CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761034Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	BLA
Application Number	761034
PDUFA Goal Date	September 12, 2016
OSE RCM #	2015-2686
Reviewer Name(s)	Mona Patel, Pharm.D., Senior Risk Management Analyst
DRISK Team Leader	Naomi Redd, Pharm. D., Team Leader
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	April 21, 2016
Subject	Evaluation to determine if a REMS is necessary
Established Name	atezolizumab
(Proposed) Trade Name	Tecentriq
Applicant	Genentech Inc.
Therapeutic Class	humanized programmed death-ligand 1 (PD-L1) blocking antibody
Formulation(s)	injection
Dosing Regimen	1200 mg administered as an intravenous infusion over 60 minutes every 3 weeks

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Tecentriq® (atezolizumab) is necessary to ensure the benefit of this product outweighs its risk. Genentech Inc., submitted a Biologics License Application (BLA) 761034 for Tecentriq (atezolizumab) for the treatment of patients with locally advanced or metastatic urothelial carcinoma (b) (4)

(b) (4)

The risks associated with the use of atezolizumab are immune-related pneumonitis, hepatitis, and endocrinopathies along with immune-mediated colitis, diabetes mellitus, infections, and infusion-related reactions. The applicant did not submit a REMS with this application but submitted a Medication Guide and a proposed pharmacovigilance plan.

This reviewer is not recommending a REMS to ensure the benefits of atezolizumab outweigh its risks. The risks seen with this drug will be communicated through labeling. The Medical Officer concurs with this recommendation.

1 Introduction

Genentech Inc., submitted a Biologics License Application (BLA 761034) for atezolizumab with the proposed indication for the treatment of patients with locally advanced or metastatic urothelial carcinoma (b) (4)

(b) (4)

This application is under review in the Division of Oncology Products 1 (DOP-1). The applicant did not submit a REMS with this application but proposed risk minimization measures that included product labeling, a Medication Guide and an enhanced pharmacovigilance plan.

2 Background

2.1 PRODUCT INFORMATION[1]

Tecentriq (atezolizumab) is a new molecular entity, humanized programmed death-ligand 1 (PD-L1) blocking antibody. The sponsor proposed the following indication: treatment of patients with locally advanced or metastatic urothelial carcinoma (mUC) (b) (4) FDA revised the indication to be for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy (b) (4); or, who have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

The proposed dosing schedule for patients with locally advanced or metastatic urothelial carcinoma is 1200 mg administered as an intravenous infusion over 60 minutes every 3 weeks until disease progression or unacceptable toxicity. If the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes. The dosage formulation is 60 mg/mL solution in a single use 20 mL vial. This is a NME 505 (b)(1) application that was granted Breakthrough Therapy designation for the treatment of patients with locally advanced or metastatic urothelial bladder cancer that is PD-L1 positive, (b) (4), after progression on or intolerance to a platinum-containing chemotherapy regimen. The efficacy of the product is based upon a single-arm Phase 2 study, Study GO29293. Atezolizumab is not licensed in the United States, or any other jurisdiction. The application is under Priority review with a Prescription Drug User Fee Act (PDUFA) date of September 12, 2016.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for BLA 761034 relevant to this review:

- 2/7/2014: IND 120827 active
- 5/22/14: Breakthrough Therapy Designation granted for treatment of patients with locally advanced or metastatic urothelial bladder cancer that are PD-L1 positive
- 5/11/15: Type B Content & Format Pre-BLA Meeting
- 9/24/15: Type B Pre-BLA Meeting to discuss clinical trial results to support BLA
- 10/23/2015: Part 1 Rolling Submission Received
- 1/12/2016: Part 2 Rolling Submission Received

[1] Clinical Overview (section 2.5), atezolizumab

- 2/1/2016: Applicant Orientation Presentation
- 3/18/2016: Midcycle Meeting
- 3/23/2016: A Post Mid-cycle meeting was held between FDA and Genentech via teleconference. The FDA informed Genentech Inc., that based on the currently available data a REMS was not needed for atezolizumab

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

According to the American Cancer Society (ACS), urinary bladder cancer represents approximately 5% of all new cancers in the United States. It is the fourth most common cancer in men and is less common in women. For 2016, the ACS estimates that there will be 76,960 new cases of bladder cancer (58,950 in men and 18,010 in women) and 16,390 deaths from bladder cancer (11,820 in men and 4,570 in women). It is estimated that men are about 3-4 times more likely to get bladder cancer during their lifetime than women. Overall, the chance men will develop this cancer during their life is about 1 in 26. For women, the chance is about 1 in 88. Bladder cancer occurs mainly in older people. About 9 out of 10 people with this cancer are over the age of 55, and the average age at time of diagnosis is 73. Whites are diagnosed with bladder cancer about twice as often as African Americans or Hispanics.[2] According to the National Cancer Institute's SEER database, between 2005-2011, in the United States, the 5 year survival rate for patients diagnosed with bladder cancer was 77%.[3]

3.2 Description of Current Treatment Options

The 2016 National Comprehensive Cancer Network guidelines recommend treatment for bladder cancer to include platinum-based (cisplatin or carboplatin) combination chemotherapy (i.e., with a taxane or other drugs including gemcitabine, vinorelbine, irinotecan, and doxorubicin).[4] Cisplatin is the only drug FDA approved for bladder cancer. Combination chemotherapy is the preferred regimen in the first-line setting of patients with urothelial carcinoma with single-agent platinum-based chemotherapy reserved for the second-line setting. Both cisplatin and carboplatin have a Boxed Warning. There are currently no approved second-line therapies for urothelial carcinoma in the United States and only one approved agent (vinflunine) in the European Union.

See table 1 in Appendix A for a summary of therapies that are used to treat patients with urothelial carcinoma. There are no approved products in the United States for second-line therapy for urothelial

[2] http://www.cancer.org/cancer/bladdercancer/detailedguide/bladder-cancer-key-statistics

[3] http://seer.cancer.gov/statfacts/html/urinb.html

[4] http://www.nccn.org/professionals/physician_gls/PDF/bladder.pdf (2016)

carcinoma. Therefore, if approved atezolizumumab would fulfill an unmet medical need to treat this disease.

4 Benefit Assessment[5,6,7]

The evidence of clinical benefit for atezolizumab in locally advanced or metastatic urothelial carcinoma (mUC) is derived from Study GO29293. In Cohort 2 of this study, 310 patients, identified using the Ventana PD-L1 (SP142) CDx Assay, with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy for metastatic disease; or, who have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy, were treated with atezolizumab. Patients received an intravenous infusion of 1200 mg of atezolizumab every 3 weeks until unacceptable toxicity, disease progression or symptomatic progression.

Patients enrolled in this cohort had a median age of 66 years. Ninety-one percent of patients were white, 78% were male. Twenty-six percent had non-bladder urothelial carcinoma and 78% of patients had metastases to the lungs, liver and bone. Forty percent of patients had received ≥ 2 prior therapies in the metastatic setting. The median duration of response had not been reached by the data cutoff date. The primary endpoint was objective response rate (ORR) as assessed by an independent review facility (IRF) using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Objective response rate was 14.8% in all patients in Cohort 2. Complete response was 5.5% and partial response was 9.4%. For the secondary endpoint of Duration of Response (DoR), median DoR had not been reached at the time of data cutoff for the ORR analysis. The results were clinically meaningful and statistically significant.

5 Risk Assessment & Safe-Use Conditions[6,7]

The safety of atezolizumab at the 1200 mg dose to be administered every three weeks was evaluated in 1189 safety-evaluable patients from Study GO29293. Adverse event data was summarized by system organ classes (SOCs) and preferred terms from the Medical Dictionary for Regulatory Activities (MedDRA) version 17.1. The intensity of AEs was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0.

Death associated with atezolizumab occurred in 5 patients (0.9%) due to sepsis, pneumonitis, and intestinal obstruction. Atezolizumab was discontinued for adverse reactions in 3.2% of the 310 patients in Study GO29293. Sepsis led to discontinuation of drug in 0.6% of patients. Adverse reactions leading

[5] Draft clinical review by Dr. Yang-Min (April 1, 2016)

[6] March 18, 2016 Midcycle Slides by Drs. Yang-Min Ning & Daniel Suzman

[7] Tecentriq (atezolizumab) draft label, April 20, 2016

to interruption of atezolizumab occurred in 27% of patients; the most common (>1.5%) were liver enzyme increase, urinary tract infection, diarrhea, fatigue, and altered mentation.

Serious adverse reactions occurred in 45% of patients. The most frequent serious adverse reactions (reported in at least 2.5% of patients) were urinary tract infection, hematuria, acute kidney injury, intestinal obstruction, venous thromboembolism, urinary obstruction, pyrexia, and pneumonia.

5.1 Serious Adverse Reactions

Immune-mediated Pneumonitis-Pneumonitis occurred in 1.1% (6/523) of patients with urothelial carcinoma who received atezolizumab. The median time to onset was 2.6 months and the median duration was 15 days. 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. Treatment was withheld in all cases. Five patients were treated with corticosteroids and pneumonitis resolved in three patients. Corticosteroids were administered at a dose of 1 to 2 mg/kg/day prednisone equivalents for Grade 2 or greater pneumonitis followed by a corticosteroid taper. Atezolizumab was to be permanently discontinued for Grade 3 or 4 pneumonitis.

Immune-mediated Hepatitis-Hepatitis occurred in 1.3% (2/521) of patients with urothelial carcinoma who received atezolizumab. The median time to onset was 1.1 months. Of these patients, one patient died from hepatitis, five patients had Grade 3, and one patient had Grade 2 hepatitis. Treatment was temporarily interrupted in four patients; none of these patients developed recurrence of hepatitis after resuming atezolizumab. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubin were to be monitored prior to and periodically during treatment with atezolizumab. Corticosteroids were administered at a dose of 1 to 2 mg/kg/day prednisone equivalents for Grade 2 or greater transaminase elevations, with or without concomitant elevation in total bilirubin. Atezolizumab was to be permanently discontinued for Grade 3 or 4 immune-mediated hepatitis.

Immune-mediated Colitis-Diarrhea or colitis occurred in 20% (103/523) of patients with metastatic urothelial carcinoma who received atezolizumab. Nine patients (1.7%) developed Grade 3 or 4 diarrhea; one of these patients died in the setting of diarrhea-associated renal failure. Treatment was withheld in all cases for Grade 3 diarrhea or colitis. Corticosteroids were to be administered intravenously at a dose of 1–2 mg/kg/day and then converted to oral steroids once the patient had improved. For Grade 3 diarrhea or colitis, when symptoms improved to Grade 0 or Grade 1, steroids were to be tapered over ≥ 1 month. Treatment with atezolizumab was to be resumed if the event improved to Grade 0 or 1 within 12 weeks and corticosteroids had been reduced to the equivalent of ≤ 10 mg oral prednisone per day. Atezolizumab was to be permanently discontinued for Grade 4 diarrhea or colitis.

Immune-related Endocrinopathies-Hypothyroidism occurred in 2.5% (13/523) of patients with urothelial carcinoma who received atezolizumab. The median time to onset was 5.4 months. Twelve patients had Grade 1–2 and one patient had Grade 3 hypothyroidism. Atezolizumab was to be withheld and thyroid hormone replacement was to be initiated. Hyperthyroidism occurred in 0.6% (3/523) of patients with

urothelial carcinoma. Of the three patients, two patients had Grade 2 and one patient had Grade 1 hyperthyroidism. The median time to onset was 3.2 months (range: 1.4 to 5.8 months).

-Adrenal insufficiency occurred in 0.4% (4/1189) of patients in the safety database receiving atezolizumab. Of the four patients, two patients had Grade 3 and 2 patients had Grade 2 adrenal insufficiency. For symptomatic adrenal insufficiency, atezolizumab was to be withheld and methylprednisolone administered intravenously at a dose of 1–2 mg/kg per day followed by oral prednisone at a dose of 1–2 mg/kg per day or an equivalent once symptoms had improved. Steroids were to be tapered over ≥ 1 month when symptoms improved to ≤ Grade 1. Atezolizumab could be resumed if the event improved to ≤ Grade 1 within 12 weeks and corticosteroids had been reduced to the equivalent of ≤ 10 mg oral prednisone per day and the patient was stable on replacement therapy, if required.

Diabetes Mellitus-Diabetes mellitus occurred in 0.2% of patients with urothelial carcinoma who received atezolizumab. Treatment was to be withheld for Grade 3 hyperglycemia and then resumed when metabolic control was achieved on insulin replacement therapy.

Infections-Severe infections, including sepsis, occurred in 37% of patients with urothelial carcinoma who have received atezolizumab. Grade 3 or 4 infection occurred in 53 (10%) patients, while two patients died due to infections. Urinary tract infections were the most common cause of Grade 3 or higher infection, occurring in 38 (7.3%) patients. Antibiotics was to be initiated for suspected or confirmed bacterial infections.

Infusion-related Reactions-Severe infusion reactions occurred in 1.7% (9/523) of patients with urothelial carcinoma who have received atezolizumab. Atezolizumab was to be discontinued in patients with severe or life-threatening infusion reactions and the rate of infusion was to be interrupted or slowed in patients with mild or moderate infusion reactions.

6 Expected Postmarket Use

Atezolizumab will be administered in the inpatient and outpatient infusion setting and the likely prescribers will be oncologists. Treatment will likely be provided in treatment centers and use will be under the supervision of healthcare providers who should be familiar with the risks and management of adverse events of PD-L1 inhibitors such as nivolumab and pembrolizumab as they are the likely prescribers of such drugs. The patient and/or caregiver will utilize a Medication Guide to recognize symptoms with the risks associated with atezolizumab and the Medication Guide will provide guidance to report the adverse events to their healthcare provider.

7 Risk Management Activities Proposed by the Applicant

Genentech, Inc., proposed a Medication Guide with labeling and routine pharmacovigilance. The sponsor did not submit a REMS or propose any other risk management activities.

8 Evaluating the Need for a REMS

There are currently no approved second-line treatment options for urothelial carcinoma. The disease is serious and life-threatening, and there is an unmet medical need for drugs to treat this disease. The DOP-1 is proposing that the indication for atezolizumab is for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy (b) (4) or, who have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

The anticipated duration of use for atezolizumab is 1200 mg administered as an intravenous infusion over 60 minutes every 3 weeks until disease progression or unacceptable toxicity.

The Medical Officer included in his review that the efficacy data for atezolizumab supports accelerated approval for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy for metastatic disease; or, who have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. The objective response rate was 14.8% in all patients in cohort 2. Complete response was 5.5% and partial response was 9.4%. These results were considered clinically meaningful and statistically significant.

The risks associated with the use of atezolizumab are immune-related pneumonitis, hepatitis, and endocrinopathies along with immune-mediated colitis, diabetes mellitus, infections, and infusion-related reactions. Other PD-L1 inhibitors such as pembrolizumab and nivolumab have similar immune-related risks. Along with infusion reactions, the most commonly seen adverse events seen with nivolumab are immune-mediated pneumonitis, colitis, hepatitis, endocrinopathies, nephritis & renal dysfunction, rash, and encephalitis. With pembrolizumab, immune-related pneumonitis, colitis, hepatitis, endocrinopathies, and nephritis and renal dysfunction were listed under the Warnings & Precautions section of the labeling.

The adverse events for atezolizumab are immune-related pneumonitis, hepatitis, and endocrinopathies along with immune-mediated colitis, diabetes mellitus, infections, and infusion-related reactions. These adverse events will be communicated through labeling and in the Warnings & Precautions section.

9 Conclusion & Recommendations

Based on the available efficacy and safety data, anticipated prescribing population, and patient population for use of this drug, DRISK and DOP1 agree that the benefit-risk profile is acceptable and a REMS is not necessary for atezolizumab to ensure the benefits outweigh the risks. At the time of this

review, evaluation of safety information and labeling was still ongoing. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile.

10 Appendices

10.1 Materials Reviewed

The following is a list of materials informing this review:

- Genentech Inc., Clinical Overview (section 2.5), atezolizumab
- Draft clinical review by Dr. Yang-Min (April 1, 2016)
- March 18, 2016 Midcycle Slides by Drs. Yang-Min Ning & Daniel Suzman
- Tecentriq (atezolizumab) draft label, April 12, 2016

10.2 TABLES

Table 1: Therapies Currently Used to Treat Urothelial Carcinoma

Product Trade Name (Generic), Year of Approval	Approved Indications	Dosing/Administration	Important Safety and Tolerability Issues	Risk Management
cisplatin[8] 1978	In combination therapy for metastatic testicular and ovarian tumors, advanced bladder cancer	Bladder Cancer: 50 to 70 mg/m2 IV per cycle once every 3 to 4 weeks depending on the extent of prior exposure to radiation therapy and/or prior chemotherapy.	*Cumulative renal toxicity, Ototoxicity, Anaphylactic-like reactions,* nephrotoxicity, ototoxicity, hematologic, gastrointestinal, serum electrolyte disturbances, hyperuricemia, neurotoxicity, ocular toxicity, anaphylactic-like reactions, hepatotoxicity	*Boxed Warning*
Paraplatin (carboplatin)[9]	Ovarian carcinoma	360 mg/m2 IV on day 1 every 4 weeks	*Bone Marrow Suppression, anaphylactic-like reactions, anemia,* increased ototoxicity with aminoglycosides, emesis, increased peripheral neurotoxicity in elderly, loss of vision, allergic reactions	*Boxed Warning*
Doxil (doxorubicin)[10] 1995	Ovarian Cancer, AIDS-related Kaposi's Sarcoma, Multiple Myeloma	Dosing Varies by Indication	*Cardiomyopathy & Infusion-related Rxns,* Hand-Foot Syndrome, Secondary Oral Neoplasms, embryo-fetal toxicity	*Boxed Warning*
Abraxane (paclitaxel)[5]	Breast cancer, NSCLC,	Dosing Varies by Indication	*Neutropenia*, nervous system, sepsis,	*Boxed Warning* *Patient*

[8] Cisplatin US Package Insert (2/2015)

[9] Paraplatin (carboplatin) US Package Insert (7/2010)

[10] Doxil (doxorubicin) US Package Insert (4/2015)

[5] Abraxane (paclitaxel) US Package Insert (7/2015)

2005	Pancreatic		pneumonitis, hepatic impairment, albumin	*Information*
Taxotere (docetaxel)[6] 1996	Breast cancer, NSCLC, Hormone Refractory Prostate Cancer, Gastric Adenocarcinoma, Squamous Cell Carcinoma of the Head and Neck Cancer	Dosing Varies By Indication	*Toxic Deaths, hepatotoxicity, neutropenia, hypersensitivity reactions, and fluid retention,* acute myeloid leukemia, cutaneous & neurologic reactions, eye disorders, asthenia	*Boxed Warning* *Patient Information*
Gemzar (gemcitabine)[7] 1996	Ovarian Cancer, Breast Cancer, NSCLC, Pancreatic Cancer	Dosing Varies	Myelosuppression, Pulmonary Toxicity & Respiratory Failure, Hemolytic-Uremic Syndrome, Hepatic Toxicity, Embryo-fetal Toxicity, Capillary leak syndrome	

[6] Taxotere (docetaxel) US Package Insert (12/2015)

[7] Gemzar (gemcitabine) US Package Insert (6/2014)

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/s/

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04/21/2016

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Concur