CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA Number:	BLA 761,041
Drug Name:	Atezolizumab (Tencentriq™)
Indication(s):	Non-Small Cell Lung Cancer
Applicant:	Hoffmann-La Roche, Inc./Genentech, Inc.
Date(s):	Submission Date: 2/19/2016
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Keywords: PD-L1, Overall Survival, Logrank Test, Randomization

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1. EXECUTIVE SUMMARY

Atezolizumab (TECENTRIQ™) is a programmed death-ligand (PD-L1) blocking antibody that has been granted Accelerated Approval for the treatment of patients with locally advanced or metastatic urothelial carcinoma in May 2016 based on single arm studies demonstrating beneficial tumor response rate and durability of response. In the current supplement Biologic License Application (sBLA), the applicant seeks a regular approval of atezolizumab for use in treating patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after failure with platinum-containing chemotherapy.

The efficacy for the proposed indication was based on the results of Study OAK, a phase 3, open-label, multicenter, randomized trial investigating the efficacy and safety of atezolizumab compared with docetaxel in patients with non-small cell lung cancer after failure with platinum-containing chemotherapy. The primary efficacy endpoint was overall survival (OS). A total of 1225 eligible patients were randomized 1:1 to receive either atezolizumab or docetaxel. Atezolizumab demonstrated a statistically significant improvement in OS as compared with docetaxel in the primary efficacy population of the first randomized 850 patients. Median OS was 13.8 months for patients assigned to atezolizumab and 9.6 months for those assigned to docetaxel (Hazard Ratio 0.74; 95% CI: 0.63, 0.87; p=0.0004). A similar statistically significant benefit on OS was observed in the pre-specified PD-L1 selected population, i.e., ≥1% of tumor cells or tumor-infiltrating immune cells (n=463), with a hazard ratio of 0.74 (95% CI: 0.59, 0.94; p=0.012). The OS data from all 1225 randomized patients will be submitted later as a post marketing requirement/commitments (PMR/PMC).

These efficacy results were supported by a randomized multinational, randomized, multicenter, open-label phase 2 study with histologically or cytologically proven locally advanced or metastatic NSCLC after platinum failure, Study POPLAR. In this phase 2 study, a total of 287 patients were randomized 1:1 to receive either atezolizumab or docetaxel. The primary efficacy endpoint was also OS. The pre-specified final OS analysis with 153 deaths showed a difference of 1.9 months in median survival favoring the atezolizumab arm (Hazard Ratio 0.77; 95% CI: 0.55, 1.07); however, the OS result was not statistically significant (p=0.11). An exploratory updated OS analysis with 200 deaths showed an improvement of 2.9 months in median survival (Hazard Ratio 0.69; 95% CI: 0.52, 0.92).

Although atezolizumab demonstrated an OS advantage over docetaxel, the judgment on the clinical meaningfulness of the treatment effect in OS observed in studies OAK and POPLAR in light of the toxicities is deferred to the clinical review team.

2. INTRODUCTION

2.1 Overview

Atezolizumab is an Fc-engineered, humanized, monoclonal antibody targeting human programmed death-ligand 1 (PD-L1) on tumor-infiltrating immune cells (ICs) and tumor cells (TCs). The efficacy claim of the current supplement BLA submission is based on a phase 3 randomized study (OAK) and a phase 2 randomized study (POPLAR) (Table 1). The applicant also submitted two single arm studies (BIRCH and FIR) and a phase 1 study expansion cohort

(PCD4989g) to further support the BLA. Study OAK is entitled "A phase III, open-label, multicenter, randomized study to investigate the efficacy and safety of atezolizumab (anti-PD-L1 antibody) compared with docetaxel in patients with non-small cell lung cancer after failure with platinum-containing chemotherapy". The primary efficacy endpoint was OS. The secondary endpoints included progression-free survival (PFS), objective response rate (ORR), duration of response (DOR), and patient-reported outcomes. Study POPLAR is entitled "A phase II, open-label, multicenter, randomized study to investigate the efficacy and safety of MPDL3280A (anti-PD-L1 antibody) compared with docetaxel in patients with non-small cell lung cancer after platinum failure". The patient population and study design are similar in studies OAK and POPLAR.

Table 1: Overview of Studies OAK and POPLAR

Study name	**Phase and Design**	**Treatment period**	**Follow-Up period**	**Treatment arms (number of randomized subjects)**	**Study Population**
OAK	Phase 3, randomized, open-label	Atezolizumab treatment as long as patients were experiencing clinical benefit as assessed by an investigator; Docetaxel treatment until disease progression per RECIST v1.1 or unacceptable toxicity.	Follow-up data capture, including survival status and subsequent anti-cancer therapies until death, loss of follow-up, withdrawal of consent, or study termination by the study Sponsor, whichever occurred first.	Atezolizumab (n=612) Docetaxel (n=613)	Patients with locally advanced or metastatic NSCLC after failure with platinum-based chemotherapy
POPLAR	Phase 2, randomized, open-label	Treated until loss of clinical benefit as assessed by the investigator	Follow-up for survival post treatment discontinuation as long as the patient remained alive, or until the end of the study	Atezolizumab (n=143) Docetaxel (n=144)	Patients with locally advanced or metastatic NSCLC who have progressed during or following a platinum-containing regimen.

The original protocol of pivotal study OAK was finalized on 07 November 2013 and was subsequently amended five times. The original statistical analysis plan (SAP) was dated

November 21, 2013 and amended once at December 10, 2015. Major changes to the study protocol and SAP are summarized in Table 2. Section 3.2 provides details on the efficacy evaluation based on data from Study OAK.

Table 2. Summary of Study OAK Protocol and SAP Amendments

Protocol Version	Protocol changes
Version 2 (10 February 2014)	For E.U. Countries only
Version 3 (5 August 2014)	• 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. • Modified treatment duration for MPDL3280A to allow patients to be treated until patients are no longer experiencing clinical benefit • Added a pilot study with 50 patients to collect PRO data. • Changed the frequency of tumor assessments after 36 weeks from every 12 weeks to every 9 weeks to be more consistent with clinical practice in NSCLC.
Version 4 (2 December 2014)	• Increased sample size from 850 to 1100 to allow for testing patients with TC3 or IC3 as first hierarchy • Modified the multiplicity adjustment procedure accordingly.
Version 5 (6 October 2015)	• Updated the management of gastrointestinal, dermatologic, endocrine, pulmonary toxicity, hepatotoxicity, potential pancreatic or eye toxicity and other immune-mediated AEs
Version 6 (28 January 2016)	• Changed the primary analysis to the first 850 randomized patients in the ITT population and the TC1/2/3 or IC1/2/3 subgroup among these 850 patients.
SAP Version	**SAP changes**
Version 2 (10 December 2015)	• Revised type I error control plan • Revised the primary population for efficacy to the first 850 randomized patients

The original protocol of Study POPLAR was finalized on 30 April 2013 and was subsequently amended five times. The SAP was dated 14 July 2015. Major changes to the study protocol are summarized in Table 3. Section 3.3 provides details on the efficacy evaluation based on data from Study POPLAR.

Table 3. Summary of Study POPLAR Protocol Amendments

Protocol Version	Protocol changes
Version 2 (29 July 2013)	• Modified inclusion and exclusion criteria. • Modified interim analyses to clarify that the planned interim analyses at 30 and 60 death events will not lead to an early termination of the study because of superior efficacy but the Sponsor IMC may recommend stopping based on safety or an unacceptable risk-benefit profile.
Version 3 (30 January 2014)	• Revised to reflect the continuation of enrollment of patients until a minimum of approximately 54 patients considered PD-L1 positive (IHC 2 or 3) are accrued. In the case of the prevalence of PD-L1 positive patients is <18%, up to a maximum of approximately 300 total patients may be enrolled.
Version 4 (21 May 2014)	• Modified treatment duration to allow patients to be treated until loss of clinical benefit • Modified the frequency of tumor assessments after 36 weeks from every 12 weeks to every 9 weeks • Modified the timing of the interim safety and efficacy analyses from 30 and 60 death events to 30 and 100 death events. • Replaced the terms "PD-L1 positive" and "PD-L1 negative" with "PD-L1 IHC 2/3" and "PD-L1 IHC 0/1" respectively. • Modified the statistical section given the current enrollment trend. The expected sample size is 285 total patients and 55 PD-L1 IHC2/3 patients.
Version 5 (25 July 2014)	• Changed the safety follow-up period to the original 90 days to maintain a consistent follow-up period throughout the study.
Version 6 (24 February 2015)	• Adjusted the event threshold for the primary analysis to approximately 180 death events and convert the originally planned analysis at 150 death events to an interim analysis. • Clarified the stratification by PD-L1 IHC status based on PD-L1 expression in tumor-infiltrating immune cells. • In addition to the primary analyses on the ITT population and the subgroup of patients with PD-L1 IHC 2 or IHC 3 expression status in tumor-infiltrating immune cells, subgroup analyses will be performed based on other categories of PD-L1 expression (e.g., including expression on tumor cells).

This review focuses on studies OAK and POPLAR.

2.2 Data Sources

Electronic submission including protocols, statistical analysis plan, study reports, and analysis datasets for this BLA submission (clinical cutoff date: 30 January 2015 and 8 May 2015 for Study POPLAR) can be accessed via this EDR link: \\CDSESUB1\evsprod\BLA761041\0001 and the updated survival analysis data and report for Study POPLAR (clinical cutoff date: 1 December 2015) are accessible via this EDR link: \\CDSESUB1\evsprod\BLA761041\0012.

Electronic submission including protocols, statistical analysis plan, report summarizing the topline data, and OS analysis dataset for Study OAK can be accessed via this EDR link: \\CDSESUB1\evsprod\BLA761041\0026.

3. STATISTICAL EVALUATION

The phase 2 study POPLAR was the Applicant's original focus for this submission to support an accelerated approval of atezolizumab. However, based on the pre-specified statistical analysis plan, the OS results in study POPLAR were not statistically significant. During the BLA review, the applicant provided top-line OS results of the phase 3 study, OAK, which showed a significant OS improvement for atezolizumab over docetaxel. FDA considered the OS results from the OAK study as the basis for a full approval. This review assessed the efficacy results of both OAK and POPLAR studies.

3.1 Data and Analysis Quality

The data and analysis quality of studies OAK and POPLAR was acceptable for the reviewer to perform the statistical review. This reviewer was able to reproduce the primary analysis datasets from the raw datasets.

For study POPLAR, it has been noted that a major amendment of protocol (version 6) and the study SAP were made after results of the pre-specified final OS analysis were available to the Applicant. Therefore, the review team considered any changes of analysis plan made post data un-blinding as exploratory. See details in Section 3.3.

3.2 Evaluation of Efficacy in Study OAK

3.2.1 Study Design and Endpoints

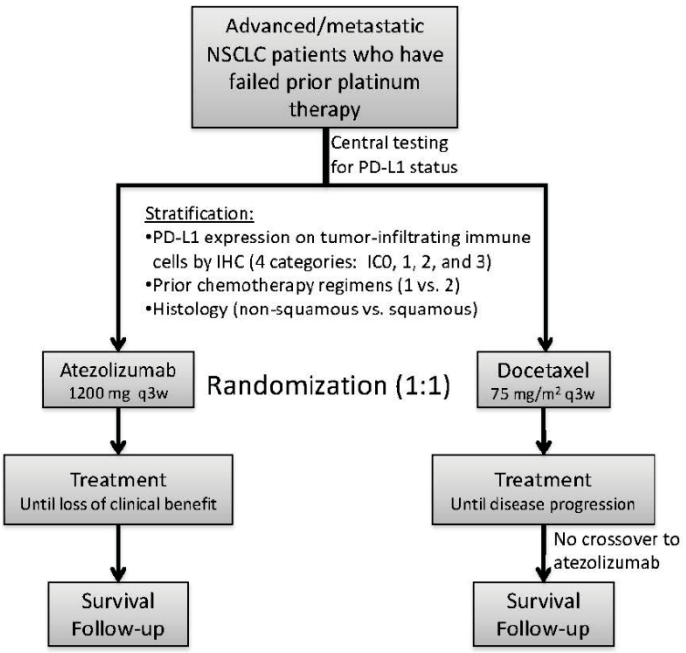
3.2.1.1 Overall Study Design

Study OAK was a multinational, multicenter, randomized, open-label, Phase 3 study to evaluate the efficacy and safety of atezolizumab compared to docetaxel in patients with locally advanced or metastatic NSCLC who have progressed during or following a platinum-containing regimen.

The primary efficacy endpoint was OS. Patients were randomized in a 1:1 ratio through an interactive voice/web response system (IxRS) to receive atezolizumab or docetaxel using a stratified permuted block randomization schedule. Randomization was stratified by the following three factors.

- PD-L1 expression on tumor-infiltrating immune cells (IHC 0 vs. IHC 1 vs. IHC 2 vs. IHC 3)
- Number of prior chemotherapy regimens (1 vs. 2)
- Histology (non-squamous vs. squamous)

The trial design is presented in Figure 1.



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

Figure 1. OAK Study Design

[Source: SAP Figure 1]

3.2.1.2 Schedule of Assessments

Based on Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1, radiographic assessment of disease status was planned every 6 weeks for 36 weeks following randomization and every 9 weeks thereafter until disease progression, death, or loss of follow-up. All patients were to be followed for survival and new anti-cancer therapy information unless the patient requests to be withdrawn from follow-up.

3.2.1.3 Efficacy Endpoints

Primary endpoints:

- OS

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-Lift Questionnaire Core 30 (EORTC QLQ-C30) and the EORTC Lung Cancer Module (QLQ-LC13)

Overall survival was defined as the time from randomization to death from any cause.

Progression-free survival was defined as the time from randomization to investigator-assessed disease progression or death from any cause, whichever occurred first.

Objective response rate was defined as the 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 was defined as the time from the first occurrence of a confirmed objective response to the time of disease progression, as determined by the investigator using RECIST v1.1 criteria, or death, whichever occurred first.

Patient reported outcome measures were collected using EORTC QLQ C-30 and QLC LC-13.

Time to deterioration (TTD) in patient-reported lung cancer symptoms (cough, dyspnea, chest pain, arm/shoulder pain) was to be examined. 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.

Reviewer's Comments

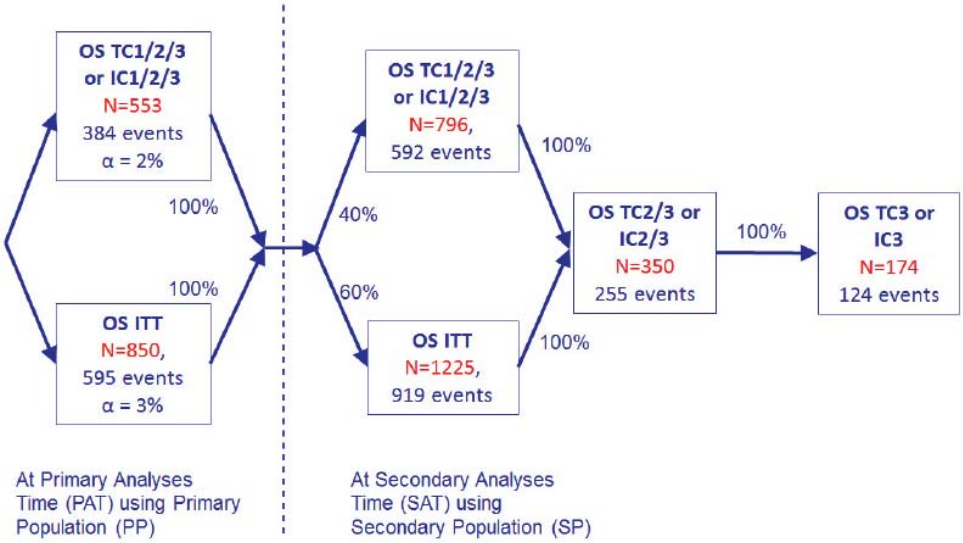
- *As this is an open-label study, the results of patient reported outcome (PRO) endpoints could be biased and not interpretable.*
- *Per the statistical analysis plan, there were no alpha (type-I error rate) adjustments for the multiple tests for the secondary endpoints.*

3.2.1.4 Sample Size Determination

An enrollment of 850 patients in the ITT population was initially planned in this study 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 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 recent data from study POPLAR, the primary OS analyses in OAK were modified and 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 were to 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 was to be hierarchically passed to the 1225 ITT patients and its PD-L1 expression subgroups (see Figure 2).



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

Figure 2. OAK Type I Error Control Plan

[Source: SAP Figure 2]

The estimated power and number of events needed for the proposed design of the first 850 patients (Table 4) and the overall ITT population (Table 5) 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%

Table 4. Power and Minimum Detectable Difference for the Primary Population

Analyses Population	No. of Patients/ Expected No. of Events	Target OS HR [a]	Two-sided Type I Error	Power	MDD
PP ITT	850/595	0.73 (median from 10 to 13.7 months)	3%	95.3%	0.837
PP TC1/2/3 or IC1/2/3	553/384	0.63 (median from 10 to 15.9 months)	2%	98.6%	0.789

HR = hazard ratio; IC = tumor-infiltrating immune cell; ITT = intent to treat; MDD = minimum detectable difference; OS = overall survival; PAT = Primary Analyses Time; PP = Primary Population; TC = tumor cell.

[a] The lower median applies to the docetaxel arm and the higher median, the atezolizumab arm.

[Source: SAP Table 1]

Table 5. Power and Minimum Detectable Difference for the Secondary Population

Analyses Population	No. of Patients/ Expected No. of Events	Target OS HR[a]	Two-sided Type I Error [b]	Power	MDD
SP ITT	1225/919	0.73 (median from 10 to 13.7 months)	1.2%	99.0%	0.847
			1.8%	99.4%	0.856
			3%	99.6%	0.867
SP TC1/2/3 or IC1/2/3	796/592	0.63 (median from 10 to 15.9 months)	0.8%	99.8%	0.804
			1.2%	99.9%	0.813
			2%	100%	0.826
SP TC2/3 or IC2/3	350/255	0.58 (median from 10 to 17.2 months)	0.8%	95.5%	0.717
			1.2%	96.7%	0.730
			1.8%	97.6%	0.743
			2%	97.8%	0.747
			3%	98.5%	0.762
			5%	99.2%	0.782
SP TC3 or IC3	174/124	0.53 (median from 10 to 18.9 months)	0.8%	81.1%	0.621
			1.2%	84.7%	0.637
			1.8%	87.9%	0.654
			2%	88.6%	0.658
			3%	91.4%	0.677
			5%	94.2%	0.703

HR = hazard ratio; IC = tumor-infiltrating immune cell; ITT = intent to treat; MDD = minimum detectable difference; OS = overall survival; SAT = Secondary Analyses Time; SP = Secondary Population; TC = tumor cell.

[a] The lower median applies to the docetaxel arm and the higher median, the atezolizumab arm.

[b] The different alpha values for each population corresponds to every possible value of alpha combination when the alpha is passed from the previous testing hierarchy.

[Source: SAP Table 2]

As shown in Table 4, the primary efficacy analyses were to be conducted when approximately 595 deaths have occurred in the first 850 randomized patients. The secondary efficacy analyses will be conducted when approximately 919 deaths have occurred in all the 1225 randomized ITT population (Table 5).

3.2.1.5 Interim Analyses

There was no interim analysis planned for efficacy evaluation.

3.2.2 Statistical Methodologies

3.2.2.1 Efficacy Analysis Population

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 (≥1%) or IC1/2/3(≥1%), TC2/3(≥5%) or IC2/3 (≥5%), and TC3 (≥50%) or IC3 (≥10%) 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 comments

The central lab re-reading PD-L1 status retrospectively to determine PD-L1 subgroups using the stepwise algorithm was not the same lab evaluating IC status at randomization, per the Applicant's response to the FDA's IR (September 22, 2016). Some inconsistencies were observed.

In addition, it has been noted that the study randomization was not stratified by TC status. Therefore, there is a potential bias of patient imbalance between treatment arms within each PD-L1 subgroup as defined above, particularly for subgroups with small sample size.

3.2.2.2 Efficacy Analysis Methods

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.

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/should 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.

3.2.3. Patient Disposition, Demographic and Baseline Characteristics

3.2.3.1 Patients Disposition

Patient disposition information was not provided in the current submission of topline dataset and will be included in the complete clinical study report as post marketing requirement/commitments (PMR/PMC).

3.2.3.2 Demographic and Baseline Characteristics

The demographic and baseline characteristics for the primary population (the first 850-randomized patients) and the PD-L1 sub-population (TC1/2/3 or IC1/2/3) of the primary population are presented in Table 6. 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 were ECOG PS 1 and 37% were ECOG PS 0. The TC1/2/3 or IC1/2/3 subpopulation had similar characteristics.

Table 6. Summary of Demographics and Baseline Disease Characteristics in the Primary Population

	ITT		TC1/2/3 or IC1/2/3	
	Atezolizumab (N=425)	**Docetaxel (N=425)**	**Atezolizumab (N=241)**	**Docetaxel (N=222)**
Age (years)				
Median	63	64	63	64
Range	33, 82	34, 85	35, 82	39, 85
Age category, n (%)				
<65	235 (55)	218 (51)	138 (57)	101 (46)
≥65	190 (45)	207 (49)	103 (43)	121 (55)
Sex, n (%)				
Male	261 (61)	259 (61)	157 (65)	126 (57)
Female	164 (39)	166 (39)	84 (35)	96 (43)
Race, n (%)				
White	302 (71)	296 (70)	184 (76)	159 (72)
Asian	85 (20)	95 (22)	33 (14)	46 (21)
Black or African American	5 (1)	11 (3)	4 (2)	4 (2)
Others	33 (8)	23 (5)	20 (18)	13 (5)
Region, n (%)				
US	114 (27)	133 (31)	79 (33)	83 (37)
Non-US	311 (73)	292 (69)	162 (67)	139 (63)
Histology (eCRF), n (%)				
Squamous	112 (26)	110 (26)	70 (29)	60 (27)
Non-Squamous	313 (74)	315 (74)	171 (71)	162 (73)
Baseline ECOG PS, n (%)				
0	155 (36)	160 (38)	90 (37)	85 (38)
1	270 (64)	265 (62)	151 (63)	137 (62)
Smoking History, n (%)				
Current	59 (14)	67 (16)	37 (15)	33 (15)
Never	84 (20)	72 (17)	39 (16)	38 (17)
Previous	282 (66)	286 (67)	165 (69)	151 (68)
Number of prior therapies (IxRS)				
1	320 (75)	320 (75)	174 (72)	164 (74)
2	105 (25)	105 (25)	67 (28)	58 (26)
IC score (IxRS)				
0	156 (37)	157 (37)	34 (14)	21 (10)
1	171 (40)	171 (40)	113 (47)	108 (49)
2	51 (12)	51 (12)	48 (20)	49 (22)
3	47 (11)	46 (11)	46 (19)	44 (20)

[Source: Supplemental reports report for study OAK Table 1]

Reviewer's comments

- *The demographics and baseline disease characteristics were balanced between the two treatment arms in the ITT population; however, as TC status was not a randomization stratification factor, several demographic characteristics (age group, sex, and race) were different (≥5%) between the two arms in the TC1/2/3 or IC1/2/3 subpopulation. A sensitivity analysis of OS in this PD-L1 subgroup is performed with adjustment of the unbalanced baseline characteristics (see Section 3.2.4.1). The results are consistent with the primary finds.*

- *Per the study SAP, the stratification factor data used in the primary analyses included IC levels per IxRS, the number of prior chemotherapy regimens per IxRS, and histology per eCRF. Following the intent-to-treat principle, all stratification data used in the primary analyses should be obtained from IxRS instead of eCRF, and eCRF-based stratification data could be used in a sensitivity analysis. The discrepancies between eCRF-based and IVRS-based histology data are summarized in Table 7.*

Table 7. Discordance of Histology Data, between eCRF and IxRS

	ITT		TC1/2/3 or IC1/2/3	
	Atezolizumab (n=425)	**Docetaxel (n=425)**	**Atezolizumab (n=241)**	**Docetaxel (n=222)**
Histology, n (%)				
Discordance	11 (2.6%)	5 (1.2%)	5 (2.1%)	4 (1.8%)
Concordance	411 (97.4%)	420 (98.8%)	236 (97.9%)	218 (98.2%)

3.2.4 Results and Conclusions

3.2.4.1 Primary Efficacy Endpoint

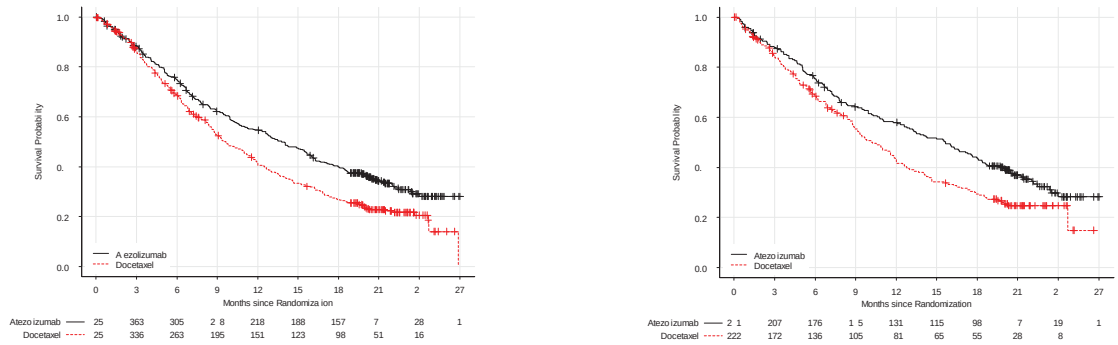
Overall survival was the primary efficacy endpoint of study OAK. The primary OS analysis was conducted when 569 death events of the primary population (n=850) occurred at the study cut-off date of 7 July 2016. The median follow-up time was around 21 months in both arms. A statistically significant improvement 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. The results are summarized in Table 8 and the Kaplan-Meier curves are shown in Figure 3.

As commented in Section 3.2.3.2, following the intent-to-treat principle, the primary analysis of OS was based on stratification data collected from the IxRS instead of from the eCRFs.

Table 8. Summary of Overall Survival Results, FDA's Analyses

	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 (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.



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

Figure 3. Study OAK: Kaplan-Meier Curves of Overall Survival

[Source: Supplemental reports report for study OAK Figures 1 and 2]

Reviewer's comment

This reviewer has performed three sensitivity analyses for OS as summarized in Table 9 below. Results from sensitivity analyses are consistent with the primary findings.

Table 9. Summary of FDA's OS Sensitivity Analyses

Sensitivity analysis for OS	**ITT** **HR (95% CI)**	**TC1/2/3 or IC1/2/3** **HR (95% CI)**
1: Unstratified analysis	0.73 (0.62, 0.86)	0.72 (0.58, 0.91)
2: Among all treated patients, per actual treatment received	0.75 (0.63, 0.89)	0.75 (0.59, 0.95)
3. For the TC1/2/3 or IC1/2/3 subpopulation analysis, use a cox model adjusted for age, sex, and race	NA	0.75 (0.59, 0.95)

3.2.4.2 Secondary Efficacy Endpoints

The secondary endpoints in this study included progression-free survival and objective response rate.

Reviewer's comments

This review focuses on the primary endpoint, OS. All secondary endpoint data from 1225 randomized patients will be required for submission as post marketing requirement/commitments (PMR/PMC). In addition, no PRO data are submitted for this study in this submission.

3.2.5 Conclusions for Efficacy based on Study OAK

Study OAK demonstrated a statistically significant improvement in OS (a 4.2-month difference in median; HR=0.74, p=0.0004) from atezolizumab compared to docetaxel in the ITT population and a similar OS benefit in the TC1/2/3 or IC1/2/3 subpopulation. Results from sensitivity analyses for OS were consistent with the primary findings.

3.3 Evaluation of Efficacy in Study POPLAR

3.3.1 Study Design and Endpoints

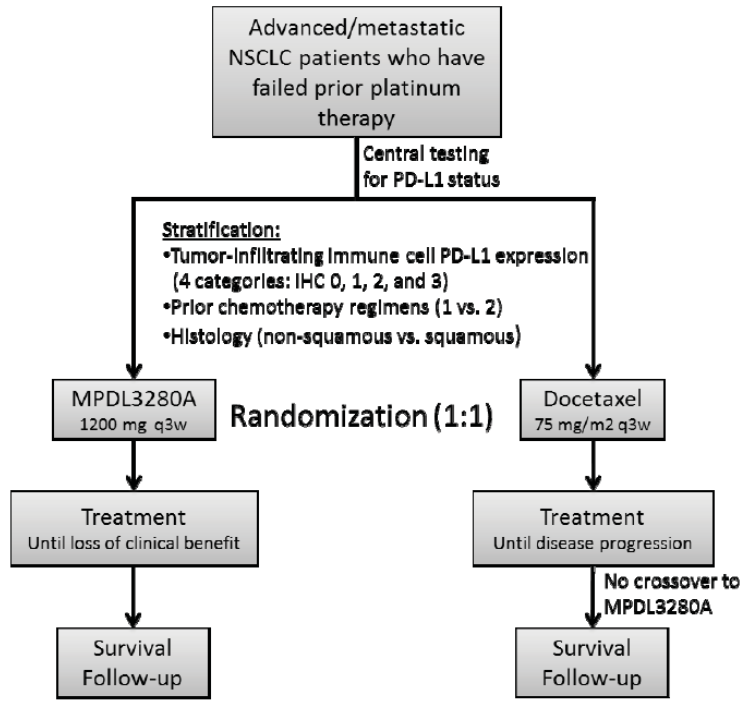
3.3.1.1 Overall Study Design

Study POPLAR was a multinational, multicenter, randomized, open-label, Phase 2 study to evaluate the efficacy and safety of atezolizumab compared to docetaxel in patients with locally advanced or metastatic NSCLC who have progressed during or following a platinum-containing regimen.

The primary efficacy endpoint was OS. Patients were randomized in a 1:1 ratio through an IxRS to receive atezolizumab or docetaxel using a stratified permuted block randomization schedule. Randomization was stratified by the following two factors.

- PD-L1 expression on tumor-infiltrating immune cells (IHC 0 vs. IHC 1 vs. IHC 2 vs. IHC 3)
- Number of prior chemotherapy regimens (1 vs. 2)
- Histology (non-squamous vs. squamous)

The trial design is presented in Figure 4.



IHC = immunohistochemistry; NSCLC = non–small cell lung cancer; PD-L1 = programmed death–ligand 1; q3w = every 3 weeks.

Figure 4. POPLAR Study Design

[Source: Protocol Figure 1]

3.3.1.2 Schedule of Assessments

Based on RECIST version 1.1, radiographic assessment of disease status was planned every 6 weeks for 36 weeks and every 9 weeks thereafter until disease progression, death, or loss of follow-up. Survival follow-up information was to be collected via telephone calls, patient medical records, and/or clinical visits approximately 3 months until death, loss to follow-up, or study termination by the Applicant. All patients were to be followed for survival and new anti-cancer therapy information unless the patient requested to be withdrawn from follow-up.

3.3.1.3 Efficacy Endpoints

Primary endpoints:

- OS

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
- PFS, ORR, DOR based on modified RECIST criteria

- Patient-reported outcomes as assessed by the European Organization for Research and Treatment of Cancer Quality-of-Lift Questionnaire Core 30 (EORTC QLQ-C30) and the EORTC Lung Cancer Module (QLQ-LC13)

Overall survival was defined as the time from randomization to death from any cause.

Progression-free survival was defined as the time from randomization to investigator-assessed disease progression or death from any cause, whichever occurred first.

Objective response rate was defined as the 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 was defined as the time from the first occurrence of a confirmed objective response to the time of disease progression, as determined by the investigator using RECIST v1.1 criteria, or death, whichever occurred first.

Patient reported outcome measures were collected using EORTC QLQ C-30 and QLC LC-13.

Time to deterioration (TTD) in patient-reported lung cancer symptoms (cough, dyspnea, chest pain, arm/shoulder pain) was to be examined. 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.

Modified RECIST was derived from RECIST v 1.1 and immune-related response criteria (irRC). The differences between the modified RECIST and RECIST 1.1 are summarized in Table 10.

Table 10. Modified RECIST and RECIST v1.1: Summary of Changes

	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 ≥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

Reviewer's Comments

- *As this is an open-label study, the results of patient reported outcome endpoints could be biased and not interpretable.*

- *Per the statistical analysis plan, there were no alpha (type-I error rate) adjustments for the multiple tests for the secondary endpoints.*

3.3.1.4 Sample Size Determination

The primary purpose of this phase 2 study was to estimate OS and PFS hazard ratios in the PD-L1-selected subset and in the overall ITT population. Based on PD-L1 expression prevalence estimates, the study was expected to enroll 285 patients with 55 PD-L1 IC2/3 patients.

The power and 95% CIs for OS and PFS in the overall ITT population and in the PD-L1 IC2/3 subpopulation (Table 11) were based on the following assumptions:

- Event times ~ exponentially distributed
- Median PFS in the control arm ~ 3 months
- Median OS in the control arm ~ 8 months
- Enrollment period ~ 8 months

Patients were to be followed until approximately 150 deaths in the overall ITT population have occurred.

Table 11. Power and 95% CI for Proposed Study Design for True Underlying OS and PFS HR 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)

* CIs are based on the assumption that the point estimate is equal to the true value of the HR assumed.

[Source: Study Protocol version 5 Tables 15 and 16]

Reviewer's comments

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. The Applicant submitted efficacy analyses results based on 150 deaths to the FDA on 10 April 2015 and discussed with the FDA regarding revising the number of death events from 150 to 180 at the type B meeting held on 12 May 2015. At the meeting, the FDA stated that the agency considers the OS analysis based on approximately 150 deaths as the final OS analysis, and an updated analysis based on more deaths (180) would be considered as an exploratory analysis. Furthermore, at the meeting, the FDA stated that OS,

PFS and other efficacy analyses results in PD-L1 subgroups would be considered as supportive or exploratory.

In addition, on 11 July 2016, the Applicant responded to the FDA's information request with regards to the protocol amendment above, and admitted that they have looked at the analysis results based on 150 deaths before initiating protocol amendment to increase event number from 150 to 180. Given that, 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 considered as exploratory.

3.3.1.5 Interim Analyses

There were two interim safety and efficacy analyses planned when approximately 30 and 100 death events in the overall ITT population occurred. Analyses were performed on both the overall and the PD-L1-selected subpopulations. These analyses would not lead to an early termination of the study because of superior efficacy. A small alpha of 0.0001 was spent for each of the interim analyses of OS. The final OS analysis was to be conducted at the 4.98% level of significance when approximately 150 death events occurred. A sponsor's internal monitoring committee (IMC) was to evaluate the interim safety and efficacy data.

Reviewer's comments

Though in the protocol v6, SAP, and CSR, the Applicant considered the 150 death analysis as the third interim analysis, we consider it as the final analysis as commented in the section 3.3.1.4.

3.3.2 Statistical Methodologies

3.3.2.1 Efficacy Analysis Population

The primary efficacy analysis population was the ITT population, defined as all patients randomized into the study. Patients were to be classified according to assigned treatment group, regardless of the actual treatment received.

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

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

The PD-L1 subsets were determined based on IC levels from stratification and TC levels derived from raw percentage staining scores at enrollment (Table 12)

Table 12. Criteria for PD-L1 Expression Assessment

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

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

[Source: CSR Table 1]

Reviewer's comment

It has been noted that the study randomization was not stratified by TC status, and TC score was derived from raw percentage staining score at enrollment retrospectively. Therefore, there is a potential patient imbalance between treatment arms within each PD-L1 subgroup as defined above, particularly for subgroups with a small sample size.

Furthermore, in the study protocol, there was no multiplicity adjustment for efficacy analyses by PD-L1 status. The SAP specified a testing hierarchy for OS to control type I error starting with the subgroup of TC2/3 or IC2/3, followed by TC1/2/3 or IC1/2/3, followed by ITT, and then TC3 or IC3. However, given that the SAP was finalized after the Applicant has looked analysis results based on 150 deaths including various PD-L1 subgroups, PD-L1 subgroup analyses are considered as exploratory.

3.3.2.2 Efficacy Analysis Methods

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 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.

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.

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. As estimate of ORR and its 95% CI were calculated 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.

PFS, ORR, and DOR analyses using modified RECIST criteria were limited to the atezolizumab arm only, with no comparison with the docetaxel arm.

EORTC QLQ C-30 and QLQ-LC13 assessments were intended per protocol to be collected at cycle 1 day 1, one day 1 of each subsequent cycle, and at the treatment discontinuation vist, which is within 30 days after the last treatment dose. Completion and compliance rates were to be summarized at each time point by treatment arm with reasons for missing data, when available.

Summary statistics of linear transformed score were reported for all the items and subscales according the EORTC scoring manual guidelines. The mean change of the linear transformed scores from based 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 analyzed using the same methods as PFS. 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/should 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.

3.3.3. Patient Disposition, Demographic and Baseline Characteristics

3.3.3.1 Patients Disposition

From 5 August 2013 until 31 March 2014, a total of 287 patients from 61 clinical sites in 13 countries were randomized to receive either atezolizumab or docetaxel in a 1:1 randomization ratio. Ten patients (8 in the docetaxel arm and 2 in the atezolizumab arm) did not receive study treatment. As of the 30 January 2015 data cut-off date for the primary final survival analysis agreed by the FDA, 4 patients (2.8%) in the docetaxel arm and 30 patients (20.8%) in the atezolizumab arm were still receiving the study treatment. A further 45 patients (31.5%) in the docetaxel arm and 38 patients (26.4%) 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) have withdrawn from the study due to reasons other than death.

Among the 277 patients receiving study treatment, 243 patients have discontinued treatment. The primary reason for treatment discontinuation was disease progression in both arms as summarized in Table 13.

Table 13. Summary of Reasons for Treatment Discontinuation, Among Patients Treated

	Atezolizumab (N=142) n (%)	Docetaxel (N=135) n (%)	Total (N=277) n (%)
On Treatment	30 (21)	4 (3)	34 (12)
Discontinued From Treatment	112 (79)	131 (97)	243 (88)
Due to Disease Progression	97 (68)	84 (62)	181 (65)
Due to Death	2 (1)	1 (<1)	3 (1)
Due to AE	11 (8)	30 (22)	41 (15)
Due to Physician Decision	0	9 (7)	9 (3)
Due to Withdrawal by Subject	2 (1)	7 (5)	9 (3)

[Source: CSR Table 15]

3.3.3.2 Demographic and Baseline Characteristics

The demographic and baseline characteristics are presented in Table 14. The median age was 62 years old (range 36–84 years). Fifty-nine percent of the randomized patients were males, and seventy-nine percent were white. Eligible patients had ECOG PS 0-1 (68% of the patients were ECOG PS 1 and 32% were ECOG PS 0).

Table 14. Summary of Demographics and Baseline Disease Characteristics

	Atezolizumab (n=144)	Docetaxel (n=143)
Age (years)		
Median	62	62
Range	(42, 82)	(36, 84)
Age category, n (%)		
<65	87 (60%)	87 (61%)
≥65	57 (40%)	56 (39%)
Sex, n (%)		
Male	93 (65%)	76 (53%)
Female	51 (35%)	67 (47%)
Race, n (%)		
White	110 (76%)	116 (81%)
Asian	23 (16%)	13 (9%)
Black or African American	3 (2%)	4 (3%)
Others	8 (6%)	10 (7%)
Region, n (%)		
US	66 (46%)	66 (46%)
Non-US	78 (54%)	77 (54%)
Number of prior therapies, n (%)		
1	93 (65%)	96 (67%)
2	51 (35%)	47 (33%)
Disease histology, n (%)		
Squamous	49 (34%)	48 (34%)
Non-Squamous	95 (66%)	95 (66%)
Disease status, n (%)		
Locally advanced	8 (6%)	5 (4%)
Metastatic	136 (94%)	138 (96%)
Baseline ECOG PS, n (%)		
0	48 (33%)	46 (32%)
1	96 (67%)	97 (68%)
Smoking History, n (%)		
Non-smoker	27 (19%)	29 (20%)
Ex-smoker	92 (64%)	93 (65%)
Current Smoker	25 (17%)	21 (15%)
IC score		
IC0	62 (43%)	63 (44%)
IC1	53 (36%)	54 (38%)
IC2	19 (13%)	18 (13%)
IC3	10 (7%)	8 (6%)

[Source: CSR Tables 18, 19, and 20]

Reviewer's comments

- *The demographics and baseline disease characteristics are balanced between the two treatment arms, except the proportion of men is higher in the atezolizumab arm.*
- *The protocol specified primary OS analysis was stratified by the PD-L1 IC score collected on IxRS, number of prior chemotherapy regimens and histology type from eCRFs. The discrepancies between eCRF-based and IVRS-based stratification data are summarized in Table 15. Following the intent-to-treat principle, the Agency's standard is to use all IxRS-*

based stratification data in the primary analysis, and CRF-based stratification data could be used in a sensitivity analysis.

Table 15. Discordance of Stratification Data, between eCRF and IxRS

	Atezolizumab (n=144)	Docetaxel (n=143)
Number of prior chemo regimens, n (%)		
Discordance	0	0
Concordance	144 (100%)	143 (100%)
Histology, n (%)		
Discordance	2 (1.4%)	1 (0.7%)
Concordance	142 (98.6%)	142 (99.3%)

[Source: The applicant's response to the information request dated 28 April 2016]

3.3.3.3 Post-Study Treatment Anti-Cancer Therapy

There was 20% in the atezolizumab arm and 13% in the docetaxel arm having at least one non-protocol anti-cancer treatment post study treatment as of the clinical cutoff date of 30 January 2015, as listed in Table 16.

Table 16. Post-Study Treatment Systemic Anti-Cancer Therapy

	Atezolizumab (n=144)	Docetaxel (n=143)
Any systemic anti-cancer therapy	29 (20%)	19 (13%)
Afatinib	0	1 (<1%)
Carboplatin	3 (2%)	4 (3%)
Cisplatin	3 (2%)	1 (<1%)
Docetaxel	22 (15%)	0
Erlotinib Hydrochloride	2 (1%)	2 (1%)
Etoposide	1 (<1%)	0
Gefitinib	3 (2%)	1(<1%)
Gemcitabine	4 (3%)	7 (5%)
Gemcitabine Hydrochloride	1 (<1%)	3 (2%)
Irinotecan Hydrochloride	1 (<1%)	0
Mitomycin	0	1(<1%)
Paclitaxel	2 (1%)	2(1%)
Paclitaxel Albumin	1 (<1%)	0
Panitumumab	1(<1%)	0
Pemetrexed	1(<1%)	1(<1%)
Pemetrexed Disodium	1 (<1%)	2(1%)
Poziotinib	0	1(<1%)
Vinorelbine Tartrate	1(<1%)	2(1%)
Vinorelbine	1 (<1%)	2 (1%)

3.3.3.5 Protocol deviations

A total of 35 patients (18 in the atezolizumab arm and 17 in the docetaxel arm) had major protocol deviations during the study as of the cutoff date 30 January 2015. Thirteen patients (6 in the atezolizumab and 7 in the docetaxel arm) had at least one eligibility violations. Twenty-three (10 in the atezolizumab and 13 in the docetaxel arm) had at least one study procedure violations.

Reviewer's comment

One patient who did not sign the informed consent was not counted as a major deviation by the review team. A sensitivity analysis of OS has been performed by excluding patients with major protocol deviations. Results were consistent to the primary findings (see Section 3.3.4.1).

3.3.4 Results and Conclusions

In the clinical study report, the applicant provided the final efficacy analysis of OS based on approximately 180 death events and the OS analysis based on approximately 150 death events was considered as the third interim analysis. As discussed in section 3.3.1.4, the review team considered the protocol initially pre-specified analysis based on approximately 150 events as the primary analysis. Therefore, in this review, the primary OS analysis and its associated sensitivity analyses are based on the data cutoff for 150 events. The analysis based on approximately 180 deaths is considered as an exploratory supportive updated analysis. During the BLA review, the Applicant submitted another survival update with 200 deaths using a cutoff date of 1 December 2015, which is included in this review as another exploratory supportive analysis.

3.3.4.1 Primary Efficacy Endpoints

Overall survival was the primary efficacy endpoint of the pivotal study POPLAR. The pre-specified final OS analysis was conducted when 153 death events occurred at the study cut-off date of 30 January 2015. An improvement in OS for patients in the atezolizumab arm compared to patients in the docetaxel arm was observed but was not statistically significant, with a 2.9-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 17 and the Kaplan-Meier curves are shown in Figure 5.

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

As commented in Section 3.3.3.2, following the intent-to-treat principle, the primary analysis of OS is based on stratification data collected from the IxRS instead of from the eCRFs.

Table 17. FDA's Primary Analysis of Overall Survival, in the ITT Population

	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

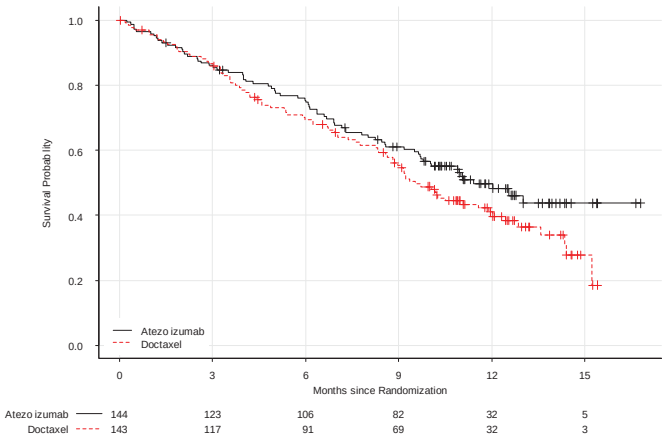


Figure 5. Study POPLAR, Kaplan-Meier Curves of Overall Survival, in the ITT Population

[Source: CSR Figure 18]

OS updated analyses

With an additional 3-month follow-up of OS (cutoff date: 8 May 2015), an updated OS analysis was performed with 173 death events. Another update on OS was performed with a median follow-up of 22 months (cutoff date: 1 December 2015). Results of both updated OS analyses are summarized in Table 18 and Figure 6.

Table 18. Updated Overall Survival, in the ITT Population

	Atezolizumab (N=144)	Docetaxel (N=143)
Update 1 (8 May 2015)		
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)	
Update 2 (1 December 2015)		
Number of deaths, n (%)	90 (63)	110 (77)
Median (95% CI), in months	12.6 (9.7, 16.0)	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]

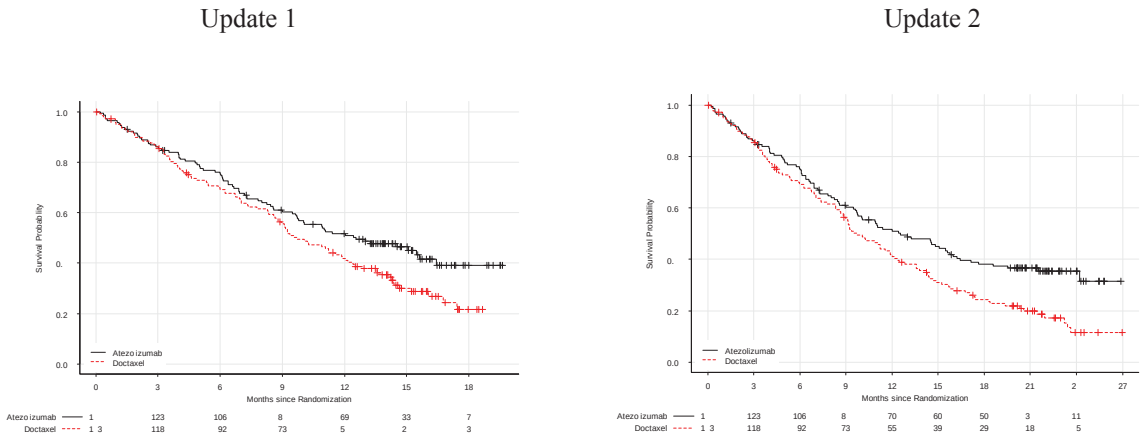


Figure 6. Study POPLAR, Kaplan-Meier Curves of Updated Overall Survival, in the ITT Population

[Source: CSR Figure 4 and OS supplemental results report Figure 1]

Reviewer's Comments

The updated OS analyses are considered as exploratory as commented in Section 3.3.1.4.

Sensitivity Analyses

The applicant has performed an un-stratified analysis of OS, and the results were consistent to the primary findings, with a HR of 0.77 (95% CI: 0.56, 1.06).

This reviewer performed additional sensitivity analyses on overall survival, as summarized in Table 19.

Table 19. FDA's OS sensitivity analyses

OS Sensitivity Analyses (cutoff 1/30/2015)	N	Median (Ate v. Doc)	HR (95% CI)
1. Considering patients censored due to lost to follow-up of survival or withdrawing consent as events at 3 months after the date of last known alive.	287	11.1 vs. 9.1	0.72 (0.53, 0.99)
2. Considering patients censored due to lost to follow-up of survival or withdrawing consent in the Atezolizumab as events at 3 months after the date of last known alive.	287	11.1 vs. 9.5	0.81 (0.58, 1.11)
3. Excluding patients not treated	277	12.0 vs. 9.7	0.77 (0.55, 1.06)
4. Excluding patients with major deviations	252	12.6 vs. 9.2	0.66 (0.46, 0.93)
5. Excluding patients off treatment early by physician's decision	284	11.4 vs. 9.4	0.73 (0.53, 1.02)
6. Excluding patients not treated, with major protocol deviation, or off treatment early by physician's decision	242	12.6 vs. 9.2	0.63 (0.44, 0.90)

Reviewer's Comment

Results from multiple sensitivity analyses of OS are consistent to the primary findings. In addition, results of OS sensitivity analyses using the updated data (cutoff 12/1/2015, detailed results not included) are consistent to the primary updated findings.

3.3.4.2 Secondary Endpoints

Secondary efficacy endpoints included progression-free survival and objective response rate. No multiplicity adjustment was pre-specified for multiple endpoints. Therefore, all the p-values 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 and 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 20. FDA's PFS Analysis Results, in the ITT Population

	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.

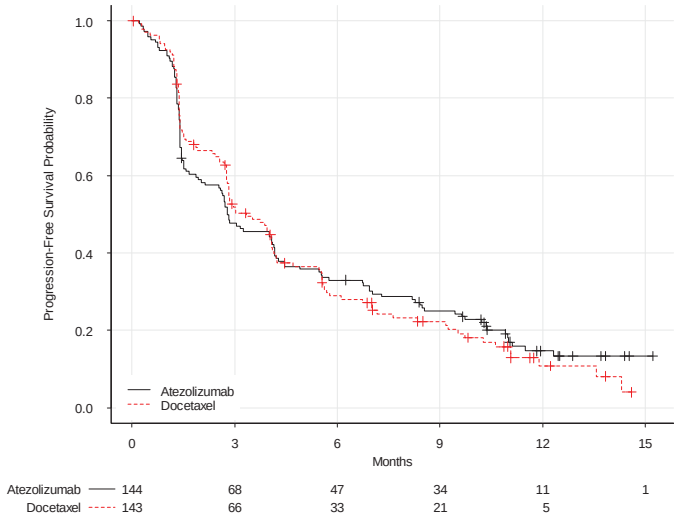


Figure 7. Study POPLAR, Kaplan-Meier Curves of Progression-Free Survival, in the ITT Population

[Source: CSR Figure 21]

Objective Response Rate per Investigator Assessment

As of the cutoff date for the primary OS analysis (30 January 2015), per investigator assessment using RECIST v1.1 criteria, the objective response rate was 15.4% and 14.6% in the docetaxel arm and the atezolizumab arm, respectively. The median response duration was 7.8 months in the docetaxel arm and not reached in the atezolizumab arm at that time. With an additional 10-month follow-up, as of the cutoff date for the second OS update (1 December 2015), the median

response duration was 18.6 months among the responders in the atezilizumab arm and 7.2 months among the responders in the docetaxel arm. See Table 21 for detailed information.

Table 21. Objective Response Rate, in the ITT population

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

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

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

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. A total of 211 patients (114 in the atezolizumab arm and 97 in the docetaxel arm) had deterioration of at least one lung cancer symptoms. The analysis of time to lung cancer symptoms deterioration did not show a compelling difference between the two treatment arms. Please note that no differences in PRO outcomes in this open-label study do not 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.

3.3.5 Conclusions for Efficacy based on Study POPLAR

The phase 2 study POPLAR showed a 1.9-month numerical improvement in OS (HR=0.77) from atezolizumab compared to docetaxel but did not reach the statistical significance at the pre-specified final analysis. Updated OS analyses with longer follow-up showed a consistent benefit of atezolizumab on survival compared to docetaxel. Results from sensitivity analyses for OS were consistent with the results of the primary analysis. No benefit on PFS and ORR from atezolizumab compared to docetaxel was observed; however, the median duration of response in the atezolizumab arm appears to be longer than that in the docetaxel arm.

3.4 Evaluation of Safety

Please refer to the clinical evaluations of this application for safety results and conclusions for safety.

3.5 Benefit-Risk Assessment

Please refer to clinical evaluations of this application for a benefit-risk evaluation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Tables 22 and 23 summarize OS results by gender, race, age, and region for studies OAK and POPLAR, respectively.

Table 22. 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.

Table 23. 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 median	Docetaxel median	HR[a] (95% CI)	Atezolizumab median	Docetaxel median	HR[a] (95% CI)
Overall	287	11.4	9.5	0.77 (0.56, 1.06)	12.6	9.7	0.68 (0.51, 0.89)
Gender							
Male	169	11.1	8.8	0.64 (0.43, 0.95)	12.0	9.0	0.60 (0.42, 0.86)
Female	118	13.0	13.6	0.99 (0.57, 1.67)	15.1	13.6	0.74 (0.47, 1.16)
Race							
White	226	11.0	9.2	0.79 (0.56, 1.12)	11.1	9.2	0.71 (0.52, 0.96)
Non-White	61	NR	11.9	0.72 (0.32, 1.59)	NR	11.9	0.60 (0.30, 1.19)
Region							
US	132	12.6	10.5	0.73 (0.45, 1.16)	15.6	9.7	0.63 (0.41, 0.96)
Non-US	155	11.4	9.2	0.80 (0.52, 1.24)	12.0	9.4	0.71 (0.49, 1.04)
Age							
<65	175	13.0	10.5	0.79 (0.52, 1.19)	13.0	11.2	0.70 (0.48, 1.01)
≥65	112	11.4	9.1	0.75 (0.46, 1.23)	12.0	9.1	0.65 (0.42, 0.99)

[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

4.2 Other Special/Subgroup Populations

Exploratory analyses of OS in studies OAK and POPLAR by baseline ECOG PS level, smoking status, and number of metastatic organ systems are presented in Tables 24 and 25, respectively.

Table 24. 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)
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.

Table 25. Study POPLAR Additional OS Subgroup Analyses

		Primary OS Analysis (cutoff 1/30/2015)			Updated OS analysis (cutoff: 12/1/2015)		
Subgroup	n	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.

OS by PD-L1 status

The results of exploratory subgroup analyses based on PD-L1 status for studies OAK and POPLAR are summarized in Tables 26 and 27, respectively.

Table 26. Study OAK OS Subgroup Analyses by PD-L1 Status

PD-L1	n	Atezolizumab median	Docetaxel median	HR[a] (95% CI)
TC3 or IC3	137	20.5	8.9	0.41 (0.27, 0.64)
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.

Table 27. 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)
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)
TC0 and IC0	92	9.7	9.7	1.12 (0.65, 1.95)	9.7	9.7	0.88 (0.55, 1.43)

[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

Reviewer's comments

All the subgroup analyses presented in this section are considered exploratory or hypothesis generating and no formal inference may be drawn.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There are no major statistical issues with the pivotal study phase 3 OAK. The study met its primary endpoint of OS and the results appeared consistent across sensitivity analyses and no apparent outliers were observed in subgroup analyses.

Study POPLAR was a phase 2 study and the primary purpose of this study was to estimate OS and PFS hazard ratios; therefore, the study was not designed to detect a statistically significant benefit in OS with an adequate power. The final analysis of OS was pre-specified to be conducted after 150 death events occurred. However, after the survival results based on 150 death events were available to the Applicant, the Applicant amended the study protocol and SAP to increase the number of death events for the final OS analysis from 150 to 180, and considered the original final analysis with 150 events as the third interim analysis. Given that the amendment of event number was made post the pre-specified analysis, the review team considered the analysis based on 150 death events in the ITT population as the primary analysis, and updated OS analyses with more death events as exploratory. The OS results at the pre-specified final analysis (150 deaths) showed a separation of Kaplan-Meier curves favoring atezolizumab, but did not reach the statistical significance.

5.2 Collective Evidences

The pivotal study OAK met its primary efficacy objective statistically. In the primary efficacy population (n=850), 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) in the intent-to-treat (ITT) population. A similar OS improvement was observed from the pre-specified TC1/2/3 or IC1/2/3 subpopulation. Results from sensitivity analyses for OS were consistent with the results of the primary analysis, and no apparent outliers were observed in subgroup analyses.

Efficacy results observed in study OAK were supported by the phase 2 study POPLAR. Study POPLAR had the same treatment regimens and patient population as those in study OAK, but with a smaller sample size. 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 was not statistically significant (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).

5.3 Conclusions and Recommendations

The applicant submitted topline results from a multicenter, phase 3, randomized, open-label clinical study (Study OAK) comparing atezolizumab to docetaxel in the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure with platinum-containing chemotherapy. Atezolizumab demonstrated a statistically significant improvement in OS as compared with docetaxel in the primary efficacy population which included the first randomized 850 patients. A similar statistically significant benefit on OS was observed in the

pre-specified PD-L1 subpopulation (TC1/2/3 or IC1/2/3). The observed OS benefit was supported by results from a phase 2 study, POPLAR. Although atezolizumab demonstrated an OS advantage over docetaxel, the judgment on the clinical meaningfulness of the treatment effect in survival observed in studies OAK and POPLAR in light of the toxicities is deferred to the clinical review team.

5.4 Labeling Recommendations

We recommend that the label include primary OS results for Study OAK and OS and ORR results for study POPLAR based on updated data post the pre-specified final analysis. Exploratory PD-L1 subgroup analysis results of OS in study OAK could be included in the text if the subgroups are considered clinically important.

SIGNATURES/DISTRIBUTIO N LIST

Primary Statistical Reviewer: Lijun Zhang, Ph.D.
Date: September 28th, 2016

Concurring Reviewer(s)

Statistical Team Leader: Shenghui Tang, Ph.D.

Biometrics Division Director: Rajeshwari Sridhara, Ph.D.

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Project Manager: Sakar Wahby
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/s/

LIJUN ZHANG
09/28/2016

SHENGHUI TANG
09/28/2016

RAJESHWARI SRIDHARA
09/28/2016

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

BLA Number: 761041 **Applicant: Genentech Inc.** **Stamp Date: 2/19/2016**

Drug Name: Atezolizumab **NDA/BLA Type: BLA (351a)**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the statistical 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.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

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/s/

LIJUN ZHANG
04/08/2016

SHENGHUI TANG
04/08/2016