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APPLICATION NUMBER:

761041Orig1s000

MEDICAL REVIEW(S)

Clinical Review
 {Chana Weinstock (Efficacy), Daniel Suzman (Safety)}
 {BLA}
 {Atezolizumab}

CLINICAL REVIEW

Application Type	BLA 505 (b) (1)
Application Number(s)	761041
Priority or Standard	Priority
Submit Date(s)	2/19/2016
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Division/Office	Division of Oncology Products 1, Office of Hematology and Oncology Products
Reviewer Name(s)	Chana Weinstock (efficacy), Daniel Suzman (safety)
Review Completion Date	10/19/2016
Established Name	Atezolizumab
(Proposed) Trade Name	TECENTRIQ™
Applicant	Hoffmann-La Roche, Inc./Genentech, Inc.
Formulation(s)	Injection for intravenous administration 1200 mg/20 mL (60 mg/mL), single-dose vials
Dosing Regimen	1200 mg administered as an intravenous infusion over 60 minutes every 3 weeks
Applicant Proposed Indication(s)/Population(s)	TECENTRIQ is a programmed death-ligand 1 (PD-L1) blocking antibody indicated for the treatment of patients with metastatic non-small cell lung cancer who have disease progression during or following platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving TECENTRIQ.
Recommendation on Regulatory Action	Traditional approval
Recommended Indication(s)/Population(s) (if applicable)	TECENTRIQ is a programmed death-ligand 1 (PD-L1) blocking antibody indicated for the treatment of patients with metastatic non-small cell lung cancer who have disease progression during or following platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving TECENTRIQ.

Disclaimer Statement: This combined review contains assessments from individual reviewers based on their best knowledge, interpretation, and analyses of the clinical data submitted to this BLA for atezolizumab. The assessments are in the best interest of patients to their best understandings of study disease, study treatment and relevant sciences. Different views and writing styles may exist among individual reviewers. Finally, the reviewers' recommendations do not necessarily reflect the final regulatory recommendation or action on this BLA from the Review Division and Review Office of FDA.

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Glossary

AC	advisory committee
AE	adverse event
ALK	anaplastic lymphoma kinase
ATA	anti-therapeutic antibody
BLA	biologics license application
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	confidence interval
CMC	chemistry, manufacturing, and controls
CRF	case report form
CSR	clinical study report
IC	immune cell
IDMC	data monitoring committee
IHC	immunohistochemistry
IND	investigational new drug
DOR	duration of response
ECG	electrocardiogram
EDC	electronic data capture
EGFR	epidermal growth factor receptor
FDA	Food and Drug Administration
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
ICH	International Conference on Harmonization
IDMC	independent data monitoring committee
imAE	immune-mediated adverse event
IND	Investigational New Drug
ISS	integrated summary of safety
IRF	Independent Review Facility
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
OSE	Office of Surveillance and Epidemiology

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OSI	Office of Scientific Investigation
PD	pharmacodynamics
PD-L1	Programmed death-ligand 1
PFS	progression-free survival
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
RECIST v1.1	Response Evaluation Criteria in Solid Tumors v1.1
SAE	serious adverse event
SAP	statistical analysis plan
TC	tumor cell
TEAE	treatment emergent adverse event
TSH	Thyroid stimulating hormone
UC	Urothelial carcinoma

1 Executive Summary

1.1. Product Introduction

Atezolizumab (TECENTRIQ) is an Fc-engineered, humanized, monoclonal antibody that directly binds to PD-L1 and blocks its interactions with the PD-1 and B7.1 receptors. The product belongs to a non-glycosylated IgG1 kappa immunoglobulin that has a calculated molecular mass of 145 kDa.

The Applicant's proposed indication for this BLA was: *"TECENTRIQ is a programmed death-ligand 1 (PD-L1) blocking antibody indicated for the treatment of patients with metastatic non-small cell lung cancer who have disease progression during or following platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving TECENTRIQ."*

The recommended dose for atezolizumab is 1200 mg, administered as an intravenous infusion over 60 minutes every 3 weeks until disease progression or unacceptable toxicity.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The clinical and statistical reviewers recommend traditional approval of atezolizumab for the proposed indication. Our review found that this BLA provides substantial evidence to support the use of atezolizumab for the treatment of patients with metastatic non-small cell lung cancer who have disease progression during or following platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving atezolizumab.

As summarized in the following Benefit-Risk Assessment (section 1.3), evidence supporting this BLA came from two randomized, controlled studies that showed consistent results in both efficacy and safety. Treatment with atezolizumab vs. docetaxel in the intended patient population in studies POPLAR and OAK resulted in a 2.9 month and a 4.2 month improvement in overall survival (OS), respectively. The median OS in POPLAR was 12.6 months (95% CI 9.7,16.0) in the atezolizumab arm compared to 9.7 months (95% CI 8.6,12.0) in the docetaxel arm [Hazard Ratio (HR)=0.69 (95% Confidence Interval (CI) 0.52,0.92)]. The median OS in OAK

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was 13.8 months (95% CI 11.8,15.7) in the atezolizumab arm compared to 9.6 months (95% CI 8.6,11.2) in the docetaxel arm HR=0.74 (95% CI 0.63,0.87); logrank p=0.0004] The result of the prespecified OS analysis of the PD-L1 selected subset in OAK was similar to the results of the primary analysis population (HR = 0.74, 95% CI 0.59, 0.94).

Overall, the evidence of improvement in overall survival (OS) combined with the demonstrated safety profile in this BLA is considered sufficient for regular approval of atezolizumab for the proposed indication. Use of the PD-L1 (SP142) assay as proposed for this BLA may identify a group of patients who may have a higher OS on atezolizumab.

1.3. **Benefit-Risk Assessment**

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Table 1: Benefit-risk assessment

Benefit-Risk Summary and Assessment

Atezolizumab, a programmed death-ligand 1 (PD-L1) blocking antibody, is recommended for regular approval for the treatment of patients with metastatic non-small cell lung cancer who have disease progression during or following platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving atezolizumab.

In the USA, standard of care for patients with metastatic non-small cell lung cancer is platinum-containing doublet chemotherapy. However, almost all patients experience disease progression during or after platinum-containing chemotherapy. For patients with EGFR or ALK genomic tumor aberrations, front-line FDA-approved targeted therapy for these aberrations is also available but the majority of patients progress during this treatment. Docetaxel is approved for second-line therapy in this setting but is associated with median OS of approximately 6-7 months as well as with considerable toxicity.

The effectiveness of atezolizumab was demonstrated in POPLAR, which was a study that enrolled 287 patients with metastatic non-small cell lung cancer who had disease progression during or following platinum-containing chemotherapy; those with EGFR or ALK genomic tumor aberrations also were required to have disease progression on FDA-approved therapy for these aberrations. Patients were randomized to receive atezolizumab (1200 mg IV) or Docetaxel (75 mg IV) every 3 weeks until radiographic disease progression, and/or clinical disease progression in the case of atezolizumab. Treatment with atezolizumab resulted in a 2.9 month improvement in overall survival (OS) compared to docetaxel; median OS 12.6 months (95% CI 9.7,16.0) vs. 9.7 months (95% CI 8.6, 12.0), HR 0.69 (95% CI 0.52,0.92)]. Study OAK was a second, similarly designed, randomized study of atezolizumab vs. docetaxel that enrolled 1225 patients with metastatic NSCLC in the same target population as POPLAR. The primary analysis population of this study was the first 850 patients enrolled. An improvement in median OS of 4.2 months was seen for atezolizumab compared to docetaxel; median OS was 13.8 months (95% CI 11.8,15.7) vs. 9.6 months (95% CI 8.6, 11.2), HR=0.74 (95% CI 0.63,0.87); logrank p=0.0004. The result of the prespecified OS analysis of a PD-L1 selected subset was similar to the results of the primary analysis population; HR = 0.74 (95% CI: 0.59, 0.94); logrank p=0.012.

The most common adverse reactions of atezolizumab seen in at least 20% of patients were fatigue, decreased appetite, dyspnea, cough, nausea, musculoskeletal pain, and constipation. The overall incidence of adverse events was 96% in both the atezolizumab and docetaxel arms. Grade 3-4 adverse events were seen in 43% of patients, which was less than the 55% incidence in the docetaxel arm. Infection and immune-related

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adverse events such as pneumonitis, hepatitis, colitis, thyroid disease, adrenal insufficiency, and diabetes were also seen with atezolizumab.

Overall, the overall survival advantage for atezolizumab over docetaxel is clinically meaningful to patients with the study disease. This represents an important, new, and non-chemotherapeutic option in this patient population. The benefit-risk profile for the approved indication is favorable.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> • Lung cancer is the leading cause of cancer-related deaths in the US, accounting for approximately 160,000 deaths in 2015. • The majority of patients present with locally advanced or metastatic disease at diagnosis, which is incurable with currently available therapeutic options. • The 5-year survival for this population is currently less than 5%. 	<p>NSCLC is a common cause of cancer-related mortality that is not yet curable and 5-year survival rates remain poor. Effective therapies are needed in this setting.</p>
Current Treatment Options	<ul style="list-style-type: none"> • In the second-line metastatic NSCLC setting, once patients have progressed on platinum-doublet chemotherapy, approved options include nivolumab or docetaxel +/- ramucirumab. Pemetrexed is approved in those with non-squamous NSCLC. • There are several targeted therapies approved under accelerated approval. For those whose tumors are positive for EGFR mutations and who have also failed first-line targeted therapy, Osimertinib is approved. For those whose tumors are positive for ALK rearrangements and who have failed targeted therapy, Ceritinib and Alectinib are approved. Pembrolizumab is approved in patients whose tumors are positive for PD-L1 as defined by an FDA-approved test. 	<p>Despite recent drug approvals, treatment options in the second-line+ metastatic NSCLC setting remain limited and these patients are considered incurable.</p>

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	<ul style="list-style-type: none"> • Treatment with with atezolizumab in the intended patient population resulted in a 2.9 month and a 4.2 month improvement in overall survival (OS) compared to docetaxel in two randomized clinical trials, POPLAR and OAK. • The median OS in POPLAR was 12.6 months (95% CI 9.7,16.0) in the Atezolizumab arm compared to 9.7 months (95% CI 8.6, 12.0) in the Docetaxel arm [Hazard Ratio (HR)=0.69 (95% Confidence Interval (CI) 0.52; 0.92)]. • The median OS in OAK was 13.8 months (95% CI 11.8,15.7) in the Atezolizumab arm compared to 9.6 months (95% CI 8.6, 11.2) in the Docetaxel arm [Hazard Ratio (HR)=0.74 (95% Confidence Interval (CI) 0.63; 0.87); logrank p=0.0004] • The result of the prespecified OS analysis of the PD-L1 selected subset in OAK was similar to the results of the primary analysis population (HR = 0.74, 95% CI: 0.59, 0.94); logrank p=0.012). 	<p>Substantial evidence of effectiveness for use of atezolizumab monotherapy in patients with non-small cell lung carcinoma who have progressed on or after platinum-doublet therapy and, where applicable, EGFR- or ALK-directed therapy, supported by similar OS improvements, was found from the two randomized, controlled studies. The results are consistent between the two studies.</p>
Risk	<ul style="list-style-type: none"> • Tolerated in most study patients • The incidence of Grade 3-4 reactions was lower in patients treated with atezolizumab compared to those treated with docetaxel, although the incidence of non-fatal serious adverse events was comparable. • Important risks include pneumonitis, hepatitis, endocrine disorders, colitis, infection, and neurological disorders. 	<p>The profile of adverse reactions associated with atezolizumab is similar to that observed in other agents targeting the PD-1/PD-L1 pathway and compares favorably to that of docetaxel.</p>
Risk Management	<ul style="list-style-type: none"> • Non-endocrine immune-mediated adverse events were largely reversible with the use of corticosteroids • A medication guide for atezolizumab describing the risks of immune-mediated adverse events will be required to better allow early 	<p>The safe use of atezolizumab can be managed through accurate labeling and routine pharmacovigilance. No REMS is required.</p>

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	recognition and initiation of treatment of these events. <ul style="list-style-type: none">• To better estimate the risk of pneumonitis and other immune-mediated events, the Applicant will fulfill a PMR to provide the safety datasets from the Phase 3 OAK trial.	

2 Therapeutic Context

2.1. Analysis of Condition

Lung cancer is the leading cause of cancer-related deaths in the US, with an estimated 158,040 death occurring in 2015, which is 26.8% of all overall cancer deaths¹. The majority of patients present with locally advanced or metastatic disease at the time of diagnosis, which is generally considered incurable. The 5-year survival for this population is less than 5%. First-line therapy for these patients has been the use of platinum-doublet chemotherapy. The median OS for patients receiving this therapy ranges from 8 to 13 months, with a 1- year survival rate of approximately 33%². Those patients whose tumors are found to be positive for EGFR activating mutations or EML4/ALK translocations, found in approximately 10% and 3% of patients with NSCLC, respectively, are also eligible for oral targeted therapies. Response rates in patients treated with these therapies are generally high, with objective response rates of approximately 60-70% and median progression-free survival of 9 to 14 months. However, the majority of patients develop treatment resistance within the first year of therapy. Despite recent advances and several new drug approvals in this setting, treatment options for those patients with NSCLC failing first-line therapy are limited (see section 2.2).

Atezolizumab is a humanized monoclonal antibody that binds directly to PD-L1, blocking its interactions with the PD-1 and B7.1 receptors. This binding results in a release of inhibition of the antitumor immune response which is mediated by PD-L1/PD-1 interaction. This drug was developed for use in a variety of tumor types, and because of initial activity demonstrated against NSCLC, further development proceeded in this setting.

2.2. Analysis of Current Treatment Options

There are several treatment options approved in the second-line setting for patients with metastatic NSCLC who have progressed on or after initial platinum-doublet chemotherapy. These options differ slightly based on tumor histology (squamous vs. non-squamous) and by mutational profile, and are summarized below. Of note, those approved under accelerated approval only at the time of this review are indicated as such.

Table 2 Approved therapy for metastatic NSCLC in the second-line setting

Product Name	Relevant Indication	Approval Date	Efficacy Information
Docetaxel	Single agent for locally advanced or metastatic NSCLC after platinum	December 1999	1. Docetaxel (n=55) vs. BSC (n=49) • mOS 7.5 m (5.5, 12.8) vs 4.6 (3.7, 6.1); HR 0.56 (0.35, 0.88); p=0.01 • mTTP 12.3 (9.0, 18.3) wks vs. 7.0 wks (6, 9.3)

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	therapy failure		<ul style="list-style-type: none"> • ORR 5.5% (1.1, 15.1) vs N/A 2. Docetaxel vs. Vinorelbine/Ifosfamide • m OS 5.7 m (5.1 , 7.1) vs. 5.6 m (4.4, 7.9); HR 0.82 (0.63,1.06); p=0.13 • mTTP 8.3 wks (7.0, 11 .7) vs. 7.6 wks (6.7, 10. 1) • ORR 5.7% (2.3, 11.3) VS. 0.8% (0.0, 4.5)
Erlotinib	Treatment of locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen	November 2004	<p>Erlotinib vs placebo</p> <ul style="list-style-type: none"> • mOS 6.7 vs. 4.7 m; HR 0.73 (0.61, 0.86); p <0.001 • mPFS 9.9 wks vs. 7.9 wks; HR 0.59 (0.5, 0.7); p < 0.001 • ORR 8.9% VS < 1 %; p < 0.001
Pemetrexed	Locally Advanced or Metastatic Nonsquamous Non-Small Cell Lung Cancer after prior chemotherapy as a single-agent	September 2008	<p>Pemetrexed vs. Docetaxel</p> <ul style="list-style-type: none"> • Nonsquamous NSCLC- OS in months- 9.3 (7.8,9.7) vs. 8.0 (6.3,9.3), adjusted HR 0.78 (0.61,1.00)
Ceritinib	Accelerated approval- anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib	April 2014	<ul style="list-style-type: none"> • ORR- investigator 54.6% (47,62), BIRC 43.6% (36,52) • DOR- investigator assessed 7.4 months (5.4,10.1), 7.1 months (5.6, NE)
Ramucirumab	In combination with docetaxel, for treatment of metastatic NSCLC with disease progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA approved therapy for these aberrations prior to receiving ramucirumab	December 2014	<p>Ramucirumab/Docetaxel vs Placebo/Docetaxel</p> <ul style="list-style-type: none"> • mOS 10.5 (0.95, 11.2) vs 9.1 (8.4, 10.0); HR 0.86 (0.75, 0.98) p = 0.024 • mPFS 4.5 (4.2, 5.4) vs 3.0 (2.8, 3.9) ; HR 0.76 (0.68, 0.86) p < 0.001 • ORR 23% (20, 26) VS. 14% (11, 17); p < 0.001
Nivolumab	Metastatic non-small cell lung cancer and	Squamous-March	<p>1. Squamous NSCLC- nivolumab vs. docetaxel</p> <ul style="list-style-type: none"> • mOS 9.2 (7.3,13.3) vs. 6.0 (5.1,7.3); HR 0.59 (0.44,

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	<p>progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving OPDIVO</p>	<p>2015 Non-squamous- October 2015</p>	<p>0.79) p=0.00025 2. Non-Squamous NSCLC- Nivolumab vs. docetaxel <ul style="list-style-type: none"> mOS 12.2 (9.7,15.0) vs. 9.4 (8.0,10.7); 0.73 (0.60, 0.89) p=0.0015 ORR 19% (15,24) vs. 12% (9,17) P=0.02 PFS 2.3 vs. 4.2 months, p+0.39 </p>
Pembrolizumab	<p>Accelerated approval- patients with metastatic NSCLC whose tumors express PD-L1 as determined by an FDA-approved test and who have disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations.</p>	<p>October 2015</p>	<ul style="list-style-type: none"> ORR 41% (29,54)
Osimertinib	<p>Accelerated approval- metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC), as detected by an FDA-approved test, who have progressed on or after EGFR TKI therapy</p>	<p>November 2015</p>	<ul style="list-style-type: none"> ORR 59% (54,64)
Alectinib	<p>Accelerated approval- anaplastic lymphoma kinase</p>	<p>December 2015</p>	<p>Study 1-</p> <ul style="list-style-type: none"> ORR- IRC 38% (28,49), investigator 46% (35,57) DOR in months- IRC 7.5 (4.9, NE), investigator NE

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(ALK)-positive, metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib		(4.9, NE) Study 2- <ul style="list-style-type: none"> • ORR- IRC 44% (36.53), investigator 48% (39,57) • DOR in months- IRC 11.2 (9.6, NE), investigator 7.8 (7.4,9.2)
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(References 3-11)

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Atezolizumab received accelerated approval by the FDA on May 18, 2016 for the treatment of locally advanced or metastatic urothelial carcinoma with disease progression during or following platinum-containing chemotherapy, or with disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. The use of atezolizumab in NSCLC in the second-line setting is the second indication for which atezolizumab is being reviewed by the FDA. There is no development program at this point in non-malignant diseases.

3.2. Summary of Presubmission/Submission Regulatory Activity

The regulatory history occurring prior to and during submission of BLA 761041 is summarized below in Table 3.

Table 3: Regulatory history for BLA 761041

Date	Activity
April 11, 2011	<ul style="list-style-type: none"> • IND 111271 submitted for MPDL3280A/atezolizumab. • IND-enabling trial was PCD4989g "A Phase I, Open-Label, Dose-Escalation Study of the Safety and Pharmacokinetics of MPDL3280A Administered Intravenously as a Single Agent to Patients with Locally Advanced or Metastatic Solid Tumors or Hematologic Malignancies."
February 12, 2013	<ul style="list-style-type: none"> • Type B meeting held with FDA to discuss data from PCD4989g and the development plan to support accelerated approval in second-line NSCLC. Preliminary efficacy results from PCD4989g showed 8/38 patients with NSCLC having PRs (21%). • Plans for studies GO28625 (FIR), GO28754 (BIRCH), and GO28753 (a phase 2/3 trial that was eventually divided into separate phase 2 study POPLAR and phase 3 study OAK) were discussed.

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Date	Activity
	<ul style="list-style-type: none"> The importance of studying atezolizumab in the second-line setting, rather than the up-front setting, was emphasized.
March 26, 2013	<ul style="list-style-type: none"> IND 117296 submitted for atezolizumab in the treatment of NSCLC with four ongoing studies enrolling 2L + NSCLC patients and six planned ongoing studies enrolling 1L NSCLC patients.
October 22, 2013	<ul style="list-style-type: none"> Type B meeting held to discuss trial design for OAK and BIRCH to support accelerated and regular approval, respectively, for atezolizumab in 2L+ NSCLC.
December 9, 2014	<ul style="list-style-type: none"> Type C meeting; applicant proposed revisions to the definition of PD-L1-positivity and modifications to analysis plans for BIRCH and OAK. Applicant discussed the companion diagnostic, which would assess PD-L1 in both tumor cells and in immune cells, and the algorithm for rescore patients' tumor specimens based on TC3 or IC3 for PD-L1 positivity.
January 28, 2015	<ul style="list-style-type: none"> Breakthrough therapy determination granted for atezolizumab for treatment of patients with locally advanced or metastatic NSCLC that is PD-L1 selected with disease progression on or after platinum-based chemotherapy and appropriate targeted therapy if EGFR or ALK positive.
May 12, 2015	<ul style="list-style-type: none"> Pre- BLA meeting held. FDA stated that despite other regulatory activity in 2L NSCLC, the possibility of obtaining accelerated approval remained if substantial improvement over available therapies was demonstrated; i.e. if the lower bound of the 95% CI around the observed effect exceeds the upper bound of the 95% CI observed with currently available therapies. FDA stated that it would consider the POPLAR OS analysis at approximately 150 events as the final survival analysis but would review data from a later unplanned OS analysis based on approximately 180 events as well.
August 7, 2015	<ul style="list-style-type: none"> FDA provided written feedback on the Sponsor's proposal to use efficacy data from BIRCH to support an approval (b) (4)
November 10, 2015	<ul style="list-style-type: none"> Pre-BLA meeting held to discuss BIRCH results, (b) (4) and from supporting studies POPLAR, FIR, and Study PCD4989g (NSCLC cohort) and to determine if these results provided sufficient clinical evidence to form the basis of a BLA submission. Prior to the formal meeting, on October 29, 2015, FDA held an informal teleconference with the Applicant to further discuss the

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Date	Activity
	<p>path towards accelerated approval for atezolizumab based on the current landscape of available therapy for 2L treatment of patients with NSCLC, including the recent traditional approval of nivolumab.</p> <ul style="list-style-type: none">• Applicant responded with a proposed submission of a BLA for atezolizumab for accelerated approval in 2L+ TC3 NSCLC.• Applicant also proposed to modify the Phase 3 study OAK to conduct the primary analysis based on the 850 initially enrolled patients, with topline results anticipated to be available for submission in Q3 2016, during the BIRCH BLA review. FDA agreed with this approach.
November 19, 2015	<ul style="list-style-type: none">• Part 1 of BLA 761041 submitted.
February 19, 2016	<ul style="list-style-type: none">• Part 2 of BLA 761041 submitted. After initial review of the efficacy data, FDA held 3 informal teleconferences with the Applicant in March and April 2016 to discuss shifting the review focus of BLA 761041 from considering Study BIRCH as pivotal to now considering Study POPLAR as pivotal.• Applicant agreed to submit a revised product label with an indication statement supported by the data from Study POPLAR as an amendment to BLA 761041.• Applicant also agreed to submit top-line efficacy data from OAK one month before PDUFA date of October 19, 2016.
August 29, 2016	<ul style="list-style-type: none">• Applicant submitted topline efficacy results from the Phase 3 Study OAK to the BLA. Datasets supporting these results submitted on September 16, 2016.

Reviewer comment: *Due to the shifting landscape of drug approval in the metastatic NSCLC 2L+ space, there was much discussion about which study should be used as the pivotal trial for efficacy, with BIRCH initially being designated as the pivotal trial for this BLA submission for accelerated approval consideration. However, after initial review of the submitted data, the decision was made to use POPLAR as the pivotal trial in support of the BLA, given its randomized, controlled design, with confirmatory evidence to be supplied by OAK topline results as soon as they were available but before the PDUFA goal date for the review. The line of therapy in which this would be approved (second-line vs. third-line), and whether this would be approved in a PD-L1 selected subgroup, was also discussed. Ultimately, the data supported second-line + and PD-L1 unselected population. See sections 5 and 6 for further details. An additional complication was the shifting landscape of the proposed PD-L1 diagnostic assay, which initially assigned a score based on analysis of immune cells only but later was redesigned to analyze PD-L1 staining in tumor cells as well.*

3.3. Foreign Regulatory Actions and Marketing History

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None as of this review completion.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

To evaluate the Applicant's compliance, the Applicant and two POPLAR study sites were selected for audit by OSI. The first site, 248415 in the USA (clinical investigator Louis Fehrenbacher), was selected since it was the highest-enrolling site. A second site, 258690 in Poland (clinical investigator Aleksandra Szczesna), was selected due to having a lower-than expected reported number of TEAEs. Among sites that enrolled at least 5 subjects, the median number of TEAEs per subject was 7.6 (SD 3.9). Site 258690 enrolled 8 patients but only had 2.75 TEAEs/subject.

The inspections of the 2 clinical investigators each found evidence of regulatory violations. However, based upon a preliminary review of available information these violations do not appear to have affected data reliability or subject safety. Based on the available audit information, OSI concluded that the submitted data from the key study POPLAR appear reliable in support of this BLA.

Additionally, there were two sites initially chosen for inspection when the BLA was originally submitted with BIRCH as the pivotal study. Those sites were inspected by OSI and no significant inspectional findings based on the clinical inspection summary were identified. The Applicant was also audited by OSI; final review of the Genentech inspection found no issues of concern.

4.2. Product Quality

No significant issues were identified regarding the CMC part of the application.

Clinical Microbiology

Not applicable.

4.4. Nonclinical Pharmacology/Toxicology

There are no data available on the use of atezolizumab in pregnant women. See the Pharmatox Review and CDTL review for details.

4.5. Clinical Pharmacology

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There were no significant clinically related issues identified in the clinical pharmacology review.

4.5.1. Mechanism of Action

Atezolizumab is a humanized monoclonal antibody (IgG1) that directly binds to PD-L1 and blocks its interactions with the PD-1 and B7.1 receptors. This results in a release of PD-L1/PD-1 mediated inhibition of the antitumor immune response. In mouse tumor models, inhibition of PD-L1 activity was associated with an increase in activated cytotoxic T cells and a decrease in tumor growth.

4.5.2. Pharmacodynamics

No issues were identified.

4.5.3. Pharmacokinetics

Exposures to atezolizumab increased dose proportionally over the dose range of 1 mg/kg to 20 mg/kg, including the fixed dose of 1200 mg administered every 3 weeks. Based on a population analysis that included 472 patients in the dose range, the typical population clearance was 0.20 L/day, volume of distribution at steady state was 6.9 L, and the terminal half-life was 27 days. The population PK analysis suggests steady state is obtained after 6 to 9 weeks (2 to 3 cycles) of repeated dosing. The systemic accumulation in area under the curve (AUC), maximum concentration (C_{max}) and trough concentration (C_{min}) was 1.91, 1.46 and 2.75-fold, respectively.

4.6. Devices and Companion Diagnostic Issues

Data regarding outcomes based on PD-L1 expression status in studies POPLAR and OAK showed a trend toward increased OS in patients with the highest level of PD-L1 IHC scores, i.e. TC3/IC3, suggesting that a complementary diagnostic based on PD-L1 expression may be appropriate. [See Table 5: PD-L1 expression in immune cells (IC) and tumor cells (TC) used in study POPLAR (source: BLA 761041 section 2.5, clinical overview). There were some inconsistencies between OAK PD-L1 subgroup assignments based on re-reads of the same assay, potentially leading to unreliable results. However, the review team has determined that the inconsistencies and variability is within the range of expected for re-reads of these assay results. As such, these data are robust enough to support a complementary diagnostic claim; for full details please see the corresponding CDRH review for BLA 761041.

4.7. Consumer Study Reviews

Not applicable.

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5 Sources of Clinical Data and Review Strategy

Table of Clinical Studies

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Table 4 summarizes key information about the four studies for which information was submitted in support of this BLA. As discussed in section 3, BIRCH was originally submitted as the primary study to support efficacy but after review of the submitted data, the decision was made to designate the randomized phase 2 study POPLAR as the primary study in support of efficacy, with supportive efficacy evidence from the other three listed studies, BIRCH, FIR, and PCD4989g. Safety results were analyzed from all relevant studies as well as from a larger database containing data from patients with urothelial bladder dosed with Atezolizumab. Once the topline efficacy results from the phase 3 study OAK became available during the review cycles, these data were analyzed as well.

Table 4 Studies of Atezolizumab in NSCLC submitted in support of BLA 761041

Study	Study Design	Study Population	Dosing Schedule	Study Endpoints	No. of Patients Enrolled
POPLAR (GO28753)	Phase II, global, multicenter, open-label, randomized, controlled	Patients with locally advanced, metastatic, or recurrent NSCLC who have failed one (2L) or two (3L) prior platinum-containing regimens. Patients were unselected for PD-L1.	Atezolizumab 1200 mg IV q3w vs. Docetaxel 75 mg/m ² q3w	Overall survival	Total n = 287 Atezolizumab = 142 vs Docetaxel=135
BIRCH (GO28754)	Phase II, global, multicenter, single arm	Patients with locally advanced or metastatic NSCLC who were treatment-naïve (in metastatic setting; 1L), progressed during or after one (2L) or more (3L+) prior treatment ^a . Patients were PD-L1 selected (TC2/3 or IC2/3).	Atezolizumab 1200 mg IV q3w	IRF-assessed ORR per RECIST v1.1	Total n = 667 Cohort 1; 1L=139 Cohort 2; 2L=267 Cohort 3; 3L+=253
FIR (GO28625)	Phase II, global, multicenter, single-arm	Patients with locally advanced or metastatic NSCLC who were treatment-naïve (in metastatic setting; 1L) or progressed during or after one (2L) prior platinum-containing regimen. Patients were PD-L1 selected (TC2/3 or IC2/3).	Atezolizumab 1200 mg IV q3w	Investigator-assessed ORR per modified RECIST	Total n = 138 Cohort 1; 1L = 31 Cohort 2; 2L+= 94 Cohort 3; ^b 2L+ = 13
PCD4989g	Phase Ia, multicenter, first-in-human, open-label, dose escalation, expansion	Patients with locally advanced or metastatic solid tumors (including NSCLC) and hematologic malignancies. NSCLC cohort included PD-L1 selected and unselected patients across all lines of treatment.	Weight-based dose escalation (0.01 to 20 mg/kg) and fixed 1200 mg dose, administered IV q3w for up to 1 year or loss of clinical benefit .	Investigator-assessed ORR per RECIST v1.1	N=481 entire study N=88 NSCLC cohort 1L (n = 15) 2L (n = 23) 3L+ (n = 50)
OAK (GO28915)	Phase III, global, multicenter,	Patients with locally advanced, metastatic, or	Atezolizumab 1200 mg IV	Overall survival in	Total n = 1225

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Study	Study Design	Study Population	Dosing Schedule	Study Endpoints	No. of Patients Enrolled
	open-label, randomized, controlled	recurrent NSCLC who have failed one (2L) or two (3L) prior platinum-containing regimens. Patients were unselected for PD-L1.	q3w vs. Docetaxel 75 mg/m ² q3w	first 850 enrolled patients; Overall survival in PD-L1-selected subgroup of first 850 enrolled patients	Atezolizumab =613 vs Docetaxel=612

5.2. Review Strategy

The clinical efficacy review included the following:

1. Review of the current literature on NSCLC epidemiology and treatment
2. Review of the CSR, protocols, protocol amendments and selected datasets for each submitted study.
3. Review of the Applicant's assessment of their analyses of atezolizumab's efficacy and safety in the treatment of NSCLC.
4. Review of datasets submitted by the Applicant
5. Review of patient narratives of serious adverse events and deaths
6. Review of the meeting minutes from meetings conducted during drug development
7. Assessment of the Module 2 summaries including the Summaries of Clinical Safety and Efficacy, and Module 5.3.5.3 including the Integrated Summaries of Safety and Efficacy and supporting datasets
8. Evaluation of reviews conducted by other FDA disciplines including biostatistics
9. Review of consultation reports from the Office of Scientific Investigations
10. Requests for additional information from the Applicant and review of Applicant responses
11. Formulation of the benefit-risk analysis and recommendations
12. Review and evaluation of proposed labeling
13. Key analysis findings to be included in the label were conveyed to the Applicant during the labeling review, and agreements reached before the final labeling.
14. Once OAK topline results became available at the end of the review cycle, supporting datasets in module 5.3.5.3 were reviewed and analyzed and integrated into the review and into labeling recommendations.

The clinical safety review focused on the 142 patients treated with atezolizumab in POPLAR with additional analyses of adverse events of special interest (AESIs) including immune-mediated adverse events. This included detailed review and analysis of data including the CSR, CRFs, narratives and datasets. The safety review focused on data available as of the data cut-

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off of May 5, 2015. Adverse events that occurred within 30 days following discontinuation of atezolizumab were included.

The clinical review of safety was supplemented with an evaluation of AESIs in patients with non-small cell lung cancer treated with atezolizumab in the BIRCH (659 patients) and FIR (137 patients) trials, and the NSCLC cohort of the PCD4989g trial (88 patients). Study PCD4989g was analyzed based on the data cut-off of August 7, 2015. Study PCD4989g provided limited ECG/QT data. The frequency of specific, rare immune-mediated AEs were additionally obtained from Applicant safety database, comprised of 1978 atezolizumab-treated patients.

Key analysis findings to be included in the label were conveyed to the Applicant during the labeling review, and agreements reached before the final labeling.

5.3. **POPLAR**

Study Design

Overview and Objective

POPLAR was a global, multi-center, international, randomized, controlled, open-label study of atezolizumab in patients with metastatic NSCLC who had progressed on or after first-line platinum-doublet chemotherapy. The key objective was to evaluate atezolizumab's effect on overall survival.

Trial Design

Study design schematic is presented below in Figure 1:

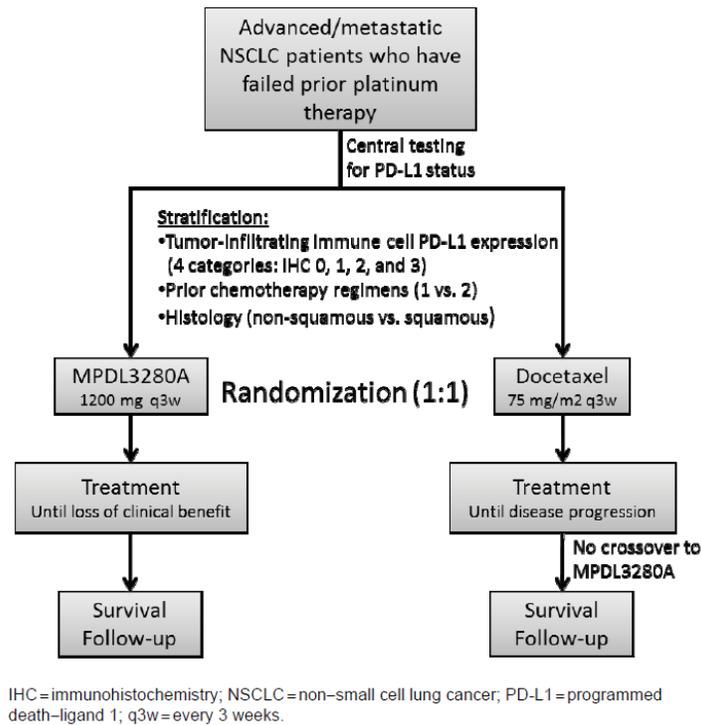
Figure 1: POPLAR trial design schema (source: Poplar protocol figure 1)

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The study was open to patients with locally advanced or metastatic NSCLC who had disease progression during or following a platinum-containing chemotherapy regimen in the metastatic setting or who had disease progression within 6 months of treatment with a platinum-containing neoadjuvant or adjuvant chemotherapy or chemoradiation.

Patients with a known epidermal growth factor receptor (EGFR) mutation in countries where treatment with EGFR tyrosine kinase inhibitors (TKIs) was the standard of care also had to experience disease progression (during or after treatment) or intolerance to treatment with erlotinib, gefitinib, or another EGFR TKI approved for the treatment of EGFR-mutant NSCLC. Patients with a known anaplastic lymphoma kinase (ALK) fusion oncogene in countries where treatment with ALK inhibitors was the standard of care also had to experience disease progression (during or after treatment) or intolerance to treatment with crizotinib or another ALK inhibitor approved for treatment of NSCLC patients having an ALK fusion oncogene.

Eligible patients were stratified by PD-L1 IC status (four categories of PD-L1 expression, referred to as IC0, IC1, IC2, and IC3, see table below), by the number of prior chemotherapy regimens (1 versus 2), and by histology (non-squamous versus squamous) and then randomized 1:1 through an IxRS to receive either atezolizumab or docetaxel.

Table 5: PD-L1 expression in immune cells (IC) and tumor cells (TC) used in study POPLAR (source: BLA 761041 section 2.5, clinical overview).

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Description of IHC Scoring Criteria	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 $\geq 1\%$ 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 $\geq 5\%$ 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 $\geq 10\%$ 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 $\geq 1\%$ and < 5% TCs	TC1
Presence of discernible PD-L1 staining of any intensity in $\geq 5\%$ and < 50% TCs	TC2
Presence of discernible PD-L1 staining of any intensity in $\geq 50\%$ TCs	TC3

IC = tumor-infiltrating immune cell; IHC = immunohistochemistry; PD-L1 = programmed death–ligand 1; TC = tumor cell.

Patients were required to be \geq age 18, with locally advanced or metastatic NSCLC and with disease progression on or after platinum-based chemotherapy. Patients were required to have measurable disease per RECIST v1.1, an ECOG performance score of 0 or 1, and controlled tumor-related pain. In addition, patients had to have adequate tumor tissue for prospective testing and determination of tumor PD-L1 expression status at a central laboratory. Tumor specimens from eligible patients were prospectively tested for PD-L1 expression by a central laboratory using the VENTANA PD-L1 (SP142) IHC assay (see section 4.6 regarding the classification of PD-L1 TC and IC scores and groupings for this study). The study enrolled all patients whose tissue was evaluable for expression testing, regardless of PD-L1 expression status. The results of PD-L1 expression status were blinded to patients, investigators and study site staff at the time of enrollment. The Applicant was blinded to individual patient PD-L1 IC scores, but had access to aggregated level data in order to monitor the prevalence of PD-L1 expression.

This study excluded patients who had a history of cardiovascular disease, HIV, active HBV/HCV, and tuberculosis, Grade ≥ 2 peripheral neuropathy, active or corticosteroid-dependent brain metastases, leptomeningeal disease, uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures. It also excluded patients who had received systemic immunostimulatory agents, other PD-1/PD-L1 targeted products, docetaxel, or systemic immunosuppressive medications.

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Docetaxel 75 mg/m² was administered intravenously on Day 1 of each 21-day cycle until disease progression per standard RECIST v1.1 or unacceptable toxicity. Atezolizumab was administered as an intravenous infusion of 1200 mg of atezolizumab on Day 1 of a 3 week cycle until unacceptable toxicity, disease progression, or symptomatic progression. For patients who met RECIST v1.1 criteria for disease progression on atezolizumab, continued treatment was allowed at the discretion of the Investigator if they met all of the following conditions: 1) Absence of symptoms and signs (including worsening of laboratory values; e.g., new or worsening hypercalcemia) indicating unequivocal progression of disease; 2) No decline in ECOG performance status from baseline; 3) Absence of tumor growth at critical anatomical sites (e.g., leptomeningeal disease) that could not be managed by protocol-allowed medical interventions; 4) Evidence of clinical benefit as assessed by the investigator.

Safety assessments were performed before each administration. See detailed safety monitoring plans and clinical tests specified for this study in Section 7.3 of this review.

Assessment of tumor response by RECIST v1.1 occurred every 6 weeks for the first 36 weeks and every 9 weeks thereafter. For patients randomized to docetaxel, assessments continued until disease progression per RECIST v1.1, regardless of whether treatment was discontinued. Patients randomized to atezolizumab underwent assessments until disease progression per modified RECIST or until treatment discontinuation (for patients who continued to receive atezolizumab following disease progression). In the absence of disease progression, tumor assessments continued regardless of whether patients started new anti-cancer therapy, until consent was withdrawn, death, or study termination by the Applicant, whichever occurred first. Follow-up data capture, including subsequent anti-cancer therapies, continued for each patient until death, loss of follow-up, withdrawal of consent, or study termination by the Applicant, whichever occurred first.

Study Endpoints of POPLAR

Primary endpoints:

- Overall survival

Secondary endpoints:

- Progression-free survival (PFS) per RECIST 1.1 as determined by investigator assessment
- Objective response rate (ORR) per RECIST 1.1 by investigator assessment
- Duration of response (DOR)
- Patient-reported outcomes as assessed by the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30 (EORTC QLQ-C30) and the EORTC Lung Cancer Module (QLQ-LC13)

The endpoints used in POPLAR are defined and explained below:

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Table 6: POPLAR study endpoints

Endpoint	Definition/ explanation
Overall survival	Time from randomization to death from any cause.
Progression-free survival	Time from randomization to investigator-assessed disease progression or death from any cause, whichever occurred first.
Objective response rate	Percentage of patients who achieved either a confirmed complete response or partial response by investigators according to RECIST 1.1 criteria as their best confirmed response, relative to patients randomized.
Duration of response	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.
Patient reported outcome measures	<p>Collected using EORTC QLQ C-30 and QLC LC-13.</p> <p>Time to deterioration (TTD) in patient-reported lung cancer symptoms (cough, dyspnea, chest pain, arm/shoulder pain) was to be examined.</p> <p>TTD of lung cancer symptoms using EORTC was defined as the time from baseline to the first time the patient’s score shows a ≥ 10-point increase above baseline in any of the following EORTC transformed scores for cough, dyspnea, chest pain, or arm/shoulder pain, whichever occurred first. An increase in a score ≥ 10 points above baseline must be held for at least two consecutive cycles or an initial score increase of ≥ 10 points is followed by death within 3 weeks from the last assessment.</p>

Reviewer’s comment: As there was no alpha (type-I error rate) adjustments for any of the secondary endpoint analyses, results of these analyses are considered exploratory.

As described above, PFS, ORR, and DOR based on modified RECIST criteria were measured for patients on the atezolizumab arm only. Key differences between the conventional RECIST v1.1 and modified RECIST criteria are shown in Table 7.

Table 7: Comparisons between RECIST v1.1 vs. modified RECIST criteria

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	RECIST v1.1	Modified RECIST
New lesions after baseline	Define progression	New measurable lesions are added into the total tumor burden and followed.
Non target lesions	May contribute to the designation of overall progression	Contribute only in the assessment of a complete response
Radiographic progression	First instance of $\geq 20\%$ increase in the sum of diameters or unequivocal progression in non-target disease	Determined only on the basis of measurable disease; may be confirmed by a consecutive assessment ≥ 4 weeks from the date first documented

Statistical Analysis Plan

POPLAR planned to enroll approximately 285 patients and approximately 55 PD-L1 IC2/3 patients, based on PD-L1 expression prevalence estimates. The power and 95% CIs for OS and PFS in the PD-L1 IC2/3 subset were based on the following assumptions: Event times are exponentially distributed, median PFS in the control arm is 3 months, median OS in the control arm is 8 months, and patients are enrolled over 8 months. As per the initial SAP, the primary OS analysis was to be performed when a total of approximately 150 deaths had been observed in the overall population.

Table 8: Power and 95% CI for proposed study design for true underlying OS and PFS values

	ITT population		PD-L1 IC2/3 subpopulation	
	OS	PFS	OS	PFS
True HR assumed	0.65	0.7	0.5	0.5
Median (months)	8 vs. 12.3	3 vs. 4.3	8 vs. 16	3 vs. 6
Number of event expected	150	247	27	45
Power of log-rank test (alpha=0.05, 2-sided)	75%	80%	44%	64%
95% CI for the observed HR*	(0.47, 0.90)	(0.54, 0.90)	(0.23, 1.06)	(0.28, 0.90)

* 95% CI for Proposed Study Design for True Underlying OS and PFS HR values

An interim efficacy analysis was to be performed when approximately 30, and 100 events in the overall population occurred. A small alpha of 0.0001 and 0.0001 was spent for the first and second planned interim analyses of OS, respectively. The primary OS analyses were to be CDER Clinical Review Template 2015 Edition
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conducted at the 4.98% level of significance.

The primary efficacy endpoint for this trial was duration (in months) of OS. Data for patients not reported as having died at the time of analysis was to be censored at the date when they were last known to be alive. Patients without post-baseline information were to be censored at the date of randomization plus 1 day. Comparison with respect to OS between the treatment arms within the ITT population was to be based on a stratified log-rank test. Both stratified and unstratified analyses were to be performed. Given the expected small sample sizes in the subsets defined on the basis of TC and IC levels, analyses in the PD-L1 selected subsets were to be based on an unstratified log-rank test.

Kaplan-Meier methodology was to be used to estimate the median OS for each treatment arm and to construct survival curves for the visual description of the difference between the treatment arms. The Brookmeyer-Crowley methodology was to be used to construct the 95% CI for the median OS for each treatment arm (Brookmeyer and Crowley 1982). The hazard ratio, λ_A/λ_B , where λ_A and λ_B represent the hazard of death in Arm A (atezolizumab) and Arm B (docetaxel), respectively, was to be estimated in the ITT population using a stratified Cox regression model with the same stratification variables used in the stratified log-rank test, including 95% CIs. An unstratified hazard ratio was to be estimated for the ITT population and for the PD-L1-selected subsets

In the protocol version 6 (24 February 2015) and SAP version 1 (14 July 2015), the Applicant increased 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.

An additional change introduced in the SAP version 1 (14 July 2015) was a procedure for a testing hierarchy for OS. This was to start with the subgroup of TC2/3 or IC2/3 at the two-sided alpha level of 4.98%. If the null hypothesis were to be rejected, the test was to continue to the TC1/2/3 or IC1/2/3 subgroup at the same 4.98% level of significance. If the null hypothesis for the test on TC1/2/3 or IC1/2/3 were to be rejected, the OS for ITT was to be tested at the two-sided significance level of 4.98%. If the null hypothesis for the test on ITT were to be rejected, the OS for TC3 or IC3 was to be tested at the two-sided significance level of 4.98%. At the time of this OS analysis, it was projected that approximately 29 events would be observed for the TC3 or IC3 subgroup, 65 events for the TC2/3 or IC2/3 subgroup, and 122 events for the TC1/2/3 or IC1/2/3 subgroup. Assuming a target HR of 0.35 for TC3 or IC3, 0.5 for TC2/3 or IC2/3, and 0.6 for TC1/2/3 or IC1/2/3, all tests will have 80% power, with a minimum detectable HR of 0.480 for TC3 or IC3, 0.616 for TC2/3 or IC2/3, and 0.699 for TC1/2/3 or IC1/2/3.

Reviewer's comment: The Applicant discussed the planned revision of the final OS analysis from the 150 event analysis to the 180 event analysis at the type B meeting held on May 12,

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2015 (see section 3). The FDA stated that the agency considers the OS analysis based on approximately 150 deaths as the final OS analysis, and that an updated analysis based on 180 deaths would be considered as an exploratory analysis only. The FDA also stated that OS, PFS and other efficacy analysis results in PD-L1 subgroups would also be considered as supportive or exploratory.

On July 11, 2016, the Applicant responded to the FDA's information request regarding the February 2015 protocol amendment, and admitted that they had looked at the analysis results based on 150 deaths before initiating the protocol amendment to increase the event number from 150 to 180. Given this information, in this review the pre-specified OS analysis based on 150 death events in the ITT population is considered as the primary analysis. Updated OS analyses with more death events are more mature data are considered as exploratory. There were two such OS updated submitted; one update with a data cutoff date of May 8, 2015 (when 173 deaths had occurred), and a second update with a data cutoff-date of January 1, 2015 (when 200 deaths had occurred). The applicant also submitted updated OS results from an additional analysis of 200 deaths. Although these data were used to assess the maturity of the OS results, these results were also considered exploratory.

For this reason, although in the protocol version 6, SAP, and CSR, the Applicant refers to the 150 death analysis as the "third interim analysis", and to the 180 event analysis of May 8, 2015 as the "final analysis", FDA considers the 150 event analysis to be the final efficacy analysis.

In the study protocol, there was no multiplicity adjustment for efficacy analyses by PD-L1 status. The SAP version 1 did specify a testing hierarchy for OS to control type I error starting in the various PD-L1 subgroups. However, since the SAP was finalized after the Applicant knew the 150 death analysis results including PD-L1 subgroup analyses, final PD-L1 subgroup analyses are considered as exploratory.

Additionally, the study randomization was stratified by IC status and not TC status. TC score was retrospectively derived from raw percentage staining score at enrollment. Therefore, there was potential for imbalance between treatment arms within each PD-L1 subgroup in terms of TC staining in each group, since this was not a pre-specified stratification factor (see demographics table in section 6).

Protocol Amendments (adapted from page 91 of POPLAR CSR)

The first version of the protocol was issued on 30 April 2013. Five subsequent amendments are summarized below;

1. Protocol Amendment 1 – 29 July 2013.

Minor corrections and modifications were made to the inclusion/exclusion criteria, laboratory assessments, and concomitant medications sections of the protocol.

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2. Protocol Amendment 2 – 30 January 2014.

The protocol was revised to continue enrolling patients until approximately 54 patients who were PD-L1–positive (IC2/3) 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.

3. Protocol Amendment 3 – 21 May 2014.

Treatment duration for atezolizumab was modified to allow patients to be treated until clinical benefit was no longer being experienced and not for a maximum of 16 cycles/12-months as initially planned. The frequency of tumor assessments after 36 weeks changed 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 changed from when 30 and 60 deaths were observed to when approximately 30 and 100 deaths had occurred. The AE/safety follow-up period changed from 90 to 30 days due to the low frequency of significant drug-related AEs following treatment discontinuation across studies.

4. Protocol Amendment 4 – 25 July 2014.

In this amendment, the safety follow-up period was changed back to the original 90 days to allow further evaluation of safety after treatment discontinuation.

5. Protocol Amendment 5 – 24 February 2015.

This protocol amendment 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. This change was made to characterize the potential delayed treatment benefit of anti–PD-L1 therapy. Additionally, while initial stratification by PD-L1 IHC status was based on PD-L1 expression on immune cells, this protocol modification allowed for subgroup analyses based on other categories of PD-L1 expression including expression on tumor cells.

Reviewer’s comment: As described previously, an IR to the Sponsor confirmed that the February 2015 protocol amendment which changed the analysis event threshold to 180 deaths from 150 deaths, and changed the subgroup analysis to allow for tumor cell PD-L1 expression, was formulated after the data monitoring committee knew the results of the 150-death analysis. For this reason, all subsequent OS analyses, including the 180-event and the 200-event analyses, are considered exploratory. The subgroup analyses based on PD-L1 expression were also changed during the February 2015 amendment, once the previous results were known. These analyses are therefore also considered exploratory.

Data Quality and Integrity: Sponsor’s Assurance

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The Sponsor assumed responsibility for data management of this study, including quality checking of the data. Data entered manually was collected via EDC using eCRFs. Sites were responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor requested data clarification from the sites, which the sites resolved electronically in the EDC system.

5.3.2. Study Results

Compliance with Good Clinical Practices

The Applicant attested that the clinical trials were conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The Applicant also specified that the trials conducted under the relevant INDs complied with FDA regulations and applicable local, state, and federal laws in the United States.

Financial Disclosure

Disclosure of the financial interests of the investigators involved in the clinical trials was submitted in the FDA form 3454. For study POPLAR, 1 sub-investigator of 822 did not submit their financial disclosure information. Overall, there were 2 out of 821 (0.002%) sub-investigators who had disclosable information. The two investigators with disclosures are identified below-

Table 9: POPLAR investigators with disclosable financial interests

Study	Site ID	#	Investigator	PI/sub-investigator or	Disclosure
GO28753			(b) (6)	Principal Investigator	Received honoraria of ~\$35,000
GO28753				Sub-Investigator	Stockholder; Owns 2000 shares of Roche holdings (worth ~\$128,000)

The disclosure was certified by Eric Olson, Vice President of Regulatory Affairs of the Applicant, showed all other investigators required to disclose a proprietary interest or a significant equity in the Applicant did not disclose any such interests and that no investigators listed in Form 3455 received significant payments of other sorts as defined in 21CFR 54.2 (f).

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Reviewer's comment: Overall, the two investigators with disclosable financial interests represent a small fraction of the total number of investigators involved in POPLAR, and patients enrolled at their sites were few. Given that POPLAR relied on overall survival as its primary endpoint, financial issues are less likely to affect the analyses that demonstrate the effectiveness of atezolizumab in NSCLC.

Patient Disposition

From August 5, 2013 until March 31, 2014, a total of 287 patients from 61 clinical sites in 13 countries were randomized 1:1 to receive atezolizumab vs. docetaxel. There were 143 patients randomized to the docetaxel arm and 144 patients to the atezolizumab arm.

Initially, a total of 527 patients were screened for POPLAR; 240 of these patients failed screening. The most common reasons for screen failure were known active or untreated CNS metastases (56 patients) or inability to provide appropriate tumor specimens for analysis (47 patients).

Reviewer's comment: The fact that the presence of CNS metastases that did not meet enrollment criteria was the most common reason for screen failure in patients screened for POPLAR is notable, as this may affect generalizability to the overall second-line metastatic NSCLC setting. This is a setting in which brain metastases are extremely common, and it is important to note that only 23 patients with brain metastases were included among the 287 patients enrolled on POPLAR, representing less than 30% of patients with brain metastases who were initially screened for enrollment.

As of the January 30, 2015, 150-event data cut-off date for the primary final survival analysis, 4 patients (3%) in the docetaxel arm and 30 patients (21%) in the atezolizumab arm were still receiving study treatment. A further 45 patients (32%) in the docetaxel arm and 38 patients (26%) in the atezolizumab arm were alive and in the survival follow-up period. A total of 17 patients (12 in the docetaxel arm and 5 in the atezolizumab arm) had withdrawn from the study for reasons other than death.

By the May 8, 2015 updated 173-event analysis, 1 patient (0.7%) in the docetaxel arm and 24 patients (17%) in the atezolizumab arm were still receiving the study treatment. A further 36 patients (25%) in the docetaxel arm and 36 patients (25%) in the atezolizumab arm were alive and in the survival follow-up period.

By the December 1, 2015 updated 200-event analysis, no patients in the docetaxel arm and 18 patients (13%) in the atezolizumab arm were still receiving the study treatment. A further 31 patients (22%) in the docetaxel arm and 36 patients (14%) in the atezolizumab arm were alive

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and in the survival follow-up period.

Reason for treatment discontinuation at each data cutoff as well as reason for initial non-treatment is given below.

Table 10: Reason for treatment discontinuation in patients on POPLAR (based on POPLAR datasets ADSL)

	Atezolizumab (n = 144) n (%)	Docetaxel (n = 143) n (%)
Randomized	144 (100)	143 (100)
Not Treated	2 (1)	8 (6)
Physician Decision	1 (<1)	0
Other ^a	1 (<1)	0
Patient Decision	0	7 (5)
Death	0	1 (<1)
Treated	142 (99)	135 (94)
Status as of January 30, 2015	(N=142) n (%)	(N=135) n (%)
On Treatment	30 (21)	4 (3)
Discontinued From Treatment	112 (79)	131 (97)
Due to Disease Progression	97 (68)	84 (62)
Due to Death	2 (1)	1 (<1)
Due to AE	11 (8)	30 (22)
Due to Physician Decision	0	7 (5)
Due to Withdrawal by Subject	2 (1)	9 (7)
Status as of May 8, 2015	(N=142) n (%)	(N=135) n (%)
On Treatment	24 (17)	1 (<1)
Discontinued From Treatment	118 (83)	134 (99)
Due to Disease Progression	102 (72)	86 (64)
Due to Death	2 (1)	1 (<1)
Due to AE	12 (8)	31 (23)
Due to Physician Decision	2 (1)	7 (5)
Due to Withdrawal by Subject	0	9 (7)
Status as of December 1, 2015	(N=142) n (%)	(N=135) n (%)
On Treatment	18 (13)	0 (0)
Discontinued From Treatment	124 (87)	135 (100)
Due to Disease Progression	107 (75)	86 (64)
Due to Death	2 (1)	1 (<1)

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	Atezolizumab (n = 144) n (%)	Docetaxel (n = 143) n (%)
Due to AE	13 (9)	31 (23)
Due to Physician Decision	2 (1)	10 (5)
Due to Withdrawal by Subject	0	7 (5)

³One patient on Atezolizumab was randomized in error initially; error was listed as “CKD-EPI too low”; the patient was not treated for that reason. By later data cut-offs, this patient had died.

The numbers in the above table were calculated using the dataset ADSL provided by the applicant, and were found to correlate with the disposition tables in the POPLAR CSR for both the January 2015 and May 2015 data cut-off dates as well as with the disposition table in the supplemental results report for the December cut-off date.

Overall, the disposition of patients did not differ markedly between the two study arms, with the following exceptions:

1. There were 7 patients randomized to the docetaxel arm but not treated due to patient decision. As this was an open-label study, the withdrawal of patients from control arm prior to treatment is not unexpected. None of these patients received subsequent immunotherapy as per dataset ACM; in fact, as per dataset ACM these patients did not receive subsequent anticancer therapy at all.

Reviewer’s comment: A sensitivity analysis was performed to assess if these patient withdrawals affected the OS analysis; these were found to not have a significant effect on overall OS results.

2. The ADSL database was matched with the AAE dataset as well as patient narratives to ensure that all patients listed as discontinuing therapy due to AEs in the table above as of the May 8, 2015 data cut-off date were accounted for; this was in fact verified.

Reviewer’s comment: Docetaxel patients were more likely to withdraw due to adverse events than those on the atezolizumab arm, but due to the cytotoxic nature of this chemotherapy, this is not unexpected.

3. As of the May 8, 2015 data cut-off date, there were 9 patients on the docetaxel arm, compared to none on the atezolizumab arm, who discontinued treatment due to “physician decision”. Review of the CRFs for these patients revealed that in six of these cases, the patient was thought to have clinical progression and/or lack of efficacy benefit by the investigator despite not meeting criteria for PD. However, in 3 cases, patients were discontinued from therapy due to physician decision to stop prior to the protocol-specified length of therapy. In one patient, therapy was stopped after having received a prolonged course of therapy, for 16 cycles, on study day 358. However, in two cases, patients were discontinued from therapy after 6 cycles only, due to physician decision, as this was listed as

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the standard number of cycles of docetaxel that the physician was accustomed to using in this setting.

Reviewer’s comment: A sensitivity analysis was performed to assess if this early treatment discontinuation for patients on the docetaxel arm affected the OS analysis, and this was found to have no significant effect on OS.

4. Withdrawal due to progressive disease events was higher at all data cutoff points on the atezolizumab arm than on the docetaxel arm.

Reviewer’s comment: This result is notable, especially given the fact that patients on the atezolizumab arm were allowed to be treated beyond RECIST v1.1-defined progressive disease. In fact, 61 patients (42%) randomized to the atezolizumab arm were treated beyond RECIST v1.1-defined progression. The fact that withdrawals due to progressive disease were more common on the atezolizumab arm, yet there was still an OS advantage seen for atezolizumab overall (see primary efficacy endpoint evaluation) may signify that there is a different response pattern and/or different response kinetics, and that survival benefit may persist for these patients beyond duration of treatment and in fact beyond the point where ‘progressive disease’ has developed.

This issue is also likely reflected in the PFS difference discussed below, as atezolizumab had an inferior median PFS than docetaxel (although this difference was not statistically significant).

Table 11: Study POPLAR patient withdrawals from study (source: dataset ADSL)

	Atezolizumab (n=144) n (%)	Docetaxel (n=143) n (%)
Study disposition as of January 30, 2015		
Still on treatment	30 (21)	4 (3)
Alive and in survival follow-up	38 (26)	45 (32)
Died	71 (49)	82 (57)
Discontinued study for reasons other than death	5 (3)	12 (8)
Lost to follow-up	1 (<1)	0
Other ^a	1(<1)	0
Withdrawal by subject	3 (2)	12 (8)
Study disposition as of May 8, 2015		
Still on treatment	24 (17)	1 (<1)
Alive and in survival follow-up	36 (25)	36 (25)
Died	78 (54)	93 (65)
Discontinued study for reasons other than death	6 (4)	13 (9)
Lost to follow-up	1 (<1)	1 (<1)
Withdrawal by subject	5 (4)	12 (8)
Study disposition as of December 1, 2015		

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	Atezolizumab (n=144) n (%)	Docetaxel (n=143) n (%)
Still on treatment	18 (13)	0
Alive and in survival follow-up	31 (22)	20 (14)
Died	89 (62)	108 (76)
Discontinued study for reasons other than death	6 (4)	15 (10)
Lost to follow-up	1 (<1)	2 (1)
Withdrawal by subject	5 (4)	13 (9)

^aReason for study discontinuation in one patient with progressive disease on atezolizumab was initially listed as 'other' but was changed to 'withdrawal by subject in subsequent datasets; this reflects listed CRF reason.

By the May 8, 2015 data cutoff date, there were 19 patients who were lost to follow-up or withdrew from study. Only one of these patients had a BOR of PR; all others had BOR of SD or PD. The patient with a PR was on Docetaxel and later withdrew from treatment and from study without evidence of progressive disease (259313-213083). Otherwise, there were 4 patients on the Docetaxel arm and 5 on the atezolizumab arm who discontinued therapy because of progressive disease who later withdrew from the study or were lost to follow-up (1 per arm).

Reviewer comment: Withdrawals from the study in patients with progressive disease were relatively rare and happened with similar frequency in each arm; overall this is not expected to significantly affect study outcome.

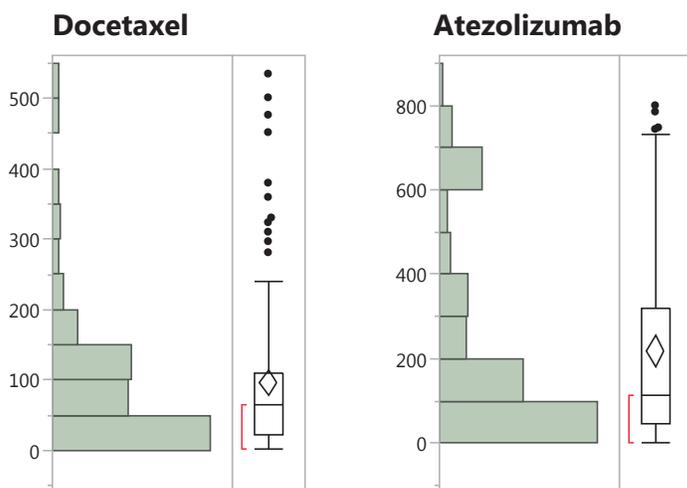
Table 12: Study POPLAR treatment duration (source: dataset ADSL, January 1, 2015 data cut-off)

Duration of treatment (days)	Docetaxel (n=135)	Atezolizumab (n=142)
Mean	96	220
Median	65	112
25% Quartiles	22,110	45,321

Treatment duration, in days:

Figure 2: POPLAR treatment duration (source: dataset ADSL, January 1, 2015 data cut-off)

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Reviewer’s comment: *Patients were treated for a longer mean and median time on atezolizumab, likely due to a combination of factors including the open-label nature of the trial, the improved toxicity profile of atezolizumab compared to docetaxel, the fact that patients on atezolizumab were allowed to be treated beyond progression while those on docetaxel were not, and the efficacy difference between arms.*

Protocol Violations/Deviations

In terms of major protocol deviations, based on the January 30, 2015 (150-event) cutoff date, a total of 35 patients (18 in the atezolizumab arm and 17 in the docetaxel arm) had major protocol deviations during the study.

By the May 8, 2015 (180 event) cutoff date, there were 41 deviations reported in 37 patients, with 4 patients having >1 each. Table 13 shows the breakdown of protocol deviations by arm and type.

Table 13: Study POPLAR, major protocol deviations (Source: dataset ADV, May 8, 2015 data cutoff)

	Atezolizumab (n = 144)	Docetaxel (n = 143)
Protocol Deviations	17 patients (11.8%);	20 patients (14%);
Total number	19 violations	22 violations
Eligibility Violations	10 violations; 9 patients (tests or labs outside windows-4, prior prohibited therapy-1, no signed ICF-1, excluded positive viral test-1, does not meet prior NSCLC therapy requirements-1, CNS metastases-	14 violations; 12 patients (CNS metastases-5, tests or labs outside window or outside limits-4, excluded autoimmune disease-2, prior prohibited therapy-1, other-1, does not meet prior NSCLC therapy

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	Atezolizumab (n = 144)	Docetaxel (n = 143)
	1,other-1)	requirements-1)
Study procedure violations	9 violations, 8 patients (prohibited concomitant therapy-2, other-2, missed assessment or assessment out of window-5)	8 violations, 8 patients (missed assessments-7, expired drug-1)

Based on the review of the reported violation types, key protocol violations that were thought to affect overall efficacy assessments were identified in 33 patients. These violations include those who missed protocol-scheduled protocol assessments, those who did not meet previous lines of therapy for NSCLC treatment, as well as those listed under “Other” in Table 15.

Reviewer’s comment: A sensitivity analysis was performed to assess if inclusion of the results of the patients with major protocol deviations affected the final OS analysis, both using the data cut-off date of January 30, 2015 as well as the updated data cut-off date of May 8, 2015; efficacy results for OS were not found to be significantly affected in either case.

Table of Demographic Characteristics

The following represents the baseline characteristics of the POPLAR analysis population. The median age of patients enrolled on the study was 62 years old (range 36-84 years); sixty-one percent of the randomized patients were males; seventy-nine percent were white; sixty-eight percent were ECOG PS 1 and 32% were ECOG PS 0.

Table 14: Study POPLAR, demographics characteristics of the primary analysis population (source: dataset ADSL, May 2015 cut-off)

Demographic Parameters	Docetxel (N=143) n (%)	Atezolizumab (N= 144) n (%)	Total (N=287) n (%)
Sex			
Male	76 (53%)	93 (65%)	169 (61%)
Female	67 (47%)	51 (35%)	118 (41%)
Age			
Mean years (SD)	61.7 (9.4)	61.4 (9.2)	61.5 (9.3)
Median (years)	62	62	62
Min, max (years)	36,84	(42,82)	36,84
Age category			
<65	87 (60%)	87 (61%)	174 (61%)
≥65	57 (40%)	56 (39%)	113 (39%)
Race			
White	116 (81%)	110 (76%)	226 (79%)

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Demographic Parameters	Docetxel (N=143) n (%)	Atezolizumab (N= 144) n (%)	Total (N=287) n (%)
Black or African American	4 (3%)	3 (2%)	7 (2%)
Asian	13 (9%)	23 (16%)	36 (13%)
American Indian or Alaska Native	1 (0.7%)	0	1 (0.3%)
Native Hawaiian or Other Pacific Islander	0	2 (1%)	2 (0.7%)
Other/Unknown	9 (6%)	6 (4%)	15 (5%)
Tobacco use			
Never	29 (20%)	27 (19%)	56 (20%)
Current	21 (15%)	25 (17%)	46 (16%)
Previous	93 (65%)	92 (64%)	185 (65%)
ECOG PS			
0	46 (32%)	48 (32%)	94 (32%)
1	97 (68%)	96 (67%)	193 (68%)

Reviewer’s comment- Baseline demographics were generally well-balanced between arms, although there were more males and more Asians on the atezolizumab arm. There were very few Black or African-American patients enrolled on the study (7 total), which could affect generalizability and applicability of study results to the US population.

Table 15: Other Baseline Characteristics (Source: ADSL, May 2015 cutoff)

Disease characteristic	Docetaxel (N=143)	Atezolizumab (N= 144)	Total (N=287)
Disease Extent			
Metastatic	138 (97%)	136 (94%)	274 (95%)
Locally Advanced	5 (4%)	8 (6%)	13 (5%)
Histology			
Squamous	48 (34%)	49 (34%)	97 (34%)
Non-Squamous	95 (66%)	95 (66%)	190 (66%)
Metastasis site			
Visceral			
Liver	33 (23%)	33 (23%)	66 (23%)
Bone	46 (32%)	35 (24%)	81 (28%)
Brain	15 (10%)	8 (6%)	23 (8%)
Pleural effusion	27 (19%)	41 (28%)	68 (24%)
Lung	125 (87%)	132 (92%)	257 (90%)
Number of prior therapies			
One	96 (67%)	93 (65%)	189 (66%)
Two or more	47 (33%)	51 (35%)	98 (34%)

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Disease characteristic	Docetaxel (N=143)	Atezolizumab (N= 144)	Total (N=287)
EGFR			
positive	8 (6%)	11 (8%)	18 (7%)
negative	74 (52%)	74 (51%)	148 (52%)
unknown	61 (43%)	61 (42%)	122 (43%)
EML4/ALK			
positive	3 (2%)	0	3 (1%)
negative	55 (38%)	59 (41%)	114 (40%)
unknown	85 (59%)	83 (58%)	168 (59%)

Reviewer’s comment: Baseline disease-related characteristics were well-distributed between arms. Of note, only a small number of patients were known to have tumors that tested positive for EGFR mutation or ALK rearrangements, although in 43% and 59% of patients overall, the status of these targetable genetic alterations were unknown. Although the protocol allowed patients to enroll with treated and clinically stable brain metastases, few patients with brain metastases were included in the analysis population (8%); as noted previously, patients with brain metastases were likely to be excluded from enrollment completely due to not meeting the eligibility criteria related to baseline stability of these brain metastases. This may impact the generalizability of these results to a more general, non-study population.

Table 16: PD-L1 staining at baseline (source: dataset ADSL, May 8, 2015 cut-off)

	Control Group (N=143)	Treatment Group (N= 144)	Total (N=287)
IC levels			
0	63 (44.1%)	62 (43.1%)	125 (43.6%)
1	54 (37.8%)	53 (36.8%)	107 (37.3%)
2	18 (12.6%)	19 (13.2%)	37 (12.9%)
3	8 (5.6%)	10 (6.9%)	18 (6.3%)
TC levels			
0	82 (57.3%)	96 (66.7%)	178 (62%)
1	21 (14.7%)	19 (13.2%)	40 (13.9%)
2	25 (17.5%)	14 (9.7%)	39 (13.6)
3	15 (10.5%)	15 (10.4%)	30 (10.5%)
IC1/2/3 or TC1/2/3			
IC1/2/3 or TC1/2/3	102 (71.3%)	93 (64.6%)	195 (67.9%)
TC0 and IC0	41 (28.7%)	51 (35.4%)	92 (32.1%)
IC 2/3 or TC 2/3			
IC 2/3 or TC 2/3	55 (38.5%)	50 (34.7%)	105 (36.6%)
IC 0/1 or TC 0/1	88 (61.5%)	94 (65.3%)	182 (63.4%)
IC3 or TC3			

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	Control Group (N=143)	Treatment Group (N= 144)	Total (N=287)
IC3 or TC3	23 (16.1%)	24 (16.7%)	47 (16.4%)
IC 0/1/2 or TC 0/1/2	120 (83.9%)	120 (83.3%)	240 (83.6%)

Reviewer’s comment: *The above data represent the distribution of patients when different cutoff points are used in defining PD-L1 positivity. Since PD-L1 expression at various levels may have prognostic implications, and to balance the staining groups between arms, the study was designed with PD-L1 expression at baseline as a stratification factor. As explained previously, the pre-specified stratification of PD-L1 was based on immune cell staining only. Analysis of tumor cell immune staining was not prespecified but was added during protocol amendment 5, which allowed for additional analyses to be done on subgroups that were not pre-specified.*

Adding the TC staining did in fact change the makeup of those included in the various staining subgroups, since correlation between levels of TC and IC staining is far from exact. In an extreme example, it is noted that among the highest-expressing subgroups of TC3 and IC3, there was almost no overlap of patients; i.e. there is only 1 patient of 47 in the highest-staining subgroup of TC3/IC3 who had both TC3 and IC3 levels of staining; all others were included in this highest-staining subgroup because they either had TC3 or IC3 staining, not both.

IC staining was a prespecified study stratification factor, and as expected, IC staining is well-balanced between arms in all levels of staining. Importantly, however, although stratification was pre-specified by IC staining and not TC staining, there appears to be a generally balanced distribution of patients in various TC staining subgroups between arms. The exception is in the TC2 subgroup, which was found approximately 8% more commonly in the Docetaxel arm, and in the TC0 subgroup, which was found approximately 9% more commonly in the Atezolizumab arm. On the one hand, this finding would be expected to bias the final OS result in favor of the Docetaxel arm, as more of the biomarker-positive patients are included in this arm and are not exposed to Atezolizumab, the therapy that would be expected to target PD-L1 expression. Alternatively, if higher levels of TC PD-L1 expression is indeed a poor prognosticator¹², then this would in theory bias the final OS results in favor of the Atezolizumab arm.

Overall, the relatively small numbers of patients represented by this imbalance, as well as the competing effects of this imbalance as described above, are unlikely to have a significant effect on the final efficacy results.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Using dataset ACM at the May 2015 data cutoff, the following analyses were undertaken of

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concomitant and/or subsequent medication use:

1. Concomitant pain medication
2. Concomitant systemic steroid use
3. Subsequent cancer-related systemic therapy

A search of narcotic and analgesic pain medications used in the treatment phase of therapy revealed that 84 atezolizumab and 62 docetaxel patients were started on analgesic pain medications over the course of the study. However, this appears to be partially driven by the fact that patients on the atezolizumab arm were generally on study therapy for a longer period of time, with median start day for use of pain medications of day 37 (range 2-430) and mean day 84.9 (95% CI 71-99) for patients on atezolizumab compared to median start day of 32 (range 2-435) and mean day 66.7 (95% CI 55-79) for patients on docetaxel.

Reviewer's comment: The fact that narcotic and analgesic pain medication was more commonly used in the atezolizumab arm may be a reflection of the fact that these patients were generally on study therapy and/or alive for a longer period of time. See above section on mean and median duration of therapy for Docetaxel vs. Atezolizumab .

As expected, likely driven by toxicity management for suspected immune-mediated adverse events, systemic steroid use in the treatment phase of therapy (for reasons other than chemotherapy prophylaxis or contrast prophylaxis or treatment of brain metastases) was more common among the atezolizumab arm vs. the docetaxel arm (31 patients vs. 24 patients). Systemic steroid use in patients on Atezolizumab had a median start date of day 68, mean day 101 (95% CI 86-117) vs patients on the Docetaxel arm, with a median start day 58, mean day 98 (95% CI 57-138). However, systemic steroid use in terms of absolute number of times systemic steroids were used per arm was far more common on the atezolizumab arm, with use of new systemic steroids occurring in 110 instances on atezolizumab as opposed to 32 instances on the docetaxel arm.

Reviewer's comment: The disproportionate use of systemic steroids in this setting is known and expected as a result of per-protocol toxicity management of immune-related AEs (see section 8.5.14, and is essentially common to all immunotherapy trials; effects on efficacy have been discussed previously¹³ and any effects would be expected to bias the result away from atezolizumab.

Data on subsequent cancer therapies were reviewed for both arms. At the time of primary analysis for OS on January 30, 2015, 29 patients on the atezolizumab arm (20%) and 19 on the docetaxel arm (13%) had received least one non-protocol anti-cancer treatment post study treatment. The table below presents updated data on anticancer therapy received by patients up to May 8, 2015, which was the date of the first updated OS analysis and corresponds with data in the POPLAR CSR. At that point, 58 patients (40%) initially randomized to atezolizumab had received 102 post-protocol anticancer therapies, and 59 patients (41%) initially randomized to docetaxel had received 109 therapies post-protocol anticancer therapies. Patients on the

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docetaxel arm were not allowed to cross over to atezolizumab on protocol.

Table 17: Subsequent anti-cancer therapies (source: ACM, data cutoff date May 8, 2015).

	Atezolizumab (n=144)	Docetaxel (n=143)
Total	58 patients, 106 therapies	59 patients, 109 therapies
Lines	Mean 1.8	Mean 1.8
1	32	28
2	12	14
3	9	11
4	5	3
5	0	1
Chemotherapy	54 patients, 85 therapies	45 patients, 73 therapies
Carboplatin	8 (6%)	10 (7%)
Cisplatin	5 (3%)	3 (2%)
Docetaxel	39 (27%)	2 (1%) ^a
Etoposide	1 (<1%)	1 (<1%)
Gemcitabine	12 (8%)	24 (17%)
Irinotecan	3 (2%)	2 (1%)
Paclitaxel	4 (3%)	5 (3%)
Mitomycin	0	1 (<1%)
Nab-paclitaxel	3 (2%)	0
Pemetrexed	6 (4%)	9 (6%)
Vinorelbine	4 (3%)	16 (11%)
Targeted therapy	17 patients, 17 therapies	19 patients, 20 therapies
Afatinib	1 (<1%)	2 (1%)
Bevacizumab	1 (<1%)	0
Ceritinib	1 (<1%)	1 (<1%)
Cetuximab	0	1 (<1%)
Crizotinib	0	1 (<1%)
Dovitinib	0	1 (<1%)
Erlotinib	8 (6%)	12 (8%)
Gefitinib	3 (2%)	1 (<1%)
Panitumumab	1 (<1%)	0
Poziotinib	0	1 (<1%)
Ramucirumab	2 (1%)	0
Immunotherapy	0	7 patients, 7 therapies
Atezolizumab	0	2 (1%)
Lambrolizumab	0	1 (<1%)
MEDI4736	0	1 (<1%)
Nivolumab	0	3 (2%)
Other investigational	0	8 patients, 9 therapies

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	Atezolizumab (n=144)	Docetaxel (n=143)
agent/unknown		
AM0010 (Recombinant IL-10)	0	1 (<1%)
BB1608 (cancer stem cell inhibitor)	0	2 (1%)
BGJ398 (FGFR inhibitor)	0	1 (<1%)
NUC-1031 (Gemcitabine protide)	0	1 (<1%)
Unknown	0	4 (3%)

^a Two patients on the docetaxel arm subsequently received docetaxel- one was re-challenged in the 5th line of therapy, and one continued as 3rd line of therapy after discontinuing treatment on the protocol.

Reviewer’s comment- Subsequent therapies were well-balanced between the two arms; an almost identical number of patients received subsequent cancer therapies in both arms (40.3% atezolizumab vs. 41.3% docetaxel); median lines of therapy were 1.8 in each patient receiving post-study anti-cancer therapy. Docetaxel patients were less likely to receive post-study chemotherapy than were atezolizumab patients. Although crossover was not allowed on protocol, 7 patients received subsequent anti-PD-L1 or anti PD-1 immunotherapy, including two who received atezolizumab. This may bias OS results in favor of the docetaxel arm, although the number of patients who received subsequent immunotherapy is small.

Efficacy Results – Primary Endpoint

The primary efficacy endpoint of the study was overall survival, which as per the original protocol was planned to occur when a total of approximately 150 deaths had been observed in the overall population. Interim efficacy analyses were to be performed when approximately 30 and 100 death events were observed. However, as described earlier, protocol amendment 5 dated February 24, 2015 changed the 150 event analysis to a third interim analysis and planned an additional 180 event analysis as the final OS analysis.

An information request was sent to the Applicant to ascertain whether this protocol amendment was made before or after the February 6, 2015 IMC meeting to review the results of the 150 event analysis was known; the Applicant responded that data from the 150 event analysis, which was originally specified as the final analysis, was known before protocol version 6 was initiated.

Below are included include OS analyses from the pre-specified primary analysis results (150 event), the first updated analysis (173 event), as well as the final updated analysis (200 events). Because the 150 event analysis was prespecified and additional analyses were not prespecified and were performed after study results were known, these additional analyses are considered exploratory only. P-value is therefore reported for the prespecified primary analysis (150

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event) but no p-value is reported for the first updated analysis (173 event) or the final updated analysis (200 event).

The pre-specified final OS analysis was conducted when 153 death events occurred at the study cut-off date of 30 January 2015. This demonstrated an improvement in median OS for patients in the atezolizumab arm compared to patients in the docetaxel arm; however, this result was not statistically significant, with a 1.9-month difference in median OS and a HR of 0.77 (95% CI: 0.56, 1.06; stratified two-sided log rank p-value =0.11). The results are summarized in Table 18 and the Kaplan-Meier curves are shown in Figure 3: **Study POPLAR, Kaplan-Meier Curves of Overall Survival in the ITT population (data cutoff date January 30, 2015).**

The median follow-up time for patients on the study was approximately 12 months in both arms as of the clinical cutoff date of January 30, 2015. At that point, a total of 18 patients (5 in the atezolizumab arm and 12 in the docetaxel arm) were lost to follow up, withdrew consent from study, or discontinued study due to a reason other than death.

Additionally as per FDA standard practice which follows the intent-to-treat principle, the primary analysis of OS is based on stratification data collected from the IxRS instead of from the eCRFs; this reassigned three patients based on discordance between stratification and eCRF histologic classification; 2 out of the 144 atezolizumab patients (1.4%), and 1 out of the 143 docetaxel patients (0.7%).

Table 18: Primary overall survival analysis in the POPLAR ITT population (data cutoff date January 30, 2015)

	Atezolizumab (N=144)	Docetaxel (N=143)
Number of deaths, n (%)	71 (49)	82 (57)
Median (95% CI), in months	11.4 (9.7, NE)	9.5 (8.6, 11.9)
Hazard ratio (95% CI) ^a	0.77 (0.55, 1.07)	
P-value ^b	0.11	

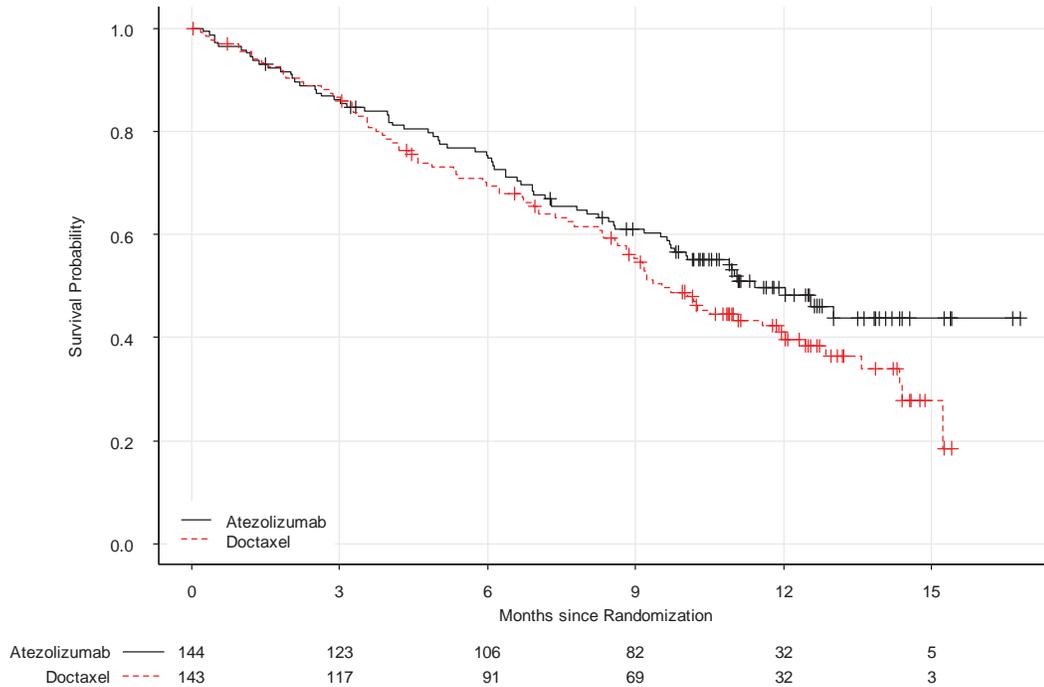
^a Hazard ratio was obtained from a Cox proportional hazards model stratified by PD-L1 IC status, number of prior chemo regimens, and histology as collected from IxRS.

^b P-value was calculated from a log-rank test stratified by PD-L1 IC status, number of prior chemo regimens, and histology as collected from IxRS.

NE: Not Estimable

Figure 3: Study POPLAR, Kaplan-Meier Curves of Overall Survival in the ITT population (data cutoff date January 30, 2015)

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The two updated OS analyses were performed when data had matured. The May 8, 2015 (173 death event) update was done with an additional 3 months of follow-up had occurred. The December 1, 2015 (200 death event) update was done when approximately 7 additional months of follow-up had occurred, corresponding to a median of 22 months of follow-up. Results of these updated OS analyses are presented below.

Figure 4: First updated OS cutoff May 8, 2015; 173 deaths

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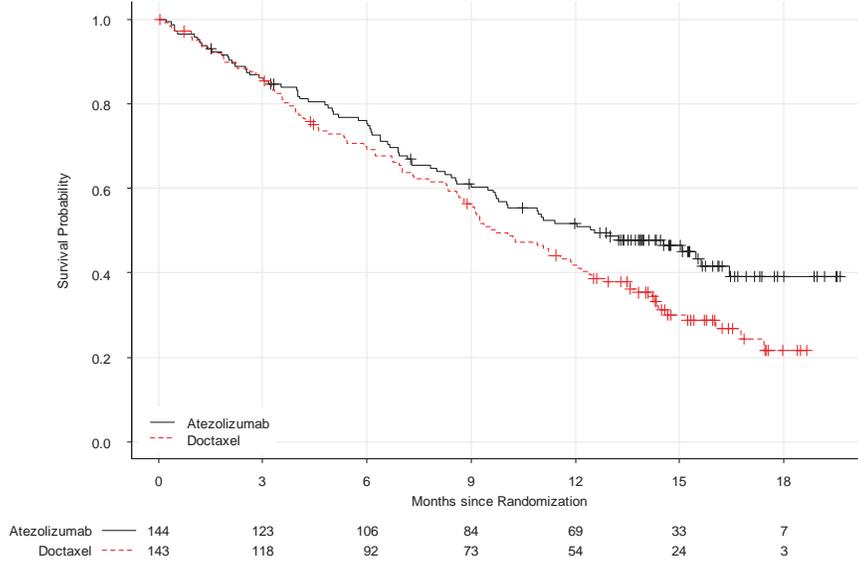
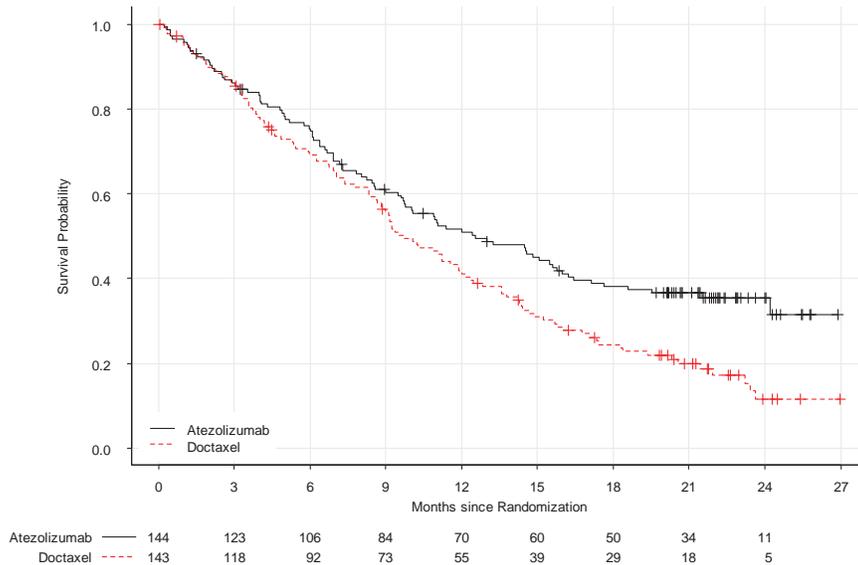


Figure 5: Second (final) updated OS cutoff December 1, 2015; 200 deaths



The median OS for each of the three analyses (primary analysis in addition to the two updates) are presented below.

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Figure 6: Median overall survival at each data cut-off; primary (January 30, 2015), first update (May 8, 2015), second and final update (December 1, 2015)

	Atezolizumab (N=144)	Docetaxel (N=143)
<u>Final preplanned analysis (1 Jan 2015)</u>		
Number of deaths, n (%)	71 (49)	82 (57)
Median (95% CI), in months	11.4 (9.7, NE)	9.5 (8.6, 11.9)
Hazard ratio (95% CI)	0.77 (0.55, 1.07)	
P-value	0.11	
<u>Update 1 (8 May 2015)</u>		
Number of deaths, n (%)	78 (54)	95 (66)
Median (95% CI), in months	12.6 (9.7, 16.4)	9.7 (8.6, 12.0)
Hazard ratio (95% CI) ^a	0.73 (0.54, 1.00)	
<u>Update 2 (1 December 2015)</u>		
Number of deaths, n (%)	90 (63)	110 (77)
Median (95% CI), in months	12.6 (9.7, 15.8)	9.7 (8.6, 12.0)
Hazard ratio (95% CI) ^a	0.69 (0.52, 0.92)	

^a Hazard ratio was obtained from a Cox proportional hazards model stratified by PD-L1 IC status, number of prior chemo regimens, and histology as collected from IxRS.

[Source: The applicant's response to the FDA's 26 April 2016 Information Request; OS update supplemental results report]

Reviewer's comment: The final preplanned analysis (150 event) showed a 1.9 month improvement in OS, although this did not reach statistical significance. As the data matured, the actuarial difference in OS between arms improved to 2.9 months. Additionally, the 95% CI surrounding the HR in the updated analyses (May 2015 and December 2015) did not cross 1.00. However, due to the fact that these analyses were not preplanned, these results are considered exploratory.

Data Quality and Integrity – Reviewers' Assessment

The data and analysis quality study POPLAR was acceptable to perform the efficacy review. Analyses were producible from the raw datasets provided in the BLA submission.

Efficacy Results – Secondary and other relevant endpoints

Secondary Endpoints

CDER Clinical Review Template 2015 Edition
 Version date: November 5, 2015 for initial rollout (NME/original BLA reviews)

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Secondary endpoints included progression-free survival and overall response rates. Analyses of these endpoints are presented below. Of note, these analyses are considered exploratory since no multiplicity adjustment was pre-specified for multiple endpoints. Therefore, all the p-values presented are nominal.

Progression-Free Survival

At the time of the primary OS analysis, the median duration of PFS per investigator assessment was 3.4 months in the docetaxel arm vs. 2.8 in the atezolizumab arm (HR=0.99; 95% CI: 0.75, 1.30). The results are summarized in Table 20 and the Kaplan-Meier curves are shown in Figure 7.

Table 19: PFS, final preplanned analysis (datat cutoff January 30, 2015)

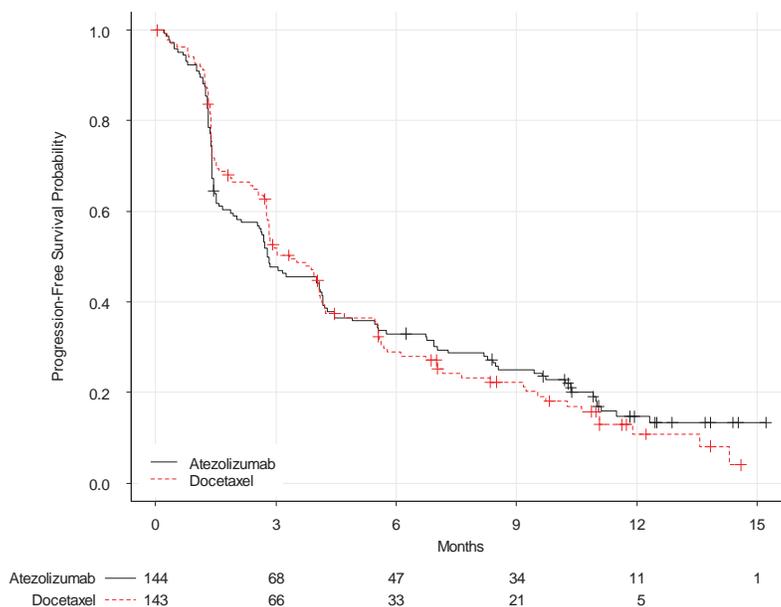
	Atezolizumab (N=144)	Docetaxel (N=143)
Number of PFS events, n (%)	119 (83)	110 (77)
Disease progression	103 (72)	83 (58)
Deaths without progression	16 (11)	27 (19)
Median (95% CI), in months	2.8 (2.1, 4.1)	3.4 (2.8, 4.1)
Hazard ratio (95% CI) ^a	0.99 (0.75, 1.30)	
Nominal P-value ^b	0.92	

^a Hazard ratio was obtained from a Cox proportional hazards model stratified by PD-L1 IC status, number of prior chemo regimens, and histology as collected from IxRS.

^b P-value was calculated from a log-rank test stratified by PD-L1 IC status, number of prior chemo regimens, and histology as collected from IxRS.

Table 20: Study POPLAR, Kaplan-Meier Curves of Progression-Free Survival, in the ITT Population (January 30, 2015 cutoff date) (source: CSR figure 21)

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Objective Response Rate per RECIST v1.1; Duration of Response per RECIST v1.1

The objective response rate per RECIST v1.1 criteria as assessed by investigator, as of the final OS analysis (December 1, 2015), was 14.7% and 15.3% in the docetaxel arm and the atezolizumab arm, respectively. The responders on atezolizumab had a point estimate for median response duration that was over double that of responders on docetaxel, although the 95% confidence intervals overlapped [18.6 months (95% CI 11.6,NE) vs. 7.2 months (95% CI 5.6,12.5)]. On the atezolizumab arm, 50% (n=11) of responders had ongoing responses at the time of final updated OS analysis of December 1, 2015, vs. 14% (n=3) of responders on the docetaxel arm.

Table 21: Objective Response Rate in the ITT population (Source: POPLAR CSR Tables 50 and Supplemental results report Table 6)

	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%)

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(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

There was only one patient in POPLAR with best overall response of CR; this patient was on the atezolizumab arm. This was an investigator-assessed confirmed CR by RECIST v1.1 (as well as a CR by modified RECIST). The patient had an EGFR exon 19 deletion, and had lung-only metastases, with TC0 and IC1 PD-L1 staining.

Of note, as per the ARS dataset submitted as part of the 150-event analysis, one patient (213111) on the docetaxel arm was initially considered to be a confirmed responder with a best overall response of PR. This was later changed to a best overall response of PD in the later datasets (May 2015 and December 2015) since the patient actually had a new lesion at the date of response confirmation and should not have been considered a confirmed RECIST v1.1 responder initially. An IR to the Applicant dated July 12, 2016 confirmed that this patient's initial classification as a confirmed responder was erroneous. This discrepancy accounts for the 22 confirmed responders reported at the time of the January 30, 2015 analysis; this was corrected in later datasets, and number of confirmed responders on docetaxel ultimately decreased to 21.

Characteristics of responders and observed responses:

- Overall, there were responders whose tumors displayed all levels of TC and IC staining in both the atezolizumab arm and the docetaxel arm, including TC0 and IC0. Both the atezolizumab and the docetaxel arms had 4 responders each who were in the TC0 and IC0 subgroup.
- No patient on either arm with brain metastases at baseline had a confirmed PR or CR.
- Three patients on the atezolizumab arm with bone metastases had best overall confirmed responses of PR; in two patients the bone lesion was included as a non-target lesion and was still listed as present at the time that the PR was recorded; the other patient had bone

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metastases at baseline but the lesions were not included as target or non-target lesions for purposes of response assessment. No bone scan was done to follow these lesions subsequently in any of these cases.

- There were five responders on the Atezolizumab arm with liver lesions at baseline. Four had documented tumor shrinkage in the liver, and three had disappearance of their liver lesions- including one patient with disappearance of 19mm and 32 mm lesions (the patient eventually died of an AE), another with disappearance of a 140 mm liver lesion (the patient eventually died of PD), and another with disappearance of a 37 mm liver lesion (the patient was alive and still being treated at the final December 2015 data cutoff date).

Reviewer's comments: The fact that median PFS did not differ between arms and in fact favored docetaxel, and the fact that the median DOR was increased compared to docetaxel, was not unexpected given known response patterns seen in NSCLC with inhibition of the PD-1/PD-L1 pathway⁷.

Overall response rate, progression-free survival, and duration of response by modified RECIST

These endpoints were measured in the atezolizumab arm only. Overall, there were 3 patients who were categorized as responders based on modified RECIST, both with best overall response of PR by modified RECIST, who did not have a PR by RECIST v1.1. One patient would otherwise have had a best overall response by RECIST v1.1 of PD, the other two would have otherwise had a best overall response of SD. There were 18 additional patients with best overall responses of SD by modified RECIST who by RECIST v1.1 criteria would have had a BOR of PD.

Patient Reported Outcomes

Patient reported outcomes evaluation was based on data collected using EORTC QLQ-C30 and QLQ-LC13. The compliance rates for QLQ-C30 among patients who were alive and still on study treatment in both arms are higher than 90% at each assessment. At assessments up to cycle 14, the compliance rates for QLQ-LC13 were higher than 80%.

Deterioration of lung cancer symptoms was defined as a ≥ 10 -point increase above baseline. The analysis of time to lung cancer symptoms deterioration did not show a compelling difference between the two treatment arms.

Reviewer's comment: The fact that there were no obvious differences in patient-reported outcomes demonstrated between arms in this open-label study should not be interpreted to mean that atezolizumab had no decrement in patient's health-related quality of life compared to docetaxel since the Applicant did not plan to test specific hypotheses related to the PRO outcomes.

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Dose/Dose Response

Patients receiving atezolizumab in POPLAR received a fixed dose of 1200 mg atezolizumab. Therefore, no dose-response relationship can be explored.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

Among the 21 responders on Docetaxel, median time to response was 1.4 months (1-8.4); mean was 2.2 months. Among the 22 responders on atezolizumab, median time to response was 2.8 months (1.3-14.5), mean 3.8 months (source: ATE, December 1, 2015 data cut-off).

Reviewer's comment: The fact that responses may take longer to occur on atezolizumab compared to docetaxel may have clinical relevance for patients in whom an immediate clinical response is desired. It is also noted that late responses may occur on atezolizumab, with one patient developing a confirmed response over 14 months after beginning therapy.

Durability of Response

See above section on duration of response. As mentioned, on the Atezolizumab arm, 50% (n=11) of responders had ongoing responses at the time of final OS analysis of December 1, 2015, vs. 14% (n=3) of responders on the docetaxel arm. Landmark analysis of 12-month event-free rate as of the final updated OS analysis (December 1, 2015), was 63% for patients on the atezolizumab arm (95% CI:42,83) vs. 37% for patients on the docetaxel arm (95% CI:16,60) (source: POPLAR supplemental results report).

Persistence of Effect

See above sections on duration of response and durability of response.

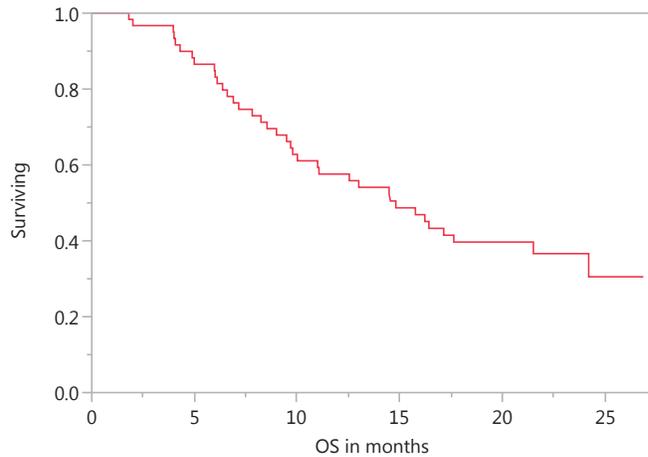
Additional Analyses Conducted on the Individual Trial

Subset analyses relevant to study POPLAR, including demographic subset analyses as well as subset analyses by disease characteristics, are discussed in detail in section 6.

There were 61 patients treated beyond investigator-assessed RECIST v1.1-defined PD on Atezolizumab. As of the final updated analysis of December 1, 2015, median OS in these patients was 14.8 months (range 1.8-26.9); 4 of these patients were still being treated with atezolizumab, and 24 were still alive.

Figure 7: POPLAR: Kaplan-Meier plot for patients treated beyond progressive disease on atezolizumab

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5.4. OAK

5.4.1. Study Design

Overview and Objective

OAK was a global, multi-center, international, randomized, controlled, open-label study of atezolizumab in patients with locally advanced or metastatic NSCLC who had progressed on or after prior platinum-containing chemotherapy regimens. The key objective was to evaluate the effect of atezolizumab on overall survival.

Trial Design

The study schema for OAK is presented below:

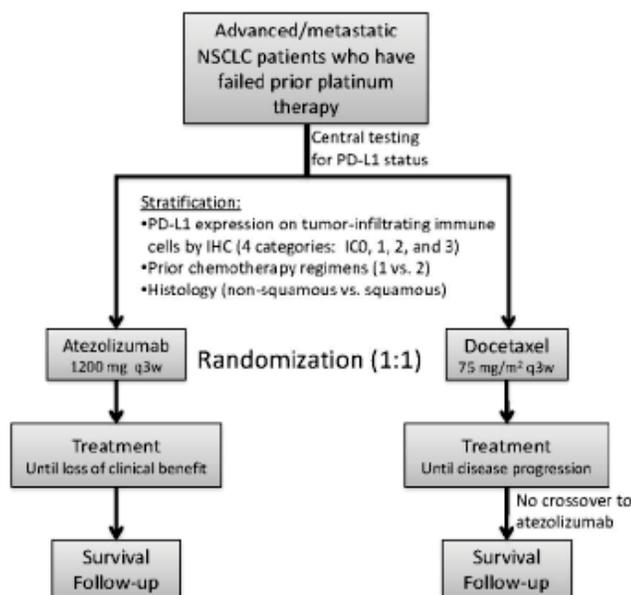
Figure 8: OAK trial design (Source: OAK SAP)

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HC=immunohistochemistry; IC=tumor-infiltrating immune cell; NSCLC=non-small cell lung cancer; PD-L1=programmed death-ligand 1; q3w=every 3 weeks.

The study was open to patients with locally advanced or metastatic NSCLC who had disease progression during or following a platinum-containing chemotherapy regimen in the metastatic setting or who had disease progression within 6 months of treatment with a platinum-containing neoadjuvant or adjuvant chemotherapy or chemoradiation. Patients with a known epidermal growth factor receptor (EGFR) mutation in countries where treatment with EGFR tyrosine kinase inhibitors (TKIs) was the standard of care had to also experience disease progression (during or after treatment) or intolerance to treatment with erlotinib, gefitinib, or another EGFR TKI approved for the treatment of EGFR-mutant NSCLC. Patients with a known anaplastic lymphoma kinase (ALK) fusion oncogene in countries where treatment with ALK inhibitors was the standard of care had to also experience disease progression (during or after treatment) or intolerance to treatment with crizotinib or another ALK inhibitor approved for treatment of NSCLC patients having an ALK fusion oncogene. Eligible patients were stratified by PD-L1 IC status (four categories of PD-L1 expression, referred to as IC0, IC1, IC2, and IC3, see table below), by the number of prior chemotherapy regimens (1 versus 2), and by histology (non-squamous versus squamous) and then randomized 1:1 to receive either atezolizumab or docetaxel.

Patients were required to be \geq age 18, with locally advanced or metastatic NSCLC and with disease progression on or after platinum-based chemotherapy. Patients were required to have measurable disease per RECIST v1.1, an ECOG performance score of 0 or 1, and controlled tumor-related pain. In addition, patients had to have adequate tumor tissue for prospective testing and determination of tumor PD-L1 expression status at a central laboratory. Patients

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who did not have tissue specimens meeting eligibility requirements were allowed to undergo a biopsy during the screening period. See Section 4.6 regarding the classification of PD-L1 TC and IC scores and groupings for this study. Tumor specimens from eligible patients were prospectively tested for PD-L1 expression by a central laboratory using the VENTANA PD-L1 (SP142) IHC assay. The study enrolled all patients whose tissue was evaluable for expression testing, regardless of PD-L1 expression status. The results of PD-L1 expression status were blinded to patients, investigators and study site staff at the time of enrollment. The Applicant was blinded to individual patient PD-L1 IC scores, but had access to aggregated level data in order to monitor the prevalence of PD-L1 expression.

This study excluded patients who had a history of cardiovascular disease, HIV, active HBV/HCV, and tuberculosis, Grade ≥ 2 peripheral neuropathy, active or corticosteroid-dependent brain metastases, leptomeningeal disease, uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures. It also excluded patients who had received systemic immunostimulatory agents, other PD-1/PD-L1 targeted products, docetaxel, or systemic immunosuppressive medications.

Docetaxel 75 mg/m² was administered intravenously on Day 1 of each 21-day cycle until disease progression per standard RECIST v1.1 or unacceptable toxicity. Atezolizumab was administered as an intravenous infusion of 1200 mg of atezolizumab on Day 1 of a 3 week cycle until unacceptable toxicity, disease progression, or symptomatic progression. For patients who met RECIST v1.1 criteria for disease progression on atezolizumab, continued treatment was allowed at the discretion of the Investigator if they met all of the following: 1) Absence of symptoms and signs (including worsening of laboratory values; e.g., new or worsening hypercalcemia) indicating unequivocal progression of disease; 2) No decline in ECOG performance status from baseline; 3) Absence of tumor growth at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions; 4) Evidence of clinical benefit as assessed by the investigator.

Safety assessments were performed before each administration. Assessment of tumor response by RECIST v1.1 occurred every 6 weeks for the first 36 weeks and every 9 weeks thereafter. For patients randomized to docetaxel, assessments continued until disease progression per RECIST v1.1, regardless of whether treatment was discontinued. Patients randomized to atezolizumab underwent assessments until disease progression per modified RECIST or until treatment discontinuation (for patients who continued to receive atezolizumab following disease progression). In the absence of disease progression, tumor assessments continued regardless of whether patients started new anti-cancer therapy, until consent was withdrawn, death, or study termination by the Applicant, whichever occurred first. Follow-up data capture, including subsequent anti-cancer therapies, continued for each patient until death, loss of follow-up, withdrawal of consent, or study termination by the Applicant, whichever occurred first.

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Study Endpoints of OAK

Primary endpoint:

- Overall survival

Secondary endpoints:

- Progression-free survival per RECIST 1.1 as determined by investigator assessment
- Objective response rate per RECIST 1.1 by investigator assessment
- Duration of response
- Patient-reported outcomes as assessed by the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30 (EORTC QLQ-C30) and the EORTC Lung Cancer Module (QLQ-LC13)

Study endpoints were defined as follows:

Figure 9: Definition of OAK study endpoints

Endpoint	Definition/ explanation
Overall survival	Time from randomization to death from any cause.
Progression-free survival	Time from randomization to investigator-assessed disease progression or death from any cause, whichever occurred first.
Objective response rate	Percentage of patients who achieved either a confirmed complete response or partial response by investigators according to RECIST 1.1 criteria as their best confirmed response, relative to patients randomized.
Duration of response	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.
Patient reported outcome measures	<p>Collected using EORTC QLQ C-30 and QLC LC-13.</p> <p>Time to deterioration (TTD) in patient-reported lung cancer symptoms (cough, dyspnea, chest pain, arm/shoulder pain) was to be examined.</p> <p>TTD of lung cancer symptoms using EORTC was defined as the time from baseline to the first time the patient’s score shows a ≥ 10-point increase above baseline in any of the following EORTC transformed scores for cough, dyspnea, chest pain, or arm/shoulder pain, whichever occurred first. An increase in a score ≥ 10 points above baseline must be held for at least two consecutive cycles or an initial score increase of ≥ 10 points is followed by death within 3 weeks from the last assessment.</p>

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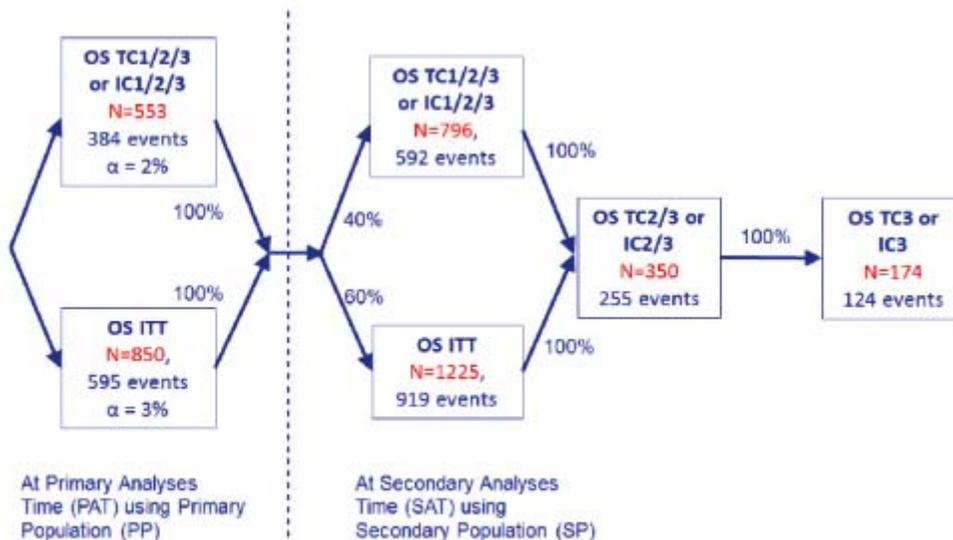
Statistical Analysis Plan

Enrollment of 850 patients in the ITT population was initially planned for study OAK so that approximately 255 PD-L1 IC2/3 patients and 425 PD-L1 IC1/2/3 patients would be enrolled. With emerging data external to this study, the sample size of study OAK was increased to approximately 1100 patients (up to a maximum of 1300) in order to ensure enrollment of at least 220 patients with PD-L1 TC3 or IC3 status, assuming a 20% prevalence of the TC3 or IC3 subgroup. The final enrollment in OAK was 1225 patients.

Based on further emerging data, this time from study POPLAR, the primary OS analyses in OAK were again modified back to the original sample size of 850, with primary analyses to be conducted on the first 850 randomized patients. If the null hypothesis in this primary OS analysis was rejected, the OS secondary analyses for the 1225 randomized ITT patients would then be tested.

To control the type I error rate in the evaluation of OS in the primary and secondary populations, alpha was split between the ITT population and the TC1/2/3 or IC1/2/3 subgroup of the first 850 randomized patients. Depending on the outcome of the primary OS comparisons, alpha would be hierarchically passed to the 1225 ITT patients and its PD-L1 expression subgroups (see Figure 10: OAK Type 1 Error Control Plan (Source: OAK SAP) below.

Figure 10: OAK Type 1 Error Control Plan (Source: OAK SAP)



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

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The estimated power and number of events needed for the proposed design of the first 850 patients and the overall ITT population were based on the following assumptions:

- Event times ~ exponentially distributed
- 24-month dropout rate for both arms ~ 7.5%
- Median OS in the docetaxel arm ~ 10 months for the ITT and PD-L1 subgroups
- Prevalence rate for TC1/2/3 and IC1/2/3: 65%
- Power for the primary analysis of OS in the ITT and TC1/2/3 or IC1/2/3 of the first 850 patients: >95%
- Power for the secondary analysis OS in the ITT, TC1/2/3 or IC1/2/3, TC2/3 or IC2/3, TC3 or IC3 of the 1225 randomized patients: >80%

The primary efficacy analyses were to be conducted when approximately 595 deaths occurred in the first 850 randomized patients. The secondary efficacy analyses were to be conducted when approximately 919 deaths occurred in all the 1225 randomized ITT population. There was no interim analysis planned for efficacy evaluation.

The primary population (PP) for efficacy analyses was the first 850 randomized ITT patients, regardless of whether they received any study drug. The PP patients were to be analyzed according to the treatment assigned at randomization by the IxRS.

The secondary population (SP) for efficacy analyses consisted of all 1225 randomized ITT patients, regardless of whether they received any study drug. The SP patients were to be analyzed according to the treatment assigned at randomization by the IxRS.

The PD-L1 expression subgroups of TC1/2/3 or IC1/2/3, TC2/3 or IC2/3, and TC3 or IC3 were determined retrospectively from a central laboratory based on the stepwise TC to IC algorithm for the PP and SP. The stepwise reads were completed prior to the primary analysis.

Reviewer's comment: Similar to the randomization in POPLAR, OAK randomization occurred based on IC status at enrollment. TC score for each patient was determined retrospectively, using data at enrollment, but was not a stratification factor. Therefore, the potential exists for patient imbalance between treatment arms within each PD-L1 subgroup as defined above, particularly for subgroups with small sample size.

The primary endpoint OS was summarized using Kaplan-Meier survival curves, and compared between the two treatment arms using a log-rank test stratified by randomization stratification factors, i.e., IC levels, the number of prior lines of therapy, and histology. The hazard ratio (HR) with a two-sided 95% confidence interval was derived from a stratified Cox proportional hazards model with the same stratification factors used in the stratified log-rank test.

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Other endpoints included PFS, ORR, DOR, and patient-reported outcomes.

Progression-free survival was compared using a stratified log-rank test, and the estimation of PFS curves for the two treatment groups was generated using the Kaplan-Meier method. Patients who were alive and have not experienced disease progression at the time of analysis were censored at the time of the last tumor assessment. Patients with no post-baseline tumor assessment were censored at the randomization date plus 1 day. Disease progression was determined based on investigator assessment using RECIST 1.1. In addition, in the primary analyses of PFS, data for patients with a PFS event who missed two or more scheduled assessments immediately prior to the PFS event were censored at the last tumor assessment prior to the missed visits. PFS was analyzed using the same methodologies as OS.

ORR per RECIST1.1 was compared between the two treatment arms for all randomized patients using the Mantel-Haenszel test stratified with the same stratification factors as used in the primary analysis of OS. 95% CIs for the difference in ORRs between the two arms were computed using the normal approximation to the binomial distribution. An estimate of ORR and its 95% CI were calculated for the ITT population and PD-L1 subpopulations using the Clopper-Pearson method for each arm.

Duration of response was estimated using Kaplan-Meier method among patients who have experienced a confirmed object response as assessed by investigator. No formal hypothesis testing was to be performed as DOR is based on a non-randomized subset of patients.

Patient-reported outcomes of lung cancer-related symptoms (i.e., cough, dyspnea, fatigue, pain in chest, pain in arm/shoulder), patient functioning, and HRQoL were assessed using EORTC QLQ C-30 and QLQ-LC13. Completion and compliance rates were to be summarized at each time point by treatment arm.

Summary statistics of linear transformed score was to be reported for all the items and subscales according the EORTC scoring manual guidelines. The mean change of the linear transformed scores from baseline was also to be assessed. Only patients with a baseline assessment and at least one on-treatment post-baseline assessment were to be included in the analysis.

Time to deterioration of lung cancer symptoms using EORTC scale was to be summarized using the Kaplan-Meier method. Patients were to be censored at the last time when they completed an assessment for cough, dyspnea (single item), dyspnea (subscale items), chest pain, and arm/shoulder pain if they have not deteriorated. If no post-baseline assessment was performed, patients were to be censored at the randomization date plus 1 day. Estimates of the treatment effect were to be expressed as HRs using a stratified Cox model including 95% CI for ITT and as unstratified HRs for the PD-L1 subgroups. Time to deterioration analyses were to be performed in patients with non-missing baseline measurement.

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Reviewer's comment: As per FDA's agreement with the Applicant, topline results only were submitted for study OAK, and, as such, data related to secondary endpoint calculations were not submitted as part of this BLA. These data will be required for submission as a post marketing requirement/ post marketing commitment (PMR/PMC).

Protocol Amendments

The protocol of for OAK was finalized on November 7, 2013 and subsequently underwent 5 protocol amendments. The original statistical analysis plan (SAP) was dated November 21, 2013 and amended once, on December 10, 2015. These amendments are summarized below:

1. Protocol amendment 1 - 10 February 2014

Revisions for E.U. Countries

2. Protocol amendment 2- 5 August 2014

This version of the protocol added exclusion criterion regarding known PD-L1 status from other clinical trials to ensure a natural distribution of the prevalence of PD-L1 expression levels.

The treatment duration for atezolizumab was modified to allow patients to be treated until loss of clinical benefit.

A pilot study was added with 50 patients to collect PRO data.

The frequency of tumor assessments after 36 weeks was changed from every 12 weeks to every 9 weeks to be more consistent with clinical practice in NSCLC.

3. Protocol amendment 3 - 2 December 2014

This version of the protocol increased sample size from 850 to 1100 to allow for testing patients with TC3 or IC3 as first hierarchy, with associated modification to the multiplicity adjustment procedure.

4. Protocol amendment 4 - 6 October 2015

This version of the protocol updated the management of immune-mediated AEs including gastrointestinal, dermatologic, endocrine, pulmonary toxicity, hepatotoxicity, potential pancreatic or eye toxicity.

5. Protocol amendment 5 - 28 January 2016

In this version of the protocol, the primary analysis was changed back 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.

Additionally, version 2 of the statistical analysis plan was submitted on December 10, 2015. This version revised the type I error control plan and revised the primary population for efficacy to the first 850 randomized patients.

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Version date: November 5, 2015 for initial rollout (NME/original BLA reviews)

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Data Quality and Integrity: Sponsor's Assurance

The Applicant assumed responsibility for data management of this study, including quality checking of the data. Data entered manually was collected via EDC using eCRFs. Sites were responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor requested data clarification from the sites, which the sites resolved electronically in the EDC system.

5.4.2. Study Results

Compliance with Good Clinical Practices

The Applicant attested that the clinical trials were conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The Applicant also specified that the trials conducted under the relevant INDs complied with FDA regulations and applicable local, state, and federal laws in the United States.

Financial Disclosure

Data on financial disclosures for 1812 out of 1827 (99.2%) principal investigators and sub-investigators were available for Study OAK. A signed financial disclosure was not obtained for 15 sub-investigators in 7 sites; reason given in all cases was “error in oversight”. There were 62 patients in total enrolled at these sites.

Of the investigators who responded, disclosable financial interests were recorded by 3 out of 1812 (0.166%) investigators in Study OAK. These disclosures are summarized in the following table;

Table 22: Financial disclosures for Study OAK (Source: BLA 761041: Overview and Summary of findings, 1.3.4)

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Clinical Site Number	Number of Patients Enrolled at Site	Investigator Name	Investigator Type	Disclosure
263614	(b) (6)	(b) (6)	Principal Investigator	Received honoraria of ~\$35,000
263627			Sub-Investigator	Owens shares of Roche holdings worth more than \$50,000
263898			Sub-Investigator	Received honoraria of \$99,935

Reviewer’s comment: *As in POPLAR, the small number of investigators and patients in OAK potentially affected by financial conflicts of interests, as well as the use of OS as the primary outcome measure, is not expected to have a significant effect on overall study outcome.*

Patient Disposition

Patient disposition information was not provided in the current submission of topline data and will be included in the complete clinical study report as a PMR/PMC.

Protocol Violations/Deviations

Information on protocol violations and deviations was not provided in the current submission of topline data and will be included in the complete clinical study report as a PMR/PMC.

Table of Demographic Characteristics

The following represents the baseline characteristics of the OAK primary analysis population; i.e. the first 850 patients enrolled. In the primary population, the median age was 64 years old (range 33-85 years); sixty-one percent of the randomized patients were males; seventy percent were white; sixty-three percent had an ECOG PS of 1, and 37% had an ECOG PS of 0.

Table 23: Baseline demographic characteristics for study OAK (source: supplemental results report, dataset ASLOS)

Demographic Parameters	Docetxel (N=425)	Atezolizumab (N= 425)	Total (N=850)
Sex			
Male	259 (61%)	261 (61%)	520 (61%)
Female	166 (39%)	164 (39%)	330 (39%)
Age			

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Demographic Parameters	Docetxel (N=425)	Atezolizumab (N= 425)	Total (N=850)
Mean years (SD)	63 (9.2)	63 (9.4)	63 (9.3)
Median (years)	64	63	64
Min, max (years)	34, 85	33,82	33,85
Race			
White	296 (70%)	302 (71%)	598 (70%)
Black or African American	11 (3%)	5 (1%)	16 (2%)
Asian	95 (22%)	85 (20%)	180 (21%)
American Indian or Alaska Native	2 (0.5%)	1 (0.2%)	3 (0.4%)
Native Hawaiian or Other Pacific Islander	2 (0.5%)	2 (0.5%)	4 (0.5%)
Other/Unknown/multiple	19 (5%)	30 (7%)	15 (5%)
Tobacco use			
Never	72 (17%)	84 (20%)	156 (18%)
Current	67 (16%)	59 (14%)	126 (15%)
Previous	286 (67%)	282 (66%)	568 (67%)
ECOG PS			
0	160 (38%)	155 (36%)	315 (37%)
1	265 (62%)	270 (67%)	535 (63%)

Table 24: Disease characteristics for study OAK (Source: dataset ASLOS)

N	Docetaxel (N=425)	Atezolizumab (N= 425)	Total (N=850)
Number of prior therapies			
One	320 (75%)	320 (75%)	640 (75%)
Two or more	105 (25%)	105 (25%)	210 (25%)
EGFR			
positive	43 (10%)	42 (10%)	85 (10%)
negative	310 (73%)	318 (75%)	628 (74%)
unknown	72 (17%)	65 (15%)	137 (16%)
EML4/ALK			
positive	0	2 (0.5%)	2 (0.2%)
negative	201 (38%)	223 (52%)	424 (50%)
unknown	224 (59%)	200 (47%)	424 (50%)

Baseline characteristics are also presented for the TC1/2/3 or IC1/2/3 subpopulation, which had similar characteristics to the ITT population.

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Table 25: Baseline demographic characteristics for TC1/2/3 or IC1/2/3 subpopulation of OAK (Source: dataset ASLOS)

	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)

Reviewer's comment: The fact that IC, and not TC, status was a randomization factor may have been a factor that led to several imbalances between arms in the TC1/2/3 or IC1/2/3 subpopulations. The demographic characteristics that were ≥5% different between the two arms were age group, sex, and race in this subpopulation.

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The following represent the number of patients at various PD-L1 cutoff levels:

Table 26: PD-L1 expression subgroups, OAK primary analysis population (source: dataset ASLOS)

	Docetaxel (N=425)	Atezolizumab (N=425)	Total (N=850)
IC1/2/3 or TC1/2/3			
IC1/2/3 or TC1/2/3	222 (52%)	241 (57%)	195 (67.9%)
TC0 and IC0	199 (47%)	180 (42%)	92 (32.1%)
IC 2/3 or TC 2/3			
IC 2/3 or TC 2/3	136 (32%)	129 (30%)	105 (36.6%)
IC 0/1 or TC 0/1	284 (67%)	290 (68%)	182 (63.4%)
IC3 or TC3			
IC3 or TC3	65 (15%)	72 (17%)	137 (16%)
IC 0/1/2 or TC 0/1/2	356 (84%)	348 (82%)	704 (83%)

Reviewer’s comment: Despite the fact that TC status was not used as a stratification factor initially, the various PD-L1 staining subgroups at various cutoff points did appear to be similarly distributed between arms. There were only 13 patients out of the 1,225 enrolled patients with overlapping TC3 and IC3 expression; out of 174 total TC3/IC3 patients. This is consistent with the very small number of patients on POPLAR with overlapping TC3 and IC3 expression.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Detailed information on treatment compliance, concomitant medications, and rescue medication use was not provided in the current submission of topline data and will be included in the complete clinical study report as a PMR/PMC.

Efficacy Results - Primary Endpoint

The primary efficacy endpoint of OAK was overall survival in the first 850 randomized patients. This analysis was conducted when 569 death events of this population had occurred, with a median follow-up time of approximately 21 months (data cut-off date July 7, 2016). A statistically significant improvement in OS for patients in the atezolizumab arm compared to patients in the docetaxel arm was observed in both the ITT population and the TC1/2/3 or IC1/2/3 subpopulation. There was a 4.2 month improvement in median OS in the ITT population and a 5.4 month improvement in median OS in the TC1/2/3 or IC1/2/3 subpopulation. The results are summarized in Table 27 and the Kaplan-Meier curves are shown in Figure 11.

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Of note, the analysis of OS performed by the FDA and shown below, as per the intent-to-treat principle, used stratification data obtained from IxRS instead of eCRF. Stratification factors specified in the study SAP included IC levels per IxRS, the number of prior chemotherapy regimens per IxRS, and histology per eCRF. There was some discordance between the eCRF and IxRS-based histologic classification, with 11 patients (2.6%) on the atezolizumab arm in the ITT population as well as 5 patients (1.2%) in the docetaxel ITT population exhibiting discordance. There were 5 patients on the atezolizumab arm (2.1%) and 4 on the docetaxel arm (1.8%) with discordance of eCRF and IxRS histologic classification in the TC 1/2/3 or IC 1/2/3 arms.

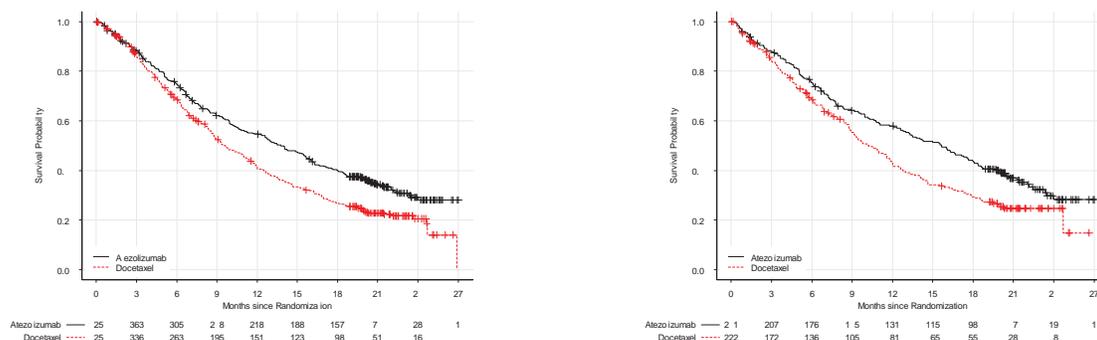
Table 27: OAK primary OS analyses, ITT and PD-L1 selected groups

	ITT population		TC1/2/3 or IC1/2/3	
	Atezolizumab (N=425)	Docetaxel (N=425)	Atezolizumab (N=241)	Docetaxel (N=222)
Number of deaths, n (%)	271 (64%)	298 (70%)	151 (63%)	149 (67%)
Median OS (95% CI), in months	13.8 (11.8, 15.7)	9.6 (8.6, 11.2)	15.7 (12.6, 18.0)	10.3 (8.8, 12.0)
Hazard ratio (95% CI) ^a	0.74 (0.63, 0.87)		0.74 (0.59, 0.94)	
P-value ^b	0.0004		0.012	

^a Hazard ratio was obtained from a Cox proportional hazards model stratified by PD-L1 IC status, number of prior chemo regimens, and histology as collected from IxRS.

^b P-value was calculated from a log-rank test stratified by PD-L1 IC status, number of prior chemo regimens, and histology as collected from IxRS.

Figure 11: Kaplan-Meier curves of OS in the ITT and PD-L1 selected subgroups of OAK (Source: Supplemental reports report for study OAK Figures 1 and 2)



(a) ITT

(b) TC1/2/3 or IC1/2/3

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Reviewer's comment: The improvement in median OS was statistically significant in OAK, confirming the effect that had been seen previously in the smaller study POPLAR. This was true for both the ITT population as well as the PD-L1-selected subgroup. Of note, the differences in point estimates of median OS and difference between arms appear to show that the PD-L1-selected subgroup may derive more benefit overall than the non-selected subgroup, which may be driven by OS results of the highest PD-L1 expressing subgroup of TC3 or IC3, as will be discussed below.

Data Quality and Integrity - Reviewers' Assessment

The data and analysis quality study OAK was acceptable for to perform the efficacy review. Analyses were producible from the raw datasets provided in the BLA submission.

Efficacy Results - Secondary and other relevant endpoints

The secondary endpoints in this study included progression-free survival and objective response rate. However, this BLA submission included topline efficacy results only. All secondary endpoint data from 1225 randomized patients will be required for submission as a PMR/PMC.

Dose/Dose Response

Patients on the atezolizumab arm of OAK received a fixed dose of 1200 mg IV every 3 weeks. Therefore, no dose-response relationship can be explored.

Durability of Response

Analyses of response durability will be performed when the complete OAK data is submitted as part of a PMR/PMC.

Persistence of Effect

Analyses of persistence of effect will be performed when the complete OAK data is submitted as part of a PMR/PMC.

Additional Analyses Conducted on the Individual Trial

Subset analyses relevant to study OAK, including demographic subset analyses as well as subset analyses by disease characteristics, are discussed in detail in section 6.

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5.5. Additional Trials Submitted in Support of Efficacy

Data from 3 additional studies were submitted as supportive evidence of activity of atezolizumab in NSCLC. These studies were single-arm studies, and all included measurement of ORR as the primary efficacy endpoint. For further details of study design, please refer Table 4 Studies of Atezolizumab in NSCLC submitted in support of BLA 761041. These studies included patients in both first-line NSCLC as well as later lines of therapy. BIRCH and FIR only included patients who were PD-L1 selected, with a cutoff of TC2/3 or IC2/3.

Objective response rate was measured differently in each study;

- **BIRCH**- IRF-ORR per RECIST v1.1
- **FIR**- Investigator-assessed ORR per modified RECIST
- **PCD4989g (NSCLC cohort)**- Investigator-assessed ORR per RECIST v1.1

Table 28: Efficacy results; BIRCH, FIR, PCD4989g (source: BLA 761041 Integrated summary of efficacy; Nov 10, 2015 pre-BLA meeting background material)

Efficacy endpoint	BIRCH		FIR	PCD4989g
	1L n=139	2L+ n=520	2L+ n=94	All lines of therapy N=88
ORR (95% CI)	19% (13,27)	17% (14,21)	17% (10, 26)	23% (15,33)
ORR in TC3/IC3 (95% CI)	26% (16, 39)	25% (20,31)	24% (11,40)	50% (28,72)
Median PFS (Months) (95% CI)	5.5 (3.0, 6.9)	2.8 (1.5, 3.5)	2.7 (1.5,3.5)	3.8 (2.6, 10.0)
Median DOR (months) (95% CI)	8.5 (5.6,NE)	8.3 (6.9, NE)	NE (10.4, NE)	17.3 (14.2, 24.7)
Median OS (months) (95% CI)	14.0 (14.0, NE)	NE (11.2, NE)	10.6 (5.7, NE)	16.5 (13.7, 22.0)

NE: not evaluable

Reviewer's comment: The broad clinical development program of atezolizumab in NSCLC, and the consistency of observed results across trials, contributed to the totality of evidence that was taken into account in support of efficacy results for the NSCLC indication.

6 Integrated Review of Effectiveness

6.1. Assessment of Efficacy Across Trials

6.1.1. Primary Endpoints

The prespecified primary OS analysis for study POPLAR showed a difference of 1.9 months in median survival favoring the atezolizumab arm compared to the docetaxel arm (HR= 0.77); however, this result did not reach statistical significance (p=0.11). An exploratory updated OS

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analysis with an additional 10 months of follow up (200 deaths) showed an improvement of 2.9 months in median survival between arms (HR= 0.69).

Study OAK demonstrated a statistically significant OS improvement for atezolizumab as compared to docetaxel in its primary efficacy population of the first 850 randomized patients. Median OS was 13.8 months for patients assigned to atezolizumab and 9.6 months for those assigned to docetaxel (HR= 0.74; p=0.0004), for a difference of 4.2 months in median survival favoring atezolizumab. A similar OS improvement was observed in the pre-specified PD-L1 selected subpopulation of TC1/2/3 or IC1/2/3.

6.1.2. Secondary and Other Endpoints

For study POPLAR, secondary efficacy endpoints included progression-free survival, objective response rate, and duration of objective response. Median investigator-assessed progression-free survival at the time of the primary OS analysis was 3.4 months in the docetaxel arm vs. 2.8 in the atezolizumab arm (HR=0.99; 95% CI: 0.75, 1.30). The objective response rate per RECIST v1.1 criteria as assessed by investigator, as of the final OS analyses was 14.7% and 15.3% in the docetaxel arm and the atezolizumab arm, respectively. The responders on atezolizumab had a point estimate for median response duration that was over double that of responders on docetaxel, although the 95% confidence intervals overlapped [18.6 months (95% CI 11.6,NE) vs. 7.2 months (95% CI 5.6,12.5)]. On the Atezolizumab arm, 50% (n=11) of responders had ongoing responses at the time of final OS analysis of December 1, 2015, vs. 14% (n=3) of responders on the docetaxel arm.

For study OAK, response data were not submitted with this BLA and will be evaluated when complete study results and dataset are submitted as part of a PMR/PMC.

6.1.3. Subpopulations

Subgroup analyses were performed for studies POPLAR and OAK and are presented below. Of note, as these were not prespecified in the statistical analysis plan of either study, they should be considered exploratory in nature and results should be interpreted with caution.

Table 29 and Table 30 summarize OS results by gender, race, age, and region for studies POPLAR and OAK.

Table 29: Study POPLAR OS Subgroup Analyses by Gender, Race, Age, and Region

Subgroup	n	Primary OS Analysis (cutoff 1/30/2015)			Updated OS analysis (cutoff: 12/1/2015)		
		Atezolizumab	Docetaxel	HR ^a	Atezolizumab	Docetaxel	HR ^a
		median	median	(95% CI)	median	median	(95% CI)
Overall	287	11.4	9.5	0.77 (0.56, 1.06)	12.6	9.7	0.68 (0.51, 0.89)

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Subgroup	n	Atezolizumab median	Docetaxel median	HR ^a (95% CI)
Gender				
Male	169	11.1	8.8	0.64 (0.43, 0.95)
Female	118	13.0	13.6	0.99 (0.57, 1.67)
Race				
White	226	11.0	9.2	0.79 (0.56, 1.12)
Non-White	61	NR	11.9	0.72 (0.32, 1.59)
Region				
US	132	12.6	10.5	0.73 (0.45, 1.16)
Non-US	155	11.4	9.2	0.80 (0.52, 1.24)
Age				
<65	175	13.0	10.5	0.79 (0.52, 1.19)
≥65	112	11.4	9.1	0.75 (0.46, 1.23)

^a Hazard ratios were estimated from unstratified Cox proportional hazards models. A hazard ratio < 1 indicates a lower risk of disease progression with atezolizumab compared to docetaxel.

NR=Not Reached

Table 30: Study OAK OS Subgroup Analyses by Gender, Race, Age, and Region, in the Primary Efficacy ITT Population

Subgroup	n	Atezolizumab median	Docetaxel median	HR ^a (95% CI)
Overall	850	13.8	9.6	0.73 (0.62, 0.87)
Gender				
Male	520	12.6	9.2	0.79 (0.64, 0.97)
Female	330	16.2	11.2	0.64 (0.49, 0.85)
Race				
White	598	12.8	8.6	0.72 (0.60, 0.88)
Non-White	252	15.7	12.5	0.75 (0.55, 1.03)
Region				
US	247	15.7	8.2	0.58 (0.42, 0.78)
Non-US	603	13.5	10.5	0.80 (0.66, 0.98)
Age				
<65	453	13.2	10.5	0.80 (0.64, 1.00)
≥65	397	14.1	9.2	0.66 (0.52, 0.83)

^a Hazard ratios were estimated from unstratified Cox proportional hazards models. A hazard ratio < 1 indicates a lower risk of disease progression with atezolizumab compared to docetaxel.

Reviewer's comment: While few definitive conclusions may be drawn from the above subgroup analyses of OS in these populations (due to lack of prespecification and lack of

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alpha allocation in the statistical analysis plan), the reviewer does note that;

- 1. Generally, the OS improvement appears to be consistent across demographic subgroups for both POPLAR and OAK.**
- 2. The ≥ 65 year old patients in both POPLAR and OAK did not appear to have inferior hazard ratios of OS on atezolizumab compared to docetaxel when compared to those < 65 .**

Additional subgroup analyses for POPLAR and OAK, based on disease characteristics, are presented below;

Table 31: Study POPLAR Additional OS Subgroup Analyses

Subgroup	n	Primary OS Analysis (cutoff 1/30/2015)			Updated OS analysis (cutoff: 12/1/2015)		
		Atezolizumab median	Docetaxel median	HR ^a (95% CI)	Atezolizumab median	Docetaxel median	HR ^a (95% CI)
Histology							
Squamous	97	10.1	8.6	0.85 (0.51, 1.41)	10.1	8.6	0.66 (0.41, 1.04)
Non-Sq	190	NR	10.2	0.74 (0.49, 1.12)	14.8	10.9	0.69 (0.49, 0.98)
ECOG PS							
0	94	NR	12.5	0.73 (0.39, 1.37)	19.5	12.2	0.57 (0.33, 0.97)
1	193	10.9	8.8	0.82 (0.56, 1.18)	10.9	8.8	0.74 (0.53, 1.03)
# of prior therapies							
1	189	12.6	9.4	0.68 (0.45, 1.01)	14.8	9.5	0.56 (0.39, 0.79)
2	98	9.8	9.7	1.04 (0.61, 1.78)	9.8	9.7	0.95 (0.59, 1.52)
Smoking status							
Never	56	NR	14.4	0.92 (0.36, 2.34)	NR	13.6	0.60 (0.29, 1.25)
Current	46	12.0	9.4	0.64 (0.30, 1.36)	12.0	9.4	0.57 (0.29, 1.11)
Previous	185	10.9	9.0	0.77 (0.53, 1.13)	11.0	9.0	0.71 (0.51, 1.00)

^a Hazard ratios were estimated from unstratified Cox proportional hazards models. A hazard ratio < 1 indicates a lower risk of death with atezolizumab compared to docetaxel.

Table 32: Study OAK Additional OS Subgroup Analyses

Subgroup	n	Atezolizumab median	Docetaxel median	HR ^a (95% CI)
Histology				
Squamous	222	8.9	7.7	0.73 (0.54, 0.98)
Non-Sq	628	15.6	11.2	0.73 (0.60, 0.89)
ECOG PS				
0	315	17.6	15.2	0.78 (0.58, 1.04)

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1	535	10.6	7.6	0.69 (0.56, 0.84)
# of prior therapies				
1	640	12.8	9.1	0.71 (0.59, 0.86)
2	210	15.2	12.0	0.80 (0.57, 1.12)
Smoking status				
Never	156	16.3	12.6	0.71 (0.47, 1.08)
Current	126	17.0	9.3	0.51 (0.33, 0.80)
Previous	568	12.6	9.3	0.79 (0.65, 0.97)

^a Hazard ratios were estimated from unstratified Cox proportional hazards models. A hazard ratio < 1 indicates a lower risk of death with atezolizumab compared to docetaxel.

Reviewer's comment: Subgroup analyses based on disease characteristics appear to demonstrate that OS benefits of atezolizumab are preserved across subgroups. Patients with non-squamous histology and ECOG PS of 0 lived longer on both arms in both studies.

The results of OS subgroup analysis by PD-L1 status, as well as PD-L1 groupings, are presented for both POPLAR and OAK.

Table 33: Study POPLAR OS Subgroup Analyses by PD-L1 Status

PD-L1	n	Primary OS Analysis (cutoff 1/30/2015)			Updated OS analysis (cutoff: 12/1/2015)		
		Atezolizumab median	Docetaxel median	HR ^a (95% CI)	Atezolizumab median	Docetaxel median	HR ^a (95% CI)
IC0	125	10.9	10.2	0.94 (0.58, 1.51)	10.9	10.2	0.77 (0.50, 1.16)
IC1	107	NR	10.1	0.65 (0.37, 1.14)	15.1	11.9	0.62 (0.39, 1.0)
IC2	37	9.2	6.2	0.55 (0.24, 1.24)	9.0	6.2	0.52 (0.24, 1.12)
IC3	18	NR	11.8	0.87 (0.24, 3.19)	14.2	11.8	0.64 (0.21, 1.95)
IC2/3	55	9.5	7.0	0.64 (0.32, 1.27)	9.5	7.0	0.57 (0.30, 1.06)
IC0/1	232	12.0	10.1	0.79 (0.55, 1.14)	13.0	10.2	0.70 (0.51, 0.96)
TC3 or IC3	47	NR	11.1	0.46 (0.19, 1.06)	NR	11.1	0.45 (0.21, 0.95)
TC0/1/2 and IC0/1/2	240	11.0	9.4	0.85 (0.60, 1.20)	11.1	9.4	0.73 (0.54, 0.99)
TC2/3 or IC2/3	105	13.0	7.4	0.56 (0.33, 0.94)	15.1	7.4	0.50 (0.31, 0.80)
TC0/1 and IC0/1	182	11.1	10.3	0.94 (0.63, 1.42)	11.4	11.2	0.80 (0.56, 1.14)
TC1/2/3 or IC1/2/3	195	NR	9.1	0.63 (0.42, 0.94)	15.1	9.2	0.59 (0.41, 0.83)

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TC0 and IC0	92	9.7	9.7	1.12 (0.65, 1.95)	9.7	9.7	0.88 (0.55, 1.43)
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^a Hazard ratios were estimated from unstratified Cox proportional hazards models. A hazard ratio < 1 indicates a lower risk of death with atezolizumab compared to docetaxel. NR=Not Reached

Table 34: Study OAK OS Subgroup Analyses by PD-L1 Status

PD-L1	n	Atezolizumab median	Docetaxel median	HR ^a (95% CI)
IC0	313	10.1	8.4	0.81 (0.62, 1.05)
IC1	342	14.2	11.6	0.71 (0.55, 0.93)
IC2	102	14.3	11.5	0.86 (0.53, 1.40)
IC3	93	18.8	8.6	0.49 (0.28, 0.83)
TC3 or IC3	137	20.5	8.9	0.41 (0.27, 0.63)
TC0/1/2 and IC0/1/2	704	12.6	9.8	0.82 (0.68, 0.98)
TC2/3 or IC2/3	265	16.3	10.8	0.67 (0.49, 0.90)
TC0/1 and IC0/1	574	12.7	9.2	0.77 (0.63, 0.94)
TC0 and IC0	379	12.6	8.9	0.75 (0.59, 0.96)

^a Hazard ratios were estimated from unstratified Cox proportional hazards models. A hazard ratio < 1 indicates a lower risk of death with atezolizumab compared to docetaxel

Analyses from both POPLAR and OAK showed consistency of effect that was preserved through all staining subgroups, both based on the pre-specified IC staining as well as the exploratory TC and IC staining subgroups. The benefit of atezolizumab over docetaxel on prolonging OS did appear to be more pronounced when looking at the higher PD-L1-expression groupings. In particular, the TC3 or IC3 subgroup in POPLAR, at the time of the final updated analysis of December 1, 2016 had a HR for risk of death compared to docetaxel of 0.45 (95% CI 0.21, 0.95), with median OS not reached in this subpopulation for those on atezolizumab. This effect was mirrored in the OAK data as well, with the HR for the TC3/IC3 subgroup being 0.41 (95% CI 0.27, 0.63). Median OS for those in this subgroup on atezolizumab compared to docetaxel was 20.5 months vs. 8.9 months. It is for this reason that the Applicant has proposed the use of a complimentary diagnostic at the TC3/IC3 cutoff to help predict those patients who are most likely to respond to atezolizumab.

However, the survival advantage for patients on atezolizumab compared to docetaxel appeared to be preserved even in patients with PD-L1 expression levels of zero using the combined IC or TC classification system. Initial analysis of POPLAR at the final preplanned January 30, 2015 cutoff showed a HR for risk of death with atezolizumab compared to docetaxel in the TC0/IC0 subgroup of 1.12 (95% CI 0.65, 1.95) in the TC0/IC0 subgroup. At the final updated analysis of December, the HR in this subgroup had decreased to 0.88 (95% CI 0.55, 1.43). This effect was preserved in the OAK analysis, with a HR for death on atezolizumab compared to docetaxel for the TC0/IC0 subgroup of 0.75 (95% CI 0.59, 0.96). This was similar to the HR seen in the overall

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population, and in the overall population excluding the highest staining levels, i.e. the TC 0/1/2 and IC 0/1/2 subgroup, which was 0.82 (95% CI 0.68, 0.98).

Reviewer’s comments: Efficacy results on OS with atezolizumab in the tested NSCLC population do not appear to be driven exclusively by results in the highest-expressing TC3/IC3 subpopulation of PD-L1, despite the fact that they seemed to derive benefit from atezolizumab treatment compared to docetaxel that was strikingly higher than those in all other measured subgroups.

An exploratory analysis was done for patients with actionable genetic aberrations; i.e. EGFR mutations or EML4/ALK translocations, included in POPLAR and OAK. These were patients who had progressed on an FDA-approved prior targeted therapy in addition to progression on or after platinum-doublet based chemotherapy. These patients are included in the proposed labelled population for atezolizumab due to their inclusion in the efficacy analysis populations of both POPLAR and OAK. Of note, due to extremely small numbers of patients with known ALK rearrangements (n=5 overall on POPLAR and OAK), these patients were included in the combined analysis and not analyzed separately.

Figure 12: Kaplan-Meier curves for OS in patients with EGFR and EML4/ALK targetable genetic aberrations

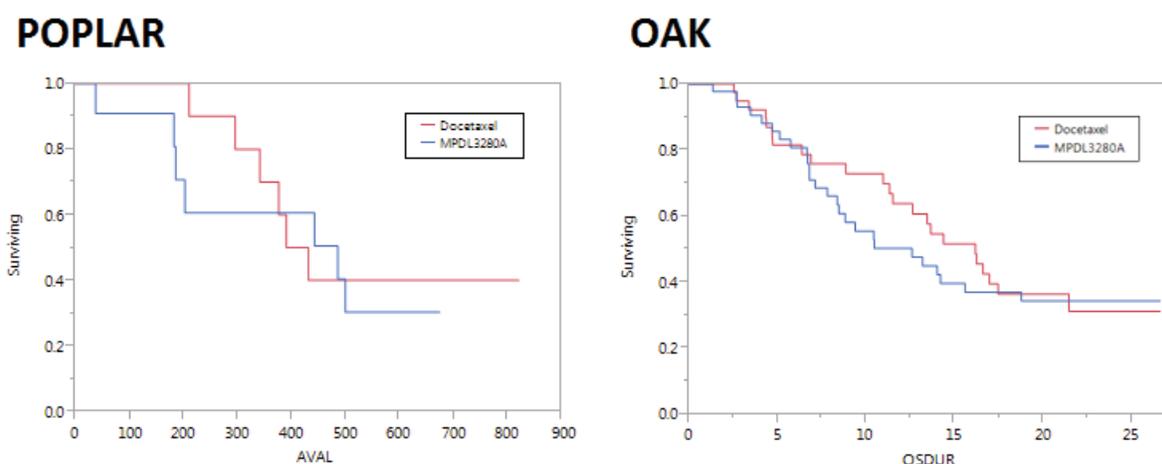


Table 35: Study POPLAR: OS in patients with EGFR and EML4/ALK targetable genetic aberrations

Subgroup	Primary OS Analysis (cutoff 1/30/2015)			Updated OS analysis (cutoff: 12/1/2015)				
	n	Atezolizumab median	Docetaxel median	HR (95% CI)	n	Atezolizumab median	Docetaxel median	HR (95% CI)
EGFR or ALK	21	NR	NR	2.12 (0.46, 11.0)	21	14.6	13.5	1.30 (0.40, 4.19)

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mutation									
EGFR and ALK wild type	93	11.1	8.3	0.65 (0.38, 1.11)	95	12.6	8.8	0.55 (0.34, 0.88)	
unknown	173	11.4	9.2	0.78 (0.52, 1.18)	171	12.4	10.1	0.69 (0.48, 0.99)	

Table 36: Study OAK: OS in patients with EGFR and EML4/ALK targetable genetic alterations

Subgroup	n	Atezolizumab median	Docetaxel median	HR (95% CI)
EGFR or ALK mutation	87	12.6	14.4	1.13 (0.64, 1.99)
EGFR and ALK wild type	374	15.5	9.3	0.65 (0.50, 0.84)
unknown	389	12.3	8.9	0.78 (0.61, 0.98)

Reviewer’s comment: *As these were not prespecified subset analyses, the above results, which seem to show a trend towards worsened HR for death in patients with EGFR or ALK genetic aberrations who received atezolizumab, should be interpreted with caution. These results are also uninterpretable due to (1) confounding factors; (2) small sample size in the mutation subgroup; (3) large percentage of patients with unknown mutation status; and (4) the fact that the HR 95% confidence intervals of the mutation group include 1.*

Additionally, it is relevant to note that the one CR in study POPLAR occurred in a patient with known EGFR exon 19 deletion. No other patients with EGFR or ALK genetic aberrations who received atezolizumab had confirmed responses. There were 3 confirmed PRs in this patient population in study POPLAR who received docetaxel; one in a patient with EGFR exon 19 deletion, and 2 in patients with ALK rearrangements.

As there are other targeted therapies approved in the second-line setting for patients with actionable genetic alterations who have developed resistance to first-line targeted therapy, the clinician may wish to take the totality of these data into account when deciding to treat these patients with atezolizumab vs. other approved therapies, especially those targeted therapies that are approved under accelerated approval for treatment of patients with resistance to initial targeted therapy.

6.1.4. Dose and Dose-Response

Not applicable as there was only one dose administered to patients on both POPLAR and OAK; 1200 mg IV every 3 weeks.

6.1.5. Onset, Duration, and Durability of Efficacy Effects

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Data on time to onset of response is available from POPLAR; this demonstrates that median time to onset of response on atezolizumab was almost double that of median time to onset of response in docetaxel- 84 days (range 40-442) vs. 43 days (range 30-257). However, responses seen with atezolizumab on study POPLAR were longer and more durable than those seen with docetaxel, with median duration of response of 18.6 months for the atezolizumab (95% CI- 11.6, NE) compared to 7.2 months (95% CI- 5.6, 12.5) for the docetaxel arm.

Response data from OAK is was not submitted as part of this BLA and will be submitted as part of the required PMR/PMC, along with full efficacy and safety data.

6.2. Additional Efficacy Considerations

6.2.1. Considerations on Benefit in the Postmarket Setting

Not applicable.

6.2.2. Other Relevant Benefits

Not applicable.

6.3. Integrated Assessment of Effectiveness

Efficacy of atezolizumab vs. docetaxel was studied in two randomized, multicenter trials in patients with metastatic non-small cell lung cancer with disease progression on or after platinum-based doublet chemotherapy. The first study was the phase 2 study POPLAR, which randomized 287 patients 1:1 to atezolizumab 1200 mg IV every 3 weeks or to docetaxel 75 mg IV every 3 weeks. The pre-specified final OS analysis showed a difference of 1.9 months in median survival favoring the atezolizumab arm compared to the docetaxel arm (HR= 0.77); however, the OS result did not reach statistical significance (p=0.11). An exploratory updated OS analysis with an additional 10 months follow up (200 deaths) showed an improvement of 2.9 months in median survival (HR= 0.69).

The pivotal phase 3 study OAK had the same treatment regimens and patient population as those in study POPLAR, but with a larger sample size of 1225 patients. In the primary efficacy population (the first 850 randomized patients), atezolizumab demonstrated a statistically significant improvement in OS as compared with docetaxel. Median OS was 13.8 months for patients assigned to atezolizumab and 9.6 months for those assigned to docetaxel (HR= 0.74; p=0.0004), for a difference of 4.2 months in median survival favoring atezolizumab. A similar OS improvement was observed in the pre-specified PD-L1 selected subpopulation of TC1/2/3 or IC1/2/3.

Overall, the OS benefit demonstrated in the above trials represents a clinically meaningful improvement over docetaxel in this disease setting. The review team concludes that these

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results, along with the safety profile (reviewed in section 7), provide substantial evidence to support approval of atezolizumab for the proposed indication. Full efficacy and safety data for OAK will be submitted by the applicant as a PMR/PMC, with anticipated submission time in March 2017.

7 Review of Safety

7.1. Safety Review Approach

The safety of atezolizumab was primarily evaluated in Trial POPLAR, a multi-center, 1:1 randomized trial of atezolizumab monotherapy compared with docetaxel in patients with non-small cell lung cancer who have progressed on or after platinum-based chemotherapy. A total of 143 patients were randomized to docetaxel and 144 patients were randomized to atezolizumab. This review focused on the 135 patients who received at least one dose of docetaxel and the 142 patients who received at least one dose of atezolizumab with a data cut-off of May 8, 2015. Additional follow-up on these patients is provided by the 90 day safety update with data cut-off of December 1, 2015.

The safety review was supplemented with a pooled evaluation of the following trials:

1. BIRCH: a Phase II multicenter single-arm trial of atezolizumab monotherapy in patients with locally advanced or metastatic NSCLC with PD-L1 expression on tumor or tumor-infiltrating immune cells (659 patients) [Data cut-off May 28, 2015]
2. PCD4989g: a Phase I, multicenter, first-in-human dose-escalation study of atezolizumab in patients with locally advanced or metastatic solid tumors or hematologic malignancies. (481 patients of whom 88 were patients with non-small cell lung cancer) [Data cut-off August 7, 2015]
3. FIR: a Phase 2 multi-center, single-arm trial of atezolizumab in patients with locally advanced or metastatic PD-L1-positive non-small cell lung cancer (NSCLC). (137 patients). [Data cut-off January 7, 2015]
4. BIRCH: a Phase 2 multi-center, single-arm study of atezolizumab in patients with PD-L1-positive locally advanced or metastatic non-small cell lung cancer. (667 patients). [Data cut-off May 28, 2015]

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Adverse events of special interest were closely evaluated due to class effect of immune-mediated events in checkpoint inhibitors.

7.2. Review of the Safety Database

The safety database included 135 patients who received at least one infusion of docetaxel and 142 patients who received at least one infusion of atezolizumab.

The Applicant mapped and coded verbatim adverse events (AE) terms for Trial POPLAR using MedDRA version 18.0.

APPEARS THIS WAY ON ORIGINAL

Reviewer comments:

- 1..... T
here were no significant discrepancies identified between the dataset and the information provided in the Clinical Study Report.
- 2..... T
he Applicant’s categorization of data and coding methods were deemed appropriate.
- 3..... P
ooled safety data regarding immune-mediated adverse events for NSCLC and all patients treated with atezolizumab were examined in an integrated manner (see section 8.4)
- 4..... T
he clinical review of safety assessed the adequacy of the Applicant’s mapping of AE verbatim terms to MedDRA preferred terms (PT) for 100% of the POPLAR raw AE data set. The review used manual matching of all verbatim and MedDRA PTs to assess the acceptability of the Applicant mapping from the verbatim term to MedDRA PT. The PTs listed in the dataset adequately represented the investigator-recorded term and did not raise any significant issues.
- 5..... A
random audit of 5% of the AE case report forms to assess the completeness and verify the accuracy of the raw AE datasets did not raise any significant issues.
- 6..... T
o review the AE datasets, the following terms were pooled:

Table 37: Pooled terms

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Pooled term	Preferred Terms
Diarrhea	Colitis Diarrhea
Abdominal pain	Abdominal pain Abdominal pain upper Abdominal pain lower Flank pain
Fatigue	Asthenia Fatigue Lethargy
Urinary tract infection	Cystitis Urinary tract infection Pyuria
Decreased appetite	Appetite disorder
Vomiting	Vomiting Retching
Back pain	Back pain Neck pain
Musculoskeletal pain	Musculoskeletal pain Musculoskeletal chest pain Myalgia
Rash	Rash Rash maculopapular Rash pruritic Dermatitis Dermatitis exfoliative Eczema Erythema Rash erythematous Rash papulosquamous Acne
Cough	Cough Productive cough Upper airway cough syndrome
Sepsis	Sepsis Bacteremia
Dyspnea	Dyspnoea exertional Dyspnoea

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Pneumonia	Lower respiratory tract infection Respiratory tract infection bacterial Respiratory tract infection Pneumonia Lobar pneumonia Lung infection
Upper respiratory tract infection	Bronchitis Bronchitis viral Bronchitis bacterial Rash pruritic Bronchiolitis
Venous thromboembolism	Pulmonary embolism Deep vein thrombosis Embolism Embolism venous Jugular vein thrombosis Venous occlusion
Insomnia	Insomnia Sleep disorder
Hematuria	Cystitis haemorrhagic Renal hemorrhage Haematuria
Pyrexia	Pyrexia Tumor-associated fever
Oral candidiasis	Oral fungal infection Oral candidiasis Fungal oesophagitis
Peripheral edema	Peripheral oedema Localized oedema Generalized oedema Swelling Peripheral swelling
Peripheral neuropathy	Peripheral sensory neuropathy Neuropathy peripheral Neuralgia Hypoaesthesia Paraesthesia

7.2.1. Overall Exposure

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Within the safety population, the median number of doses received in the atezolizumab arm was 6 (1 to 28) and the median duration of therapy was 3.7 months (0-19 months) as of the May 2015 cutoff date (Table 41). In the docetaxel arm, the median number of doses was 4 (1-26) and the median duration of therapy was 2.1 months (0-17 months).

Table 38: Safety Population, Size and Denominators

Clinical Trial Groups	Atezolizumab arm (n=142)	Docetaxel arm (n=135)
Number of doses received		
Mean (SD)	9.6 (8.0)	5.3 (4.8)
Median (Min, Max)	6 (1-28)	4 (1-26)
Treatment duration (months)		
Mean (SD)	6.2 (5.7)	3.1 (3.5)
Median (Min, Max)	3.7 (0-19)	2.1 (0-17)
Treatment duration (months)		
0-3	59 (41.5%)	82 (60.7%)
>3-6	26 (18.3%)	32 (23.7%)
>6-12	27 (19.0%)	16 (11.9%)
>12	30 (21.1%)	5 (3.7%)
Dose Interruptions/Delays		
Any modification	53 (37.3%)	56 (41.5%)
Delay due to AE	34 (24%)	28 (20.1%)
Dose reduction due to AE (docetaxel only)	N/A	19 (14.1%)
Missed dose	12 (8.5%)	11 (8.1%)

Data cut-off 5-8-15: Source AEX.xpt

At the time of the database lock, 17% of patients on the atezolizumab arm and 0.7% of patients on the docetaxel arm were continuing with study treatment..

Reviewer comments: Overall, the size of the safety population and the extent of exposure were adequate and generally allowed sufficient characterization of AEs associated with atezolizumab and docetaxel in the target population.

7.2.2. Relevant characteristics of the safety population:

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The safety and efficacy populations were similar. Refer to Section 6.1.2 for additional details regarding the efficacy population.

The demographics and baseline characteristics of the safety population are shown in Figure 2 and Table 42:

Figure 13: Safety Population Age

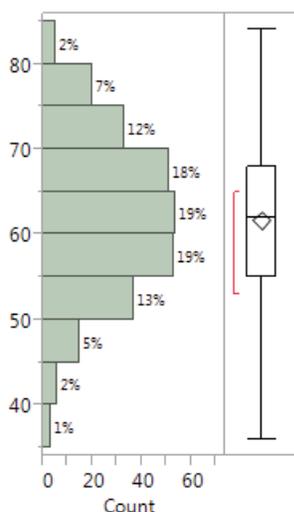


Table 39: Safety Population Demographics

	Atezolizumab	Docetaxel	Total
N	142	135	277
Mean (SD)	61.6 (9.1)	61.97 (9.2)	(61.7) 9.1
Minimum	42	36	36
Maximum	82	84	84
Median	62	62	62

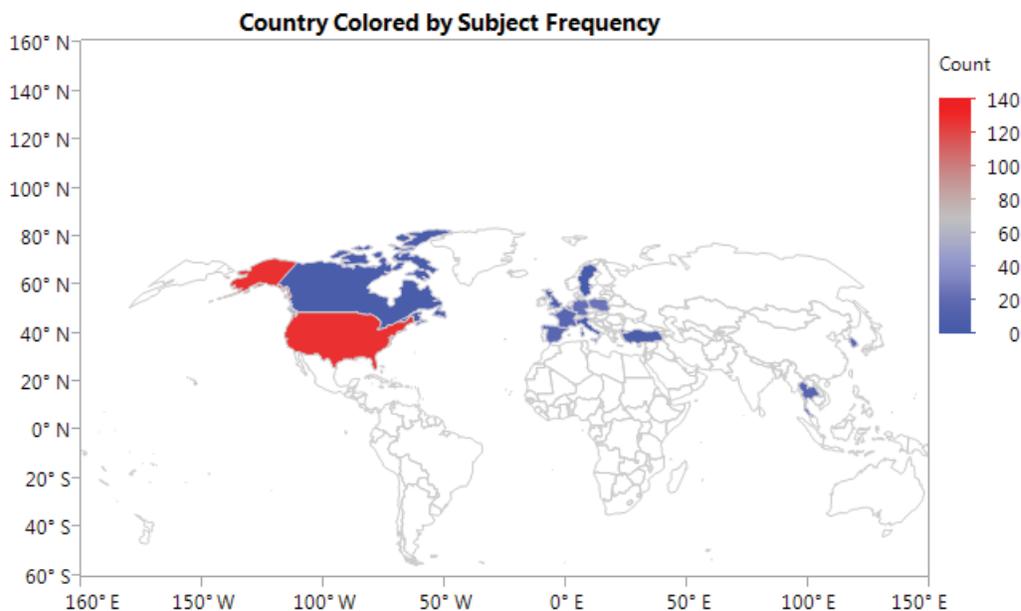
		Atezolizumab	Docetaxel	Total
		Count (%)		
Age Group	Age under 65 years	87 (61.3%)	81 (60%)	168 (60.6%)
	65 <= Age <75	43 (30.3%)	41 (30.4%)	84 (30.3%)
	Age 75 and over	12 (8.5%)	13 (9.6%)	25 (9.0%)
Sex	Female	49 (34.5%)	62 (45.9%)	111 (40.1%)
	Male	93 (65.5%)	73 (54.1%)	166 (59.9%)
Race	Asian	23 (16.2%)	13 (9.6%)	36 (13%)

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	Black Or African American	3 (2.1%)	4 (3.0%)	7 (2.5%)
	White	108 (76.1%)	109 (80.7%)	217 (78.3%)
	Other/unknown	8 (5.6%)	8 (5.9%)	16 (5.8%)
Ethnicity	Not Hispanic Or Latino	138 (97.2%)	125 (92.6%)	263 (95.0%)
	Hispanic Or Latino	3 (2.1%)	6 (4.4%)	9 (3.3%)
	Unknown/Not Reported	1 (0.7%)	4 (3.0%)	5 (1.8%)

US patients (46.6%) were the plurality of study subjects, followed by Poland (9.4%) and Germany (8.3%)(Figure 3):

Figure 14: Safety Population Geography



The trial excluded patients with a history of autoimmune disease with the exception of patients with a history of autoimmune hypothyroidism on a stable dose of thyroid replacement hormone and patients with controlled Type 1 diabetes mellitus on a stable insulin regimen. Additionally, the trial excluded patients with a history of pulmonary fibrosis or pneumonitis, although radiation pneumonitis in a radiation field was permitted.

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Reviewer note: The safety database was adequate to represent the expected target population of U.S. patients with bladder cancer who have progressed following platinum-based therapy. Of note, as discussed above, this trial did not include those with a history of autoimmune disease. The trial did not enroll extensively in non-US and non-European countries. The trial did not enroll large numbers of non-Caucasian patients. Thus, the safety results may not extend to these populations.

7.2.3. Adequacy of the safety database:

The size of the safety database and duration of atezolizumab and docetaxel exposure were sufficient to characterize the safety of atezolizumab and docetaxel for treatment of a serious and life-threatening condition with the expectation of updated safety data from this trial and from the ongoing randomized phase III study, OAK. OAK will evaluate atezolizumab compared with docetaxel in a similar patient population to that of POPLAR.

Demographics and disease characteristics of the study subjects were adequately representative of the target population of patients with NSCLC that has progressed during or following a platinum-containing regimen.

7.3. Adequacy of Applicant's Clinical Safety Assessments

7.3.1. Issues Regarding Data Integrity and Submission Quality

During the review of the urothelial carcinoma BLA (4-5-2016) the Office of Scientific Investigations reported that there were several adverse events that were documented in source at an inspected site but were not included in the safety database. A teleconference was held with the Applicant on 4-14-2016. The Applicant reported that several adverse events were entered late by the site. Given this issue, the Applicant performed an audit for the POPLAR trial and did not find significant issues regarding data integrity.

7.3.2. Categorization of Adverse Events

Safety and tolerability assessment was based on the frequency of deaths, adverse events (AEs), serious adverse events (SAEs), AEs leading to discontinuation, AEs leading to dose delay, select AEs, clinical laboratory assessments (hematology, serum chemistry, and liver and thyroid function tests), and vital sign measurements. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 18.0. The MedDRA preferred terms (PT) and the corresponding verbatim terms included in the datasets were reviewed to check for accuracy of MedDRA coding using random audit. Comparison of the applicant's MedDRA PTs to the verbatim terms did not show significant discrepancies. Adverse events and laboratory

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values were graded for severity using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.

The Applicant identified adverse events of special interest (AESIs) based on pre-defined criteria based on the known mechanism of action of atezolizumab. See section 8.5 for more details regarding these events.

The Applicant further identified immune-mediated AEs based on the following pre-defined criteria: patients who required the use of systemic corticosteroids within 30 days after the AE onset date (based on the concomitant medication CRF) with no clear alternate etiology. Systemic corticosteroids specifically excluded steroids administered via the following routes: inhaled, intranasal, intravitreal, ophthalmic, otic, per vagina, and topical.

Safety data was available only for the 30-day post-discontinuation time point.

Immune-mediated adverse events (IMAE) were defined as AEs within 30 days prior to initiation of systemic corticosteroid therapy that did not resolve within that time period.

Reviewer note: *The Applicant's definition of AEs of special interest and immune-mediated AEs were pre-defined and adequate to evaluate class effect AEs. See section 7.1 for terms that were pooled for the purpose of this review.*

7.3.3. Routine Clinical Tests

In POPLAR (GO 28753), the following assessments were planned starting on Cycle 1 Day 1 and continued on Day 1 of each Cycle and at treatment discontinuation:

- Vital signs including temperature, blood pressure, heart rate, respiratory rate, oxygen saturation by pulse oximetry at rest (also amount of supplemental oxygen if applicable) within 72 hours of dosing.
- AEs continuously throughout the study.
- Physical examination and physical measurements including weight, and ECOG performance status.
- CBCs with differential, including WBC, lymphocyte count, ANC, hemoglobin, hematocrit, and platelet count (results were to be obtained prior to dosing on infusion days).
- Serum chemistry tests (BUN or serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, phosphate, chloride, glucose and LDH), (results were to be obtained prior to dosing on infusion days).
- Liver function tests including AST, ALT, total bilirubin, alkaline phosphatase, albumin (results were to be obtained prior to dosing on infusion days).

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- Serum sample for auto-antibody, anti-drug antibody testing, PK sampling, and immune cell profile (atezolizumab patients only)

The following were performed only at screening and treatment discontinuation:

- Thyroid function testing including TSH (obtain free T3 and free T4 if abnormal result).
- Coagulation panel

Pregnancy screening was performed only prior to Cycle 1 for women of childbearing potential.

- Pregnancy test performed every 6 weeks on study or more frequently as per local standards.

Patients were assessed for toxicity prior to each dose. All visits had to occur within 3 days of the schedule date. All AEs were collected until 30 days following the last administration of study treatment or until study discontinuation/termination or until initiation of subsequent anti-cancer therapy, whichever occurred first. Patients were contacted at 30 days after the last dose of study treatment to determine if any new AEs had occurred. After this period, investigators reported any death, serious adverse event, or any other adverse event of concern that were considered to be related to prior study treatment. All AEs were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4.0).

Reviewer note:

Routine clinical testing of patients enrolled in the trial, including efforts to elicit adverse event data by monitoring laboratory tests, vital signs, and oxygen saturation appear to have been adequate with the exception of thyroid function. Thyroid function testing, which included thyroid stimulating hormone (TSH), free T3, and free T4 levels, was routinely performed in POPLAR only at screening and at treatment discontinuation. Immune checkpoint therapy, including ipilimumab, nivolumab, and pembrolizumab, has been associated with a high frequency of endocrine events with thyroiditis/hypothyroidism. Other studies of checkpoint inhibitors have measured thyroid function more frequently (e.g. every 3 cycles [6 weeks] in Study CA209057 of nivolumab in non-squamous non-small cell lung cancer). Thus, the frequency of thyroid adverse events in POPLAR may underestimate the true incidence of thyroiditis/hypothyroidism.

7.4. Safety Results

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Table 43 presents the overview of safety in POPLAR and the pooled safety population including all patients on PCD4989g and the atezolizumab-treated patients in FIR, BIRCH, POPLAR, and IMVigor 210.

Table 40: Integrated Summary of Safety

Total number of patients with at least one:	POPLAR (n = 142)	All NSCLC (n =1026)	All patients (n = 1848)
Grade 5 AE	6 (4.2%)	34 (3.3%)	54 (2.9%)
Grade 3-4 AE	57 (40%)	405(40%)	782 (42%)
SAE	50 (35%)	384 (37%)	713 (39%)
AE leading to treatment discontinuation	11 (7.7%)	64 (6.2%)	137 (7.4%)
imAE	10 (7.4%)	77 (7.5%)	141 (7.6%)

7.4.1. Deaths

Table 44 summarizes total deaths in POPLAR. Listed deaths include deaths during treatment and occurring up to 100 days of the last dose of study drug as of the database lock date (May 8, 2015).

Table 41: Cohort 2 Deaths on Study

	Atezolizumab (N = 142)	Docetaxel (N = 135)
Total deaths	76 (54%)	92 (68%)
Deaths within 30 days of last dose or prior to next therapy	9 (6.3%)	4 (3.0%)
Death attributed to disease progression	66 (47%)	85 (63%)

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Death attributed to other/unknown (including those occurring up to 30 days after last dose of study drug)	1(2.2%)	3 (2.2%)
--	---------	----------

Death associated with atezolizumab occurred in 10 patients (due to pneumothorax, ulcer hemorrhage, intestinal perforation, pulmonary embolism (2 patients), pneumonia, and cardiac failure. Due to the potential for late-onset immune-related toxicity, deaths occurring up to 30 days after the last dose of atezolizumab were studied. Brief summary narratives for these patients are provided in Table 45.

Table 42: Brief Summaries of Related Deaths

Adverse event	Brief case description
Pneumothorax Patient 202002	A 62 year-old female with adenocarcinoma to the right upper lobe and underlying COPD and emphysema developed Grade 3 bronchial infection on Day 299, treated with amoxicillin and oxygen therapy. She subsequently developed Grade 3 spontaneous pneumothorax on Day 320. Per the investigator, there was no radiologic evidence of pneumonitis. She was intubated and ventilated and pneumothorax drainage was performed but was unsuccessful. She died on Day 331.
Ulcer hemorrhage Patient 203024	A 53 year-old man with adenocarcinoma to the central right lung and left lower lobe as well as right pleural effusion and bone developed Grade 3 ulcer hemorrhage on Day 74. He was not on systemic steroids but was receiving dipyron, an analgesic reported to have lower risk of gastrointestinal bleeding than NSAIDs. He died on Day 75 despite transfusions.
Autoimmune hemolysis/Large intestinal perforation Patient 211004 Reviewer note: Note that patient was on ongoing high-dose corticosteroids that could have led to	A 51 year-old man with adenocarcinoma to right upper lobe, pleura, mediastinum, and skin developed Grade 3 hemolysis on Day 12 with hemoglobin decreasing to 6.4 g/dL, elevated LDH, and Coombs' test positivity. He was treated with methylprednisolone up to 16mg PO QID with improvement in his hemolysis. Methylprednisolone was weaned to 16mg QD ongoing. Atezolizumab was interrupted and restarted on Day 50 (Cycle 3). On Day 83, he developed diverticulitis. On Day 153, he was hospitalized with acute abdominal pain and CT demonstrated free air. He underwent emergency laparotomy, however died on Day 175.

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intestinal perforation.	
Pulmonary Embolism Patient 212006	A 60 year-old man with adenocarcinoma to right lower lobe and anterior abdominal peritoneum with pleural and pericardial effusions and prior history of pulmonary embolism and DVT on LMWH developed worsening of his embolism on Day 4 with evidence of right heart strain. He received alteplase, however died on the same day. Autopsy confirmed that the extent of his pulmonary embolism was greater than that seen on his earlier CT pulmonary angiogram.
Pneumonia Patient 212009	A 67 year-old woman with squamous carcinoma to the mediastinum and right lung developed Klebsiella oxytoca pneumonia beginning Day 26 and resulting in hospitalization on Day 41. She was treated with antibiotics and discharged. On Day 61, she was again hospitalized for pneumonia and died on Day 75.
Pulmonary Embolism Patient 213071	A 67 year-old man with squamous carcinoma to bone, brain, liver, spleen, and bilateral lung with pleural effusion developed Grade 3 pneumonia on Day 2. On Day 9, the patient represented with respiratory distress and was diagnosed with pulmonary embolism. He died on Day 10.
Cardiac Failure Patient 213080	A 70 year-old woman with squamous carcinoma to the liver developed ST-elevation MI on Day 14 and died on Day 16. Autopsy demonstrated marked pulmonary edema, cardiac biventricular dilatation, and congestive changes of the liver.
Other deaths >30 days	
“Death” Patient 207019 Reviewer note: It is likely that cachexia secondary to dysphagia was directly related to the patient’s death. The etiology of the patient’s dysphagia is unclear and a relationship to atezolizumab is possible.	A 68 year-old man with squamous carcinoma to bilateral lung, right adrenal gland, and bone developed Grade 4 dysphagia on Day 13 with subsequent cachexia. He was hospitalized and discharged on Day 28. On Day 33, he died during insertion of a central venous catheter for parenteral nutrition. No autopsy was performed.
Pneumonia Patient 207009	A 56 year-old man with squamous carcinoma to the right lung, liver, and lymph nodes developed pneumonia after the last dose of atezolizumab on Day 396, but on or prior to Day 442. Per phone contact with the caregiver, the patient died on Day

	442 due to pneumonia prior to admission to the hospital.
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7.4.2. Serious Adverse Events

Non-fatal serious adverse events (SAEs) occurred in 35% of patients who received atezolizumab and 34% of patients who received docetaxel. The most frequent serious adverse reactions (>2% of atezolizumab-treated patients) were pneumonia, dyspnea, pleural effusion, and venous thromboembolism. Table 46 summarizes these common SAEs including SAEs occurring in >2% of docetaxel-treated patients.

Table 46: Serious Adverse Events (Cohort 2) [Database cut-off 5-5-15]

Pooled term	Atezolizumab % (n)	Docetaxel % (n)
SAEs occurring in >2% of atezolizumab-treated patients		
Pneumonia	9.6 (14)	2.2 (3)
Dyspnea	4.9 (7)	0.7 (1)
Pleural effusion	3.5 (5)	0
Venous thromboembolism	2.1 (3)	4.4 (6)
SAEs occurring in >2% of docetaxel-treated patients		
Febrile neutropenia	0	5.2 (7)
Sepsis	0	3.0 (4)
Neutropenia	0	2.2 (3)
Hemoptysis	0.7 (1)	2.2 (3)

7.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Table 47 below provides information on the 6 patients who permanently discontinued atezolizumab due to an adverse event.

Dose interruptions occurred in 34 (24%) patients in the AE dataset. These interruptions are

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discussed further in Section 8.5.

Table 47: Adverse Events Resulting in Permanent Discontinuation

	POPLAR N = 142
Any Adverse Event Leading to Permanent Discontinuation	6 (4.2%)
Dyspnea	2 (1.4)
Aspiration pneumonia	1 (0.7)
Elevated AST	1 (0.7)
Autoimmune arthritis	1 (0.7)
Stress/anxiety	1 (0.7)

7.4.4. Significant Adverse Events

Adverse events of special interest (AESIs) were pre-defined as described in Section 7.5. POPLAR, 41 atezolizumab-treated patients (29%) experienced an AESI, compared to 40 patients (30%) treated with docetaxel. Eight of the atezolizumab-treated patients (5.6%) experienced a Grade 3-4 AESI, compared to four (3%) of the docetaxel-treated patients. The most common AESIs in atezolizumab-treated patients were skin disorders (16%) and endocrine events (6%), the majority of which were hypothyroidism. The most common AESIs in docetaxel-treated patients were Grade 1-2 peripheral neuropathy, occurring in 16 patients (12%). See Section 8.4.5 for discussion of severe (Grade 3-4) adverse events and Section 8.5 for further discussion of adverse events by system.

7.4.5. Treatment Emergent Adverse Events and Adverse Reactions

The most common adverse events (>20% of atezolizumab-treated patients) were fatigue, decreased appetite, dyspnea, cough, nausea, musculoskeletal pain, and constipation. The most common Grade 3-4 adverse events (>2% of atezolizumab-treated patients) were pneumonia, hypoxia, fatigue, musculoskeletal pain, and arthralgia. (Table 48).

Infections, including high-grade pneumonia, occurred at a high rate in atezolizumab-treated patients in this study compared to docetaxel-treated patients. Based on the system organ classification term "infections and infestations," 42% of patients who received atezolizumab experienced an event compared to 33% of those who received docetaxel. With regards to pneumonia, the difference in incidence between the two arms is not explained by exposure duration alone, as the number of patient years at risk in the atezolizumab arm was 84 compared to 46 in the docetaxel arm, however the incidence of pneumonia was 18% vs 4% respectively for all-grades and 6.3% vs 1.5% for Grades 3-4.

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Table 43: Grade 1-4 Adverse Reactions in $\geq 10\%$ of Patients treated with either Atezolizumab or Docetaxel

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	Atezolizumab N = 142		Docetaxel N = 135	
Adverse Reaction	Grades 1-4 (%)	Grades 3 – 4 (%)	Grades 1-4 (%)	Grades 3 – 4 (%)
All Adverse Reactions	96	43	96	55
Gastrointestinal Disorders				
Diarrhea	18	1.4	29	3
Constipation	20	0	24	0.7
Nausea	22	0.7	33	0
Vomiting	13	0	13	0
Abdominal pain	9	0	10	0.7
General Disorders and Administration				
Fatigue	46	3.5	54	9.6
Pyrexia	18	0	13	0
Peripheral edema	11	0	15	0
Insomnia	13	0	8	1.5
Infections and Infestations				
Pneumonia	18	6.3	4.4	1.5
Febrile neutropenia	0	0	8	8
Metabolism and Nutrition Disorders				
Decreased appetite	35	1.4	21	0
Weight decreased	11	0	7	0
Musculoskeletal and Connective Tissue Disorders				
Back pain	14	1.4	9	0.7
Musculoskeletal pain	22	2.8	21	4.4
Arthralgia	16	2.1	9	1.5
Nervous System Disorders				
Peripheral neuropathy	7	0.7	25	5
Respiratory, Thoracic, and Mediastinal Disorders				

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Dyspnea	32	7	24	1.5
Cough	30	0.7	25	0
Hypoxia	4.2	4.2	0.7	0
Skin and Subcutaneous Tissue Disorders				
Rash	19	1.4	18	0.7
Pruritis	9	0	3.7	0
Alopecia	2.1	0	39	0.7

7.4.6. Laboratory Findings

Laboratory events in the alb.xpt databased were assessed per CTCAE v4.0 criteria. Abnormalities in hematology tests were primarily Grade 1 to 2 in severity. The most common Grade 3 and 4 hematologic abnormalities in the atezolizumab-treated patients were hyponatremia (13%), lymphopenia (12%), hyperglycemia (8%), anemia (5%), and hypoalbuminemia (Table 49). Abnormal laboratory values of all-grades that occurred more commonly (>5% difference between arms) in the atezolizumab-treated patients compared to the docetaxel-treated patients included hyponatremia (48% vs 28%), hypokalemia (18% vs 11%), increased ALT (31% vs 9%), increased AST (33% vs 14%), increased total bilirubin (10% vs 4%), increased alkaline phosphatase (42% vs 24%), increased creatinine (84% vs 69%), and hypercalcemia (13% vs 5%). Abnormalities in liver function tests in atezolizumab-treated patients were primarily Grade 1 to 2 in severity. The most common Grade 3-4 liver function test abnormalities were increased ALT and AST (3% each). There were two cases of Hy's Law identified through laboratory screening, however one of these patients had an alternative etiology for their liver test abnormalities. Grade 3-4 increased creatinine occurred in 1% of patients. The most common Grade 3-4 electrolyte abnormalities were hyponatremia (13%) and hyperglycemia (8%). Grade 3-4 lymphopenia was noted in 12% of atezolizumab-treated patients, however there was no clear association between lymphopenia and infection.

Table 49: Incidence of Grade 3-4 Laboratory Abnormalities

Laboratory Test	Grades 3-4 N (%)	
	Atezolizumab N =142	Docetaxel N = 135
Hyponatremia	17 (13%)	10 (8%)

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Lymphopenia	17 (12)	35 (26)
Hyperglycemia	12 (8)	23 (17)
Anemia	7 (5)	9 (7)
Hypoalbuminemia	7 (5)	1 (1)
Increased ALT	3 (2)	1 (1)
Increased AST	3 (2)	0
Hypokalemia	2 (1)	5 (4)
Increased Alkaline phosphatase	2 (1)	1 (1)
Increased Creatinine	1 (1)	3 (2)
Increased Total Bilirubin	0	1 (1)
Hypercalcemia	0	0

Laboratory Test	All Grades N (%)	
	Atezolizumab N =142	Docetaxel N = 135
Anemia	96 (72%)	111 (87%)
Lymphopenia	78 (59)	90 (70)
Hyponatremia	64 (48)	37 (28)
Hypoalbuminemia	64 (48)	63 (49)
Increased Alkaline phosphatase	56 (42)	32 (24)
Increased AST	44 (33)	19 (14)
Increased ALT	41 (31)	12 (9)
Hypocalcemia	29 (22)	31 (24)
Increased Creatinine	27 (19)	19 (14)
Hypokalemia	24 (18)	14 (11)
Hypercalcemia	17 (13)	7 (5)
Increased total bilirubin	14 (10)	5 (4)

7.4.7. Vital Signs

Based on analyses of mean value and mean change from baseline at each cycle, no clinically meaningful differences in systolic blood pressure, diastolic blood pressure, heart rate, or temperature were observed during the course of treatment with atezolizumab.

7.4.8. Electrocardiograms (ECGs)

Safety ECGs and/or triplicate ECGs were not collected in POPLAR. Therefore, no QT

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prolongation effect can be assessed for patients in POPLAR. In study PCD4989g, digitized 12-lead ECGs were collected in triplicate for patients enrolled in the dose-expansion cohorts at screening, 30 minutes before and after end of infusion on Day 1 of Cycles 1 and 4, and at treatment discontinuation. There was no relationship between atezolizumab concentration and change in QTcF at atezolizumab concentrations up to the geometric mean C_{max} following four doses of atezolizumab 20 mg/kg administered once every three weeks. After examination of events of seizure/convulsion, syncope/presyncope, QTc prolongation, and tachycardia, no event was determined to be associated with an abnormal ECG finding and none were potentially related to an arrhythmia.

7.4.9. QT

Refer to Section 7.4.8 and Clinical Pharmacology Review for additional details.

7.4.10. Immunogenicity

Anti-therapeutic antibodies (ATAs) were assessed at multiple time-points in patients in the atezolizumab arm in POPLAR. Of those sampled, 135 patients were considered evaluable, 83/88 in PCD, . 73 patients (54%) were considered ATA-positive. ATA positivity had only a minor impact on atezolizumab exposure, yielding a 13.6% increased clearance in a population PK analysis. Incidence of adverse events in POPLAR, by anti-therapeutic antibody (ATA) status is presented in Table 50.

Table 50: Adverse Effect Incidence by Presence of Anti-therapeutic Antibodies

	POPLAR	
	ATA positive N= 73 (%)	ATA negative N=62 (%)
Any AE	68 (93%)	61 (98%)
Grade 1-2 AE	36 (49%)	37 (60%)
Grade 3-5 AE	32 (44%)	24 (39%)
AESI	22 (30%)	19 (31%)

Table 51: AESIs in NSCLC trials

BIRCH		FIR		PCD4989g NSCLC Cohort	
ATA positive N= 240 (%)	ATA negative N= 384 (%)	ATA positive N=73 (%)	ATA negative N= 63 (%)	ATA positive N= 21 (%)	ATA negative N= 62 (%)
67 (28%)	101 (26%)	15 (23%)	16 (25%)	7 (33%)	19 (31%)

Reviewer note: No significant impact of anti-therapeutic antibodies on safety or efficacy were

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noted. Refer to the Clinical Pharmacology Review for additional details.

7.5. Analysis of Submission-Specific Safety Issues

Class effects associated with anti-PD-1/anti-PD-L1 drugs, including nivolumab and pembrolizumab, are primarily immune-related and include pneumonitis, colitis, hepatitis, hypophysitis, renal failure/nephritis, hyper/hypothyroidism. The Applicant thus identified adverse events of special interest (AESIs) in categories comprising endocrine, GI, hepatic, pulmonary, renal, and skin toxicities, as well as infection and hypersensitivity reactions. These included

1. Conditions suggestive of an autoimmune disorder
2. Grade 3 or greater acute infection
3. Grade 3 or greater events suggestive of hypersensitivity
4. Grade 3 or greater rash or pruritis
5. Grade 3 or greater diarrhea
6. Grade 2 or greater colitis
7. Grade 3 or greater LFT elevations
8. Grade 2 or greater LFT elevations with symptoms
9. Grade 2 or greater dyspnea not attributable to UBC
10. Grade 2 or greater hypoxia
11. Grade 2 or greater pleural effusion
12. Grade 2 or greater pericardial effusion
13. Cases of potential drug-induced liver injury as defined by Hy's Law
14. Suspected transmission of an infectious agent by the study drug

In POPLAR, the Applicant identified 41 patients (29%) in the atezolizumab arm and 40 patients (30%) in the docetaxel arm who experienced at least one AESI. The most common AESIs in the atezolizumab arm were rash (15%), hypothyroidism (6%), and hepatic events (6% all-grade, 3% Grade 3-4 events).

Additionally, the Applicant identified immune-mediated adverse events (imAEs) as those in which the date of systemic corticosteroid initiation was on or up to 30 days after the AE onset date, the date of corticosteroid initiation was prior to the AE resolution date, and no clear alternate etiology could be identified. The incidence of these events is shown in Table 51 below. Across the integrated safety database, including NSCLC and patients with other malignancies treated on the PCD4989g, BIRCH, FIR, and POPLAR trials, the most common imAEs were pneumonitis and rash, which each occurred in 1.2% of patients. Incidence of corticosteroid administration is discussed in more detail in section 7.5.16.

Reviewer note: *The incidence of immune-mediated adverse events appears consistent with those noted with other PD-1/PD-L1 inhibitors.*

Table 51: Immune-mediated Adverse Events (>0.5%) in Patients with NSCLC Treated with Atezolizumab

ImAEs	All NSCLC (n = 1027)
Pneumonitis	18 (1.8%)
Rash ¹	11 (1.1%)
Dyspnea	8 (0.8%)
AST increased	7 (0.7%)
ALT increased	6 (0.6%)

1: includes dermatitis, rash maculopapular, rash pruritic

7.5.1. Pneumonitis

Six patients (4.2%) treated with atezolizumab developed pneumonitis or interstitial lung disease, of which 3 cases were Grade 3, one was Grade 2, and two were Grade 1. In one patient (213018), the documented AEs were Grade 3 hypoxia and dyspnea, however the patient was treated with prednisone with an indication of pneumonitis. In another patient (213053), the documented AE was Grade 3 hypoxia, however this occurred on a background of ongoing lung infiltration, which began 26 days prior. The median day of onset for the first event for these six patients was day 142 (range: 20-359). One of these events was ongoing and a date of resolution (and therefore duration) was not available for this patient. In the remaining 5 patients, the median duration of the first event was 18 days (range: 8-70). Four patients were treated with corticosteroids and one patient was treated only with azithromycin.

Dyspnea or exertional dyspnea was reported in 32 patients of which 7 cases were Grade 3-4. Eleven of these patients were treated with corticosteroids, however there was no clear radiographic evidence of pneumonitis in these cases aside from the patient (213018) described above.

BIRCH

Twenty-five patients (3.8%) treated with atezolizumab developed pneumonitis or interstitial lung disease. One patient died due to pneumonitis. Eleven cases were Grade 3 or 4 and 13 cases were Grade 1 or 2. The median day of onset for the first event for these 25 patients was Day 25 (range: 3-343). Nine of these events were ongoing and a date of resolution (and therefore duration) was not available for these patients. In the remaining 16 patients, the median duration of the first event was 25 days (range: 13-401). Thirteen patients were treated with corticosteroids. Pneumonitis recurred in 4 patients.

FIR

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{BLA}

{Atezolizumab}

Two patients (1.5%) treated with atezolizumab developed pneumonitis or interstitial lung disease. One patient developed Grade 3 pneumonitis at Day 94, which was unresolved at the time of the patient's death on Day 145 despite treatment with corticosteroids. A second patient experienced Grade 1 pneumonitis at Day 217, which resolved with drug interruption.

Patient 181207 died due to respiratory failure on Day 21 and had received corticosteroids for an indication of pneumonitis. A lung biopsy demonstrated organizing lung injury with intra-alveolar fibroplasia, however the patient had concomitant evidence of rapid disease progression, suggesting an alternative etiology for the patient's respiratory decline. One patient was treated for Grade 2 dyspnea with corticosteroids, however there was no radiographic evidence of pneumonitis.

PCD4989g

Five patients (5.7%) treated with atezolizumab developed pneumonitis or interstitial lung disease. All cases were Grade 1 or Grade 2. No patients discontinued therapy due to pneumonitis; one patient interrupted therapy. Three patients were treated with corticosteroid therapy. Two patients experienced Grade 3 hypoxia and one patient developed Grade 2 dyspnea and were treated with corticosteroids, however on review of these narratives, there was not clear radiologic evidence of pneumonitis in these cases. Dyspnea or exertional dyspnea was reported in 17 patients. One patient (101716) died due to acute respiratory failure. On review of this narrative, this appears to be disease progression.

Reviewer note: *In conclusion, the incidence of pneumonitis was 4.2% in POPLAR. The median date of onset was Day 142. In all patients with NSCLC, the incidence was 38/1027 (3.7%). There was one case of fatal pneumonitis.. Atezolizumab was permanently discontinued in 4/1027 patients and interrupted in 24/1027 patients. Steroids were used in 20 of the 38 patients, of whom one died and 26 recovered. Overall, the incidence of pneumonitis appears consistent or lower than that noted with other PD-1/PD-L1 inhibitors.*

7.5.2. Hepatitis

Safety Database

Table 52 below presents the incidence of Grade 3-4 liver function test abnormalities in the safety database, comprising 1848 patients with multiple tumor types in several studies. On-study labs were not available for all patients.

Table 52: Liver Function Test Abnormalities in the Adverse Event Datasets

	Grade 3-4 AST	Grade 3-4 ALT	Grade 3-4 bilirubin
Total	40/1750 (2.3%)	43/1752 (2.5%)	28/1752 (1.6%)

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N = 1848			
POPLAR N = 142	3/134	3/134	0/134
FIR N = 137	4/129	5/129	2/129
BIRCH N = 659	5/632	6/633	3/633
IMvigor Cohort 1 N = 119	3/110	5/110	2/110
IMvigor Cohort 2 N = 310	7/284	6/284	4/284
PCD4989g N = 481	18/461	18/462	17/462

POPLAR

All	Combined NSCLC	
	Grade 1-4	Grade 3-4
	75 (7.3%)	23 (2.2%)
	POPLAR N = 142	
	Grade 1-4	Grade 3-4
All	10 (7%)	4 (2.8%)
AST Increased	6 (4.6)	3 (2.1)
ALT Increased	5 (3.5)	2 (1.4)
AKP Increased	4 (2.8)	1 (0.7)
Elevated Bilirubin/Hyperbilirubinemia	1 (0.7)	0
Hepatitis	1 (0.7)	0
Liver function test abnormal	1 (0.7)	1 (0.7)
	BIRCH N = 659	
	Grade 1-4	Grade 3-4
All	50 (7.6%)	14 (2.1%)
AST Increased	25 (3.8)	5 (0.8)
ALT Increased	21 (3.2)	2 (0.3)
GGT Increased	11 (1.7)	5 (0.8)
AKP Increased	8 (1.2)	1 (0.2)
Elevated Bilirubin/Hyperbilirubinemia	6 (0.9)	1 (0.2)
Transaminases Increased	3 (0.5)	0

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Liver function test abnormal	3 (0.5)	0
Hepatic enzyme increased	2 (0.3)	1 (0.2)
Drug-induced liver injury	1 (0.2)	0
Hepatic function abnormal	1 (0.2)	0
Hepatotoxicity	1 (0.2)	0
Hepatic failure	1 (0.2)	1 (0.2)
	FIR N = 137	
	Grade 1-4	Grade 3-4
All	7 (5.1%)	4 (2.9%)
AST Increased	6 (4.4)	3 (2.2)
ALT Increased	6 (4.4)	3 (2.2)
AKP Increased	3 (2.2)	1 (0.7)
	PCD4989g (NSCLC) N=88	
	Grade 1-4	Grade 3-4
All	8 (9.1%)	1 (1.1%)
ALT increased	3 (3.4)	0
Transaminases increased	2 (2.3)	0
Hepatocellular injury	2 (2.3)	0
Autoimmune hepatitis	1 (1.1)	1
Hepatic steatosis	1 (1.1)	0
AST increased	1 (1.1)	0

Table 53 below provides information on the incidence of hepatic adverse events in the POPLAR, BIRCH, FIR trials and the NSCLC cohort of the PCD4989g, including laboratory abnormalities that were reported as adverse events. In total, 232 events occurred in 116 patients out of 1027 patients with NSCLC treated with atezolizumab. The median day of onset for the first event was 29 days (range: 1-784). Many events were ongoing or unresolved prior to death and a date of resolution (and therefore duration) was not available for 41 patients. The median duration of the first event in the remaining 75 patients was 17 days (range: 0-91). Of note, of the 10 patients with hepatic adverse events in the POPLAR trial, only two had liver metastases at baseline.

Corticosteroids were administered to treat 64 events in 10 patients. In a review of the narratives of these patients, 8 (0.8%) were determined to have experienced immune-mediated hepatitis. Of these patients, four had Grade 3 events, three had Grade 2, and one had Grade 1. The median time to onset for the first event was 25 days (range: 15-147 days).

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POPLAR

Two patients developed liver enzyme elevations that appeared to be immune-mediated. Patient 213019 developed Grade 3 AST and ALT elevations on Day 127 and subsequently received a course of systemic corticosteroids and mycophenolate mofetil. However, the ALT event worsened to Grade 4 on Day 155 despite continued and increased steroids, leading to discontinuation of atezolizumab. A liver biopsy on Day 162 demonstrated minimally active interface hepatitis with portal and focal periportal fibrosis. She died on Day 185 due to brain metastasis progression with ongoing hepatitis.

Patient 213102 developed an influenza-like illness on Day 12 with concomitant Grade 3 AST elevation and Grade 2 bilirubin and alkaline phosphatase elevations. She developed a Grade 3 rash on Day 17. Abdominal right upper quadrant ultrasound was normal. She received systemic corticosteroids and atezolizumab was temporarily held. Hepatic adverse events resolved on Day 29 except for elevated alkaline phosphatase, which resolved on Day 50.

BIRCH

There were two cases in which patients had concurrent elevation in transaminases and bilirubin meeting the laboratory criteria for Hy's Law (bilirubin > 2xULN (grade 2) and ALT/AST > 3xULN (Grade 2) without concomitant elevated alkaline phosphatase) in BIRCH. Patient 308001 experienced progressive elevations in her LFTs beginning Day 44, however she was found to have progressive liver metastases. Patient 305005 developed Grade 5 hepatic failure on Day 290 in the context of esophageal perforation and respiratory failure. She died on the same day and no autopsy was performed.

FIR

There was one case in which the patient met laboratory criteria for Hy's Law in FIR. Patient 102605 developed disseminated intravascular coagulation with microangiopathic hemolytic anemia and portal vein thrombosis. He died on Day 91; autopsy additionally demonstrated diffuse hepatic infiltration of tumor. Although corticosteroids were initially administered, this was not considered a case of autoimmune hepatitis.

PCD4989g

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{BLA}

{Atezolizumab}

There were no cases that met laboratory criteria for Hy's Law in NSCLC patients in PCD4989g. Patient 101515 developed a Grade 3 pruritic rash on Day 23 and received systemic corticosteroids. She then developed a recurrent rash and Grade 4 autoimmune hepatitis, confirmed by liver biopsy, on Day 32. She received a second course of corticosteroids and then event resolved 21 days later. Atezolizumab was temporarily interrupted without recurrence upon reinitiation. All other hepatic events were of Grade 1 or 2 severity.

Reviewer note: *In conclusion, hepatic adverse events occurred in 10 (7%) of patients in POPLAR, including 4/142 (2.8%) Grade 3-4 hepatic adverse events. In all patients with NSCLC treated with atezolizumab, hepatic adverse events occurred in 75 (7.3%) of patients, including 23 (2.2%) with Grade 3-4 hepatic adverse events. In all patients with NSCLC treated with atezolizumab, the median day of onset for the first event was Day 29 with a median duration of 17 days. In all patients with NSCLC for whom on-study laboratory values were available (983 patients), the incidence of Grade 3-4 AST, ALT, and total bilirubin elevation were 1.6%, 1.7%, and 0.8% respectively. Atezolizumab was interrupted in 6/1027 patients. Steroids were used for hepatic events in 10/1027 (1.0%) of patients, of whom all patients recovered. Atezolizumab was held in four patients and then restarted; none of these patients experienced recurrent hepatitis. Overall, the incidence of hepatitis appears consistent or lower than that noted with other PD-1/PD-L1 inhibitors.*

7.5.3. Diarrhea/Colitis

Table 56 below provides information on the incidence of diarrhea in NSCLC-treated patients.

Table 56: Diarrhea/Colitis Adverse Events in NSCLC

	POPLAR N = 277			
	Atezolizumab (N =142)		Docetaxel (N = 135)	
	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4
All	26 (18%)	2 (1.4%)	4 (29%)(3.0%)	4 (3%)
Diarrhea	24 (17)	1 (0.7)	38 (28)	4 (3)
Colitis	2 (1.4)	1 (0.7)	1 (0.7)	0
	BIRCH (N = 659)			
	Grade 1-4		Grade 3-4	
All	121 (19%)		8 (1.2%)	
Diarrhea	112 (17)		5 (0.7)	
Colitis	8 (1.2)		3 (0.5)	
Frequent bowel movements	1 (0.8)		0	

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	FIR (N = 137)	
	Grade 1-4	Grade 3-4
All	29 (21%)	2 (1.5%)
Diarrhea	28 (20)	2 (1.5)
Colitis	1 (0.7)	0
	PCD4989g (N = 88)	
	Grade 1-4	Grade 3-4
All	21 (24%)	0
Diarrhea	21 (24%)	0

POPLAR

In atezolizumab-treated patients, 34 events of diarrhea or colitis occurred in 26 patients. The median day of first event onset was day 26 (range: 1-343). 3 events were unresolved. Among the 23 patients in whom the event had resolved and in whom data was available, the median duration was 8 days (range: 1-367). Drug was interrupted in 1 patient; no patient withdrew due to diarrhea. Among the 2 patients with Grade 3 diarrhea, the drug was interrupted in one patient and continued in the other; both patients were treated with corticosteroids with resolution of the event.

BIRCH

173 events of diarrhea or colitis occurred in 128 patients. The median day of onset was day 48 (range: 1-387). Among the 117 patients in whom the event had resolved and in whom data was available, the median duration was 3 days (range: 1-193). Drug was interrupted due to diarrhea in 13 patients and was discontinued in one patients.

Patient 317036 developed Grade 3 colitis on Day 196 and was hospitalized. The event resolved, however recurred on Day 211, whereupon she was treated with corticosteroids. Endoscopy with biopsy demonstrated duodenitis and she was rehospitalized on Day227. Atezolizumab was discontinued. Infectious workup was negative and she was treated with infliximab, with subsequent improvement. However the colitis as well as treatment with corticosteroids continued and the colitis remained unresolved as of the DCO.

FIR

In atezolizumab-treated patients, 38 events of diarrhea or colitis occurred in 29 patients. The median day of first onset was 43 (range 1-426). Five events were unresolved. Among the 24 patients in whom the event had resolved and in whom data was available, the median duration

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was 6 days (range: 1-80). Atezolizumab was interrupted in one patient and was not discontinued in any patient. Steroids were not administered for diarrhea or colitis in any patients.

PCD4989g

In atezolizumab-treated patients, 24 events of diarrhea occurred in 21 patients. Colitis was not reported. All events were grade 1-2. The median day of the first event onset was day 73 (range; 2-430). Two events were unresolved. Among the 19 patients in which the event had resolved and in whom data was available, the median duration was 15 days (range; 1-171). Atezolizumab was not interrupted or discontinued in any patient. Steroids were not administered for diarrhea or colitis in any patient.

Reviewer note: *In conclusion, the incidence of diarrhea or colitis was 18% in POPLAR. The median date of onset was Day 26. Patients with NSCLC from BIRCH, FIR, and the Phase 1 study are discussed in this section. In all patients with bladder cancer, the incidence was 197/1027 (19%). The majority of these events were grade 1-2 and most were of short duration. One patient required infliximab therapy for persistent colitis. Atezolizumab was permanently discontinued in 2/1027 pts and interrupted in 15/1027 patients. Steroids were used in only 4 patients; one of these patients also required infliximab for persistent colitis.*

7.5.4. Thyroid Disease

Due to the infrequency of the event, analyses were combined across all atezolizumab-treated patients with NSCLC. In all studies, 46 events of hypothyroidism or increased TSH were reported in 42 patients. The median time of onset was 145 days (range 15-337). The event was reported as resolved in 10 patients. In these patients, the median duration was 22 days (range: 13-199). The dose was interrupted in 7 patients; atezolizumab was not discontinued for hypothyroidism in any patient. Three patients developed Grade 3 hypothyroidism. Patient 315007 (BIRCH) developed Grade 3 hypothyroidism on Day 236, atezolizumab was interrupted, and was hospitalized. Levothyroxine was administered and the event resolved by Day 248. Patient 305023 (BIRCH) developed Grade 3 hypothyroidism on Day 216 with concomitant elevated blood CPK, muscle cramps, and myxedema. Atezolizumab was interrupted and he recovered with levothyroxine treatment. Patient 201003 (POPLAR) had baseline hypothyroidism and developed Grade 3 hypothyroidism on Day 147. Levothyroxine dose was increased and she recovered.

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Table 59 below provides information on thyroid function tests at baseline and on study for Atezolizumab-treated patients in POPLAR, which were combined due to the relatively small number of patients with a follow-up TSH. On study includes the treatment period and the 30 day safety follow-up visit.

Table 59: Thyroid Stimulating Hormone (TSH) Changes in POPLAR (Only patients with on-study value included)

	N = 138
	Baseline
TSH > ULN and over baseline value	10 (7.2%)
TSH > 3x ULN and over baseline value	4 (2.9)
TSH > 10xULN and over baseline value	1 (0.7)

Reviewer note: *In conclusion, the incidence of hypothyroidism was 42/1027 (4.1%) in all NSCLC patients treated with atezolizumab. The median date of onset was Day 145. TSH was elevated at least 10-fold over ULN in 1/138 (0.7%) patients with available follow-up laboratory values in POPLAR. Overall, while the incidence of hypothyroidism appears consistent or lower than other PD-1/PD-L1 agents, TSH was routinely evaluated only at baseline and end-of-study, thus this incidence likely underestimates the true incidence of hypothyroidism. The Applicant has agreed to a Post-Marketing Requirement (PMR) as a component of the BLA for atezolizumab in bladder cancer (BLA 761034) to assess TSH more frequently (every 6 weeks) in one large trial.*

7.5.5. Hyperglycemia/Diabetes Mellitus

No cases of likely immune-mediated diabetes mellitus (as identified by low C-peptide and/or auto-antibodies) were noted in FIR, POPLAR, BIRCH or PCD4989g datasets as of the data cutoffs. The Applicant provided a drug safety update indicating seven cases of new onset diabetes mellitus suggestive of immune-mediated islet cell destruction. Two cases occurred in patients with non-small cell lung cancer (including one case in a patient in BIRCH that occurred after the data cutoff), one in a patient with renal cell carcinoma, one in a patient with breast cancer, three with an unspecified advanced solid tumor. In two cases, GAD65 auto-antibodies were positive. Two patients had low C-peptide. Three patients presented with ketoacidosis. Insulin was started in all cases and six of the seven patients resumed atezolizumab.

Hyperglycemia (Combined analysis)

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Thirty-eight events of “hyperglycemia” during the treatment period were reported in 23 patients of a combined analysis of atezolizumab-treated NSCLC patients in POPLAR, BIRCH, FIR, and PCD4989g. The median time of onset was 76 days (range: 1-170). Seventeen cases were reported as resolved with a median duration of 22 days (range: 4-126). Five patients experienced Grade 3-4 events. Patient 211004 (POPLAR) experienced Grade 3 hyperglycemia in the setting of high-dose steroids administered for autoimmune hemolysis. Patient 210014 (POPLAR) had a history of diabetes mellitus on two oral agents and developed Grade 3 hyperglycemia on day 43 without a clear precipitant. Hyperglycemia resolved following addition of metformin. Patient 314011 (BIRCH) had a history of baseline Type 2 insulin-dependent diabetes mellitus and developed Grade 3 hyperglycemia on Day 23, in the setting of concurrent Grade 2 hyperthyroidism. Hyperglycemia resolved on Day 55. Patient 301017 (BIRCH) had a history of insulin-dependent Type 2 diabetes mellitus and developed Grade 3 hyperglycemia in the setting of high-dose corticosteroids for pneumonitis. Patient 102102 (PCD4989g) had a history of Type 2 diabetes on metformin and developed Grade 3 hyperglycemia on day 254 without a clear precipitant and was not reported as having resolved at completion of the study. following discontinuation of atezolizumab for disease progression on day 66.

Reviewer note: *In conclusion, there were one case of likely immune-mediated diabetes mellitus that occurred in the BIRCH trial after the data cut-off. The incidence of hyperglycemia among in the NSCLC safety database was 23/1027 patients (2.2%). In POPLAR, the incidence of Grade 3-4 hyperglycemia was lower in patients receiving atezolizumab than in patients receiving docetaxel, likely due to the use of pre- and post-infusion corticosteroid use with docetaxel. . In all patients treated with atezolizumab in the Applicant’s database (N = 1978), there were two cases of confirmed immune-mediated diabetes mellitus. Overall, the incidence of diabetes mellitus is consistent with other PD-1/PD-L1 inhibitors.*

7.5.6. Adrenal Insufficiency

Two patients in the BIRCH trial developed adrenal insufficiency. Patient 313032 developed Grade 2 on day 158 treated with fludrocortisone and hydrocortisone. The event is ongoing. Patient 36007 developed Grade 1 adrenal insufficiency on day 2. He was treated with dexamethasone, however died on day 30 due to disease progression. The event was ongoing at that time. Neither patient had adrenal metastases at screening.

No patients in the POPLAR, FIR, or NSCLC population of PCD4989g reported adrenal insufficiency. Patients were examined for reports of the adverse events hyponatremia and hyperkalemia. Nine patients experienced concomitant adverse events of hyponatremia and hypokalemia. One patient (183804) did experience a concomitant adverse event of dehydration, however there were no concomitant reports of hypotension in these patients.

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There were a number of reports of fatigue and diarrhea, but these could not be distinguished from concomitant conditions.

Reviewer note: *Two patients with non-small cell lung cancer developed adrenal insufficiency as discussed above. Overall, the incidence of immune-mediated adrenal insufficiency appears similar to other PD-1/PD-L1 inhibitors.*

7.5.7. Hypophysitis

No cases of hypophysitis or pituitary dysfunction were reported in BIRCH, FIR, or POPLAR.

PCD4989g

Patient 121018 developed dizziness, lethargy, and confusion and was found to have a hypothalamic mass which was thought to be an inflammatory lesion. She was treated with high dose dexamethasone with reduction in the size of the lesion. Laboratory tests showed pituitary deficiency. It is unclear if hormone replacement was used, but there are no reports of hormone replacement in the concomitant medications. She permanently discontinued atezolizumab.

Reviewer note: *There were no cases of hypophysitis in patients with NSCLC. There was one case of likely immune-mediated hypophysitis in the PCD4989g bladder cancer cohort as described above. Overall, the incidence of hypophysitis appears similar to other PD-1/PD-L1 inhibitors.*

7.5.8. Other Endocrinopathies

POPLAR

There were no other endocrinopathies noted in POPLAR.

BIRCH

There were no other endocrinopathies noted in BIRCH.

FIR

One patient (182110) developed Grade 1 primary hypogonadism as manifested by a low testosterone level and normal or elevated LH/FSH on Day 22.

PCD4989g

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Grade 1 hypogonadism was reported on day 703 in patient 102009 and is ongoing. Dosing was unchanged. This was not considered an AESI. The Applicant reports that no further details are available regarding this event.

7.5.9. Neurological Disorders

Neurological disorders of concern are presented in the table below. This table does not include all neurological adverse events, but instead includes adverse events designed as AESIs by the Applicant or neurological events that have been seen with other PD-1/PD-L1 inhibitors.

POPLAR

Most neurologic events in atezolizumab-treated patients in the POPLAR trial were Grade 1-2 peripheral neuropathy that occurred at a lower rate than in the docetaxel-treated patients. No patient received corticosteroids for a neurologic event.

BIRCH

Grade 2 optic neuritis was reported in a patient with NSCLC enrolled in the BIRCH study on day 89. Atezolizumab was discontinued for disease progression on day 85 and she received dexamethasone for brain metastasis-related edema on day 105. Optic neuritis remained unresolved at the time of death.

Patient 314006 developed Grade 3 vestibular neuronitis on Day 408. Brain MRI did not reveal evidence of metastases. He was treated with corticosteroids, however the event remained unresolved. Atezolizumab was not interrupted.

Patient 313047 developed Grade 3 encephalitis on Day 16, manifested by fever, convulsions, and neck adenopathy. She was treated with antivirals, antibiotics, and anticonvulsants. MRI was reportedly normal and the remainder of her infectious workup was negative. She was treated with corticosteroids. Atezolizumab was interrupted. The event resolved on Day 28.

Patient 317099 developed Grade 3 peripheral motor neuropathy on Day 15, which resolved by Day 87 without treatment.

Patient 304024 developed Grade 3 paraplegia on Day 12. Lumbar puncture and auto-immune antibody panel were negative. MRI demonstrated a small nodular focus of enhancement in the right occipital lobe as well as a lesion in the right cervical hemisphere. He received intravenous immunoglobulin with improvement in paraplegia. On Day 39, he discontinued the study for progressive disease. It is unclear whether the lesions seen on MRI represented CNS metastases or an autoimmune phenomenon.

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Three patients received steroids for peripheral neuropathy or polyneuropathy. Patient 307024 experienced Grade 2 worsening of pre-existing polyneuropathy and received a single dose of dexamethasone that was listed as indicated for nausea/vomiting. Both events in the two patients receiving steroids for peripheral neuropathy were reported as Grade 1.

FIR

Grade 3 Guillain-Barre syndrome was reported in a patient with NSCLC enrolled in the FIR study on day 247. Atezolizumab was discontinued and she was treated intravenous immunoglobulin. The event resolved by day 282. Of note, she experienced concurrent hepatitis and hyperthyroidism.

Patient 173703 experienced Grade 3 monoparesis of the right leg on Day 10. Neurologic examination showed a positive Babinski reflex, but MRI demonstrated no evidence of ischemia, metastasis, or spinal compression. He received dexamethasone with resolution of the monoparesis by Day 18. Atezolizumab was continued without interruption.

PCD4989g

Most neurologic events in patients in PCD4989g with NSCLC were Grade 1-2 peripheral neuropathy. Patient 102128 experienced Grade 4 seizures on Day 16 in the setting of cerebellar metastases and venous sinus thrombosis of the right sigmoid sinus and internal jugular vein. She died on the same day. No patient was treated with corticosteroids for a neurologic event.

Table 44: Neurologic Events in NSCLC patients treated with atezolizumab

	PCD4989g N = 88		POPLAR N = 142		BIRCH N = 659		FIR N=137	
	G1-4	G3-4	G1-4	G3-4	G1-4	G3-4	G1-4	G3-4
Confusional state ¹	4	0	2	1	13	5	9	2
Transient ischemic attack/Stroke	0	0	0	0	12	6	0	0
Neuropathy ²	8	1	12	1	52	2	11	0
Ataxia	0	0	0	0	3	0	0	0
Paraplegia ³	0	0	0	0	1	1	3	1
Encephalitis	0	0	0	0	1	1	0	0

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Vestibular neuronitis	0	0	0	0	1	1	0	0
Subarachnoid Hemorrhage	0	0	0	0	1	1	0	0
8 th Nerve paralysis	1	0	0	0	1	1	0	0
Vocal cord paralysis	0	0	0	0	3	1	1	1
Optic neuritis	0	0	0	0	1	0	0	0
Myelopathy	0	0	0	0	1	1	0	0
Seizure	1	1	0	0	0	0	1	0
Guillain-Barre Syndrome	0	0	0	0	0	0	1	1

1 Includes: altered state of consciousness, mental status changes, depressed level of consciousness, disturbance in attention, confusion state, encephalopathy, hallucination, delirium

2 Includes: polyneuropathy, hypoesthesia, neuralgia, diabetic neuropathy, paresthesia, peripheral sensory neuropathy, peripheral neuropathy

3 Includes: paraplegia, diplegia, hemiparesis, monoparesis

Reviewer note: *In conclusion, the incidence of neurologic adverse events in NSCLC patients treated with atezolizumab was 145/1027 (14%) while the incidence of Grade 3-4 events was 29/1027 (2.8%). The majority of these events were confusional state/delirium that may have been related to infection or peripheral neuropathy that may have been related to prior platinum therapy. There were five cases of immune-mediated neurologic disorders (optic neuritis, Guillain-Barre syndrome, encephalitis, vestibular neuronitis, and right leg monoparesis) in the BIRCH and FIR trials. Overall, the incidence of neurologic events appears consistent with other PD-1/PD-L1 inhibitors.*

7.5.10. Musculoskeletal Disorders

Grade 2 polymyalgia rheumatic was reported on day 176 in a patient on the FIR trial. The patient received prednisone and atezolizumab was continued. The event improved to Grade 1, but remained ongoing.

Grade 2 autoimmune arthritis was reported on day 112 in a patient on the POPLAR trial. Atezolizumab was discontinued and the patient was treated with prednisone. The arthritis improved to Grade 1 by day 176, but remained ongoing.

Grade 3 dermatomyositis was reported on day 75 in a patient on the BIRCH trial. Auto-antibody screen was positive for Anti-Sjogren's syndrome antigen A (anti-SSA). Atezolizumab was interrupted and corticosteroids were administered with resolution of the event. The event

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recurred as Grade 3 on Day 206. Atezolizumab was again interrupted and corticosteroids administered with resolution.

7.5.11. Skin Disorders

POPLAR

Grade 3 rash was reported in 2 patients. Steroids were administered in two of these patients and atezolizumab was interrupted in one, who had concomitant liver enzyme elevations.

BIRCH

Grade 3 rash was reported in 3 patients and Grade 3 psoriasis was reported in one patient. The patient with event of psoriasis, which occurred on Day 130, had no prior history of the disease. Drug was interrupted in this patient and no treatment was recorded. The event resolved by Day 253.

FIR

Grade 3 rash was reported in one patient. Only topical corticosteroids were administered and atezolizumab was not interrupted.

PCD4989g

One patient experienced a Grade 3 rash. The patient was treated with systemic corticosteroids and atezolizumab was interrupted.

Table 45: Dermatitis Events in NSCLC patients treated with atezolizumab

	PCD4989g N = 88		POPLAR N = 142		BIRCH N = 659		FIR N=137	
	G1-4	G3-4	G1-4	G3-4	G1-4	G3-4	G1-4	G3-4
Rash ¹	23	1	37	2	116	3	21	1
Dermatitis Acneiform ²	1	0			2	0	1	0
Dermatitis Bullous	0	0	0	0	0	0	2	0
Eczema			1	0	3	0	3	0
Lichen Planus					2	0	0	0

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Seborrheic Dermatitis	1	0	1	0	1	0	0	0
Photosensitivity reaction	0	0	1	0	0	0	0	0
Psoriasis	0	0	0	0	3	1	0	0
Pruritus/Generalized Pruritus	2	0	19	0	101	0	16	0
Erythema	1	0	4	0	8	0	0	0
Erythema multiforme		0			2	0		
Other ³	2	0	2	0	12	1	0	0

1Including erythematous, maculo-papular, pustular, popular, and pruritic rash and dermatitis

2Including dermatitis psoriasiform

3Including skin toxicity, skin hypopigmentation, skin hyperpigmentation, skin lesion, skin disorder, drug eruption, contact dermatitis, dermatitis exfoliative, lichenoid keratosis, skin exfoliation

Reviewer note: *In conclusion, the incidence of skin disorders (including pruritis) was 238/1027 (23%) in all NSCLC treated with atezolizumab. The majority of these events were Grade 1-2 and were of short duration. The median date of onset was Day 64 (range: 1-951). In the 144 patients in whom the event was reported as resolved, the duration was 23 days (range: 1-219). Eight patients (0.8%) developed Grade 3 rash. Atezolizumab was interrupted in 12 patients and was not discontinued in any for rash. Systemic steroids were used in three patients. Overall, the incidence of skin disorders was consistent with other PD-1/PD-L1 inhibitors.*

7.5.12. Increased Amylase and Lipase/Pancreatitis

The Applicant considered these to be AESIs.

POPLAR, FIR, PCD4989g

There were no cases of increased amylase or lipase reported in these trials.

BIRCH:

Four patients experienced Grade 3 increased amylase, lipase, or pancreatitis. Patient 313014 experienced increased amylase on Day 168. Atezolizumab was interrupted and the event resolved in 8 days without further treatment. Patient 317013 experienced increased lipase on Day 8 in the setting of a flu-like illness. Atezolizumab was not interrupted and the event lasted 4 days without further treatment. Patients 317037 had a history of porphyria which is associated with gallstones and experienced acute pancreatitis on Days 331. Atezolizumab was interrupted and the event resolved after 54 days without further treatment. No corticosteroids

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were administered. Patient 317059 experienced acute pancreatitis on Day 30 in the setting of gallstone visualized on ultrasound. Atezolizumab dosing was not changed and the event resolved in 4 days, followed by cholecystectomy.

PCD4989g

Reviewer note: *There were four cases of pancreatitis or increased amylase/lipase in all patients with NSCLC treated with atezolizumab. In one case, the preceding cause was likely gallstones, however an immune-mediated event could not be ruled out in the others. In the Applicant's database of all patients treated with atezolizumab (N = 1978), there was two additional cases of Grade 3 acute pancreatitis without plausible alternate explanations. Both patients were treated with steroids. One patient recovered, while the event was ongoing in the other. Atezolizumab was discontinued without rechallenge in both patients. Overall, the incidence of pancreatitis appears consistent with other PD-1/PD-L1 inhibitors.*

8.5.14 Infusion Reactions

A combined analysis of all NSCLC patients treated with atezolizumab in POPLAR, BIRCH, FIR and PCD4989g was performed. The terms "infusional-related reaction" or "urticaria" or "cytokine release syndrome" that occurred on an infusion day were reported in 21 patients. There were four Grade 3 events; the remainder were Grade 1-2. Patient 317018 (BIRCH) experienced a Grade 3 event on Day 22 (2nd cycle) with flushing and chest tightness and a subsequent Grade 2 event on Day 64 (Cycle 4). In both cases, corticosteroids and diphenhydramine were administered. Patient 314037 (BIRCH) experienced a Grade 3 event on Day 22 (Cycle 2) with dyspnea, tachycardia, peripheral cyanosis, and chills. He received epinephrine, corticosteroids, and diphenhydramine and was admitted to the ICU. Atezolizumab was permanently discontinued in response. Patient 305050 (BIRCH) developed Grade 3 infusion reaction on Day 65 (Cycle 4) with flushing and palpitations. On the same day, he developed Grade 3 cardiac tamponade. Atezolizumab was temporarily interrupted. It was unclear whether the tamponade was related to underlying disease or treatment. Patient 213125 (POPLAR) developed a Grade 3 infusion reaction on Day 21. Atezolizumab was temporarily interrupted.

Reviewer note: *In conclusion, the incidence of infusion reactions (as defined by the terms "infusion-related reaction" or "urticaria" or "cytokine release syndrome" occurring on the date of infusion) was 21/1027 (2%) in all patients with NSCLC treated with atezolizumab. There were four Grade 3-4 events. One patient required discontinuation while two patients required steroids for infusion reaction. Atezolizumab was interrupted in ten patients. Overall, the incidence of infusion-related reaction appears consistent with other PD-1/PD-L1 inhibitors.*

8.5.14 Corticosteroid Use

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POPLAR

Thirty-two patients (23%) received systemic corticosteroids within 30 days of an AE. 10% experienced Grade 1 or 2 AEs and 13% experienced Grade 3 or 4 AEs. Eleven of these patients (7.7%) were considered to have experienced an imAE. The most common indications for steroid use were dyspea (6%), fatigue (5.6%) cough (3.5%), and nausea (2.8%).

No patients were identified who received a non-corticosteroid immunomodulatory agent including tumor necrosis factor-alpha antagonists (e.g. adalimumab, infliximab, etanercept), interleukin-2 receptor antagonists, anti-interleukin-6 receptor antibody (e.g. tocilizumab), or mycophenelate.

BIRCH

A total of 151 patients (23%) received corticosteroids within 30 days of an AE. Of these, 80 patients (12%) experienced Grade 1-2 events and 70 patients (11%) experienced Grade 3-4 events. One patient experienced a Grade 5 event. Forty-eight of these patients (7.3%) were considered to have experienced an imAE. The most indications for steroid use were dyspnea (5.2%), fatigue (4.7%), decreased appetite (3.2%), and cough (2.4%).

One patient received infliximab for colitis as described above.

FIR

A total of 42 patients (31%) received corticosteroids within 30 days of an AE. Of these, 26 patients (19%) experienced a Grade 1-2 event and 11 patients (8%) experienced a Grade 3-4 event. Nine patients (10%) were considered to have experienced an imAE. The most common indications for steroid use were fatigue (5.5%), cough (4.5%), and dyspnea (4.5%).

No patients were identified who received a non-corticosteroid immunomodulatory agent.

PCD4989g

A total of 19 patients (22%) received corticosteroids within 30 days of an AE. Of these, 12 patients (14%) experienced a Grade 1-2 event and 7 patients (8%) experienced a Grade 3-4 event. Five patients (3.6%) experienced a Grade 5 event. Nine patients (4.4%) were considered to have experienced an imAE. The most common indications for steroid use were cough (8%), dyspnea (8%), fatigue (5.1%), and nausea (4.4%).

Reviewer note: *In conclusion, the incidence of corticosteroid use in patients with NSCLC treated with atezolizumab was 244/1027 (23.8%), of which 77 patients (7.5%) of patients received steroids for an adverse event considered possibly immune-mediated. Only one systemic non-*

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corticosteroid immunomodulatory drug was administered. Overall, the incidence of systemic corticosteroid use was somewhat lower than in trials of other PD-1/PD-L1 inhibitors. This may have led to an incidence of adverse events termed imAEs that underestimates the true incidence of immune-mediated events.

7.6. Specific Safety Studies/Clinical Trials

Subgroup analysis based on race were not performed as the study population was almost entirely Caucasian. Subgroup analyses based on age and gender in POPLAR are shown below. All common AEs appear to be similar across ages <65 years and ≥65 years, with the exception of pneumonia, in which high-grade events in atezolizumab-treated patients occurred more frequently in the older age group. Nausea and fatigue appeared to be more predominant in female patients, however there were relatively few female patients in the study.

Table 69: Grade 1-4 Adverse Events in >15% of Atezolizumab-treated Patients by Age (POPLAR)

Grade 1-4 Adverse Events in > 15% of Patients by Age				
	<65 N = 86		≥65 N = 56	
	G1-4	G3-4	G1-4	G3-4
Fatigue	30 (35%)	2 (2%)	25 (45%)	2 (4%)
Dypnea	25 (29)	4 (5)	22 (39)	6 (11)
Decreased Appetite	28 (33)	1 (1)	21 (38)	1 (2)
Cough	23 (27)	0	15 (27)	0
Pneumonia	12 (14)	2 (2)	11 (20)	7 (13)
Back pain	9 (10)	1 (1)	9 (16)	0

Table 70: Grade 1-4 Adverse Events in > 15% of Patients by Sex (POPLAR)

Grade 1-4 Adverse Events in > 15% of Patients by Sex				
	Male N=93		Female N = 49	
	G1-4	G3-4	G1-4	G3-4
Fatigue	32 (34%)	3 (3%)	23 (47%)	1 (2%)
Decreased appetite	31 (33)	1 (1)	18 (37)	1 (2)
Dyspnea	30 (32)	5 (5)	17 (35)	5 (10)

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Cough	25 (27)	0	13 (27)	0
Constipation	17 (18)	0	12 (24)	0
Diarrhea	15 (16)	1 (1)	9 (18)	0
Pyrexia	15 (16)	0	10 (20)	0
Musculoskeletal pain	22 (15)	2 (1)	15 (10)	1 (2)
Nausea	14 (15)	1 (1)	17 (35)	0

7.7. Specific Safety Studies/Clinical Trials

No studies were performed to address specific safety concerns.

7.8. Additional Safety Explorations

7.8.1. Human Carcinogenicity or Tumor Development

The Applicant did not conduct carcinogenicity studies.

7.8.2. Human Reproduction and Pregnancy

Based on its mechanism of action, atezolizumab can cause fetal harm when administered to a pregnant woman. Animal studies have demonstrated that inhibition of the PD-L1/PD-1 pathway can lead to increased risk of immune-related rejection of the developing fetus resulting in fetal death. Females of reproductive potential are advised to use effective contraception during treatment with atezolizumab and for at least five months after the last dose.

7.8.3. Pediatrics and Assessment of Effects on Growth

Atezolizumab has not been studied in a pediatric population. The Applicant has been granted a waiver of pediatric studies based on the low incidence of non-small cell lung cancer in the pediatric population.

7.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

In the PCD4989g Phase I study, the maximum tolerated dose of atezolizumab was not reached and no dose-limiting toxicities were observed at any dose. The maximum dose evaluated was 20 mg/kg, therefore doses greater than 20 mg/kg of atezolizumab should be considered

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overdose. There was no evidence that suggests a risk for dependence of atezolizumab. No cases of withdrawal symptoms were reported during human clinical trials.

7.9. Safety in the Postmarket Setting

7.9.1. Safety Concerns Identified Through Postmarket Experience

Atezolizumab was approved on May 18, 2016 for the treatment of locally advanced or metastatic bladder cancer who have progressed following a platinum-containing regimen. No new safety concerns have been identified through the postmarket experience at this time.

7.9.2. Expectations on Safety in the Postmarket Setting

Patients with autoimmune disorders, except those with Type 1 diabetes mellitus or hypothyroidism on stable hormone replace, were excluded from trials evaluating atezolizumab. Thus, off-label use in these patients would constitute a safety concern regarding immune-mediated adverse events.

The true incidence of hypothyroidism may be higher than that reported in the trials reviewed here. The Applicant will perform TSH evaluation (b) (4) in one planned trial to better estimate the incidence of hypothyroidism as a post-marketing requirement.

7.10. Additional Safety Issues From Other Disciplines

No additional safety issues from other disciplines were raised during the review. Refer to the pharmaco-metrics review for additional discussion of anti-drug antibodies and exposure-toxicity relationship.

7.11. Integrated Assessment of Safety

The safety profile of atezolizumab in patients with non-small cell lung cancer who have progressed following treatment with a platinum-based regimen is acceptable. The size of the safety database and duration of atezolizumab exposure were sufficient to characterize the safety of atezolizumab for treatment of a serious and life-threatening condition with the exception of updated safety data from completed Phase 3 trial, OAK, which will be obtained as a PMR as well as additional data regarding the incidence of thyroid toxicity, which is currently being obtained via an ongoing PMR. Notable toxicities included a high incidence of infections, including pneumonia and upper respiratory tract infections. Incidences of immune-mediated adverse events, including pneumonitis, hepatitis, and diarrhea/colitis, were similar to or lower than other checkpoint inhibitors such as nivolumab and pembrolizumab. This reviewer does not recommend a risk evaluation and mitigation strategy (REMS) given the current safety

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profile of atezolizumab and the experience of the medical community in managing immune-mediated adverse reactions, based on use of other FDA-approved immune-modulating agents, such as nivolumab and pembrolizumab. Recommendations for safe and effective use of atezolizumab, including monitoring for immune-mediated adverse events, will be made in labeling, including a patient medication guide.

8 Advisory Committee Meeting and Other External Consultations

There were no safety or efficacy issues identified for the proposed indication and for the product itself. The safety profile of atezolizumab is similar to that of two similar products currently marketed in the USA. The demonstrated benefit-risk profile for atezolizumab is favorable in the intended patient population. Therefore, this application was not referred to the Oncologic Drugs Advisory Committee.

9 Labeling Recommendations

9.1. Prescribing Information

Based on our review findings and the Applicant's submitted initial and revised labels during the review, the clinical and statistical reviewers recommended the following for the final label of atezolizumab for this BLA.

a) Section 5:

- *Pneumonitis*
 - Added two pneumonitis cases from POPLAR considered hypoxia or dyspnea by the Applicant
 - Provided additional details on management and outcome of all cases
- *Hepatitis*
 - Added one case of severe autoimmune hepatitis from PCD4989g
 - Provided additional details on management and outcome of all cases
- *Infection*
 - Pooled cases of pneumonia and respiratory infection

b) Section 6:

- Adverse events, including serious adverse events, were updated to reflect pooled terms.
- Frequency of laboratory abnormalities were recalculated based on CTCAE toxicity grades rather than a shift table.

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c) Section 14:

- FDA included OS data from OAK with associated p-value, and from the 200-event analysis of POPLAR with no associated p-value.
-
- FDA excluded a proposed [REDACTED] (b) (4)
[REDACTED] A summary of those results were included in the text.

9.2. Patient Labeling

Refer to final patient labeling.

9.3. Nonprescription Labeling

Refer to nonprescription labeling.

10 Risk Evaluation and Mitigation Strategies (REMS)

There were no REMS proposed for atezolizumab.

10.1. Safety Issue(s) that Warrant Consideration of a REMS

N/A

10.2. Conditions of Use to Address Safety Issue(s)

N/A

10.3. Recommendations on REMS

There were no REMS proposed for atezolizumab.

11 Postmarketing Requirements and Commitments

The FDA review team for this BLA identified the following postmarketing clinical trials or studies for the recommended approval. These requirements and commitments have been agreed by the Applicant.

PMRs:

CDER Clinical Review Template 2015 Edition
Version date: November 5, 2015 for initial rollout (NME/original BLA reviews)

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1. Provide complete datasets and clinical study report for the Phase 3 trial OAK.
Final Report Submission Date: March 2017

Previously agreed to during the urothelial carcinoma BLA:

2. Conduct a clinical trial to evaluate the effect of atezolizumab on thyroid function tests and clinical thyroid disease. Submit the completed report, datasets, and revised labeling.

Final protocol Submission Date: May 2016

Study/Clinical Trial Completion Date: August 2020

Final Report Submission Date: February 2021

12 Appendices

12.1. References

1. Surveillance, Epidemiology, and End Results Program (SEER), Cancer Statistics. 2016, <http://seer.cancer.gov/statfacts/html/lungb.html>
2. Schiller JH, Harrington D, Belani CP, et al.: Comparison of Four Chemotherapy Regimens for Advanced Non-Small Cell Lung Cancer: N Engl J Med. 2002 Jan 10:346(2) 92-8.
3. TAXOTERE (docetaxel) injection, for intravenous use, Prescribing Information.
4. Tarceva[®] (erlotinib) tablets, for oral use, Prescribing Information
5. ALIMTA (pemetrexed) injection, for intravenous use, Prescribing Information.
6. CYRAMZA (ramucirumab) injection, for intravenous use, Prescribing Information.
7. OPDIVO (nivolumab) injection, for intravenous use, Prescribing Information.
8. KEYTRUDA (pembrolizumab) injection, for intravenous use, Prescribing Information
9. ZYKADIA(ceritinib) Capsules, oral, Prescribing Information.
10. TAGRISSO (osimertinib) tablets, oral, Prescribing Information.
11. ALECENSA (alectinib) Capsules, oral, Prescribing Information.
12. Zhang, Y., Kang, S., Shen, J., et. al. (2015). Prognostic Significance of Programmed Cell Death 1 (PD-1) or PD-1 Ligand 1 (PD-L1) Expression in Epithelial-Originated Cancer: A Meta-Analysis. *Medicine*, 94(6), e515.
<http://doi.org/10.1097/MD.0000000000000515>
13. Horvat TZ, Adel NG, Dang TO, et. al. Immune-Related Adverse Events, Need for Systemic Immunosuppression, and Effects on Survival and Time to Treatment Failure in Patients With Melanoma Treated With Ipilimumab at Memorial Sloan Kettering Cancer Center. *J Clin Oncol*. 2015 Oct 1;33(28):3193-8. doi:

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10.1200/JCO.2015.60.8448. Epub 2015 Aug 17. PubMed PMID:26282644.

12.2. Financial Disclosure

The covered studies for this BLA are POPLAR and OAK. Since these studies relied on overall survival as a primary endpoint, financial issues are less likely to affect the analyses of the effectiveness of atezolizumab in the intended patient population.

Covered Clinical Study (Name and/or Number): POPLAR

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: <u>821</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>2</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u> Significant payments of other sorts: <u>1</u> Proprietary interest in the product tested held by investigator: <u>1</u> Significant equity interest held by investigator in S Sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>N/A</u>		

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Covered Clinical Study (Name and/or Number): OAK

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: <u>1815</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>3</u>		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u></p> <p>Significant payments of other sorts: <u>2</u></p> <p>Proprietary interest in the product tested held by investigator: <u>1</u></p> <p>Significant equity interest held by investigator in S</p> <p>Sponsor of covered study: <u>0</u></p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>N/A</u>		

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHANA WEINSTOCK
10/13/2016

SEAN N KHOZIN
10/14/2016

DANIEL L SUZMAN
10/14/2016

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 761041

Applicant: Genentech

Stamp Date: 06/09/16

Drug Name: Atezolizumab

NDA/BLA Type: 351(a)

On initial overview of the BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			1.14.1
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			5.3.5.3
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			5.3.5.3
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			2.5, Clinical overview- Section 6- Benefits and risks conclusions
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number: PCD4989g Study Title: A Phase I, Open-Label, Dose-Escalation Study of the Safety and Pharmacokinetics of Atezolizumab (MPDL3280A) Administered Intravenously as a Single Agent to Patients With Locally Advanced or Metastatic Solid Tumors or Hematologic Malignancies Sample Size: 481 (473 PK-evaluable) Arms: 0.3 to 20 mg/kg, including a 1200 mg flat dose q3w Location in submission: 2.7.2 SCP section 3.6	X			Proposed dose is 1200 mg IV every 3 weeks
EFFICACY					

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?	X			Original application had pivotal study as single-arm study BIRCH with supportive randomized data from phase II POPLAR study. Applicant revised application to make POPLAR pivotal study.
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?	X			
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			90 day safety update provided.
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (<i>e.g.</i> , label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Section 1.9.1- Requested waiver. The Sponsor submitted to the Agency an Agreed iPSP on 6 February 2015 (Serial No. 0225). The Agency confirmed agreement to the agreed iPSP in a correspondence dated 8 May 2015.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?				
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			SDTM
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?				
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? X yes_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

No review issues have been identified.

Chana Weinstock, MD	6/9/2016
Reviewing Medical Officer	Date
Sean Khozin, MD	6/9/2016
Clinical Team Leader	Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHANA WEINSTOCK
06/09/2016

SEAN N KHOZIN
06/09/2016