients with no post-baseline tumour assessment were censored at the randomisation date plus one day.[4]

As of 08-May-2015 data cut-off date, after a median follow-up was 14·8 months in the atezolizumab group and 15·7 months in the docetaxel group, the median PFS rate was 2.7 months (95% CI 2.0, 4.1) for atezolizumab and 3.0 months (95% CI 2.8, 4.1) for docetaxel, with the PFS curves crossing at about 4 months. The stratified HR indicated that PFS was not statistically different between the treatment groups (HR = 0.94; 95% CI 0.72, 1.23; p=0.65).[4] Similar results were observed in the TC1/2/3 and IC1/2/3 sub-population. The median PFS rate was 2.8 months (95% CI 2.6, 5.5) for atezolizumab and 3.0 months (95% CI 2.8, 4.1) for docetaxel (HR= 0.85; 95% CI 0.63, 1.16; p=0.31.[4]

Objective Response Rate

ORR was defined as the percentage of patients who achieved either a confirmed complete or partial response (CR or PR) by investigators according to RECIST 1.1 criteria as their best confirmed response, relative to patients randomized. Estimates of ORR and its 95% CI, for the ITT population and PD-L1 subgroups, were calculated using the Clopper-Pearson method. ORR was compared between the two arms using the stratified Mantel-Haenszel test, with the same stratification factors as used in the analysis of OS (i.e., PD-L1 expression levels, number of previous chemotherapy regimens, and histology). Normal approximation to the binomial distribution was used to estimate the 95% CIs for the difference in ORRs between the two study groups.[6]

As of 08-May-2015 data cut-off date, 21/144 (14.6%) patients in the atezolizumab group and 21/143 (14.7%) patients in the docetaxel group achieved an objective response. At the data cut-off date, 12/21 (57%) responders in the atezolizumab group and 5/21 (24%) of responders in the docetaxel group had an ongoing response.[4] As of 01-Dec-2015 data cut-off, ORR was 15.3% (95% CI 9.8, 22.2) in the atezolizumab group and 14.7% (95% CI 9.3, 21.6) in the docetaxel group. Additional ORR data obtained at 30-Jan-2015 and 01-Dec-2015 data cut-off dates is presented in Table 6.19.[6]

Table 6.19: Objective response rate and duration of response in POPLAR trial (ITT population)

	Atezolizumab (n=144)	Docetaxel (n=143)
ORR as of the primary survival analysis (cutoff: 1/30/2015)		
Best Overall Response, n (%)		
CR	0	0
PR	21 (14.6%)	22 (15.4%)
SD	57 (39.6%)	61 (42.7%)
PD	54 (37.5%)	40 (28%)
NE or Missing	12 (8.3%)	20 (14.0%)
ORR, n (%)	21 (14.6%)	22 (15.4%)
(95% CI)	(9.3, 21.4)	(9.9, 22.4)
Nominal P-value (chi-square)	0.85	
Duration of response	n=21	n=22
Median (95% CI), in months	NR (5.6, NE)	7.8 (2.9, 12.9)
Range	2.1+, 13.2+	1.4+, 12.9
ORR as of the 2nd survival update (cutoff: 12/1/2015)		
Best Overall Response, n (%)		
CR	1 (0.7%)	0
PR	21 (14.6%)	21 (14.7%)
SD	53 (36.8%)	50 (35.0%)
PD	59 (41.0%)	50 (35.0%)
NE or Missing	10 (6.9%)	22 (25.4%)
ORR, n (%)	22 (15.3%)	21 (14.7%)
(95% CI)	(9.8, 22.2)	(9.3, 21.6)
Duration of response	n=22	n=21
Median (95% CI), in months	18.6 (11.6, NE)	7.2 (5.6, 12.5)
Range	2.7, 23.6+	1.5+, 19.8+

NR: Not reached; NE: not evaluable; +: censoring

[Source: POPLAR CSR Tables 50 and Supplemental results report Table 6]

CI = confidence interval; **CR** = complete remission; **ITT** = intention-to-treat; **ORR=** objective response rate; **OS** = overall survival; **PD** = progressive disease; **PFS** = progression-free survival; **PR** = partial remission; **SD** = stable disease

Source: [FDA Statistical Reviews, page 34][6]

In the long-term (3-year) analysis of POPLAR data (07-April-2017 data cut-off), the ORR was 15 % in both atezolizumab and docetaxel arms in the ITT population, but the median duration of response was reported to be 22.3 months (95 % CI 11.6, 31.1) in the atezolizumab group, as compared with 7.2 months (95 % CI: 5.8, 12.2) in the docetaxel group.[38]

Duration of response

DOR was defined as the time from the first occurrence of a confirmed objective response to the time of disease progression, as assessed by the investigator using RECIST v1.1 criteria, or death, whichever occurred first. Kaplan-Meier method was used to estimate duration of response among patients with an objective response.[6] Patients without assessment after baseline were considered non-responders. DOR was censored at the date of the first occurrence of complete or partial response plus one day if no tumour assessments were done after the first response.[4]

As of 08-May-2015 data cut-off date, the median DOR was 14.3 months (95% CI 11.6, non-estimable) in the atezolizumab group, when compared with 7.2 months (95% CI 5.6, 12.5) in the docetaxel group. The increased durability of response in the atezolizumab group was statistically significant (HR=0.41; 95% CI 0.18, 0.96; p=0.034).[4] As of 01-Dec-2015 data cut-off, the median DOR was 18.6 months among the responders in the atezolizumab group and 7.2 months among the responders in the docetaxel group.[6] Additional data on DOR obtained at 30-Jan-2015 and 01-Dec-2015 data cut-off dates is presented in Table 6.19.

Quality of Life

Global health status or HRQoL, functioning, and lung cancer symptoms (cough, dyspnea, chest pain, arm/shoulder pain) were assessed by the EORTC QLQ-C30 and LC13 questionnaires.[6,7] The compliance rates for QLQ-C30 among patients who were alive and still on study treatment were reported to be higher than 90% in both arms are at each assessment. At assessments up to cycle 14, the compliance rates for QLQ-LC13 were reported to be higher than 80%.[6]

No clinically meaningful change (improvement or decline) from baseline was observed for patients in the atezolizumab arm during the study period in global health status, functioning (physical, role, emotional, cognitive, and social) or any of the symptom subscales, indicating that atezolizumab did not have a detrimental impact on health related quality of life (HRQoL).[7] Deterioration of lung cancer symptoms was defined as a 10-point or higher increase above the baseline. Deterioration of at least one lung cancer symptoms was reported in 211 patients (114 in the atezolizumab group and 97 in the docetaxel group).[6]

Harms

Safety was a secondary outcome in the POPLAR trial. AEs were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Laboratory safety assessments included monitoring hematology and blood chemistry.[4]

Of the 287 patients randomized in the POPLAR trial, 142 patients in the atezolizumab group and 135 patients in the docetaxel group received at least one dose of protocol-specified treatment and were included in the safety analysis. Table 6.20 summarizes safety outcomes and AEs that was reported in at least 10% of treated patients.[4]

As of 08-May-2015 data cut-off, AEs of any cause were reported in 136/142 (96%) patients in the atezolizumab group and 130/135 (96%) patients in the docetaxel group. The most common AEs of any grade included fatigue (20.4% with atezolizumab versus 34.8% with docetaxel) and decreased appetite (17.6% with atezolizumab versus 15.6% with docetaxel). Grade 3 or 4 AEs occurred in 40.0% of patients in the atezolizumab group and 53.0% of those in the docetaxel group. The proportion of patients with treatment-related grade 3 or 4 AEs was 11% in the atezolizumab group

and 39% in the docetaxel group. Grade 5 AEs was reported in 4% of patients in each treatment group (Table 6.20).[4]

The incidence of non-fatal serious AEs was comparable between the two study groups (35% with atezolizumab and 34% with docetaxel). AEs of any grade leading to treatment withdrawal were observed in 8% of patients in the atezolizumab group and 22% of those in the docetaxel group. The incidence of treatment-related AEs leading to treatment withdrawal was 1% and 18% in the atezolizumab and docetaxel groups, respectively. AEs leading to dose modifications, delay or interruption were reported in 11% of patients who received atezolizumab and 24% of patients who received docetaxel (Table 6.20).[4]

Table 6.20: Adverse events in POPLAR trial (Safety Population)

	Atezolizumab (n=142)	Docetaxel (n=135)
Total patients with at least one adverse event	136 (96%)	130 (96%)
Total events	1354	1325
Treatment-related adverse events	95 (67%)	119 (88%)
Grade 3 or 4 adverse events	57 (40%)	71 (53%)
Treatment-related grade 3 or 4 adverse events	16 (11%)	52 (39%)
Grade 5 adverse events	6 (4%)	5 (4%)
Treatment-related grade 5 adverse events	1 (1%)	3 (2%)
Serious adverse events	50 (35%)	46 (34%)
Adverse events leading to withdrawal from treatment	11 (8%)	30 (22%)
Treatment-related adverse events leading to withdrawal from treatment	2 (1%)	24 (18%)
Adverse events leading to dose modification or interruption	34 (24%)	44 (33%)
Treatment-related adverse events leading to dose modification or interruption	15 (11%)	32 (24%)

Adverse events in at least 10% of patients

	Atezolizumab (n=142)	Docetaxel (n=135)
Alopecia	2 (1.4%)	51 (37.8%)
Fatigue	29 (20.4%)	47 (34.8%)
Nausea	17 (12.0%)	37 (27.4%)
Diarrhea	10 (7.0%)	30 (22.2%)
Anemia	8 (5.6%)	22 (16.3%)
Decreased appetite	25 (17.6%)	21 (15.6%)
Asthenia	9 (6.3%)	18 (13.3%)
Vomiting	8 (5.6%)	16 (11.9%)
Constipation	7 (4.9%)	16 (11.9%)
Peripheral neuropathy	1 (0.7%)	15 (11.1%)
Neutropenia	1 (0.7%)	15 (11.1%)

Source:[Fehrenbacher, Lancet 2016, Table 2 and Table S2 (appendix)][4] Reprinted from The Lancet, 387(10030), Fehrenbacher L, Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial, 1837-46, Copyright (2016), with permission from Elsevier

6.4 Ongoing Trials

[Table 6]: Ongoing trials off atezolizumab (Tecentriq) in NSCLC.

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Study: IMpower210 Phase III, multicenter, open-label, randomized, controlled Sample size = 563 Locations: China, Korea, Republic of, Malaysia, Singapore, Thailand Study Start Date: July 31, 2016 Estimated Study Completion Date: April 30, 2019 Funding: Hoffmann-La Roche	Key Inclusion Criteria: • Aged 18 years or older • Histologically documented locally advanced or metastatic NSCLC • •Disease progression during or following treatment with a prior platinum-containing regimen • measurable disease per RECIST criteria(version 1.1) • ECOG performance status of 0 or 1 Key Exclusion Criteria: • Active or untreated CNS metastases • Prior treatment with or hypersensitivity to study drug(s) or related compounds	Arm 1: Atezolizumab 1200 mg IV Q3W Arm 2: Docetaxel 75 mg/m2 Q3W	Primary: OS Secondary: PFS ORR DOR AES Minimum Observed Serum Concentration (Cmin) of Atezolizumab QoL

AE = adverse events; **CNS** = central nervous system; **ECOG** = Eastern Cooperative Oncology Group; s; **IV** = intravenous; **mg =** milligram**; mg/m^2** = milligram per square meter of body surface; **NSCLC** = non-small cell lung cancer; **ORR** = objective response rate; **OS**= overall survival; **PFS** = progression-free survival; **Q3W** = once every three weeks; **QoL** = quality of life; **RECIST**: Response Evaluation Criteria in Solid Tumours, version 1.1

7 SUPPLEMENTAL QUESTIONS

The following supplemental question were identified during development of the review protocol as relevant to the pCODR review of Atezolizumab as monotherapy, in the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who have progressed on or after systemic chemotherapy.:

- Summary and critical appraisal of the Manufacturer-submitted indirect treatment comparison of pharmacological interventions used as second or higher lines of treatment for locally advanced/metastatic NSCLC

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

7.1 Summary and critical appraisal of the Manufacturer-submitted indirect treatment comparison of pharmacological interventions used as second or higher lines of treatment for locally advanced/metastatic non-small cell lung cancer

7.1.1 Objective

The pCODR-conducted literature search did not identify any RCTs that included a direct, head-to-head comparison between atezolizumab and other potentially relevant immunotherapy agents for the treatment of advanced or metastatic NSCLC who have failed on prior systemic chemotherapy, i.e., nivolumab and pembrolizumab.

In the absence of direct comparative evidence, indirect comparison (ITC) of atezolizumab with relevant comparators in the aforementioned patient population was required. The objective of this section is to summarize and critically appraise the Manufacturer-submitted ITC that provides evidence for the efficacy of atezolizumab versus available immunotherapy options in patients with advanced or metastatic NSCLC.

7.1.2 Findings

Review of Manufacturer's ITC[8]

7.1.2.1 Objectives of ITC

The objective of the Manufacturer's ITC was to evaluate the relative efficacy and safety of second and further lines of therapy for locally advanced/metastatic NSCLC, through a network meta-analysis (NMA) of randomized controlled trials (RCTs) identified through a systematic literature review (SLR).[8]

The submitted ITC used the intention-to-treat population of 1225 patients from the Phase III OAK trial (secondary ITT population), investigating atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer.[8] Of note, the efficacy data for the OAK secondary analysis is not publically available, at the time being.

7.1.2.2 Overview of Methods

Systematic Review[8]

The Manufacturer conducted a systematic review to identify eligible RCTs, reporting evidence of efficacy and safety of 2nd and further line treatments in NSCLC, for inclusion in the ITC.

The following data bases were searched: Medline, Medline In-Process, EMBASE, clinicaltrials.gov and the International Clinical Trials Registry Platform Search Portal were searched in March 2017 without restriction on publication year; Cochrane (CENTRAL & CDSR) was searched from January 2011 to March 2017. All retrieved citations were screened using pre-specified criteria (Table 7.1) by two independent reviewers.

Table 7.1: Study selection criteria used in the Manufacturer-submitted systematic review

Population	Adults (≥18 years) with advanced/metastatic NSCLC eligible for second-line or further-line treatments, who had received one or more prior systematic therapies
Intervention(s)/ Comparator(s)	All 2nd or further line pharmacological treatments (licensed and investigational Phase II-IV).
Outcome(s)	– OS (time-to-event) – PFS (time-to-event) – OS and PFS hazard ratios – OS survival rates at 12 months – ORR – treatment-related AEs – treatment-related serious AEs
Study design	Randomized controlled trials

AE= adverse event**; ORR=** objective response rate; **OS** = overall survival; **PFS** = progression-free survival

Source: Manufacturer submitted NMA Technical Report (OAK – ITT1225)[8]

The literature search resulted in a total of 310 publications reporting 206 RCTS. The evidence base was further reduced after exclusion of investigational and non-licenced treatments, leaving 35 RCTs reporting on relevant comparators for comparators (2nd or further line treatments), which were evaluated during the NMA feasibility assessment phase.

Assessment of Study Quality[8]

The methodological quality of the included studies (risk of bias) was assessed using the National Institute for Health and Care Excellence (NICE) quality appraisal tool. The results of the study quality assessment did not reveal low quality studies.

Indirect Treatment Comparisons[8]

The indirect comparisons were based on:

a) A Bayesian NMA (standard approach); and
b) Fractional polynomials approach by Jansen et al.[77]

Analyses were performed on the following six efficacy outcomes (OS time-to-event; PFS time-to-event; OS and PFS hazard ratios, OS survival rates at 12 months, ORR) and two safety outcomes (treatment-related AEs and treatment-related serious AEs).[8] Additionally, survival time-to-event

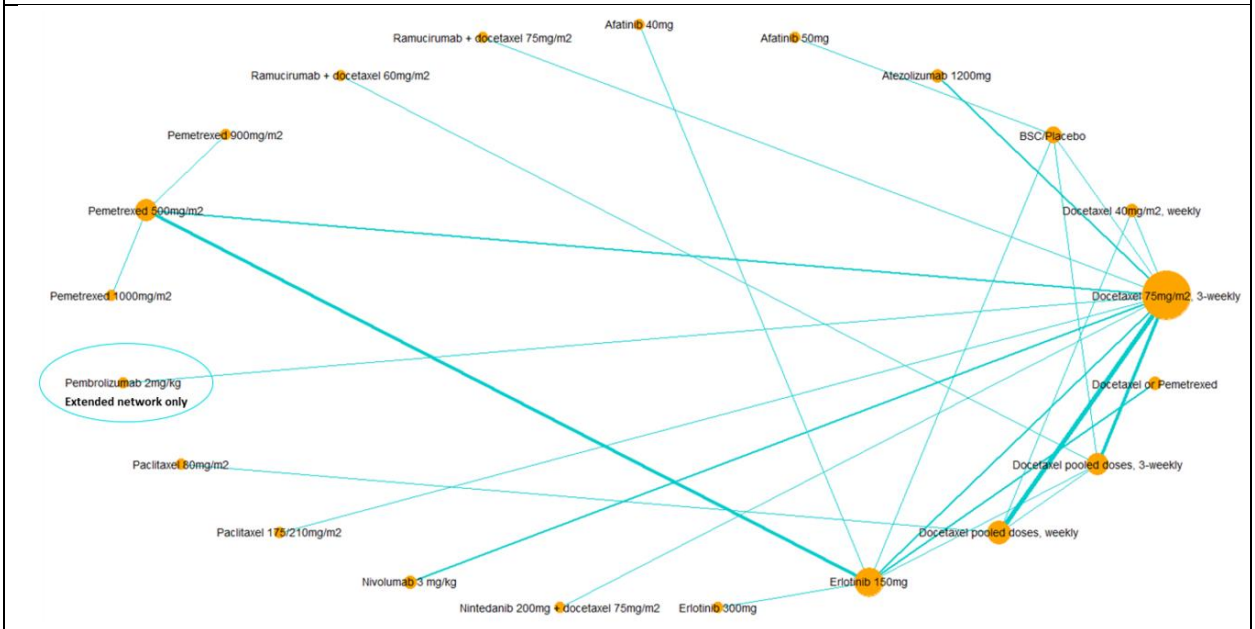
outcomes (OS and PFS) were modelled using fractional polynomials.[73] NMA was not conducted for Quality of life (QoL) outcomes, due to the scarcity of reported QoL data across the included trials.

Given the fact that in the OAK trial, 23% of patients in the docetaxel arm had switched to an immunotherapy during the follow-up period, the estimates of efficacy of atezolizumab relative to docetaxel might be confounded. Therefore, Rank Preserving Structural Failure Time models (RPSFTM) were used to adjust for estimating the true survival time of patients in the docetaxel arm in OAK trial, as if they had stayed on docetaxel for the duration of follow-up. Scenario analyses were performed in addition to the base case analysis. The best fitting model (lowest deviance information criteria [DIC]) was fixed effects for OS, switch adjusted OS, OS rate at 12-months, AEs and serious AEs, random effects informative prior for PFS and random effects vague prior for ORR.

7.1.2.3 Results of ITC[8]

The all-evidence network, which was constructed by linking treatments irrespectively of the outcome of interest, consisted of 21 active treatments based on 35 head-to-head RCTs (Figure 7.1). Eleven studies were phase II trials, 22 studies were phase III trials, and two were phase 2/3 trials. The number of trial participants ranged from 25 to 659 per arm, with 24 studies that included more than 100 patients per treatment arm.

Figure 7.1: All-evidence network diagram constructed for the purpose of the Manufacturer-submitted network meta-analysis



Source: Manufacturer submitted NMA Technical Report (OAK – ITT1225; Figure 19)[8]

Evidence networks were then constructed for each outcome of interest. These networks consisted of a subset of the depicted treatments based on the availability of data for each outcome within the 35 RCTs. Therefore, the size of the network varied depending on the data availability, as shown in Table 7.2.

Table 7.2: Size of the evidence networks for each outcome in the network meta-analyses submitted by the Manufacturer

Outcome	Size of the Network
OS	21 studies
OS (PD-L1 subgroups)	5 studies
OS rates at 12 months	34 studies
PFS (PD-L1 subgroups)	5 studies†
ORR	32 studies
PFS	20 studies
Any treatment-related AEs	9 studies
Any treatment-related serious AEs	10 studies

AE = adverse event; **ORR** = objective response rate; **OS** = overall survival; **PD-L1** = programmed death-ligand1; **PFS** = progression-free survival

†Excludes pembrolizumab for the PD-L1 negative subgroup
Source: Manufacturer submitted NMA Technical Report (OAK – ITT1225)[8]

The included RCTs investigated the following treatments: tumor programmed death ligand-1 (PD-1/PD-L1) inhibitors (atezolizumab, nivolumab and pembrolizumab); targeted therapies (afatinib, erlotinib); chemotherapy regimens (docetaxel, paclitaxel, pemetrexed); placebo/best standard care (BSC); and other/combination of therapies (ramucirumab + docetaxel, nintedanib + docetaxel). Five studies reporting on atezolizumab, nivolumab and pembrolizumab were among the included studies. These trials are listed in Table 7.3.

Table 7.3: Studies of atezolizumab, nivolumab and pembrolizumab used in the network meta-analyses submitted by the Manufacturer

Relevant studies included in the network			Sample size (ITT population)	
			Intervention	Control (docetaxel)
Atezolizumab [vs. docetaxel] 2 studies	OAK (n=1225)	Primary 850	425	425
		Total 1225†	613	612
	POPLAR (n=287)		144	143
Nivolumab [vs. docetaxel] 2 studies	CHECKMATE-057 (n=582)		292	290
	CHECKMATE-017 (n=272)		135	137
Pembrolizumab [vs. docetaxel] 1 study	KEYNOTE-010 (n=687)‡		344	343

ITT = intention-to-treat

†The submitted ITC used the intention-to-treat population of 1225 patients of the Phase III OAK trial

‡ KEYNOTE-010 was only included in the extended network

Source: Manufacturer submitted NMA Technical Report (OAK – ITT1225)[8]

Overall survival[8]

Twenty-one studies reported the hazard ratio for OS data. For the base case network, atezolizumab showed superior OS (i.e., 95% credible intervals [CrI] for the OS HR did not include

the null hypothesis value), when compared with afatinib 50mg, placebo/BSC, docetaxel 3-weekly pooled, erlotinib 300mg, erlotinib 150mg, docetaxel or pemetrexed, paclitaxel 175/210mg/m^2, pemetrexed 500mg/m^2, docetaxel 75mg/m^2 and nintedanib+docetaxel 75mg/m^2. There was no significant difference in OS when compared with ramucirumab+docetaxel 60mg/m^2, pemetrexed 900/m^2, afatinib 40mg, ramucirumab+docetaxel 75mg/m^2 and nivolumab. When the relative ranking of the different treatments were estimated using the Surface Under the Cumulative Ranking Curves (SUCRA), nivolumab showed the highest SUCRA, followed by atezolizumab.

In the extended network analysis, one additional treatment was included, i.e., pembrolizumab (KEYNOTE-010). In this analysis, nivolumab, pembrolizumab and atezolizumab showed the highest SUCRA values (95.6%, 93.8% and 87.8%, respectively). Atezolizumab showed comparable OS to pembrolizumab and nivolumab.

Overall, nivolumab was the best treatment in both networks (according to SUCRA). When OS HR results from the OAK trial were adjusted for the confounding effect of switching to another immunotherapy in the docetaxel arm, nivolumab remained to be the best treatment in both the base case and extended network.

Pairwise treatment comparison NMA results for OS are presented in in Table 7.3.

Table 7.3: NMA results for OS (network size: 21 studies)

Intervention	Comparator	OS HR (95% CrI) Base Case Network	OS HR (95% CrI) Extended Network
Atezolizumab 1200 mg	Docetaxel 75mg/m^2	0.78 (0.69, 0.88)† Switch adjusted : 0.73 (0.63, 0.85)†	0.78 (0.69, 0.88)†
	Nivolumab 3mg/kg	1.11 (0.91, 1.35) Switch adjusted : 1.03 (0.84, 1.28	1.10 (0.91, 1.34
	Pembrolizumab 2mg/kg	NA	1.08 (0.87, 1.36)

CrI = credible interval; **HR** = hazard ratio; **mg/m^2** = milligram per square meter of body surface; **mg/kg** = milligram per kilogram of body weight; **OS** = overall survival

†statistically significant difference favouring atezolizumab

Source: Manufacturer submitted NMA Technical Report (OAK – ITT1225)[8]

Progression-free survival[8]

Twenty studies reported the hazard ratio for PFS data. For the base case network, atezolizumab was found to result in a statistically better PFS, when compared with placebo/BSC, erlotinib 300mg and erlotinib 150mg. However, atezolizumab was found to be statistically significantly worse, when compared with ramucirumab+docetaxel 75mg/m^2. Based on SUCRA ranking, atezolizumab was found to be the 6th best treatment among the 15 competing treatment. Ramucirumab+docetaxel 75mg/m^2 had the highest rank, followed by nintedanib+docetaxel 75mg/m^2 and nivolumab.

Ramucirumab+docetaxel 75mg/m^2 had the highest rank, followed by nintedanib+docetaxel 75mg/m^2 and nivolumab.

In the extended network analysis, atezolizumab showed superior PFS results, when compared with placebo/BSC, erlotinib 150mg, and worse PFS results, when compared with nintedanib+docetaxel 75mg/m^2 and ramucirumab+docetaxel 75mg/m^2. No statistically significant difference in PFS was found between atezolizumab and all other interventions. According to SUCRA, ramucirumab+docetaxel 75mg/m^2 had the highest rank, followed by nintedanib+docetaxel

75mg/m^2 and nivolumab. Atezolizumab was ranked 7th out of 16 competing treatments in the extended network.

Pairwise treatment comparison NMA results for PFS are presented in in Table 7.4.

Table 7.4: NMA results for PFS

Intervention	Comparator	PFS HR (95% CrI) Base Case Network	PFS HR (95% CrI) Extended Network
Atezolizumab 1200 mg	Docetaxel 75mg/m^2	0.95 (0.85, 1.05)†	0.95 (0.85, 1.06)
	Nivolumab 3mg/kg	1.18 (0.98, 1.41)	1.18 (0.98, 1.42)
	Pembrolizumab 2mg/kg	NA	1.07 (0.88, 1.32)

CrI = credible interval; **HR** = hazard ratio; **mg/m^2** = milligram per square meter of body surface; **mg/kg** = milligram per kilogram of body weight; **NI**= not included in the network; **PFS**= progression-free survival

†statistically significant difference favouring atezolizumab

Source: Manufacturer submitted NMA Technical Report (OAK – ITT1225)[8]

Overall survival rate at 12 months[8]

Thirty-four studies reported the OS rates at 12 months. For the base case network, atezolizumab was found to have a statistically higher OS rate at 12 months, when compared with nintedanib+docetaxel 75mg/m^2, docetaxel 75mg/m^2, pemetrexed 500mg/m^2, pemetrexed 900mg/m^2, erlotinib 150mg, paclitaxel 175/210mg/m^2, pemetrexed 1000mg/m^2, docetaxel 3-weekly pooled, placebo/BSC and afatinib 50mg. Nivolumab, atezolizumab, and pembrolizumab (extended network) showed the highest SUCRA values.

Pairwise treatment comparison NMA results for 12-month OS rate are presented in in Table 7.5.

Table 7.5: NMA results for OS rate at 12 months

Intervention	Comparator	12-month OS (95% CrI) Base Case Network	12-month OS (95% CrI) Extended Network
Atezolizumab 1200 mg	Docetaxel 75mg/m^2	1.51 (1.23, 1.85)†	1.51 (1.23, 1.84)†
	Nivolumab 3mg/kg	0.84 (0.60, 1.18)	0.84 (0.60, 1.19)
	Pembrolizumab 2mg/kg	NA	1.05 (0.72, 1.51)

CrI = credible interval; **HR** = hazard ratio; **mg/m^2** = milligram per square meter of body surface; **mg/kg** = milligram per kilogram of body weight; **NI**= not included in the network; **OS** = overall survival

†statistically significant difference favouring atezolizumab

Source: Manufacturer submitted NMA Technical Report (OAK – ITT1225)[8]

Objective response rate[8]

Thirty-two studies reported the ORR data. Atezolizumab was found to have a statistically better ORR, when compared with placebo/BSC in both the base case and the extended network analyses. Paclitaxel 80mg/m^2, nivolumab and pembrolizumab (extended network) showed the highest SUCRA values. According to SUCRA, atezolizumab was ranked 7th out of 20 treatments in the base case analysis, and 8th out of 21 treatments in the extended network analysis.

Pairwise treatment comparison NMA results for ORR are presented in in Table 7.6.

Table 7.6: NMA results for ORR

Intervention	Comparator	ORR (95% CrI) Base Case Network	ORR (95% CrI) Extended Network
Atezolizumab 1200 mg	Docetaxel 75mg/m^2	1.14 (0.52, 2.45)	1.14 (0.52, 2.44)
	Nivolumab 3mg/kg	0.57 (0.18, 1.69)	0.56 (0.18, 1.65)
	Pembrolizumab 2mg/kg	NA	0.53 (0.14, 2.04)

CrI = credible interval; **HR** = hazard ratio; **mg/m^2** = milligram per square meter of body surface; **mg/kg** = milligram per kilogram of body weight; **NI** = not included in the network; **ORR** = objective/overall response rate

Source: Manufacturer submitted NMA Technical Report (OAK – ITT1225)[8]

Subgroup analysis by pD-L1 status

The results of NMAs of PD-L1 subgroups showed that OS HRs (reported in 5 studies) and PFS HRs (reported in 5 studies) in the PD-L1 negative subgroup were generally consistent with the overall population. Nivolumab had the highest SUCRA for PFS HR when considering PD-L1 positive patients only (base case and extended network).

Treatment-related adverse events

Nine studies reported on treatment-related AEs. Atezolizumab was found to have a statistically significantly lower rate of treatment-related any grade AEs, when compared with docetaxel 75mg/m^2. However, there was no statistically significant difference between atezolizumab and nivolumab in terms of incidence of AEs. Nivolumab showed the highest SUCRA value (80.3%), and atezolizumab had a SUCRA value of 69.7%.

Pairwise treatment comparison NMA results for AEs rate are presented in in Table 7.7.

Table 7.7: NMA results for treatment-related AEs

Intervention	Comparator	AEs rate (95% CrI) Base Case Network	AEs rate (95% CrI) Extended Network
Atezolizumab 1200 mg	Docetaxel 75mg/m^2	0.29 (0.22, 0.37)†	0.29 (0.22, 0.37)†
	Nivolumab 3mg/kg	1.06 (0.68, 1.67)	1.06 (0.68, 1.66)
	Pembrolizumab 2mg/kg	NA	0.72 (0.47, 1.14)

AEs= adverse events; **CrI** = credible interval; HR = hazard ratio; **mg/m^2** = milligram per square meter of body surface; **mg/kg** = milligram per kilogram of body weight; **NI**= not included in the network

†statistically significant difference favouring atezolizumab

Source: Manufacturer submitted NMA Technical Report (OAK – ITT1225)[8]

Treatment related serious adverse events

Ten studies reported on treatment-related serious AEs. Atezolizumab was found to have a statistically significant lower rate of treatment-related serious AEs, when compared with docetaxel 3-weekly pooled and docetaxel 75mg/m^2. Atezolizumab was found to be not statistically different from most other interventions in terms of serious AEs, except for nivolumab which showed a statistically lower rate of serious AEs than atezolizumab.

Pairwise treatment comparison NMA results for serious AEs rate are presented in in Table 7.8.

Table 7.8: NMA results for treatment-related AEs			
Intervention	Comparator	Serious AEs rate (95% CrI) Base Case Network	Serious AEs rate (95% CrI) Extended Network
Atezolizumab 1200 mg	Docetaxel 75mg/m^2	0.48 (0.36, 0.63)†	0.48 (0.36, 0.63)†
	Nivolumab 3mg/kg	1.68 (1.01, 2.85)‡	1.68 (1.00, 2.87)‡
	Pembrolizumab 2mg/kg	NI	0.73 (0.41, 1.27)

AEs= adverse events; **CrI** = credible interval; **HR** = hazard ratio; **mg/m^2** = milligram per square meter of body surface; **mg/kg** = milligram per kilogram of body weight; **NI**= not included in the network

†Statistically significant difference favouring atezolizumab

‡ Statistically significant difference favouring nivolumab

Source: Manufacturer submitted NMA Technical Report (OAK – ITT1225)[8]

7.1.3 Summary

The quality of the ITC provided by the Manufacturer[8] was assessed according to the recommendations made by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparisons.[78] Details of the critical appraisal are presented in Table 7.9.

Table 7.9: Adapted ISPOR Questionnaire to Assess the Credibility of an Indirect Treatment Comparison or Network Meta-Analysis†

ISPOR Questions		Details and Comments
1.	Is the population relevant?	**Yes**. The study populations of the studies included in indirect comparisons aligned with the indication under review. The Manufacturer's systematic review and NMAs included studies of adult patients with advanced/metastatic NSCLC eligible for second-line or further-line treatments, who had received one or more prior systematic therapies.
2.	Are any critical interventions missing?	**No.** The Manufacturer included all relative interventions for this patient population in the systematic review and NMAs.
3.	Are any relevant outcomes missing?	**Yes, in part.** The Manufacturer included all relative efficacy outcomes for this patient population in NMAs which include: OS HR, PFS HR, ORR, and OS rate at 12 months. They also performed NMAs on treatment-related AEs and serious AEs. However, it was noted that that HRQoL was not considered in the NMA due to the scarcity of reported HRQoL data across the included trials.
4.	Is the context (e.g., settings and circumstances) applicable to your population?	**Yes**. The settings of the included trials were relevant to that in this pCODR review.
5.	Did the researchers attempt to identify and include all relevant randomized controlled trials?	**Yes**. The Manufacturer provided a summary of the systematic literature review process used in the NMA. In the summary, the Manufacturer took adequate steps to ensure an unbiased selection of studies for inclusion in their analysis. They described the information sources they used, their search strategy, their study selection criteria, and independent double screening and data extraction.

ISPOR Questions		Details and Comments
6.	Do the trials for the interventions of interest form one connected network of randomized controlled trials?	**Yes**. The Manufacturer constructed a network of all evidence by linking treatments irrespectively of the outcome of interest. However, the evidence networks for each outcome of interest consisted of a subset of the depicted treatments based on the availability of data for each outcome.
7.	Is it apparent that poor quality studies were included thereby leading to bias?	**No.** The Manufacturer used the NICE checklist to assess the quality of all the trials that met their inclusion criteria, and reported that the results of their quality appraisal did not reveal low quality studies.
8.	Is it likely that bias was induced by selective reporting of outcomes in the studies?	**No.** There was no selective reporting of outcomes.
9.	Are there systematic differences in treatment effect modifiers (i.e. baseline patient or study characteristics that impact the treatment effects) across the different treatment comparisons in the network?	**Unclear**. In order to show between-study similarities, the Manufacturer-submitted NMA report described the distribution of seven key baseline characteristics of the study populations (median age at baseline, gender, race, smoking history, disease stage, histology, and performance status) along with a description of study design characteristics. However, no quantitative measures of between-study heterogeneity were provided to justify the *similarity* assumption (no treatment-covariate interactions) between the included trials.
10.	If yes (i.e. there are such systematic differences in treatment effect modifiers), were these imbalances in effect modifiers across the different treatment comparisons identified prior to comparing individual study results?	**Yes**. Based on the Manufacture-submitted NMA report, the study design and the patient characteristics of each RCT were investigated to detect potential effect-modifiers. The NMA feasibility analyses were conducted for each outcome, which included an assessment of the availability and the comparability of the data across the studies, and construction of a global network of possible comparisons for each outcome.
11.	Were statistical methods used that preserve within-study randomization? (No naïve comparisons)	**Yes**. The Manufacturer a Bayesian NMA (standard approach) to analyze data on outcomes of interest from the included RCTs. For survival time-to-event outcomes, additional analyses were performed using the fractional polynomials approach.
12.	If both direct and indirect comparisons are available for pairwise contrasts (i.e. closed loops), was agreement in treatment effects (i.e. consistency) evaluated or discussed?	**Yes.** The Manufacturer performed consistency assessment for the eligible outcome networks (networks that contained one or more closed loops). Evidence inconsistency (discrepancy between direct and indirect evidence) was investigated using the deviance information criterion (DIC) of the consistency and inconsistency models. A formal evaluation of consistency was not conducted for the fractional polynomials NMAs due to the complexity of the models.
13.	In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the network meta-analysis?	**Yes**. The NMA models seem to have used both direct and indirect evidence. However, for the network that contained multiple of complex closed loops (for which potential source of inconsistency could not be identified; i.e., ORR results), the authors of NMA cautioned drawing any conclusions from treatment comparisons that are linked to those closed loops.
14.	With inconsistency or an imbalance in the distribution of treatment effect modifiers across the different types of comparisons in the network of trials, did the researchers attempt to minimize this bias with the analysis?	**Unclear**. The manufacturer presented the distributions of potential effect-modifiers among the included studies. The results showed that histology might be an effect modifier. However, based on the NMA report, no statistical tests (e.g., scenario analysis) were performed to control the potential bias.

ISPOR Questions		Details and Comments
15.	Was a valid rationale provided for the use of random effects or fixed effect models?	**Yes.** Based on the submitted NMA report, the Manufacturer used both fixed- and random-effect models and reported the best fitting model (lowest DIC) for each outcome. When the difference in DIC between fixed- and random-effect models was ignorable, results for the fixed-effect model were presented.
16.	If a random effects model was used, were assumptions about heterogeneity explored or discussed?	**Unclear.** It is unclear how the Manufacturer explored the assumptions about heterogeneity. However, as mentioned above, the results of the fixed- and random-effect models were compared and the best fitting model for each outcome was presented.
17.	If there are indications of heterogeneity, were subgroup analyses or meta-regression analysis with pre-specified covariates performed?	**Yes, in part.** Subgroup analyses were performed by PD-L1 status and histology. Meta-regression analysis (to assess the impact of multiple covariates) was not performed.
18.	Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison?	**Yes**. The NMA networks for each outcome were presented in the Manufacturer's NMA report.
19.	Are the individual study results reported?	**Yes**. The effect estimates of all outcomes used in the NMA were provided in the submitted report.
20.	Are results of direct comparisons reported separately from results of the indirect comparisons or network meta-analysis?	**No**.
21.	Are all pairwise contrasts between interventions as obtained with the network meta-analysis reported along with measures of uncertainty?	**Yes.** The Manufacturer's NMA report provided the pairwise NMA results for atezolizumab versus each of the competing interventions in both 'base case' and 'extended network' analyses. Measures of uncertainty (95% CrI) were reported for estimates of effect (ratios and rates).
22.	Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome?	**Yes**. In the submitted NMA report, a hierarchy of the treatments are presented using the probability that each treatment is ranked at a certain position out of all interventions compared (rankograms). The SUCRA for each treatment was also estimated and probabilities of being best for each treatment were calculated and ranked.
23.	Is the impact of important patient characteristics on treatment effects reported?	**Yes, in part.** Subgroup analyses were performed by PD-L1 status and histology.
24.	Are the conclusions fair and balanced?	**Yes.** The submitted NMA s concluded that the OS HR of atezolizumab and nivolumab and pembrolizumab (where included) were similar; and that these three PD-1/PD-L1 inhibitors seemed to perform better than other treatment comparators in the network. In terms of subgroup analyses by PD-L1 status, results for OS HR were generally consistent with the overall population.
25.	Were there any potential conflicts of interest?	**Not reported.**
26.	If yes, were steps taken to address these?	**Not applicable.**

ISPOR Questions	Details and Comments
CrI = credible interval**; HRQoL** = health-related quality of life; **ISPOR** = International Society For Pharmacoeconomics and Outcomes Research; **NMA**= network meta-analysis; **OS** = overall survival **PFS** = progression-free survival; **SUCRA** = surface under the cumulative ranking curve † Adapted from Jansen, Value Health. 2014;17(2):157-73[78]	

7.1.4 Conclusion

The submitted ITC was conducted to assess the relative efficacy and safety of pharmacological interventions of second or greater lines of treatment for patients with advanced/metastatic NSCLC. The analysis based on the standard Bayesian approach included 35 RCTs reporting on relevant treatments that could be classified in five different treatment classes: targeted therapies, chemotherapy regimens, PD1/PD-L1 inhibitors, placebo, and others (combined therapies). Analyses were performed for two types of networks: 1) base case, and 2) extended network (included KEYNOTE-010 trial which assessed pembrolizumab in PD-L1 positive patients).[8]

Based on the results of NMAs, nivolumab was found to be the best treatment among the competing interventions with the highest SUCRA value. However, in all analyses the OS HR of atezolizumab and nivolumab and pembrolizumab (where included) were similar. These three PD-1/PD-L1 inhibitors seemed to perform better than other treatments of interest. Subgroup analyses showed that the OS HRs in subgroups of patients by PD-L1 status (positive and negative) were generally consistent with those in the overall population. In subgroup analyses by histology OS HR for the squamous subgroup was consistent with the overall population. However, the analysis of non-squamous patients only showed slightly different results: nivolumab continued to have the highest SUCRA in the base case, but when the pembrolizumab had the highest SUCRA value in the extended network. In terms of OS at 12 months, nivolumab had the highest SUCRA in the base case and the extended network).[8]

8 COMPARISON WITH OTHER LITERATURE

No comparisons with other literature were addressed in 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 atezolizumab (Tecentriq) 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.

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

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.

APPENDIX A: LITERATURE SEARCH STRATEGY AND DETAILED METHODOLOGY

Literature Search Strategies

1. Literature search via OVID platform

Database(s):EBM Reviews - Cochrane Central Register of Controlled Trials November 2017, Embase 1974 to 2017 December 19, Ovid MEDLINE(R) ALL 1946 to December 19, 2017

#	Searches	Results
1	(atezolizumab* or Tecentriq* or MPDL3280A or MPDL-3280A or RG7446 or RG-7446).ti,ab,ot,kf,kw,hw,rn,nm.	2119
2	(52CMI0WC3Y or 1380723-44-3).rn,nm.	1372
3	or/1-2	2119
4	Carcinoma, Non-Small-Cell Lung/	51766
5	(NSCLC or NSCLCs).ti,ab,ot,kf,kw,hw.	102238
6	((lung cancer* or lung carcinoma* or lung neoplasm*) adj2 (nonsmall cell or non-small cell)).ti,ab,ot,kf,kw,hw.	148217
7	(lung adj2 (adenocarcinoma* or adeno-carcinoma*)).ti,ab,ot,kf,kw,hw.	47622
8	((bronchial cancer* or bronchial carcinoma* or bronchial neoplasm*) adj2 (nonsmall cell or non-small cell)).ti,ab,ot,kf,kw,hw.	500
9	(bronchial adj2 (adenocarcinoma* or adeno-carcinoma*)).ti,ab,ot,kf,kw,hw.	260
10	((pulmonary cancer* or pulmonary carcinoma* or pulmonary neoplasm*) adj2 (nonsmall cell or non-small cell)).ti,ab,ot,kf,kw,hw.	54
11	(pulmonary adj2 (adenocarcinoma* or adeno-carcinoma*)).ti,ab,ot,kf,kw,hw.	4939
12	((lung cancer* or lung carcinoma* or lung neoplasm*) adj2 (large cell or squamous cell)).ti,ab,ot,kf,kw,hw.	7935
13	((bronchial cancer* or bronchial carcinoma* or bronchial neoplasm*) adj2 (large cell or squamous cell)).ti,ab,ot,kf,kw,hw.	112
14	((pulmonary cancer* or pulmonary carcinoma* or pulmonary neoplasm*) adj2 (large cell or squamous cell)).ti,ab,ot,kf,kw,hw.	32
15	or/4-14	208203
16	3 and 15	945
17	16 use medall	136
18	16 use cctr	52
19	*atezolizumab/ or (atezolizumab* or Tecentriq* or MPDL3280A or MPDL-3280A or RG7446 or RG-7446).ti,ab,kw.	1039
20	exp Non Small Cell Lung Cancer/	110097
21	(NSCLC or NSCLCs).ti,ab,kw.	102027
22	((lung cancer* or lung carcinoma* or lung neoplasm*) adj2 (nonsmall cell or non-small cell)).ti,ab,kw.	139936
23	(lung adj2 (adenocarcinoma* or adeno-carcinoma*)).ti,ab,kw.	32531
24	((bronchial cancer* or bronchial carcinoma* or bronchial neoplasm*) adj2 (nonsmall cell or non-small cell)).ti,ab,kw.	500
25	(bronchial adj2 (adenocarcinoma* or adeno-carcinoma*)).ti,ab,kw.	258
26	((pulmonary cancer* or pulmonary carcinoma* or pulmonary neoplasm*) adj2 (nonsmall cell or non-small cell)).ti,ab,kw.	54

27	(pulmonary adj2 (adenocarcinoma* or adeno-carcinoma*)).ti,ab,kw.	4915
28	((lung cancer* or lung carcinoma* or lung neoplasm*) adj2 (large cell or squamous cell)).ti,ab,kw.	4896
29	((bronchial cancer* or bronchial carcinoma* or bronchial neoplasm*) adj2 (large cell or squamous cell)).ti,ab,kw.	112
30	((pulmonary cancer* or pulmonary carcinoma* or pulmonary neoplasm*) adj2 (large cell or squamous cell)).ti,ab,kw.	32
31	or/20-30	207307
32	19 and 31	489
33	32 use oemezd	323
34	33 and conference abstract.pt.	168
35	limit 34 to yr="2012 -Current"	168
36	limit 35 to english language	168
37	33 not conference abstract.pt.	155
38	17 or 18 or 37	343
39	limit 38 to english language	326
40	remove duplicates from 39	201
41	36 or 40	369
42	remove duplicates from 41	360

2. Literature search via PubMed

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

Search	Query	Items found
#15	Search #1 AND #12 AND #13 Filters: English Sort by: PublicationDate	8
#14	Search #1 AND #12 AND #13 Sort by: PublicationDate	8
#13	Search publisher[sb] Sort by: PublicationDate	522307
#12	Search #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 Sort by: PublicationDate	82145
#11	Search (pulmonary cancer*[tiab] OR pulmonary carcinoma*[tiab] OR pulmonary neoplasm*) AND (large cell[tiab] OR squamous cell[tiab]) Sort by: PublicationDate	271
#10	Search (bronchial cancer*[tiab] OR bronchial carcinoma*[tiab] OR bronchial neoplasm*) AND (large cell[tiab] OR squamous cell[tiab]) Sort by: PublicationDate	542
#9	Search (lung cancer*[tiab] OR lung carcinoma*[tiab] OR lung neoplasm*) AND (large cell[tiab] OR squamous cell[tiab]) Sort by: PublicationDate	13742
#8	Search pulmonary AND (adenocarcinoma*[tiab] OR adeno-carcinoma*[tiab]) Sort by: PublicationDate	31327
#7	Search (pulmonary cancer*[tiab] OR pulmonary carcinoma*[tiab] OR pulmonary neoplasm*) AND (nonsmall cell[tiab] OR non-small cell[tiab]) Sort by: PublicationDate	144
#6	Search bronchial AND (adenocarcinoma*[tiab] OR adeno-carcinoma*[tiab]) Sort by: PublicationDate	1580
#5	Search (bronchial cancer*[tiab] OR bronchial carcinoma*[tiab] OR bronchial neoplasm*) AND (nonsmall cell[tiab] OR non-small cell[tiab]) Sort by: PublicationDate	488
#4	Search lung AND (adenocarcinoma*[tiab] OR adeno-carcinoma*[tiab]) Sort by: PublicationDate	30374
#3	Search (lung cancer*[tiab] OR lung carcinoma*[tiab] OR lung neoplasm*) AND (nonsmall cell[tiab] OR non-small cell[tiab]) Sort by: PublicationDate	51027
#2	Search NSCLC[tiab] OR NSCLCs[tiab] Sort by: PublicationDate	32139

Search	Query	Items found
#1	Search atezolizumab*[tiab] OR Tecentriq*[tiab] OR MPDL3280A[tiab] OR MPDL-3280A[tiab] OR RG7446[tiab] OR RG-7446[tiab] Sort by: PublicationDate	251

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: TECENTRIQ / atezolizumab, non small cell lung cancer

Select international agencies including:

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

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

Search: TECENTRIQ / atezolizumab, non small cell lung cancer

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: TECENTRIQ / atezolizumab, non small cell lung cancer - last 5 years

Detailed Methodology

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

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates via Ovid; Embase (1974-) via Ovid; The Cochrane Central Register of Controlled Trials (November 2017) 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 TECENTRIQ / atezolizumab and non small cell lung cancer.

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

The search is considered up to date as of May 3, 2018.

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), the European Society for Medical Oncology (ESMO), and the American Society of Hematology (ASH) 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. A member of the pCODR Methods Team made the final selection of studies to be included in the review and differences were resolved through discussion with the review team.

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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