

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**761041Orig1s000**

**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)**

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<b>Application Type</b>	BLA
<b>Application Number</b>	761041
<b>PDUFA Goal Date</b>	October 19, 2016
<b>OSE RCM #</b>	2016-170 & 2016-235
<b>Reviewer Name(s)</b>	Mona Patel, Pharm.D., Senior Risk Management Analyst
<b>DRISK Team Leader</b>	Naomi Redd, Pharm. D., Team Leader
<b>Division Director</b>	Cynthia LaCivita, Pharm.D.
<b>Review Completion Date</b>	September 28, 2016
<b>Subject</b>	Evaluation to determine if a REMS is necessary
<b>Established Name</b>	atezolizumab
<b>(Proposed) Trade Name</b>	Tecentriq
<b>Applicant</b>	Genentech Inc.
<b>Therapeutic Class</b>	humanized programmed death-ligand 1 (PD-L1) blocking antibody
<b>Formulation(s)</b>	injection
<b>Dosing Regimen</b>	1200 mg administered as an intravenous infusion over 60 minutes every 3 weeks

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## **EXECUTIVE SUMMARY**

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This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the drug Tecentriq® (atezolizumab) is necessary to ensure the benefit of this product outweighs its risk. Genentech, Inc., submitted a BLA for atezolizumab on February 19, 2016 with the proposed indication for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who are programmed death-ligand 1 (PD-L1) selected, as determined by an FDA-approved test, and who have progressed on or after platinum-containing chemotherapy. Patients with epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving atezolizumab.

The risks associated with the use of atezolizumab are immune-related pneumonitis, hepatitis, colitis, and endocrinopathies along with infection, infusion-related reactions and embryo-fetal toxicity. The applicant did not submit a REMS with this application but submitted a Medication Guide.

Atezolizumab was approved in the United States under accelerated approval on May 18, 2016 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. The adverse events for atezolizumab will be communicated in the Warnings & Precautions section of labeling which will also include when to withhold treatment, administer corticosteroids to help mitigate a risk, or permanently discontinue treatment with atezolizumab. This reviewer is not recommending a REMS to ensure the benefits of atezolizumab outweigh the risks seen with this drug. The Medical Officer concurs with this recommendation.

## **1 Introduction**

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Genentech Inc., submitted a BLA 761041 for atezolizumab with the proposed indication for the treatment of patients with locally advanced or metastatic NSCLC who are PD-L1 selected, as determined by an FDA-approved test, and who had disease progression on or after platinum-containing chemotherapy.

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 and a Medication Guide.

## 2 Background

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### 2.1 PRODUCT INFORMATION

Tecentriq (atezolizumab) is a PD-L1 blocking antibody.<sup>1</sup> The sponsor proposed the following indication: treatment of patients with locally advanced or metastatic NSCLC who are PD-L1 selected, as determined by an FDA-approved test, and who have progressed on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving atezolizumab. FDA revised the indication to be for the treatment of patients with metastatic NSCLC who are PD-L1 selected, as determined by an FDA-approved test, and who have progressed on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving atezolizumab.

The proposed dosing schedule for patients with metastatic NSCLC 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 PD-L1 positive non-small cell lung cancer (NSCLC) with disease progression on or after platinum-based chemotherapy and appropriate targeted therapy if EGFR or ALK positive. The efficacy of the product is based upon a Phase 2, multi-center, international, randomized, open-label, trial in 287 patients with metastatic NSCLC who progressed during or following a platinum-containing regimen. Atezolizumab was approved in the United States under accelerated approval on May 18, 2016 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. The application is under Priority review with a Prescription Drug User Fee Act (PDUFA) date of October 19, 2016.

### 2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for BLA 761041 relevant to this review:

- 4/11/2013: IND 117296 active
- 1/28/15: Breakthrough Therapy Designation granted for treatment of patients with PD-L1 positive non-small cell lung cancer (NSCLC) with disease progression on or after platinum-based chemotherapy and appropriate targeted therapy if EGFR or ALK positive.

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<sup>1</sup> Clinical Overview (section 2.5), atezolizumab

- 6/26/15: Type B Content & Format Pre-BLA Meeting
- 11/10/15: Type B Pre-BLA Meeting to discuss clinical trial results to support BLA
- 11/19/2015: Part 1 Rolling Submission Received
- 2/19/2016: Part 2 Rolling Submission Received
- 4/25/2016: Applicant Orientation Presentation
- 7/21/2016: 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**

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#### **3.1 DESCRIPTION OF THE MEDICAL CONDITION**

Lung cancer is the leading cause of cancer and cancer-related mortality worldwide and the leading cause of cancer related deaths in the United States (US).<sup>2</sup> In the US, lung cancer represents the second most common type of cancer.<sup>2</sup> An estimated 224,390 new cases (117,920 in men and 106,470 in women) will be diagnosed in 2016, accounting for approximately 14% of all new cancer diagnoses.<sup>2</sup> According to the American Cancer Society, lung cancer mainly occurs in older people. About 2 out of 3 people diagnosed with lung cancer are 65 or older; fewer than 2% of all cases are found in people younger than 45. The average age at the time of diagnosis is about 70. Black men are about 20% more likely to develop lung cancer (including all types) than are white men. The rate is about 10% lower in black women than in white women. According to the National Cancer Institute's SEER database, between 2006-2012, in the United States, the 5 year survival rate for patients diagnosed with lung cancer was 17.7%.<sup>3</sup>

The two major histological subtypes of lung cancer are small cell lung cancer and non-small cell lung cancer (NSCLC). NSCLC accounts for nearly 85% of all cases of lung cancer.

#### **3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS**

Docetaxel, paclitaxel, and albumin-bound paclitaxel (nab-paclitaxel) are all FDA approved for use in the first-line treatment of unresectable, locally advanced or metastatic NSCLC in combination with cisplatin (docetaxel, paclitaxel) or carboplatin (nab-paclitaxel).

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<sup>2</sup> American Cancer Society. Available at: <http://www.cancer.org/cancer/lungcancer-non-smallcell/index>. Accessed August 11, 2016

<sup>3</sup> National Cancer Institute Surveillance, Epidemiology, and End Results Program <http://seer.cancer.gov/statfacts/html/lungb.html>

Several tyrosine kinase inhibitors targeting EGFR and ALK have been shown to be effective therapy in tumors harboring such alterations. Erlotinib and afatinib, which inhibit EGFR, are FDA approved for the first-line treatment of patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations. Erlotinib is also FDA-approved for the treatment of locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen. Ramucirumab, an EGFR, is indicated in combination with docetaxel for the treatment of patients with metastatic NSCLC that is resistant to or has progressed after platinum-based chemotherapy.

Crizotinib is a small molecule inhibitor of ALK, ROS-1, and MET, and it is FDA approved for the treatment of patients with metastatic NSCLC whose tumors are ALK-positive. Ceritinib and alectinib target ALK, and it is used for the treatment of patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib.

Two PD-L1 inhibitors indicated as second-line option for the treatment of patients with metastatic NSCLC who have disease progression on or after platinum-containing chemotherapy are pembrolizumab and nivolumab. Both pembrolizumab and nivolumab have a Medication Guide and share the same immune-related risks as atezolizumab except for the infections seen with atezolizumab.

See *table 1* in Appendix A for a summary of therapies that are used to treat patients with locally advanced or metastatic NSCLC. Despite advances in the treatment options for patients with NSCLC, the majority of patients will die from their disease and 5-yr survival rates are still low. Approved chemotherapy regimens have low response rates and toxicities. There is still a need for targeted therapies and diagnostic selection methods which can identify patients who are likely to benefit from such treatment.

## 4 Benefit Assessment

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The evidence of clinical benefit for atezolizumab for the treatment of patients with metastatic NSCLC who have disease progression during or following platinum-containing chemotherapy is derived from Study Poplar. Study Poplar is a multi-center, international, randomized, open-label, trial in 287 patients with metastatic NSCLC who progressed during or following a platinum-containing regimen. Eligible patients were stratified by PD-L1 expression status in tumor-infiltrating immune cells (ICs), by the number of prior chemotherapy regimens, and by histology, and then randomized (1:1) to receive either atezolizumab administered intravenously at 1200 mg every 3 weeks or docetaxel administered intravenously at 75 mg/m<sup>2</sup> every 3 weeks.<sup>4</sup> Treatment in both arms continued until unacceptable toxicity or disease progression.

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<sup>4</sup> Draft Review by Chana Weinstock-September 11, 2016

<sup>4</sup> Tecentriq (atezolizumab) draft label, September 8, 2016

Patients enrolled in this cohort had a median age of 62 years.<sup>4</sup> Seventy-nine percent of patients were white, 59% of patients were male.<sup>5</sup> Sixty-six percent of patients had non-squamous disease, 7% had known EGFR mutation, 1% had ALK rearrangements, and most patients were current or previous smokers (80%).<sup>5</sup> Sixty-six percent of patients had previously received second-line treatment (66%).<sup>5</sup> The primary endpoint was overall survival (OS). Other efficacy outcome measures included investigator-assessed objective response rates (ORR) and Duration of Response (DoR) using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Median overall survival was 11.4 months in the atezolizumab arm versus 9.5 months in the docetaxel arm.<sup>6</sup> Overall ORR was the same (15%) in both arms.<sup>6</sup> The DoR was 18.6 months in the atezolizumab arm and 7.2 months in the docetaxel arm.<sup>6</sup> The Medical Officer and Statistical Reviewer deemed the results as clinically meaningful but not statistically significant.<sup>4</sup>

## 5 Risk Assessment & Safe-Use Conditions<sup>6,7</sup>

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The safety of atezolizumab was evaluated in 1026 patients from Study POPLAR. Death associated with atezolizumab occurred in 9 patients (6.3%) due to pulmonary embolism, pneumonia, pneumothorax, ulcer hemorrhage, dysphagia, myocardial infarction, or large intestinal perforation.<sup>5</sup> Atezolizumab was discontinued for adverse reactions in 4% of the 142 patients in Study POPLAR.<sup>5</sup> Adverse reactions leading to interruption of atezolizumab occurred in 24% of patients; the most common (>1%) were pneumonia, upper respiratory tract infection, pneumonitis, hypoxia, hypothyroidism, liver function test abnormality, acute kidney injury, and fatigue.<sup>5</sup> Serious adverse reactions occurred in 35% of patients.<sup>5</sup> The most frequent serious adverse reactions (> 2%) were pneumonia, dyspnea, pleural effusion, and venous thromboembolism.<sup>5</sup>

Adverse event data was summarized by system organ classes (SOCs) and preferred terms from the Medical Dictionary for Regulatory Activities (MedDRA) version 18.0.<sup>1</sup> The intensity of AEs was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0.<sup>1</sup>

### 5.1 Serious Adverse Reactions

*Immune-related Pneumonitis*<sup>5</sup>-Pneumonitis occurred in 3.7% (38/1027) of patients with NSCLC who received atezolizumab. The median time to onset was 3 months and the median duration was 1.4 months. Of these patients, there was one patient with fatal pneumonitis, 2 patients with Grade 4, thirteen patients with Grade 3, 11 patients with Grade 2, and 11 patients with Grade 1 pneumonitis. Treatment was withheld in 24 patients and 20 patients were treated with corticosteroids. Pneumonitis resolved in 26 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.

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<sup>6</sup> July 12, 2016 Midcycle Slides by Drs. Chana Weinstock and Daniel Suzman



*Immune-related Hepatitis*<sup>5</sup>-Hepatitis occurred in 0.8% (8/1027) of patients with NSCLC who received atezolizumab. The median time to onset was 25 days. Of these eight patients, four patients had Grade 3, three patients had Grade 2, and one patient had Grade 1 immune-related hepatitis. Treatment was temporarily interrupted in six 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-related hepatitis.

*Immune-related Colitis*<sup>5</sup>-Diarrhea or colitis occurred in 19.3% (198/1027) of patients with NSCLC who received atezolizumab. 12 patients (1.2%) developed Grade 3 colitis or diarrhea. Five patients (0.5%) had immune-mediated colitis or diarrhea with a median time to onset of 21 days. Of these patients, one had Grade 3, two had Grade 2, and two had Grade 1 immune-mediated colitis or diarrhea. Immune-mediated colitis or diarrhea resolved with corticosteroid administration in four of these patients, while the fifth patient died due to disease progression prior to resolution of colitis. Treatment was withheld in all cases for Grade 3 diarrhea or colitis. Methylprednisolone was 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 both Grade 2 and Grade 3 diarrhea or colitis, when symptoms improved to Grade 0 or Grade 1, steroids were to be tapered over  $\geq 1$  month. Treatment was to be resumed with atezolizumab if the event improved to Grade 0 or 1 within 12 weeks and corticosteroids had been reduced to the equivalent of  $\leq 10$  mg oral prednisone per day. Atezolizumab was to be permanently discontinued for Grade 4 diarrhea or colitis.

*Immune-related Endocrinopathies*<sup>5</sup>-Hypothyroidism occurred in 4.2% (43/1027) of patients with NSCLC who received atezolizumab. The median time to onset was 4.8 months. Three patients had Grade 3 and forty patients had Grade 1–2 hypothyroidism. For patients with symptomatic hypothyroidism, atezolizumab was to be withheld and thyroid hormone replacement was to be initiated. Hyperthyroidism occurred in 1.1% (11/1027) of patients with NSCLC. Eight patients had Grade 2 and three patients had Grade 1 hyperthyroidism. The median time to onset was 4.9 months. For symptomatic hyperthyroidism, atezolizumab was to be withheld and an anti-thyroid drug was to be given as needed. Treatment with atezolizumab was to be resumed when symptoms of hypothyroidism or hyperthyroidism were controlled and thyroid function was improving.

Adrenal insufficiency occurred in 0.4% (7/1978) of patients in the safety database receiving atezolizumab. Of the 7 patients, two patients had Grade 3 and four patients had Grade 2 adrenal insufficiency and one patient with Grade 1 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  $\geq 1$  month when symptoms improved to  $\leq$  Grade 1. Atezolizumab could be resumed if the event improved to  $\leq$  Grade 1 within 12 weeks and corticosteroids had been reduced to the equivalent of  $\leq 10$  mg oral prednisone per day and the patient was stable on replacement therapy, if required.

Diabetes mellitus occurred in 3 (0.3%) patients with NSCLC 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*<sup>5</sup>- Grade 3 or 4 infection occurred in 9.2% of patients compared with 2.2% in patients treated with docetaxel, while two patients died due to infections. One patient (0.7%) treated with atezolizumab 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 7.7% of patients treated with atezolizumab. Antibiotics were to be initiated for suspected or confirmed bacterial infections.

*Infusion-related reactions*<sup>5</sup>-Severe infusion reactions occurred in 1.6% (16/1027) of patients with NSCLC. 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.

*Embryo-fetal Toxicity*<sup>5</sup>- 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. Effective contraception is to be used during treatment with atezolizumab and for at least 5 months after the last dose.

## 6 Expected Postmarket Use

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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.

## 7 Risk Management Activities Proposed by the Applicant

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Genentech, Inc., proposed a Medication Guide with labeling. The sponsor did not submit a REMS but proposed to monitor adverse events through routine pharmacovigilance and labeling.

## 8 Evaluating the Need for a REMS

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Lung cancer is the leading cause of cancer and cancer-related mortality worldwide and the leading cause of cancer related deaths in the United States (US). Atezolizumab is another potential treatment option for the treatment of patients with metastatic NSCLC who have progressed on or after platinum-containing chemotherapy and patients with EGFR or ALK genomic tumor aberrations who have disease progression on FDA-approved therapy for these aberrations. Current therapy options include first line treatment with docetaxel, paclitaxel, and nab-paclitaxel and second-line treatment options such as pembrolizumab, nivolumab, and ramucirumab. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapies for these aberrations prior to receiving

atezolizumab. Erlotinib and afatinib, which inhibit EGFR, are FDA approved for the first-line treatment of patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations. Crizotinib is a small molecule inhibitor of ALK, ROS-1, and MET, and it is FDA approved for the treatment of patients with metastatic NSCLC whose tumors are ALK-positive. Ceritinib and alectinib target ALK, and it is used for the treatment of patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib.

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 efficacy of atezolizumab for the treatment of patients with metastatic NSCLC who have progressed on or after platinum-containing chemotherapy was considered clinically meaningful but not statistically significant as per FDA review. It is another treatment option for metastatic NSCLC who have progressed on or after platinum-containing chemotherapy. Median overall survival was 11.4 months in the atezolizumab arm versus 9.5 months in the docetaxel arm. Overall ORR was the same (15%) in both arms. The DoR was 18.6 months in the atezolizumab arm and 7.2 months in the docetaxel arm. The objective response rate was 14.8% in all patients in cohort 2. Complete response was 5.5% and partial response was 9.4%. Compared with other second-line treatment options, pembrolizumab had a partial response rate at 41%, nivolumab had a complete response in non-squamous NSCLC at 1.4% and partial response at 18%, and ramucirumab had median OS at 10.5 months and 4.5 months for progression-free survival.

The risks associated with the use of atezolizumab are immune-related pneumonitis, hepatitis, colitis, and endocrinopathies along with infections, infusion-related reactions and embryo-fetal toxicity. Other PD-L1 inhibitors such as pembrolizumab and nivolumab share the same immune-related risks as atezolizumab except for the infections seen with atezolizumab. Immune-mediated nephritis and renal dysfunction were unique to only pembrolizumab and nivolumab. None of the product labeling for these drugs include a Boxed Warning for any of these risks.

Ramucirumab, another second-line option for metastatic NSCLC had a Boxed Warning for hemorrhage, gastrointestinal perforation, and impaired wound healing. Gastrointestinal perforation was also shared with erlotinib, another second-line option. Cases of interstitial lung disease, renal failure, and hepatotoxicity with or w/o hepatic impairment, bullous/exfoliative skin disorders, myocardial infarction/ischemia, cerebrovascular accident, microangiopathic hemolytic anemia with thrombocytopenia, ocular disorders, hemorrhage in patients taking warfarin, and embryo-fetal toxicity were also seen with erlotinib. For crizotinib, hepatotoxicity, interstitial lung disease, QT interval prolongation, bradycardia, severe visual loss, and embryofetal toxicity were included under the Warnings & Precautions section of labeling. For ceritinib, severe or persistent gastrointestinal toxicity, hepatotoxicity, ILD, QT interval prolongation, hyperglycemia, bradycardia, pancreatitis, and embryofetal toxicity were seen. Hepatotoxicity and interstitial lung disease were common among erlotinib, crizotinib and ceritinib. Embryo-fetal toxicity was common among atezolizumab, erlotinib, crizotinib, and ceritinib.

None of the above drugs warranted risk management beyond labeling for approval. The adverse events for atezolizumab will be communicated in the Warnings & Precautions section of labeling which will also include when to withhold treatment, administer corticosteroids to help mitigate a risk, or permanently discontinue treatment with atezolizumab.

The likely prescribing population for atezolizumab will be oncologists who are familiar with the disease and adverse events seen with this drug and their management.

## **9 Conclusion & Recommendations**

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Based on the available efficacy and safety data, anticipated prescribing population, and patient population for use of this drug, DRISK and DOP1 agree that a REMS is not necessary for atezolizumab to ensure the benefits outweigh the risks. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile.

## **10 Appendices**

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### **10.1 MATERIALS REVIEWED**

The following is a list of materials informing this review:

- Genentech Inc., Clinical Overview (section 2.5), atezolizumab
- Draft Review by Chana Weinstock-September 11, 2016
- July 12, 2016 Midcycle Slides by Drs. Chana Weinstock & Daniel Suzman
- Tecentriq (atezolizumab) draft label, August 26, 2016

### **10.2 TABLES**

**Table 1: 1<sup>st</sup> and 2<sup>nd</sup> line Therapies Currently Used to Treat Non-Small Cell Lung Cancer**

Product Trade Name (Generic), Year of Approval	Approved Indication	Dosing/Administration	Important Safety and Tolerability Issues	Risk Management
Abraxane (paclitaxel) <sup>7</sup> 2005	Locally advanced or metastatic NSCLC  MOA: microtubule inhibitor	Dosing Varies by Indication	<i>Neutropenia</i> , nervous system, sepsis, pneumonitis, hepatic impairment, albumin	<i>Boxed Warning</i>  <i>Patient Information</i>
Taxotere (docetaxel) <sup>8</sup> 1996	Locally advanced or metastatic NSCLC after platinum therapy failure; and with cisplatin for unresectable, locally advanced or metastatic untreated NSCLC  MOA: microtubule inhibitor	Dosing Varies By Indication	<i>Toxic Deaths, hepatotoxicity, neutropenia, hypersensitivity reactions, and fluid retention</i> , acute myeloid leukemia, cutaneous & neurologic reactions, eye disorders, asthenia	<i>Boxed Warning</i>  <i>Patient Information</i>
Tarceva (erlotinib hydrochloride) <sup>9</sup> 2004	First-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test. (1.1)  Maintenance treatment of patients with locally advanced or metastatic NSCLC whose disease has not progressed after four cycles of platinum-based first-line chemotherapy.  MOA: EGFR	150 mg orally, on an empty stomach, once daily.	Interstitial lung disease, renal failure, hepatotoxicity with or w/o hepatic impairment, gastrointestinal perforation, bullous/exfoliative skin disorders, myocardial infarction/ischemia, cerebrovascular accident, microangiopathic hemolytic anemia with thrombocytopenia, ocular disorders, hemorrhage in patients taking warfarin, embryo-fetal toxicity	

<sup>7</sup> Abraxane (paclitaxel) US Package Insert (7/2015)

<sup>8</sup> Taxotere (docetaxel) US Package Insert (12/2015)

<sup>9</sup> Tarceva (erlotinib hydrochloride) US Package Insert (6/2016)

Product Trade Name (Generic), Year of Approval	Approved Indication	Dosing/Administration	Important Safety and Tolerability Issues	Risk Management
Gilotrif (afatinib) <sup>10</sup> 2013	First-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test  MOA: EGFR	40 mg orally, once daily	Diarrhea, bullous and exfoliative skin disorders, ILD, hepatic toxicity, keratitis, embryo-fetal toxicity	<i>Patient Information</i>
Xalkori (crizotinib) <sup>11</sup> 2011	metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test.  MOA: ALK	250 mg orally, twice daily	Hepatotoxicity, interstitial lung disease, QT interval prolongation, bradycardia, severe visual loss, embryofetal toxicity	
Zykadia (ceritinib) <sup>12</sup> 2014	ALK-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib  MOA: ALK	750 mg orally once daily	Severe or persistent gastrointestinal toxicity, hepatotoxicity, ILD, QT Interval Prolongation, Hyperglycemia, Bradycardia, Pancreatitis, Embryofetal toxicity	Patient Information
Alecensa (alectinib) <sup>13</sup> 2014	ALK-positive, metastatic NSCLC who have progressed on or are intolerant to crizotinib  MOA:ALK	600 mg orally twice daily	Hepatotoxicity, ILD, bradycardia, sever myalgia/CPK elevation, embryo-fetal toxicity	Patient Information

<sup>10</sup> Gilotrif (afatinib) US Package Insert

<sup>11</sup> Xalkori (crizotinib) US Package Insert

<sup>12</sup> Zykadia (ceritinib) US Package Insert

<sup>13</sup> Alecensa (alectinib) US Package Insert (12/2015)

Product Trade Name (Generic), Year of Approval	Approved Indication	Dosing/Administration	Important Safety and Tolerability Issues	Risk Management
Keytruda (pembrolizumab) <sup>14</sup> 2014	metastatic NSCLC whose tumors express PD-L1 as determined by an FDA-approved test and who have disease progression on or after platinum-containing chemotherapy, recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy.  MOA: PDL-1	2 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity	Immune-mediated pneumonitis, colitis, hepatitis, endocrinopathies, nephritis & renal dysfunction, adverse reactions, infusion-related reactions, embryofetal toxicity	Medication Guide
Opdivo (nivolumab) <sup>15</sup> 2014	Metastatic non-small cell lung cancer in patients with progression on or after platinum-based chemotherapy.  MOA: PDL-1	3 mg/kg every 2 weeks	Immune-mediated pneumonitis, colitis, hepatitis, endocrinopathies, nephritis & renal dysfunction, rash, encephalitis, adverse reactions, infusion reactions, embryofetal toxicity	Medication Guide
Cyramza (ramucirumab) <sup>16</sup> 2014		10 mg/kg administered by intravenous infusion over 60 minutes on day 1 of a 21-day cycle prior to docetaxel infusion.	<i>Hemorrhage, gastrointestinal perforation, impaired wound healing</i>	<i>Boxed Warning</i>

<sup>14</sup> Keytruda (pembrolizumab) US Package Insert (8/2016)

<sup>15</sup> Opdivo (nivolumab) US Package Insert (3/2015)

<sup>16</sup> Cyramza (ramucirumab) US Package Insert (4/2015)

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