CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761041Orig1s000

SUMMARY REVIEW

Division Director Summary Review

Date	October 17, 2016
From	Geoffrey Kim
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	761041
Applicant	Genentech, Inc.
Date of Submission	February 19, 2016
PDUFA Goal Date	October 19, 2016
Proprietary Name / **Non-Proprietary Name**	Atezolizumab/TECENTRIQ
Dosage Form(s) / Strength(s)	Injection for intravenous administration 1200 mg/20 mL (60 mg/mL), single-dose vials
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.*
Action/Recommended Action for NME:	Approval
Approved/Recommended Indication/Population(s) (if applicable)	Tecentriq is a humanized 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.

Material Reviewed/Consulted	**Names of discipline reviewers/Team Leaders**
Regulatory Project Manager	Sakar Wahby
Medical Officer Reviewer	Chana Weinstock (efficacy); Daniel Suzman (safety)/ Sean Khozin (CDTL)
Statistical Review	Lijun Zhang/ Shenghui Tang
CDRH	Shyam Kalavar, PhD/Eunice Lee, PhD & Reena Philip, PhD (TL)
Clinical Pharmacology Review	Wentao Fu/ Qi Liu/ Rosanne Charlab-Orbach
Pharmacometrics Review	Chao Liu/ Jingyu (Jerry Yu)
DMPP/OPDP	Nazia Fatima
OSI	Lauren Iacono-Connors
OSE/DMEPA	Tingting Gao/Alice (Chi-Ming) Tu
Patient Labeling	Rowell Medina/Barbra Fuller

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

1. **Benefit-Risk Assessment**

Benefit-Risk Summary and Assessment

I concur with the Benefit-Risk Assessment that was made by the clinical and statistical teams. All members of the review team recommended approval of this application. As summarized by the clinical and statistical team:

"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."

"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 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."

The following table is derived from the clinical and CDTL reviews. I concur with the statements presented.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• 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%.	**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.**
Current Treatment Options	• 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. 1. 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.	**Despite recent drug approvals, treatment options in the second–line+ metastatic NSCLC setting remain limited and these patients are considered incurable.**
Benefit	2. 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. 3. 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	**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**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	(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).	**randomized, controlled studies. The results are consistent between the two studies.**
Risk	4. Tolerated in most study patients 5. 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. 6. Important risks include pneumonitis, hepatitis, endocrine disorders, colitis, infection, and neurological disorders.	**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.**
Risk Management	7. Non-endocrine immune-mediated adverse events were largely reversible with the use of corticosteroids 8. A medication guide for atezolizumab describing the risks of immune-mediated adverse events will be required to better allow early recognition and initiation of treatment of these events. 9. 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.	**The safe use of atezolizumab can be managed through accurate labeling and routine pharmacovigilance. No REMS is required.**

2. Background

Summary of Presubmission/Submission Regulatory Activity
From the Clinical Review

April 2011	*IND 111271 submitted to the Division of Oncology Products 2*
February 2013	*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.*
October 2013	*Type B meeting held to discuss trial design for OAK and BIRCH to support accelerated and regular approval, respectively, for atezolizumab in 2L+ NSCLC.*
January 2015	*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*
November 2015	*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.* *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 2015	*Part 1 of BLA 761041 submitted.*
February 2016	*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 2016	*Applicant submitted topline efficacy results from the Phase 3 Study OAK to the BLA. Datasets supporting these results submitted on September 16, 2016.*

Intended Population
From the clinical review:

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 deaths[1]. 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).

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.

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 1 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 therapy failure	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) • ORR 5.5% (1.1, 15.1) vs N/A 2. Docetaxel vs. Vinorelbine/lfosfamide • 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	Erlotinib vs placebo • 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	Pemetrexed vs. Docetaxel • 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	• 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	Ramucirumab/Docetaxel vs Placebo/Docetaxel • 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 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	Squamous-March 2015 Non-squamous-October 2015	1. Squamous NSCLC- nivolumab vs. docetaxel • mOS 9.2 (7.3,13.3) vs. 6.0 (5.1,7.3); HR 0.59 (0.44, 0.79) p=0.00025 2. Non-Squamous NSCLC- Nivolumab vs. docetaxel • 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

	prior to receiving OPDIVO		
Pembrolizumab	**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.	October 2015	• ORR 41% (29,54)
Osimertinib	**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	November 2015	• ORR 59% (54,64)
Alectinib	**Accelerated approval**- anaplastic lymphoma kinase (ALK)-positive, metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib	December 2015	Study 1- • ORR- IRC 38% (28,49), investigator 46% (35,57) • DOR in months- IRC 7.5 (4.9, NE), investigator NE (4.9, NE) Study 2- • 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)

3. **Product Quality: N/A**

4. **Nonclinical Pharmacology/Toxicology: N/A**

5. **Clinical Pharmacology**

I agree with the clinical pharmacology team, who state that BLA761041 is acceptable from a clinical pharmacology perspective.

"The submission contains updated information for the incidence of anti-drug antibody (ATA). The presence of ATAs did not have a clinically significant impact on pharmacokinetics, safety or efficacy. The applicant's final population pharmacokinetic (PK) model is not considered appropriate by the Pharmacometric review team as atezolizumab showed time-dependent PK. The PK labeling (Section 12.3) is updated based on the results of the improved population PK model."

6. **Clinical Microbiology**

NA

7. **Clinical/Statistical-Efficacy**

This application is primarily supported by two randomized, multicenter, open-label studies (OAK and POPLAR) of atezolizumab in patients with locally advanced or metastaticNSCLC who have progressed during or following a platinum-containing regimen. The following is excerpted from the clinical studies section (14) of the agreed upon text in the atezolizumab (TECENTRIQ) package insert regarding the design and efficacy results of OAK and POPLAR:

Metastatic Non-Small Cell Lung Cancer

Previously Treated Metastatic NSCLC

The efficacy of TECENTRIQ was investigated in two multi-center, international, randomized, open-label trials in patients with metastatic NSCLC who progressed during or following a platinum-containing regimen. Study 2 was a trial in 1225 patients with the primary analysis population consisting of the first 850 randomized patients and Study 3 was a trial in 287 patients. In both studies, eligible patients were stratified by PD-L1 expression status in tumor-infiltrating immune cells (IC), by the number of prior chemotherapy regimens, and by histology. Patients were randomized (1:1) to receive either TECENTRIQ administered intravenously at 1200 mg every 3 weeks until unacceptable toxicity or either radiographic or clinical progression or docetaxel administered intravenously at 75 mg/m^2 every 3 weeks until unacceptable toxicity or disease progression. These studies excluded patients who had: a history of autoimmune disease, had active or corticosteroid-dependent brain metastases, administration of a live, attenuated vaccine within 28 days prior to enrollment, administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medications within 2 weeks prior to enrollment. Tumor assessments were conducted every 6

weeks for the first 36 weeks, and every 9 weeks thereafter. In Study 2, tumor specimens were evaluated prospectively for PD-L1 expression on tumor cells (TC) and IC using the VENTANA PD-L1 (SP142) Assay and the results were used to define the PD-L1 expression subgroups for the analyses described below.

In Study 2, among patients in the primary analysis population, the median age was 64 years (range: 33 to 85), and 61% of patients were male. The majority of patients were white (70%). Approximately three-fourths of patients had non-squamous disease (74%), 10% had known EGFR mutation, 0.2% had known ALK rearrangements, and most patients were current or previous smokers (82%). Baseline ECOG performance status was 0 (37%) or 1 (63%). Seventy five percent of patients received only one prior platinum-based therapeutic regimen. In Study 3, the median age was 62 years (range: 36 to 84), and 59% of patients were male. The majority of patients were white (79%). Approximately two-thirds of patients had non-squamous disease (66%), 7% had known EGFR mutation, 1% had ALK rearrangements, and most patients were current or previous smokers (80%). Baseline ECOG performance status was 0 (33%) or 1 (67%). Approximately two-thirds of patients received only one prior platinum-based therapeutic regimen.

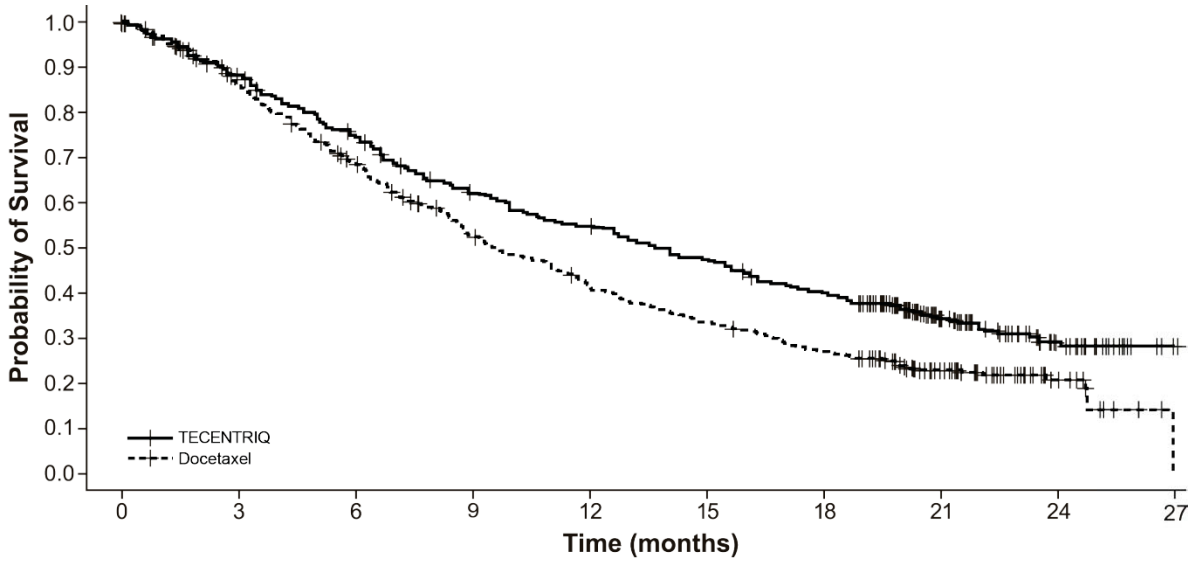
The major efficacy outcome measure of Study 2 was overall survival (OS) in the primary analysis population (first 850 randomized patients). The major efficacy outcome measure of Study 3 was overall survival (OS). Other efficacy outcome measures for Study 3 included investigator-assessed objective response rates and duration of response per RECIST v1.1. The results of Study 2 with a median follow up of 21 months are presented in Table 6 and Figure 1.

Table 6: Efficacy Results in the Primary Analysis Population from Study 2

	TECENTRIQ (n=425)	Docetaxel (n=425)
Overall Survival		
Deaths (%)	271 (64%)	298 (70%)
Median, months	13.8	9.6
(95% CI)	(11.8, 15.7)	(8.6, 11.2)
Hazard ratio[1] (95% CI)	0.74 (0.63, 0.87)	
p-value[2]	0.0004	

[1] Stratified by PD-L1 expression in tumor infiltrating immune cells, the number of prior chemotherapy regimens, and histology
[2] Based on the stratified log-rank test
CI=confidence interval

Figure 1: Kaplan-Meier Plot of Overall Survival in the Primary Analysis Population in Study 2



No. Patients at Risk

TECENTRIQ	425	407	382	363	342	326	305	279	260	248	234	223	218	205	198	188	175	163	157	141	116	74	54	41	28	15	4	1
Docetaxel	425	390	365	336	311	286	263	236	219	195	179	168	151	140	132	123	116	104	98	90	70	51	37	28	16	6	3	

Tumor specimens were evaluated prospectively using the VENTANA PD-L1 (SP142) Assay at a central laboratory and the results were used to define the PD-L1 expression subgroups for pre-specified analyses. Of the 850 patients, 16% were classified as having high PD-L1 expression, defined as having PD-L1 expression on ≥ 50% of TC or ≥ 10% of IC. In an exploratory efficacy subgroup analysis of OS based on PD-L1 expression, the hazard ratio was 0.41 (95% CI: 0.27, 0.64) in the high PD-L1 expression subgroup and 0.82 (95% CI: 0.68, 0.98) in patients who did not have high PD-L1 expression.

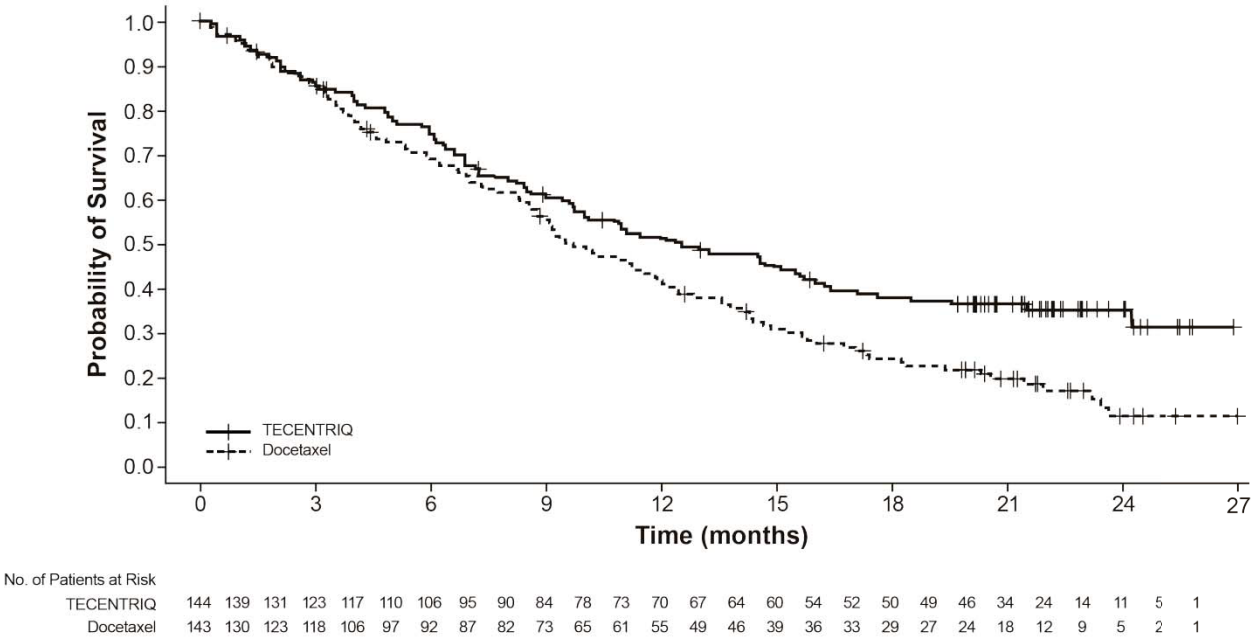
Results of an updated survival analysis in Study 3 with a median follow-up of 22 months are provided for all randomized patients (Table 7 and Figure 2).

Table 7: Efficacy Results from Study 3

	TECENTRIQ (n=144)	Docetaxel (n=143)
Overall Survival		
Deaths (%)	90 (63%)	110 (77%)
Median, months	12.6	9.7
(95% CI)	(9.7, 16.0)	(8.6, 12.0)
Hazard ratio[1] (95% CI)	0.69 (0.52, 0.92)	
Objective Response Rate[2] n (%)	22 (15%)	21 (15%)
(95% CI)	(10%, 22%)	(9%, 22%)
Complete response	1 (0.7%)	0
Partial response	21 (15%)	21 (15%)
Duration of Response[2]	n=22	n=21
Median (months)	18.6	7.2
(95% CI)	(11.6, NE)	(5.6, 12.5)

[1] Stratified by PD-L1 expression in tumor-infiltrating immune cells, the number of prior chemotherapy regimens, and histology
[2] per RECIST v1.1 (Response Evaluation Criteria in Solid Tumors v1.1)
CI=confidence interval; NE=not estimable

Figure 2: Kaplan-Meier Plot of updated Overall Survival in Study 3



8. Safety

The safety results from this trial are summarized below in the following excerpt from section 6.1 of the agreed-upon package insert:

The safety of TECENTRIQ was evaluated in Study 3, a multi-center, international, randomized, open-label trial in patients with metastatic NSCLC who progressed during or following a platinum-containing regimen, regardless of PD-L1 expression *[see Clinical Studies (14.2)]*. Patients received 1200 mg of TECENTRIQ (n=142) administered intravenously every 3 weeks until unacceptable toxicity or either radiographic or clinical progression or docetaxel (n=135) administered intravenously at 75 mg/m^2 every 3 weeks until unacceptable toxicity or disease progression. The median duration of exposure was 3.7 months (range: 0–19 months) in TECENTRIQ-treated patients and 2.1 months (range: 0–17 months) in docetaxel-treated patients.

The most common adverse reactions (≥ 20%) in patients receiving TECENTRIQ were fatigue (46%), decreased appetite (35%), dyspnea (32%), cough (30%), nausea (22%), musculoskeletal pain (22%), and constipation (20%). The most common Grade 3-4 adverse reactions (≥2%) were dyspnea, pneumonia, hypoxia, hyponatremia, fatigue, anemia, musculoskeletal pain, AST increase, ALT increase, dysphagia, and arthralgia.

Nine patients (6.3%) who were treated with TECENTRIQ experienced either pulmonary embolism (2), pneumonia (2), pneumothorax, ulcer hemorrhage, cachexia secondary to dysphagia, myocardial infarction, or large intestinal perforation which led to death. TECENTRIQ was discontinued due to adverse reactions in 4% (6/142) of patients. Adverse reactions leading to interruption of TECENTRIQ occurred in 24% of patients; the most common (>1%) were pneumonia, liver function test abnormality, upper respiratory tract infection, pneumonitis, acute kidney injury, hypoxia, hypothyroidism, dyspnea, anemia, and fatigue. Serious adverse reactions occurred in 37% of patients. The most frequent serious adverse reactions (> 2%) were pneumonia, dyspnea, pleural effusion, pyrexia, and venous thromboembolism.

Table 3 summarizes adverse reactions that occurred in at least 10% of TECENTRIQ-treated patients and at a higher incidence than in the docetaxel arm. Table 4 summarizes selected laboratory abnormalities worsening from baseline that occurred in ≥10% of TECENTRIQ-treated patients and at a higher incidence than in the docetaxel arm.

Table 3: Adverse Reactions Occurring in ≥10% of TECENTRIQ-Treated Patients with NSCLC and at a Higher Incidence than in the Docetaxel Arm (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grades 3–4]) (Study 3)

	TECENTRIQ (n=142)		Docetaxel (n=135)	
Adverse Reaction	**All grades**	**Grade 3–4**	**All grades**	**Grade 3–4**
	Percentage (%) of Patients			
General Disorders and Administration Site Conditions				
Pyrexia	18	0	13	0
Infections and infestations				
Pneumonia	18	6	4	2
Metabolism and nutrition disorders				
Decreased appetite	35	1	22	0
Musculosketal and connective tissue disorders				
Arthralgia	16	2	9	2
Back pain	14	1	9	1
Psychiatric Disorders				

Insomnia	14	0	8	2
Respiratory, thoracic and mediastinal disorders				
Dyspnea	32	7	24	2
Cough	30	1	25	0

Table 4: Selected Laboratory Abnormalities Worsening from Baseline Occurring in ≥10% of TECENTRIQ-Treated Patients with NSCLC and at a Higher Incidence than in the Docetaxel Arm (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grades 3–4]) (Study 3)

	Percentage of Patients with Worsening Laboratory Test from Baseline			
	TECENTRIQ		**Docetaxel**	
Test	All grades %	Grade 3–4 %	All grades %	Grade 3–4 %
Hyponatremia	48	13	28	8
Hypoalbuminemia	48	5	49	1
Alkaline Phosphatase increased	42	2	24	1
Aspartate aminotransferase increased	33	2	15	0
Alanine aminotransferase increased	31	2	9	1
Creatinine increased	19	1	14	2
Hypokalemia	18	2	11	4
Hypercalcemia	13	0	5	0
Total Bilirubin increased	11	0	5	1

The following Warnings and Precautions were updated in the Package Insert:

5.1 Immune-Related Pneumonitis

In 1027 patients with NSCLC who received TECENTRIQ, pneumonitis occurred in 38 (3.7%) patients. Of these patients, there was one patient with fatal pneumonitis, two patients with Grade 4, thirteen patients with Grade 3, eleven patients with Grade 2, and eleven patients with Grade 1 pneumonitis. TECENTRIQ was held in 24 patients and 21 patients were treated with corticosteroids. Pneumonitis resolved in 26 of the 38 patients. The median time to onset was 3.3 months (range: 3 days to 18.7 months). The median duration was 1.4 months (range: 0 days to 12.6+ months).

5.2 Immune-Related Hepatitis

In patients with NSCLC, Grade 3 or 4 elevation occurred in ALT (1.4%), AST (1.3%), and total bilirubin (0.6%). Immune-mediated hepatitis occurred in 0.9% (9/1027) of patients. Of these nine patients, one patient had Grade 4, four patients had Grade 3, three patients had Grade 2, and one patient had Grade 1 immune-mediated hepatitis. The median time to onset was 28 days (range: 15 days to 4.2 months). TECENTRIQ

was temporarily interrupted in seven patients; none of these patients developed recurrence of hepatitis after resuming TECENTRIQ.

5.3 Immune-Related Colitis

In 1027 patients with NSCLC who received TECENTRIQ, colitis or diarrhea occurred in 198 (19.3%) patients. Twelve patients (1.2%) developed Grade 3 colitis or diarrhea. Five patients (0.5%) had immune-mediated colitis or diarrhea with a median time to onset of 21 days (range: 12 days to 3.4 months). Of these patients, one had Grade 3, two had Grade 2, and two had Grade 1 immune-mediated colitis or diarrhea. Immune-mediated colitis or diarrhea resolved with corticosteroid administration in four of these patients, while the fifth patient died due to disease progression prior to resolution of colitis.

5.4 Immune-Related Endocrinopathies

In 1027 patients with NSCLC who received TECENTRIQ, hypothyroidism occurred in 4.2% (43/1027). Three patients had Grade 3 and forty patients had Grade 1–2 hypothyroidism. The median time to onset was 4.8 months (range 15 days to 31 months.) TSH was elevated and above the patient's baseline in 17% (54/315) of patients with follow-up measurement.

Hyperthyroidism occurred in 1.1% (11/1027) of patients with NSCLC. Eight patients had Grade 2 and three patients had Grade 1 hyperthyroidism. The median time to onset was 4.9 months (range: 21 days to 31 months). TSH was decreased and below the patient's baseline in 7.6% (24/315) of patients with a follow-up measurement.

5.6 Infection

In Study 3, a randomized trial in patients with NSCLC, infections were more common in patients treated with TECENTRIQ (43%) compared with those treated with docetaxel (34%). Grade 3 or 4 infections occurred in 9.2% of patients treated with TECENTRIQ compared with 2.2% in patients treated with docetaxel. Two patients (1.4%) treated with TECENTRIQ and three patients (2.2%) treated with docetaxel died due to infection. Pneumonia was the most common cause of Grade 3 or higher infection, occurring in 7.7% of patients treated with TECENTRIQ.

9. Advisory Committee Meeting

This efficacy supplement was not referred to a meeting of the Oncologic Drugs Advisory Committee as the application did not raise significant safety or efficacy issues that required the advice of the ODAC to make a risk-benefit assessment of atezolizumab in this patient population.

10. Pediatrics

A pediatric waiver was granted by the PeRC.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

The OSI consultants conclude: "The data from Study GO28753 was submitted to the Agency in support of BLA 761041. Two clinical sites, Dr. Aleksandra Szczesna, M.D. (Site 258690), Dr. Louis Fehrenbacher, M.D. (Site 258415), and the study sponsor, were selected for audit.

The primary efficacy endpoint, Overall Survival (OS), as reported in the application was verified with the source records generated at the inspected clinical sites. There were some significant deficiencies observed but these should not importantly impact study outcome or subject safety. The data from Study GO28753 submitted to the Agency in support of BLA 761041, appear reliable based on available information."

12. Labeling

Agreement has been reached on the physician labeling. The final indication is 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 efficacy (14) and safety (5, 6.1) sections of the package insert are discussed in prior sections of this review.

13. Postmarketing

There was no recommendation for Postmarketing Risk Evaluation and Mitigation Strategies.

The following postmarketing requirements are as follows:

3133-1 Conduct a randomized trial that will characterize the incidence, severity and response to treatment of TECENTRIQ induced immune-mediated adverse reactions, including immune-mediated pneumonitis.

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The following postmarketing commitments are as follows:

3133-2 Submit the final report and datasets for clinical trial 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" [OAK (GO28915)].

Final Report Submission: 03/2017

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

/s/

GEOFFREY S KIM
10/17/2016