CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761034Orig1s000

OFFICE DIRECTOR MEMO

Office Director Decisional Memo for Regulatory Action

Date	Electronic stamp date
From	Richard Pazdur, MD
Subject	Office Director Decisional Memo
NDA/BLA #	761034
Applicant	Genentech, Inc.
Date of Submission	January 12, 2016
PDUFA Goal Date	September 12, 2016
Proprietary/Non-Proprietary Name	Atezolizumab/TECENTRIQ
Dosage Form(s) / Strength(s)	Injection for intravenous administration 1200 mg/20 mL (60 mg/mL), single-dose vials
Action:	*Accelerated Approval*
Approved Indication/Population(s)	Tecentriq is a 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**
Division Director	Geoffrey Kim
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/Barbara 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

A favorable benefit-risk profile has been demonstrated, based on the results of study GO29293, for patients with advanced or metastatic urothelial bladder cancer who have received prior platinum-based therapy. 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; however, the durability of the responses observed with atezolizumab appears to be better than available (off-label) therapy. Currently, 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. The durable responses were observed in patients regardless of PD-L1 IC scores. Therefore, information regarding the Ventana PD-L1 (SP142) Assay will 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." I agree with the clinical and statistics review team assessment of a positive risk-benefit profile. Furthermore, all disciplines recommend approval of this application. This application will be approved under the Accelerated Approval provisions of 21 CFR 601 Subpart E.

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 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.	Substantial evidence of effectiveness for second-line use of atezolizumab monotherapy in advanced urothelial carcinoma, as supported by similar ORRs and durable 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.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
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 distributed to better allow early recognition and initiation of treatment of these events. • 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. A REMS is not necessary.

2. Background

Urothelial carcinoma is the most common malignancy in the urinary tract system and accounts for approximately 16,000 deaths yearly in the USA. 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 carcinoma. 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. The reported median survival of patients after platinum-containing therapy ranges from 5 to 10 months.

Existing (or Available) Therapies

Outside the USA, vinflunine is approved as a second-line treatment. Table 1 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 1: 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

There are no issues that would preclude approval from a product quality perspective. CMC reviewers have concluded that the drug substance (DS) and drug product (DP) manufacturing process is well controlled and should consistently deliver DS and DP of desired quality. A PMR will be a part of this approval as 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 patients' 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. See action letter for description of product quality PMRs and PMCs.

4. Nonclinical Pharmacology/Toxicology

There are no issues that would preclude approval from a nonclinical perspective. Based on the pharmacology/toxicology review, 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.

5. Clinical Pharmacology

There are no issues that would preclude approval from a clinical pharmacology perspective. Based on the clinical pharmacology review, 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.

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 administered 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

Not applicable.

7. Clinical/Statistical-Efficacy

This application is primarily supported by a multicenter, single-arm trial in 310 patients with locally advanced or metastatic urothelial carcinoma. Patients entering this trial had disease progression during or following a platinum-containing chemotherapy regimen or within 12 months of treatment with a neoadjuvant or adjuvant platinum-containing regimen. The study excluded patients who had a history of autoimmune disease or required systemic immunosuppressive medications. Tumor specimens were required in all patients. All patients received an intravenous infusion of atezolizumab, 1200 mg, every 3 weeks. Major efficacy outcome measures included confirmed ORR as assessed by independent review facility (IRF) using Response Evaluation Criteria in Solid Tumors (RECIST v1.1) and duration of response (DoR).

Visceral metastases were present in 78% of patients and 40% of patients had received greater than or equal to 2 prior regimens in the metastatic setting. Nineteen percent (19%) of patients had progressed following neoadjuvant or adjuvant therapy.

The confirmed ORR by independent review was 14.8% (95% CI: 11.1, 19.3) in all treated patients. Median DoR was not reached and response duration ranged from 2.1+ to 13.8+ months. Of the 46 responders, 37 patients had an ongoing response for greater than or equal to 6 months and 6 for greater than or equal to12 months. Tumor specimens were evaluated using the Ventana PD-L1 (SP142) Assay at a central laboratory and the results were used to define subgroups for pre-specified analyses. Patients were considered PD-L1 positive if PD-L1 stained tumor-infiltrating immune cells occupied greater than or equal to 5% of the tumor area. Of the 310 patients, 32% were classified as having PD-L1 expression of greater than or equal to 5% (defined as PD-L1 stained tumor-infiltrating immune cells [ICs] covering greater than or equal to 5% of the tumor area). The remaining 68% of patients were classified as having PD-L1 expression of less than 5% (PD-L1 stained tumor-infiltrating ICs covering less than 5% of the tumor area). The confirmed ORR was 26.0% (95% CI: 17.7, 35.7) in 100 patients whose specimens had PD-L1 expression of greater than or equal to 5% and 9.5% (95% CI: 5.9, 14.3) in 210 patients whose specimens had PD-L1 expression of less than5%. Response durations in these subgroups were similar to those noted above in all treated patients.

Table 2: Summary of Efficacy Data

	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 application were obtained from 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. Patients received 1200 mg of atezolizumab 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 of atezolizumab (greater than or equal to 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, diabetes, pancreatitis, and dermatitis/rash were also seen with atezolizumab.

9. Advisory Committee Meeting

This application was not referred to the Oncologic Drugs Advisory Committee (ODAC) 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. Postmarketing

A Risk Evaluation and Mitigation Strategy (REMS) is not necessary for approval. See action letter for PMRs and PMCs.

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/s/

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05/18/2016

RICHARD PAZDUR
05/18/2016