CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761041Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Date	October 12, 2016
From	Sean Khozin, MD, MPH
Subject	Cross-Discipline Team Leader Review
BLA #	761041
Applicant	Genentech, Inc.
Date of Submission	February 19, 2016
PDUFA Goal Date	October 19, 2016 (priority)
Proprietary Name / Established (USAN) names	Atezolizumab/Tecentriq™
Formulation	1200 mg/20 mL (60 mg/mL) single-dose vials Injection for intravenous administration
Dosing Regimen	1200 mg administered as an intravenous infusion over 60 minutes every 3 weeks
Proposed Indication(s)	TECENTRIQ is a programmed death-ligand 1 (PD-L1) blocking antibody indicated for the treatment of patients with metastatic non-small cell lung cancer who have disease progression during or following platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving TECENTRIQ.
Recommendation	*Traditional Approval*

Discipline and Consultants	**Primary/ Secondary Reviewer**
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1. Introduction

On February 19, 2016, Hoffmann-La Roche, Inc./Genentech, Inc. (heretofore referred to as the applicant) submitted a supplemental BLA (#761041) for atezolizumab (TECENTRIQ™) 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™.*

Atezolizumab, a humanized immunoglobulin (Ig)G1 mAb, targets human programmed death-ligand 1 (PD-L1) and inhibits its interaction with its receptors programmed Death-1 (PD-1) and B7.1, both of which are thought to provide inhibitory signals to T cells. Atezolizumab is undergoing clinical development for a variety of solid tumors and hematologic malignancies. On May 18, 2016, the U. S. Food and Drug Administration (FDA) gave accelerated approval to atezolizumab for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

Primary data supporting the proposed indication came from two randomized, multi-center, open label trials (OAK, n= 1225 and POPLAR, n=278) in patients with previously treated metastatic non-small cell lung cancer (NSCLC) randomized to receive atezolizumab or standard therapy (docetaxel). The applicant submitted supportive evidence from the following trials in similar and relevant patient populations with metastatic NSCLC: BIRCH (single arm, multicenter, parallel cohort; n=667), FIR (single arm, multicenter, parallel cohort; n=138), and PCD4989g (first-in-human, dose-finding, single-arm; n=481; n[NSCLC cohort]=88).[1]

2. Background

Lung cancer is the leading cause of cancer deaths in the United States, with an estimated incidence of over 220,000 new cases and approximately 160,000 deaths in 2016. About 85% of cases are NSCLC and the majority of patients present with advanced disease (stage IIIB or IV) at the time of diagnosis. The median survival of patients with advanced NSCLC with supportive care is approximately 3–6 months. Standard first-line systemic treatment in unselected patients consists of platinum-based doublet chemotherapy, with response rates of approximately 30% and a median survival of approximately 10 months. In genomically-selected patients whose tumors

[1] The applicant's original submission on September 19, 2016 was based on the results of POPLAR, BIRCH, FIR, and PCD4989g. FDA further agreed to the receipt of topline data from the randomized GO28915 (OAK) comparing atezolizumab with docetaxel for labeling consideration with submission no later than September 19, 2016, a month before the BLA Prescription Drug User Fee Act (PDUFA) date.

harbor EGFR, ALK, or ROS1 mutations, approved targeted therapy with tyrosine kinase inhibitors has shown superior clinical benefit compared to standard chemotherapy. After failure of first-line therapy, further-line therapy includes nivolumab, pembrolizumab (in PD-L1 selected patients), docetaxel +/- ramucirumab, and pemetrexed for non-squamous NSCLC. Despite improvements in patient outcomes as a result of enhanced supportive care and availability of new therapies in recent years, nearly all patients with metastatic NSCLC eventually succumb to their disease and there remains to be a high unmet medical need.

3. Nonclinical pharmacology and toxicology

The potential of PD-L1 blockade to enhance anti-tumor immunity was investigated in tumors of colorectal and melanoma origin in three different genetic strains of mice where anti-PD-L1 induced antitumor activity demonstrated by tumor responses/regression was observed. The activity of anti-PD-L1 was also evaluated in mouse infection models with initial in vivo studies assessing the efficacy of atezolizumab in mice infected with lymphocytic choriomeningitis virus (LCMV) where anti-PD-L1 administration during the chronic phase of LCMV infection appeared to enhance T-cell function and reduce viral load, although blockade of PD-L1 at the peak of the acute T-cell response and concomitant peak viremia following LCMV infection resulted in high mortality rate. Based on published and the applicant's internal these mortalities may not be unique to this specific pathway and similar to mortalities observed in this model with other PD-1 and PD-L1 inhibitors as well as IL-2.

The pharmacokinetics and toxicokinetics of atezolizumab were investigated in mice and cynomolgus monkeys. The toxicology studies were a 15-day pilot study in mice, 8- and 26-week repeat-dose studies in cynomolgus monkeys, an in vitro cytokine release assay, an in vitro hemolytic potential assay, and a tissue cross-reactivity analysis of human and cynomolgus monkey tissues. Reproductive toxicity studies (developmental or fertility) were not planned/conducted as atezolizumab is expected to have an adverse effect on pregnancy outcome. Blockage of PD L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to a fetus and to result in an increase in fetal loss. No studies have been performed to test the potential of atezolizumab for carcinogenicity or genotoxicity.

Overall, the nonclinical pharmacokinetic (PK) behavior observed for atezolizumab was consistent with that expected for a receptor-targeting humanized IgG1 monoclonal antibody with target-mediated clearance and high incidence of anti-therapeutic antibodies (ATAs). Atezolizumab exhibited biphasic disposition and nonlinearity at lower doses, potentially due to target-mediated clearance that may be further influenced by the presence of anti-therapeutic antibodies.

4. Clinical pharmacology

Clinical pharmacology characteristics of atezolizumab were investigated in the 5 clinical trials stated in the introduction section of this review. These trials investigated and characterized single- and multiple-dose pharmacokinetics of atezolizumab, the potential effect of atezolizumab serum concentration on change from baseline QTc interval (ΔQTcF), and the immunogenicity of atezolizumab.

The recommended dose of atezolizumab is 1200 mg administered as an IV infusion every 3 weeks (q3w). The single-arm supportive trial BIRCH evaluated the atezolizumab 1200 mg q3w dose level in patients metastatic NSCLC with the rationale derived from both nonclinical studies and available clinical data from first-in-human trial PCD4989g. A target serum exposure for atezolizumab was projected on the basis of nonclinical tissue distribution data in tumor-bearing mice and receptor occupancy in the tumor. These data suggested that the 15 mg/kg atezolizumab q3w regimen (or fixed-dose equivalent) for BIRCH would be sufficient to maintain appropriate exposure levels, which could potentially safeguard against both inter-patient variability and the possibility that development of ATAs could lead to sub-therapeutic levels of atezolizumab. PK simulations by the applicant using a preliminary popPK model based upon PK data obtained in PCD4989g did not suggest any clinically meaningful differences in exposure following a fixed dose or a dose adjusted for weight.

The immunogenicity of atezolizumab was evaluated in PCD4989g, BIRCH, POPLAR, and FIR. In general, ATA positivity did not have significant impact on exposure and pharmacokinetics and overall response rates (ORRs) were comparable between ATA-positive and ATA-negative patients with no conclusive impact of ATA on efficacy.

The metabolism of atezolizumab has not been directly studied. Antibodies are cleared principally by catabolism. popPK analyses indicated that the typical clearance of atezolizumab was 0.200 L/day and the typical terminal $t_{1/2}$ was 27 days. In a popPK model, body weight, albumin, tumor burden, and ATA were covariates for clearance; body weight, and albumin were covariates for central volume of distribution, and gender was a covariate for both central volume of distribution and peripheral volume of distribution.

In terms of special populations, age (21-89 years), body weight, gender, albumin levels, tumor burden, region or race, mild or moderate renal impairment (estimated glomerular filtration rate 30 to 89 mL/min/1.73 m2), mild hepatic impairment (bilirubin ≤ ULN and AST > ULN or bilirubin < 1.0 to 1.5 × ULN and any AST), level of PD L1 expression, or ECOG status had no clinically significant effect on the systemic exposure of atezolizumab. The effect of severe renal impairment (eGFR 15 to 29 mL/min/1.73 m2) or moderate or severe hepatic impairment (bilirubin > ULN and AST > ULN or bilirubin ≥ 1.0 to 1.5 × ULN and any AST) on the pharmacokinetics of atezolizumab is unknown.

5. Clinical (efficacy and safety)/statistical (efficacy)

I agree with the conclusions of the clinical efficacy (Chana Weinstock, MD) clinical safety (Daniel Suzman, MD) and statistical (Lijun Zhang, PhD) reviewers.

The efficacy and safety of atezolizumab in the intended patient population was based on the following clinical trials (Appendix A)[2]:

- OAK.[3] Global, multicenter, open- label, randomized (atezolizumab vs docetaxel), controlled clinical trial in patients with metastatic or recurrent NSCLC who have failed one (2L) or two (3L) prior platinum-containing regimens. Patients were unselected for PD-L1. The primary endpoint was overall survival. Eligible patients were stratified by PD-L1 status (four categories of PD-L1 expression in ICs) [4], by the number of prior chemotherapy regimens (1 versus 2), and by histology (non-squamous versus squamous) and then randomized 1:1 to receive either atezolizumab or docetaxel.
- POPLAR. Global, multicenter, open-label, randomized, controlled clinical trial designed to evaluate the efficacy and safety of atezolizumab vs docetaxel in patients with metastatic NSCLC who have progressed during or following a platinum-containing regimen. The primary efficacy endpoint in POPLAR was OS. Key secondary endpoints included objective response rate (ORR) per RECIST v1.1 and duration of response (DOR).
- FIR (supportive). Global, multicenter, open- label, single-arm clinical trial in patients with metastatic NSCLC who were treatment-naïve (in metastatic setting; 1L) or progressed during or after one (2L) prior platinum- containing regimen. Patients were PD-L1 selected (TC2/3 or IC2/3).
- BIRCH (supportive). Global, multicenter, open- label, single-arm clinical trial in patients with metastatic NSCLC who were treatment-naïve (in metastatic setting; 1L), progressed during or after one (2L) or more (3L+) prior treatment. Patients were PD-L1 selected (TC2/3 or IC2/3).
- PCD4989g (supportive). Dose finding clinical trial in patients with metastatic solid tumors (including NSCLC) and hematologic malignancies. NSCLC cohort included PD-L1 selected and unselected patients across all lines of treatment.

OAK and POPLAR were the primary trials for evaluation of the efficacy of atezolizumab for this application. OAK included a total of 1225 patients with the primary analysis of efficacy conducted, as per pre-specified statistical plan, on the first 850 randomized patients. POPLAR included 287 patients. In both trials, eligible patients were stratified by PD L1 expression status in ICs, by the number of prior chemotherapy regimens, and by histology. Patients were

[2] In OAK, POPLAR, BIRCH, and FIR, atezolizumab was administered at 1200 mg IV q3w based on the results of first-in-human trial PCD4989g. In OAK and POPLAR, Docetaxel was administered at 75 mg/m2 q3w.
[3] The applicant submitted topline efficacy results from OAK to the BLA on August 29, 2016 as per prior discussion with FDA. Datasets supporting the results were submitted on September 16, 2016.
[4] IC = tumor-infiltrating immune cell; TC = tumor cell

randomized (1:1) to receive either atezolizumab administered intravenously at 1200 mg every 3 weeks until unacceptable toxicity or either radiographic or clinical progression or docetaxel administered intravenously at 75 mg/m2 every 3 weeks until unacceptable toxicity or disease progression.

Both OAK and POPLAR excluded patients with a history of autoimmune disease and active or corticosteroid-dependent brain metastases. Tumor assessments were conducted every 6 weeks for the first 36 weeks, and every 9 weeks thereafter. In OAK, tumor specimens were evaluated prospectively for PD L1 expression on TCs and ICs using the Ventana PD L1 (SP142) Assay. The criteria for PD-L1 immunohistochemical categorization in atezolizumab clinical trials is shown in

Table 1.

In the primary analysis population of OAK (n=[first] 850 patients), 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,[5] 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 POPLAR, 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.

In OAK, patients in the atezolizumab arm achieved a statistically significant and clinically meaningful prolongation in OS compared with those in the docetaxel arm. The stratified log-rank hazard ratio (HR) was 0.74 (95% CI: 0.63, 0.87; p-value = 0.0004) (Figure 1). The median OS (months) in patients treated with atezolizumab (n=425) was 13.8 (95% CI: 11.8, 15.7) and in those treated with docetaxel (n=425) was 9.6 (95% CI: 8.6, 11.2). In the primary analysis population of OAK (n=850), 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. The results of POPLAR were consistent with OAK with meaningful improvement in OS (supported by key secondary endpoints of ORR and DOR) in patients treated with atezolizumab compared with docetaxel (Table 2 and Figure 2). The supportive trials (BIRCH, FIR, PCD4989g) provided further supportive evidence of the activity and tolerability of atezolizumab in the intended patient population. The results were generally consistent with the efficacy and safety profile of atezolizumab observed in OAK and POPLAR.

The primary safety analyses were based on the results of POPLAR in patients who had received (n=142) or docetaxel (n=135) (Table 3 and Table 4). The median duration of exposure was 3.7 months (range: 0–19 months) in atezolizumab-treated patients and 2.1 months (range: 0–17 months) in docetaxel-treated patients. The most common adverse events (AEs) occurring in ≥ 20% of patients receiving atezolizumab were fatigue (46%), decreased appetite (35%), dyspnea (32%), cough (30%), nausea (22%), musculoskeletal pain (22%), and constipation (20%). The most common Grade 3-4 AEs occurring in ≥2% of patients receiving atezolizumab were dyspnea, pneumonia, hypoxia, hyponatremia, fatigue, anemia, musculoskeletal pain, AST

[5] In OAK and POPLAR, patient with ALK or EGFR mutations were enrolled following progression on or after appropriate TKI therapy.

increase, ALT increase, dysphagia, and arthralgia. Atezolizumab was discontinued due to AEs in 4% of patients. AEs leading to interruption of atezolizumab 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 AEs occurred in 37% of patients. The most frequent serious AEs (> 2%) were pneumonia, dyspnea, pleural effusion, pyrexia, and venous thromboembolism.

Less frequent, but clinically relevant AE's (including immune-related AEs) were evaluated in a larger safety population (n=1027 advanced NSCLC patients treated with atezolizumab). Pneumonitis occurred in 38 (3.7%) patients (1 fatal case). Pneumonitis resolved in 26 of the 38 patients with dose interruptions and medical management (corticosteroids). 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). Immune-mediated colitis or diarrhea resolved with corticosteroid administration in four of these patients and one patient died due to disease progression prior to resolution of colitis. Hyperthyroidism occurred in 1.1% of patients.

Data supporting the complementary diagnostic Ventana PD-L1 (SP142) assay was reviewed by FDA's Center for Devices and Radiological Health and is being approved concurrently as PD-L1 expression in ≥ 50% TC or ≥ 10% IC as detected by this assay appears to be associated with enhanced survival in patients with advanced NSCLC treated with atezolizumab.

6. Advisory committee meeting

There was no advisory committee meeting for this submission because the safety profile of atezolizumab is acceptable for the intended patient population and the application did not raise any significant public health questions. Outside expertise was not necessary since there were no controversial issues that could benefit from an advisory committee discussion.

7. Other Relevant Regulatory Issues

No issues identified in areas of Application Integrity Policy, Exclusivity or Patent, Financial Disclosures, or Good Clinical Practice. A waiver of pediatric studies was granted based on the low incidence of NSCLC in the pediatric population. DRISK and OHOP/DOP1 both agreed that a REMS is not necessary for atezolizumab. Clinical inspections were conducted and raised no significant issues. The inspections focused on the applicant's control, oversight, and management of POPLAR trial. FDA's Office of Scientific Investigations (OSI) conducted the following reviews: monitoring records were reviewed from 4 clinical sites. Actions taken by the applicant to bring non-compliant clinical sites into compliance were assessed. Contract agreements and sponsor responsibility transfer agreements were reviewed as appropriate. Reporting practices for AEs, serious AEs, and protocol deviations were reviewed. An additional ten sites were reviewed for their oversight of significant adverse event and fourteen sites for protocol deviations. OSI

identified no major issues. The applicant maintained adequate oversight over the study. There was no evidence of under-reporting of AEs/SAEs.

The following post market requirement (PMR) post market commitment (PMC) were put into place for this application and agreement was reached with the applicant:

PMR

- Conduct a randomized trial that will characterize the incidence, severity and response to treatment of Tecentriq™ induced immune-mediated adverse reactions to include immune-mediated pneumonitis.

PMC

- Submit the final report and datasets for clinical trial entitled "A Phase III, Multicenter, Randomized Study of Atezolizumab Compared with Docetaxel in Patients with Non-Small Cell Lung Cancer after Failure with Platinum-Containing Chemotherapy" [OAK (GO28915)].

8. Labeling

Labeling agreements were appropriately reached between FDA and the applicant with no significant concerns or issues throughout the review and negotiation process. Below is a brief summary of FDA's clinical labeling changes to the original submission:

a) Section 5

Pneumonitis
- Added two pneumonitis cases from POPLAR considered hypoxia or dyspnea by the Applicant
- Provided additional details on management and outcome of all cases

Hepatitis
- Added one case of severe autoimmune hepatitis from PCD4989g
- Provided additional details on management and outcome of all cases

Infection
- Pooled cases of pneumonia and respiratory infection

b) Section 14:
- FDA included OS data from OAK with associated p-values, in addition to key efficacy results (OS, ORR, and DOR) from POPLAR.

- FDA excluded a proposed (b) (4) in favor of a summary narrative text describing the impact of PD-L1 expression levels on OS.

9. Recommendation/benefit-risk summary

Recommended Regulatory Action: ***traditional approval***

Benefit-risk summary

Despite recent advances in the treatment of patients with metastatic NSCLC, options for second- and further-line treatment are limited, especially in patients without targetable somatic tumor mutations or those who have disease progression following targeted tyrosine kinase inhibitor therapy. In two randomized clinical trials (OAK and POPLAR)[6] enrolling a total of 1137 patients, atezolizumab was associated with a favorable benefit-risk profile with superior efficacy demonstrated by statistically-significant and clinically-meaningful improvements in OS, as compared with standard docetaxel, in patients with metastatic NSCLC who have disease progression during or following platinum-containing chemotherapy. Treatment with atezolizumab in the intended patient population in OAK and POPLAR resulted in a 4.2 month and a 2.9 month improvement OS, respectively. The efficacy and safety of atezolizumab in the intended patient population was further supported by three other trials (BIRCH, FIR, and the first-in-human trial PCD4989g). PD-L1 expression in ≥ 50% TC or ≥ 10% IC as detected by the concurrently-approved complementary diagnostic Ventana PD-L1 (SP142) Assay appears to be associated with enhanced survival in patients with advanced NSCLC treated with atezolizumab. Atezolizumab was generally well-tolerated, with immune-related AEs that included pneumonitis, hepatitis, colitis, and endocrine disorders. These AEs appeared to be manageable with appropriate medical management and/or dose interruptions.

[6] Adequate and well-controlled as defined by 21CFR314.126(b)

Table 1. Criteria for PD-L1 expression assessments in atezolizumab clinical trials

Description of IHC Scoring Criteria	PD-L1 Expression Level
Absence of any discernible PD-L1 staining OR presence of discernible PD-L1 staining of any intensity in tumor-infiltrating immune cells 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 tumor-filtrating immune cells 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 tumor-infiltrating immune cells 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 tumor-infiltrating immune cells 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%** tumor cells	TC0
Presence of discernible PD-L1 staining of any intensity in ≥ **1% and** < **5%** tumor cells	TC1
Presence of discernible PD-L1 staining of any intensity in ≥ **5% and** < **50%** tumor cells	TC2
Presence of discernible PD-L1 staining of any intensity in ≥ **50%** tumor cells	TC3

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

Figure 1. Kaplan-Meier plot of overall survival in OAK

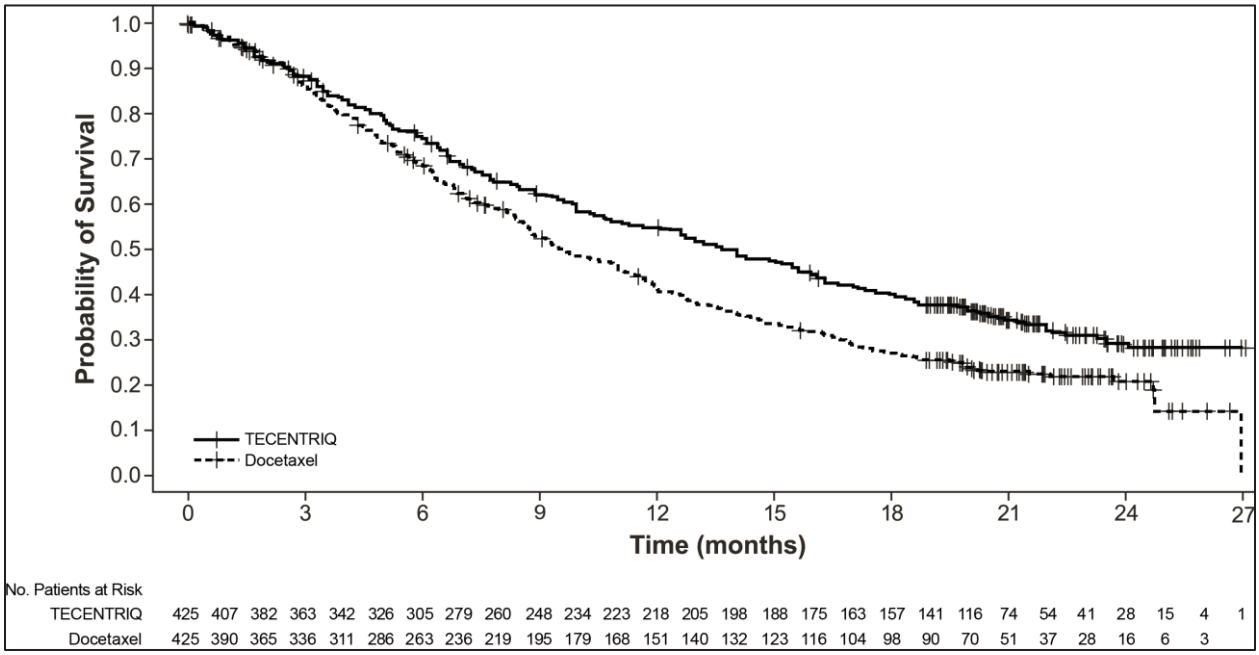

Table 2. Efficacy results in POPLAR for primary analyses of OS and key secondary endpoint of ORR and DOR

	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 OS in POPLAR

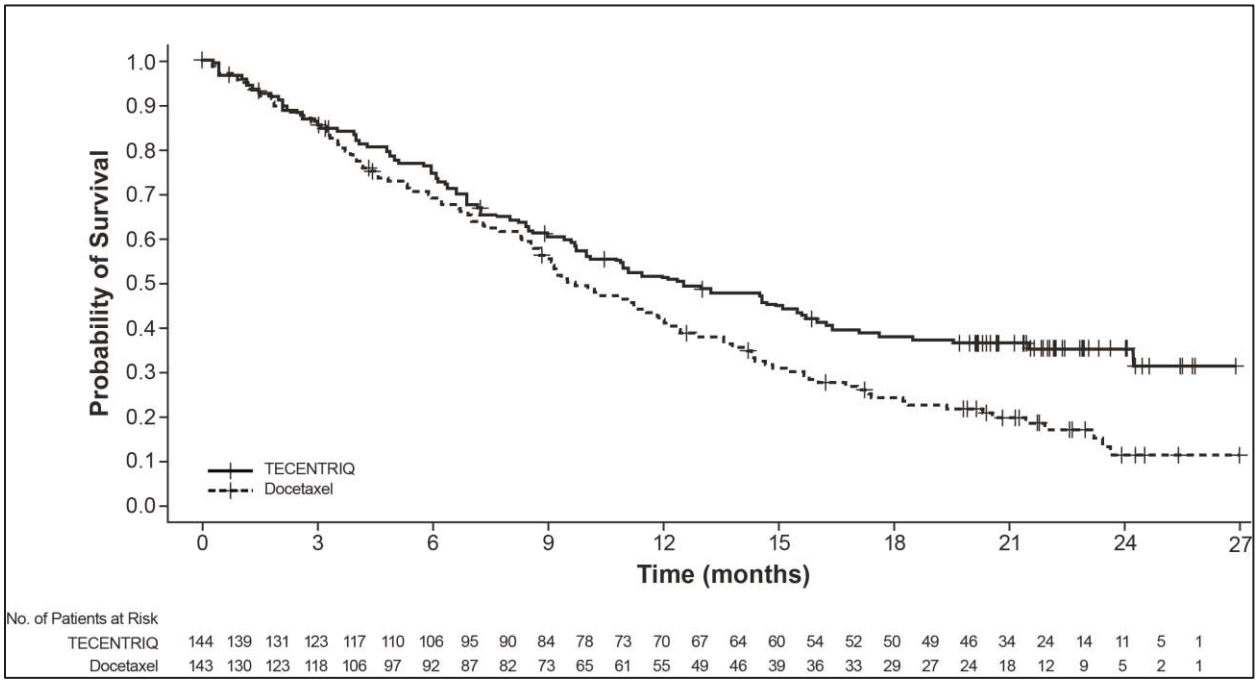

Table 3. Adverse events occurring in ≥10% of atezolizumab-treated patients in POPLAR with higher incidence than in the docetaxel arm (between arm difference of ≥5% [All Grades] or ≥2% [Grades 3–4])

	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
Musculoskeletal 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 atezolizumab-treated in POPLAR at a higher incidence than in the docetaxel Arm (between arm difference of ≥5% [All Grades] or ≥2% [Grades 3–4])

	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

Appendix A: List of clinical trials in support of the indication for BLA 761041

	Study Design	**Study Population**	**Dosing Schedule**	**Primary endpoint**	**No. of Patients Enrolled**
POPLAR (GO28753)	Global, multicenter, open-label, randomized, controlled	Patients with locally advanced, metastatic, or recurrent NSCLC who have failed one (2L) or two (3L) prior platinum-containing regimens. Patients were unselected for PD-L1.	Atezolizumab 1200 mg IV q3w vs. Docetaxel 75 mg/m^2 q3w	OS	Total n=287 Atezolizumab = 142 vs Docetaxel=135
BIRCH (GO28754)	Global, multicenter, single arm	Patients with locally advanced or metastatic NSCLC who were treatment-naïve (in metastatic setting; 1L), progressed during or after one (2L) or more (3L+) prior treatment. Patients were PD-L1 selected (TC2/3 or IC2/3).	Atezolizumab 1200 mg IV q3w	ORR assessed by independent review facility (IRF) per RECIST v1.1	Total n=667 Cohort 1; 1L=139 Cohort 2; 2L=267 Cohort 3; 3L+=253
FIR (GO28625)	Global, multicenter, single- arm	Patients with locally advanced or metastatic NSCLC who were treatment-naïve (in metastatic setting; 1L) or progressed during or after one (2L) prior platinum- containing regimen. Patients were PD-L1 selected (TC2/3 or IC2/3).	Atezolizumab 1200 mg IV q3w	Investigator-assessed ORR per RECIST 1.1	Total n=138 Cohort 1; 1L = 31 Cohort 2; 2L+= 94 Cohort 3; 2L+ = 13
PCD4989g	Multicenter, first-in- human, open-label, dose escalation, expansion	Patients with locally advanced or metastatic solid tumors (including NSCLC) and hematologic malignancies. NSCLC cohort included PD-L1 selected and unselected patients across all lines of treatment.	Weight-based dose escalation (0.01 to 20 mg/kg) and fixed 1200 mg dose, administered IV q3w for up to 1 year or loss of clinical benefit. .	Investigator-assessed ORR per RECIST v1.1	Total n=481 N=88 NSCLC cohort 1L (n = 15) 2L (n = 23) 3L+ (n = 50)
OAK (GO28915)	Global, multicenter, open-label, randomized, controlled	Patients with locally advanced, metastatic, or recurrent NSCLC who have failed one (2L) or two (3L) prior platinum-containing regimens. Patients were unselected for PD-L1.	Atezolizumab 1200 mg IV q3w vs. Docetaxel 75 mg/m^2 q3w	OS	Total n = 1225

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/s/

SEAN N KHOZIN
10/12/2016