CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761034Orig1s000

SUMMARY REVIEW

Division Director Summary Review

Date	5/17/2016
From	Geoffrey Kim
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	761034
Applicant	Genentech, Inc.
Date of Submission	January 12, 2016
PDUFA Goal Date	September 12, 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 humanized programmed death-ligand 1 (PD-L1) blocking antibody indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma* (b) (4) [redacted]
Action/Recommended Action for NME:	Accelerated 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 locally advanced or metastatic urothelial carcinoma who: • Have disease progression during or following platinum containing chemotherapy

	• Have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy

Material Reviewed/Consulted	**Names of discipline reviewers/Team Leaders**
Regulatory Project Manager	Kim Robertson
Medical Officer Reviewer	Yang-Min (Max) Ning (efficacy); Daniel Suzman (safety)/ V. Ellen Maher (CDTL)
Statistical Review	Lijun Zhang/ Shenghui Tang
Pharmacology Toxicology Review	Tiffany Ricks/ Todd Palmby
CMC Review	Xianghong Jing/ Joel Welch – Drug Substance and Drug Product (see integrated Quality review for complete Quality Review Team)
Clinical Pharmacology Review	Wentao Fu/ Qi Liu
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. Based on the results of Study GO29293, a favorable benefit-risk profile has been demonstrated for patients with advanced or metastatic urothelial bladder cancer who have received prior platinum-based therapy. Although the point estimate for the response rate may be lower than what is reported in single-arm studies involving chemotherapy or combination chemotherapy regimens in this disease setting, the durability of the responses observed with atezolizumab appears to be better than available (off-label) therapy. It is important to note that at the time of this recommendation, the data regarding the durability of response is not yet mature as there continues to be patients on Study GO29293 with ongoing responses to atezolizumab, with some responses lasting for more than a year. I recommend accelerated approval under the provisions of 21CFR 601 Subpart E. The observed response rate and response duration are reasonably likely to predict clinical benefit and the benefits of atezolizumab in this patient population outweigh its risks. The durable responses were observed in patients regardless of PD-L1 IC scores. Therefore, I agree with the recommendation that the information regarding the Ventana PD-L1 (SP142) Assay be included in the atezolizumab package insert as complementary information that can inform prescribers of these results. As summarized by the clinical and statistical team:

*"*Atezolizumab, a programmed death-ligand 1 (PD-L1) blocking antibody, is recommended for approval as a second-line therapy for locally advanced or metastatic urothelial carcinoma that has progressed during or after platinum-containing chemotherapy.

In the USA, there is no FDA approved second-line therapy for this indication. Standard of care for patients with advanced urothelial carcinoma is platinum-containing chemotherapy. However, almost all patients experience disease progression during or after platinum-containing chemotherapy. There is no effective or standard second-line therapy. Patients with progressive disease may have a limited survival time of 5-10 months. Off-label use of a few chemotherapeutics in this disease setting is associated with low response rates and short response durations along with considerable toxicities.

The effectiveness of atezolizumab is demonstrated in 310 patients with locally advanced or metastatic urothelial carcinoma who had disease progression after prior platinum-containing chemotherapy. Atezolizumab was administered intravenously at a dose of 1200 mg every 3 weeks. Confirmed ORR, as assessed by IRF per RECIST v1.1, was 14.8% (95% CI: 11.1%, 19.3%). At the data cutoff time for the ORR analysis, median

DOR in responders was not reached (range: 2.1+ to 13.8+ months). Of the 46 responders, 37 patients had ongoing responses of ≥6 months and 6 had ongoing responses of ≥12 months. ORR was also analyzed as pre-specified by PD-L1 expression status in tumor-infiltrating immune cells,

which was prospectively assayed in tumor specimens at a central laboratory. The confirmed ORR was 9.5% (95% CI: 5.9%, 14.3%) in 210 patients with a PD-L1 IC score of 0/1 and 26.0% (95% CI: 17.7%, 35.7%) in 100 patients with a PD-L1 IC score of 2/3. Response durations in the
PD-L1 subgroups were similar to those in the 310 patients.
Supportive evidence was available from additional 94 patients who were enrolled in another study cohort in a similar disease setting. The results of this small cohort are consistent with the findings from the 310 patients.
The most common adverse reactions of atezolizumab in at least 20% of patients were fatigue, decreased appetite, nausea, urinary tract infection, pyrexia, and constipation. Grade 3-4 adverse events were seen in 50% of patients. Infection and immune-related adverse events such as pneumonitis, hepatitis, colitis, thyroid disease, adrenal insufficiency, and diabetes were also seen with atezolizumab.
Overall, the atezolizumab-induced objective and durable responses are clinically meaningful to patients with the study disease. This represents an important, new, and non-chemotherapeutic option that will address an unmet medical need in this patient population. The benefit-risk profile for the approved indication is favorable. A randomized trial to verify and/or establish the benefit-risk profile of atezolizumab is ongoing."

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	• Progressive advanced urothelial carcinoma following platinum-based first line therapy has a poor prognosis, with a median survival of 6-10 months. • Approximately 15,000 deaths from advanced Urothelial carcinoma each year.	This disease is serious and life-threatening. There is a significant unmet medical need for patients with the disease.
Current Treatment Options	• There are no approved products in the USA for second-line therapy for the disease. • Off-label use of a taxane (docetaxel, paclitaxel, nabpaclitaxel), or combination of paclitaxel with gemcitabine; vinflunine is available outside the USA	All the products are palliative and have significant adverse reactions and/or intolerance. Patients generally have low response rates and short response durations. Vinflunine is associated with a survival trend compared to best supportive care.
Benefit	• Of the unenriched population of 310 patients, 14.8% had confirmed responses. The ORR was 26% in the PD-L1 IC 2/3 group and 9.5% in the PD-L1 IC 0/1 group. • Median response duration was not reached (range 2.1+, 13.8+ months). Of	Substantial evidence of effectiveness for second-line use of atezolizumab monotherapy in advanced Urothelial carcinoma, as supported by similar ORRs and durable

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	the responders, 80% (37/46) had ongoing responses of ≥6 months and 13% (6/46) had ongoing responses of ≥12 months. • In a PD-L1 enriched population of 94 patients, 25.5% of patients had confirmed responses. Median response duration was not reached (range 2.9, 26.3+ months), with responses of ≥6 months in 92% (22/24) of responders and of ≥12 months in 58% (14/24) of responders.	responses, was found from the two single-arm studies. The results are consistent between the two studies. Patients positive for PD-L1 expression in their ICs appear to have a higher response rate relative to patients negative for PD-L1 expression. Durable responses are observed in both PD-L1 positive (IC2/3) and negative (IC0/1) responders.
Risk	• Tolerated in most study patients • Important risks include hepatitis, pneumonitis, endocrine disorders, colitis, infection, and neurological disorders	The profile of adverse reactions associated with atezolizumab is similar to that observed in other PD-1 targeted products.
Risk Management	• Non-endocrine immune-mediated adverse events were largely reversible with the use of corticosteroids. • A medication guide for atezolizumab describing the risks of immune-mediated adverse events will be required to better allow early recognition and initiation of treatment of these events. (*Division Director Clarification: the medication guide will be distributed but is not required by FDA)* • To better estimate the incidence of hypothyroidism, the Applicant will fulfill a PMR for more frequent routine TSH evaluation during therapy in one planned trial.	The safe use of atezolizumab can be managed through accurate labeling and routine pharmacovigilance. No REMS is indicated.

2. Background

Summary of Presubmission/Submission Regulatory Activity

April 2011	*IND 111271 submitted to the Division of Oncology Products 2*
January 2014	*IND 120827 administratively split to the Division of Oncology Products 1 for the studies of MPDL3280A in urothelial carcinoma*
May 2014	*Breakthrough Designation granted based on preliminary evidence from 20 patients with locally advanced or metastatic UBC with a PD-L1 IHC score of 2 or 3 in their tumor specimens (as determined by the prototype PD-L1 assay). Confirmed objective response (per RECIST v1.1) rate was 50%. The median response duration was not reached (observed range: 2.9-7.5 months) at the data cutoff.*
June-Dec. 2014	*Post Breakthrough Therapy designation meetings were held to discuss the development plans and regulatory approval pathways. The single-arm study GO 29293 was proposed to support potential accelerated approval. Designs of randomized trials were discussed as well.*
May-Sep. 2015	*Pre-BLA submission meetings held and agreements were reached on the contents, format, and analyses for a BLA submission based on results from Cohort 2 of Study GO 29293 and supportive evidence from the Phase 1 UBC Cohort*
Oct.2015-Feb. 2016	*Rolling submission of the BLA initiated, with the clinical datasets and study reports submitted on January 12, 2016.*

Intended Population
From the clinical and statistical review:
Pathophysiology of Condition
"Urothelial carcinoma is the most common malignancy in the urinary tract system and accounts for approximately 16,000 deaths yearly in the USA2,3. Although most urothelial carcinomas are non-muscle invasive at diagnosis and can be managed effectively with surgical resection and/or intravesical therapies, approximately 10-15% of patients may develop invasive, locally advanced and metastatic urothelial carcinoma4. In addition, approximately 10% of patients have regionally advanced or metastatic disease at diagnosis.
Standard of care for patients with advanced disease is platinum-containing chemotherapy, such as gemcitabine and cisplatin (GC) or methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC). However, almost all patients experience disease progression or intolerance to treatment during or after platinum-containing chemotherapy. There is no efficacious or standard second-line therapy after disease progression (See Section 2.2). The reported median survival of patients after platinum-containing therapy ranges from 5 to 10 months (Table 2). Clearly, there is an unmet need for patients with this serious and life-threatening disease."

Existing (or Available) Therapies

"Outside the USA, vinflunine is approved as a second-line treatment. Table 2 summarizes key efficacy and safety information about vinflunine and other second-line chemotherapies studied or used off-label in such patients after platinum-containing chemotherapy. As shown in the table, these chemotherapeutics, either used alone or in combination, are associated with a low response rate but considerable toxicities. Except for vinflunine, response durations remain unknown or unreported. Nab-paclitaxel monotherapy was associated with a response rate of 28% and a longer survival time relatively to other agents. However, the results may not be reliably interpreted given the small sample size of a single-arm study. In addition, the heterogeneity of study patient populations is an issue among these studies, which may contribute to the varying response rates and survival times."

Table 2: Activity and Safety of Second-Line Chemotherapeutics Studied in Advanced Urothelial Carcinoma

	Vinflunine[a] +BSC	Gemcitabine + Paclitaxel[b]	Docetaxel[c]	Nab-paclitaxel[d]
Objective Response (#Evaluable Patients)	N = 185	N = 40	N = 70	N = 47
Overall Response Rate	16 (9%)	15 (38%)	5 (11%)	13 (28%)
Response Duration (mos), median	7.4	NR	NR	NR
Overall Survival*, median	6.9 months (*vs* 4.6 mos with BSC, HR 0.88 p=0.287)	7.8 months	7.0 months	10.8 months
Key Safety Issues (Grade 3 or 4 Toxicity) (%)**	Neutropenia (50%); Febrile neutropenia (6%); Anemia (19%); Fatigue (19%); Constipation (16%)	Anemia (7%)	Neutropenia (14%); Anemia (1%); Fatigue (6%); Infection (6%) Electrolyte abnormalities (6%)	Fatigue (10%); Weakness (8); Neuropathy (6%) Dyspnea (6%) Hypertension (6%)

3. Product Quality

I agree with the recommendation of approval from the CMC perspective provided in the Integrated Quality Review as follows: "The Office of Pharmaceutical Quality recommends approval of BLA 761034 for Tecentriq (atezolizumab) manufactured by Genentech, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of Tecentriq (atezolizumab) is well controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

A. Recommendation and Conclusion on Approvability

The DS and DP manufacturing process is well controlled and should consistently deliver DS and DP of desired quality. A PMR is recommended as the the current method for detecting neutralizing antidrug antibodies (ADA) is not tolerant to the presence of drug at the levels expected to be in some patents' serum at the time of sampling, leading to a reduced capability of detecting ADA. The development of a more sensitive and drug tolerant assay for the detection of neutralizing antibodies to atezolizumab would provide a more accurate measure and characterization of the patients'immune response to atezolizumab.
PMCs are recommended to perform additional characterization to assure the (b) (4) of the MCB for atezolizumab. This data will aid in evaluation of proposed (b) (4) for drug substance.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Below are the draft PMC/PMRs to be proposed to the sponsor should approvability be the recommendation.

1). Develop and validate an assay with improved sensitivity for the detection of neutralizing antibodies against atezolizumab in the presence of atezolizumab levels that are expected to be present in samples at the time of patient sampling.

2). Perform supplemental characterization of the MCB to provide additional assurance of (b) (4) the cell bank. This data should include evaluation of (b) (4) with respect to growth characteristics and product quality."

4. Nonclinical Pharmacology/Toxicology

I agree with the nonclinical pharmacology/toxicology reviewer, Tiffany Ricks Ph.D., and the team leader, Todd Palmby, Ph.D., who recommend approval for the proposed indication. From the primary pharmacology/toxicology review: "The submitted nonclinical pharmacology and toxicology studies support approval of Tecentriq for the proposed indication. The Applicant provided data demonstrating that atezolizumab binds to PD-L1 and blocks its interaction with PD-1 and B7-1 receptors. Consequently, atezolizumab relieves inhibition of immune responses, including antitumor activity and peripheral tolerance. Atezolizumab had no effects on cardiovascular, respiratory, or neurological systems in monkeys. Toxicological effects of atezolizumab administration in animals were limited to irregular menstruation in female monkeys and immune-mediated effects, including tissue damage and multi-organ inflammation. Other effects of PD-L1 blockade observed in animals, which may be relevant to patients receiving atezolizumab, consisted of enhanced inflammatory response and severity of infections and a risk of embryo-fetal toxicity, primarily an increased risk of immune-mediated abortion."

In addition, "The Pharmacology/Toxicology team recommends that the Applicant conduct a pharmacology study to further characterize the effect of atezolizumab on the immune response as a Post-Marketing Commitment (PMC). We recommend that the Applicant conduct an animal study that will measure the effect of PD-L1 inhibition on the magnitude of the primary (1st vaccination) and recall (2nd vaccination) antibody responses to antigen challenge (e.g. KLH)."

5. Clinical Pharmacology

I agree with the clinical pharmacology team, who state that BLA761034 is acceptable from a clinical pharmacology perspective.

"***Dose Selection:*** The proposed dosing regimen of atezolizumab (1200 mg every 3 weeks) is the same as the regimen used in the Phase 2 trial IMvigor 210. This dosing regimen is acceptable based on atezolizumab safety and efficacy data. In addition, the selected dosing regimen can reach a projected target steady-state Cmin (6 μg/mL) based on nonclinical tissue distribution data in tumor-bearing mice and receptor occupancy in the tumor.
Pharmacokinetics: Atezolizumab demonstrated linear pharmacokinetics (PK) at a dose range of 1-20 mg/kg. Based on data from 472 patients who received 1-20 mg/kg of atezolizumab every 3 weeks, the population PK mean estimates were as follows:
• Clearance, 0.20 L/day
• Volume of distribution at steady-state, 6.9 L
• Half-life, 27 days
• Time to reach steady state concentrations, 6 to 9 weeks (2 to 3 cycles) after 1200 mg every 3 weeks and the systemic accumulation of area under the curve (AUC), approximately 1.9-fold
Population Pharmacokinetic Analysis: Population PK analyses (n=472) showed that the following factors have no clinically important effect on the PK parameters of atezolizumab administrated at 1200 mg every 3 weeks: gender, body weight, tumor burden, serum albumin level, anti-therapeutic antibody (ATA) status, mild and moderate renal impairment, and mild hepatic impairment. Therefore, no dose adjustments based on above covariates are needed.
Exposure/Dose-Response Relationship for Efficacy and Safety at 1200 mg q3w: Steady-state exposure (AUC,ss) of atezolizumab was not a significant predictor of either probability of ORR or probability of Adverse Events (AE) in patients.
Immunogenicity: The percentages of evaluable patients tested positive ATA were 41.9% (161/384), 31.7% (139/439) and 16.7% (1/6) in Phase 2 pivotal study IMvigor 210, Phase 1 supportive study PCD4989g, and Phase 1 supportive study JO28944, respectively. The presence of ATAs did not appear to have a clinically significant impact on pharmacokinetics, safety or efficacy.
Drug-Drug interaction (DDI) potential*:* No DDI studies have been conducted.
QT prolongation: IRT-QTc review team concluded that there is no evidence from nonclinical or clinical data to suggest that atezolizumab has the potential to delay ventricular repolarization."

6. Clinical Microbiology

NA

7. Clinical/Statistical-Efficacy

This application is primarily supported by a single-arm, multicenter, open-label, two-cohort study (GO29293) of atezolizumab in patients with locally advanced or metastatic urothelial carcinoma. 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 GO29293:

TECENTRIQ was investigated in Study 1, a multicenter, open-label, two-cohort trial that included patients with locally advanced or metastatic urothelial carcinoma. In Cohort 2 of Study 1, 310 patients with locally advanced or metastatic urothelial carcinoma who had disease progression during or following a platinum-containing chemotherapy regimen or who had disease progression within 12 months of treatment with a platinum-containing neoadjuvant or adjuvant chemotherapy regimen were treated with TECENTRIQ. This study excluded patients who had: a history of autoimmune disease, active or corticosteroid-dependent brain metastases, administration of a live, attenuated vaccine within 28 days prior to enrollment, or administration of systemic immunostimulatory agents or systemic immunosuppressive medications. Patients received an intravenous infusion of 1200 mg of TECENTRIQ every 3 weeks until unacceptable toxicity or either radiographic or clinical progression. Tumor response assessments were conducted every 9 weeks for the first 54 weeks and every 12 weeks thereafter. Major efficacy outcome measures included confirmed objective response rate (ORR) as assessed by independent review facility (IRF) using Response Evaluation Criteria in Solid Tumors (RECIST v1.1) and duration of response (DoR).

In this cohort, the median age was 66 years, 78% were male, 91% patients were Caucasian. Twenty-six percent had non-bladder urothelial carcinoma and 78% of patients had visceral metastases. Sixty-two percent of patients had an ECOG score of 1 and 35% of patients had a baseline creatinine clearance of < 60 mL/min. Nineteen percent of patients had disease progression following prior platinum-containing neoadjuvant or adjuvant chemotherapy. Forty-one percent of patients had received ≥ 2 prior systemic regimens in the metastatic setting. Seventy-three percent of patients received prior cisplatin, 26% had prior carboplatin, and 1% were treated with other platinum-based regimens.

Tumor specimens were evaluated prospectively using the Ventana PD-L1 (SP142) Assay at a central laboratory, and the results were used to define subgroups for pre-specified analyses. Of the 310 patients, 32% were classified as having PD-L1 expression of ≥ 5% (defined as PD-L1 stained tumor-infiltrating immune cells [ICs] covering ≥ 5% of the tumor area). The remaining, 68% of patients, were classified as having PD-L1 expression of <5% (PD-L1 stained tumor-infiltrating ICs covering < 5% of the tumor area).

Confirmed ORR in all patients and the two PD-L1 subgroups are summarized in Table 3. The median follow-up time for this cohort was 14.4 months. In 59 patients with disease progression following neoadjuvant or adjuvant therapy, the ORR was 22.0% (95% CI: 12.3%, 34.7%).

Table 3: Summary of Efficacy from Cohort 2 of Study 1

	All Patients	PD-L1 Expression Subgroups	
	N=310	**PD-L1 Expression of < 5% in ICs[1] (N=210)**	**PD-L1 Expression of ≥ 5% in ICs[1] (N=100)**
Number of IRF-assessed Confirmed Responders	46	20	26
ORR % (95% CI)	**14.8% (11.1, 19.3)**	**9.5% (5.9, 14.3)**	**26.0% (17.7, 35.7)**
Complete Response (CR) (%)	5.5%	2.4%	12.0%
Partial Response (PR) (%)	9.4%	7.1%	14.0%
Median DoR, months (range)	NR (2.1+, 13.8+)	12.7 (2.1+, 12.7)	NR (4.2, 13.8+)
NR = Not reached + Denotes a censored value [1] PD-L1 expression in tumor-infiltrating immune cells (ICs)			

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 data described in Table 1 reflects exposure to TECENTRIQ in Cohort 2 of Study 1. This cohort enrolled 310 patients in a single arm trial with locally advanced or metastatic urothelial carcinoma who had disease progression during or following at least one platinum-containing chemotherapy regimen or who had disease progression within 12 months of treatment with a platinum-containing neoadjuvant or adjuvant chemotherapy regimen *[see Clinical Studies (14.1)]*. Patients received 1200 mg of TECENTRIQ intravenously every 3 weeks until unacceptable toxicity or either radiographic or clinical progression. The median duration of exposure was 12.3 weeks (range: 0.1, 46 weeks).
>
> The most common adverse reactions (≥ 20%) were fatigue (52%), decreased appetite (26%), nausea (25%), urinary tract infection (22%), pyrexia (21%), and constipation (21%). The most common Grade 3–4 adverse reactions (≥ 2%) were urinary tract infection, anemia, fatigue, dehydration, intestinal obstruction, urinary obstruction, hematuria, dyspnea, acute kidney injury, abdominal pain, venous thromboembolism, sepsis, and pneumonia.

Three patients (0.9%) who were treated with TECENTRIQ experienced either sepsis, pneumonitis, or intestinal obstruction which led to death. TECENTRIQ was discontinued for adverse reactions in 3.2% (10/310) of the 310 patients. Sepsis led to discontinuation in 0.6% (2/310) of patients. Adverse reactions leading to interruption of TECENTRIQ occurred in 27% of patients; the most common (> 1%) were liver enzyme increase, urinary tract infection, diarrhea, fatigue, confusional state, urinary obstruction, pyrexia, dyspnea, venous thromboembolism, and pneumonitis. Serious adverse reactions occurred in 45% of patients. The most frequent serious adverse reactions (> 2%) were urinary tract infection, hematuria, acute kidney injury, intestinal obstruction, pyrexia, venous thromboembolism, urinary obstruction, pneumonia, dyspnea, abdominal pain, sepsis, and confusional state.

Table 1 summarizes the adverse reactions that occurred in ≥ 10% of patients while Table 2 summarizes Grade 3–4 selected laboratory abnormalities that occurred in ≥ 1% of patients treated with TECENTRIQ in Cohort 2 of Study 1.

Table 1: All Grade Adverse Reactions in ≥ 10% of Patients with Urothelial Carcinoma in Study 1

	TECENTRIQ N = 310	
Adverse Reaction	All Grades (%)	Grades 3 – 4 (%)
All Adverse Reactions	96	50
Gastrointestinal Disorders		
Nausea	25	2
Constipation	21	0.3
Diarrhea	18	1
Abdominal pain	17	4
Vomiting	17	1
General Disorders and Administration		
Fatigue	52	6
Pyrexia	21	1
Peripheral edema	18	1
Infections and Infestations		
Urinary tract infection	22	9
Metabolism and Nutrition Disorders		
Decreased appetite	26	1
Musculoskeletal and Connective Tissue Disorders		
Back/Neck pain	15	2
Arthralgia	14	1
Renal and urinary disorders		
Hematuria	14	3
Respiratory, Thoracic, and Mediastinal Disorders		
Dyspnea	16	4
Cough	14	0.3
Skin and Subcutaneous Tissue Disorders		

Rash	15	0.3
Pruritus	13	0.3

Table 2: Grade 3–4 Laboratory Abnormalities in Patients with Urothelial Carcinoma in Study 1 in ≥ 1% of Patients

Laboratory Test	Grades 3–4 (%)
Lymphopenia	10
Hyponatremia	10
Anemia	8
Hyperglycemia	5
Increased Alkaline phosphatase	4
Increased Creatinine	3
Increased ALT	2
Increased AST	2
Hypoalbuminemia	1

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

5.1 Immune-Related Pneumonitis

Immune-mediated pneumonitis or interstitial lung disease, defined as requiring use of corticosteroids and with no clear alternate etiology, occurred in patients receiving TECENTRIQ. Across clinical trials, 2.6% (51/1978) of patients developed pneumonitis. Fatal pneumonitis occurred in two patients. In 523 patients with urothelial carcinoma who received TECENTRIQ, pneumonitis occurred in 6 (1.1%) patients. Of these patients, there was one patient with fatal pneumonitis, one patient with Grade 3, three patients with Grade 2, and one patient with Grade 1 pneumonitis. TECENTRIQ was held in all cases and five patients were treated with corticosteroids. Pneumonitis resolved in three patients. The median time to onset was 2.6 months (range: 15 days to 4.2 months). The median duration was 15 days (range: 6 days to 3.1+ months).

Monitor patients for signs with radiographic imaging and symptoms of pneumonitis. Administer steroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for Grade 2 or greater pneumonitis, followed by corticosteroid taper. Withhold TECENTRIQ until resolution for Grade 2 pneumonitis. Permanently discontinue TECENTRIQ for Grade 3 or 4 pneumonitis *[see Dosage and Administration (2.2)]*.

5.2 Immune-Related Hepatitis

Immune-mediated hepatitis, defined as requiring use of corticosteroids and with no clear alternate etiology, occurred in patients receiving TECENTRIQ. Liver test abnormalities occurred in patients who received TECENTRIQ. Across clinical trials (n=1978), Grade 3 or 4 elevation occurred in ALT (2.5%), AST (2.3%), and total

bilirubin (1.6%). In patients with urothelial carcinoma (n=523) Grade 3 or 4 elevation occurred in ALT (2.5%), AST (2.5%), and total bilirubin (2.1%). Immune-mediated hepatitis occurred in 1.3% of patients. Of these cases, one patient died from hepatitis, five patients had Grade 3, and one patient had Grade 2 hepatitis. The median time to onset was 1.1 months (range: 0.4 to 7.7 months). Of the seven patients with immune-mediated hepatitis, TECENTRIQ was temporarily interrupted in four patients; none of these patients developed recurrence of hepatitis after resuming TECENTRIQ.
Monitor patients for signs and symptoms of hepatitis. Monitor AST, ALT, and bilirubin prior to and periodically during treatment with TECENTRIQ. Administer corticosteroids at a dose of 1-2 mg/kg/day prednisone equivalents for Grade 2 or greater transaminase elevations, with or without concomitant elevation in total bilirubin, followed by corticosteroid taper. Withhold TECENTRIQ for Grade 2 and permanently discontinue TECENTRIQ for Grade 3 or 4 immune-mediated hepatitis *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)]*.

5.3 Immune-Related Colitis

Immune-mediated colitis or diarrhea, defined as requiring use of corticosteroids and with no clear alternate etiology, occurred in patients receiving TECENTRIQ. Across clinical trials, colitis or diarrhea occurred in 19.7% (389/1978) of all patients and in 18.7% (98/523) of patients with urothelial carcinoma. Ten patients (1.9%) developed Grade 3 or 4 diarrhea. Four patients (0.8%) had immune-mediated colitis or diarrhea with a median time to onset of 1.7 months (range: 1.1 to 3.1 months). Immune-mediated colitis resolved with corticosteroid administration in three of these patients, while the other patient died without resolution of colitis in the setting of diarrhea-associated renal failure.
Monitor patients for signs and symptoms of diarrhea or colitis. Withhold treatment with TECENTRIQ for Grade 2 diarrhea or colitis. If symptoms persist for longer than 5 days or recur, administer 1–2 mg/kg prednisone or equivalent per day. Withhold treatment with TECENTRIQ for Grade 3 diarrhea or colitis. Treat with IV methylprednisolone 1–2 mg/kg per day and convert to oral steroids once the patient has improved. For both Grade 2 and Grade 3 diarrhea or colitis, when symptoms improve to Grade 0 or Grade 1, taper steroids over ≥ 1 month. Resume treatment with TECENTRIQ if the event improves to Grade 0 or 1 within 12 weeks and corticosteroids have been reduced to the equivalent of ≤ 10 mg oral prednisone per day. Permanently discontinue TECENTRIQ for Grade 4 diarrhea or colitis *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)]*.

5.4 Immune-Related Endocrinopathies

Immune-related thyroid disorders, adrenal insufficiency, hypophysitis, and type 1 diabetes mellitus, including diabetic ketoacidosis, have occurred in patients receiving TECENTRIQ. Monitor patients for clinical signs and symptoms of endocrinopathies.

Hypophysitis

Hypophysitis occurred in 0.2% (1/523) of patients with urothelial cancer receiving TECENTRIQ. Monitor for signs and symptoms of hypophysitis. Administer corticosteroids and hormone replacement as clinically indicated. Withhold TECENTRIQ for Grade 2 or Grade 3 and permanently discontinue for Grade 4 hypophysitis *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)]*.

Thyroid Disorders

Thyroid function was assessed routinely only at baseline and the end of the study. Across clinical trials, hypothyroidism occurred in 3.9% (77/1978) of patients and in 2.5% (13/523) of patients with urothelial carcinoma. One patient had Grade 3 and twelve patients had Grade 1–2 hypothyroidism. The median time to first onset was 5.4 months (range: 21 days to 11.3 months). Thyroid stimulating hormone (TSH) was elevated and above the patient's baseline in 16% (21/131) of patients with a follow-up measurement.

Hyperthyroidism occurred in 1.0% (20/1978) of patients across clinical trials and in 0.6% (3/523) of patients with urothelial carcinoma. Of the three urothelial carcinoma patients, one patient had Grade 2 and two patients had Grade 1 hyperthyroidism. The median time to onset was 3.2 months (range: 1.4 to 5.8 months). TSH was decreased and below the patient's baseline in 3.8% (5/131) of patients with a follow-up measurement.

Monitor thyroid function prior to and periodically during treatment with TECENTRIQ. Asymptomatic patients with abnormal thyroid function tests can receive TECENTRIQ. For symptomatic hypothyroidism, withhold TECENTRIQ and initiate thyroid hormone replacement as needed. Manage isolated hypothyroidism with replacement therapy and without corticosteroids. For symptomatic hyperthyroidism, withhold TECENTRIQ and initiate an anti-thyroid drug as needed. Resume treatment with TECENTRIQ when symptoms of hypothyroidism or hyperthyroidism are controlled and thyroid function is improving *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)]*.

Adrenal Insufficiency

Adrenal insufficiency occurred in 0.4% (7/1978) of patients across clinical trials, including two patients with Grade 3, four patients with Grade 2, and one patient with Grade 1. Adrenal insufficiency resolved in two patients.

For symptomatic adrenal insufficiency, withhold TECENTRIQ and administer methylprednisolone 1–2 mg/kg per day IV followed by oral prednisone 1–2 mg/kg per day or equivalent once symptoms improve. Start steroid taper when symptoms improve to ≤ Grade 1 and taper steroids over ≥ 1 month. Resume treatment with TECENTRIQ if the event improves to ≤ Grade 1 within 12 weeks and corticosteroids have been reduced to the equivalent of ≤ 10 mg oral prednisone per day and the patient is stable on replacement therapy, if required *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)]*.

Diabetes Mellitus

New onset diabetes with ketoacidosis has occurred in patients receiving TECENTRIQ. Diabetes mellitus without an alternative etiology occurred in one (0.2%) patient with urothelial carcinoma.

Initiate treatment with insulin for type 1 diabetes mellitus. For ≥ Grade 3 hyperglycemia (fasting glucose >250–500 mg/dL), withhold TECENTRIQ. Resume treatment with TECENTRIQ when metabolic control is achieved on insulin replacement therapy *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)]*.

5.5 Other Immune-Related Adverse Reactions

Other immune-related adverse reactions including meningoencephalitis, myasthenic syndrome/myasthenia gravis, Guillain-Barré, ocular inflammatory toxicity, and

pancreatitis, including increases in serum amylase and lipase levels, have occurred in ≤ 1.0% of patients treated with TECENTRIQ.

Meningitis / Encephalitis

Monitor patients for clinical signs and symptoms of meningitis or encephalitis. Permanently discontinue TECENTRIQ for any grade of meningitis or encephalitis. Treat with IV steroids (1–2 mg/kg/day methylprednisolone or equivalent) and convert to oral steroids (prednisone 60 mg/day or equivalent) once the patient has improved. When symptoms improve to ≤ Grade 1, taper steroids over ≥ 1 month *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)]*.

Motor and Sensory Neuropathy

Monitor patients for symptoms of motor and sensory neuropathy. Permanently discontinue TECENTRIQ for any grade of myasthenic syndrome/myasthenia gravis or Guillain-Barré syndrome. Institute medical intervention as appropriate. Consider initiation of systemic corticosteroids at a dose of 1–2 mg/kg/day prednisone *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)]*.

Pancreatitis

Symptomatic pancreatitis without an alternative etiology occurred in 0.1% (2/1978) of patients across clinical trials. Monitor patients for signs and symptoms of acute pancreatitis. Withhold TECENTRIQ for ≥ Grade 3 serum amylase or lipase levels (> 2.0 ULN), or Grade 2 or 3 pancreatitis. Treat with 1–2 mg/kg IV methylprednisolone or equivalent per day. Once symptoms improve, follow with 1–2 mg/kg of oral prednisone or equivalent per day. Resume treatment with TECENTRIQ if serum amylase and lipase levels improve to ≤ Grade 1 within 12 weeks, symptoms of pancreatitis have resolved, and corticosteroids have been reduced to ≤ 10 mg oral prednisone or equivalent per day. Permanently discontinue TECENTRIQ for Grade 4 or any grade of recurrent pancreatitis *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)]*.

5.6 Infection

Severe infections, including sepsis, herpes encephalitis, and mycobacterial infection leading to retroperitoneal hemorrhage occurred in patients receiving TECENTRIQ. Across clinical trials, infections occurred in 38.4% (759/1978) of patients. In 523 patients with urothelial carcinoma who received TECENTRIQ, infection occurred in 197 (37.7%) patients. Grade 3 or 4 infection occurred in 60 (11.5%) patients, while three patients died due to infections. Urinary tract infections were the most common cause of Grade 3 or higher infection, occurring in 37 (7.1%) patients.

In a randomized trial in patients with non-small cell lung cancer, infections were more common in patients treated with TECENTRIQ (42%) compared with those treated with docetaxel (33%). Grade 3 or 4 infections occurred in 9.2% of patients treated with TECENTRIQ compared with 2.2% in patients treated with docetaxel. One patient (0.7%) treated with TECENTRIQ died due to infection, compared to two patients (1.5%) treated with docetaxel. Pneumonia was the most common cause of Grade 3 or higher infection, occurring in 6.3% of patients treated with TECENTRIQ.

Monitor patients for signs and symptoms of infection and treat with antibiotics for suspected or confirmed bacterial infections. Withhold TECENTRIQ for ≥ Grade 3 infection *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)]*.

5.7 Infusion-Related Reactions

Severe infusion reactions have occurred in patients in clinical trials of TECENTRIQ. Infusion-related reactions occurred in 1.3% (25/1978) of patients across clinical trials and in 1.7% (9/523) of patients with urothelial carcinoma. Interrupt or slow the rate of infusion in patients with mild or moderate infusion reactions. Permanently discontinue TECENTRIQ in patients with Grade 3 or 4 infusion reactions *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)]*.

5.8 Embryo-Fetal Toxicity

Based on its mechanism of action, TECENTRIQ can cause fetal harm when administered to a pregnant woman. Animal studies have demonstrated that inhibition of the PD-L1/PD-1 pathway can lead to increased risk of immune-related rejection of the developing fetus resulting in fetal death. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, advise the patient of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TECENTRIQ and for at least 5 months after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

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 IMvigor210 (GO29293) was submitted to the Agency in support of BLA 761034. Three clinical sites, Dr. Jonathan Rosenberg, M.D. (Site 268278), Dr. Ani Balmanoukian, M.D. (Site 268794), Dr. Richard Joseph, M.D. (Site 268646), and the study sponsor were selected for audit.
The primary efficacy endpoint is Objective Response Rate (ORR), the proportion of subjects that had an objective response. Objective Response, as determined by the clinical investigators, per Modified RECIST, was verified for a subset of study subjects. There were no significant deficiencies.
There were no significant inspectional findings for clinical investigators Dr. Jonathan Rosenberg, M.D., Dr. Ani Balmanoukian, M.D., Dr. Richard Joseph, M.D., and the study sponsor Genentech. The data from IMvigor210 (GO29293) submitted to the Agency in support of BLA 761034, 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 locally advanced or metastatic urothelial carcinoma who:

- Have disease progression during or following platinum-containing chemotherapy
- Have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy

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:

3081-1 Conduct "GO29294: A Phase 3, Open-label, Multicenter, Randomized Study to Investigate the Efficacy and Safety of Atezolizumab Compared with Chemotherapy in Patients with Locally Advanced or Metastatic Urothelial Bladder Cancer After Failure with Platinum-containing Chemotherapy" and provide the datasets with the final report.

Final Protocol Submission: 09/14 (Completed)
Trial Completion: 09/17
Final Report Submission: 12/17

3081-2 Develop and validate an assay with improved sensitivity for the detection of neutralizing antibodies against atezolizumab in the presence of atezolizumab levels that are expected to be present in samples at the time of patient sampling. Patient samples should be banked for storage until the improved method is available.

Final Report Submission: 06/18

3081-3 Conduct a clinical trial to evaluate the effect of atezolizumab on thyroid function tests and clinical thyroid disease. Submit the datasets with the completed report.

Final Protocol Submission: 07/16
Trial Completion: 08/20
Final Report Submission: 02/21

The following postmarketing commitments are as follows:

3081-4 Submit the median duration of response for patients who responded to atezolizumab on GO29293. This includes all patients and patients whose tumor-infiltrating cells stain IC 2/3 or IC 0/1. Submit datasets with the completed report.

Trial Completion:	03/16
Final Report Submission:	12/16

3081-5 Conduct an animal study that will measure the effect of PD-L1 inhibition on the magnitude of the primary (1st vaccination) and recall (2nd vaccination) antibody responses to antigen challenge (e.g., KLH). This study will evaluate the effect of PD-L1 inhibition on the primary immune response once steady state plasma levels have been achieved and will reassess the magnitude of the recall response after a suitable period in the presence or absence of continued dosing. The study should include, if possible, an evaluation of cytokine production by T cells at appropriate time-points.

Final Protocol Submission: 11/16
Study Completion: 07/17
Final Report Submission: 01/18

3081-6 Perform supplemental characterization of the Master Cell Bank to provide additional assurance that the cell bank was (b) (4). These data should include the evaluation (b) (4) analysis with respect to growth characteristics and product quality.

Final Report Submission: 06/17

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
05/17/2016