CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761232Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
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	761232
PDUFA Goal Date	July 12, 2022
OSE RCM #	2022-1269
Reviewer Name(s)	Till Olickal, Ph.D., Pharm.D.
Team Leader	Naomi Boston, Pharm.D.
Deputy Director	Laura Zendel, Pharm.D.
Review Completion Date	January 12, 2024
Subject	Evaluation of the need for a REMS
Established Name	Tislelizumab-jsgr
Trade Name	Tevimbra
Name of Applicant	BeiGene USA, Inc.
Therapeutic Class	Programmed death receptor-1 (PD-1) blocking antibody
Formulation(s)	100 mg/10 mL (10 mg/mL) solution in a single-dose vial
Dosing Regimen	200 mg as an intravenous infusion once every 3 weeks

Table of Contents

EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for Tevimbra (tislelizumab-jsgr) is necessary to ensure the benefits outweigh its risks. BeiGene USA, Inc. submitted a Biologic Licensing Application (BLA) 761232 for tislelizumab-jsgr with the proposed indication for the treatment of adult patients with unresectable or metastatic esophageal squamous cell carcinoma (ESCC) after prior systemic chemotherapy that did not include a programmed death-(ligand)1 [PD-(L)1] inhibitor. The serious risks associated with the use of tislelizumab-jsgr are severe and fatal immune-mediated adverse reactions, infusion-related reactions, complications of allogeneic hematopoietic stem cell transplantation (HSCT), and embryo-fetal toxicity. The Applicant did not submit a REMS or risk management plan with this application.

The Division of Risk Management (DRM) and the Division of Oncology 3 (DO3) have determined that a REMS is not necessary to ensure the benefits of tislelizumab-jsgr outweigh its risks. Based on the efficacy and safety information currently available, the clinical reviewer stated that tislelizumab-jsgr shows clinically meaningful benefit and recommends approval of tislelizumab-jsgr as a programmed death receptor-1 (PD-1) blocking antibody for the treatment of adult patients with unresectable or metastatic ESCC after prior systemic chemotherapy that did not include a PD-(L)1 inhibitor. The review team concluded that tislelizumab-jsgr provided a statistically significant and clinically meaningful improvement in overall survival (OS) compared with chemotherapy. The safety profile is similar to programmed death receptor-1 (PD-1) blocking antibodies for similar indications, which do not require a REMS. If approved, labeling will be similar to the currently approved PD-1 blocking antibodies, such as pembrolizumab (Keytruda) and nivolumab (Opdivo). Management of the adverse events of tislelizumab-jsgr will be communicated in Warnings and Precautions, Patient Counseling Information, and the Medication Guide.

1 Introduction

This review by the Division of Risk Management (DRM) evaluates whether a REMS for Tevimbra (tislelizumab-jsgr) is necessary to ensure the benefits outweigh its risks. BeiGene USA, Inc. submitted a Biologic Licensing Application (BLA) 761232 for tislelizumab-jsgr with the proposed indication for the treatment of adult patients with unresectable or metastatic esophageal squamous cell carcinoma (ESCC) after prior systemic chemotherapy that did not include a programmed death-(ligand)1 [PD-(L)1] inhibitor.[1] This application is under review in the Division of Oncology 3 (DO3). The applicant did not submit a REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Tislelizumab-jsgr is a new molecular entity (NME) BLA type 351(a) pathway application.[a] It is a programmed death receptor-1 (PD-1) blocking antibody. Tislelizumab-jsgr binds to PD-1 and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response.[1] Tislelizumab-jsgr is proposed to be supplied as 100 mg/10

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

mL (10 mg/mL) injection solution in a single-dose vial. The recommended dosage of tislelizumab-jsgr is 200 mg administered as an intravenous infusion once every 3 weeks, until disease progression or unacceptable toxicity.[b,1] Tislelizumab-jsgr was granted orphan designation on Nov 6, 2019, for the treatment of esophageal cancer. Tislelizumab-jsgr has received marketing authorization in China for various indications; the ESCC indication was approved in China on April 8, 2022.[2]

2.2 Regulatory History

The following is a summary of the regulatory history for tislelizumab-jsgr (BLA 761232) relevant to this review:

- 11/13/2017: Investigation New Drug (IND) 135699 submission for tislelizumab-jsgr received.
- 11/06/2019: Orphan designation granted for the treatment of esophageal cancer.
- 07/09/2021: BLA 761232 submission from BeiGene USA, Inc. for tislelizumab-jsgr with the proposed indication for the treatment of adult patients with unresectable or metastatic ESCC after prior systemic chemotherapy that did not include a PD-(L)1 inhibitor, received.
- 12/16/2021: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant at the Post Mid-cycle meeting that based on the currently available data, there were no safety issues that require a REMS for tislelizumab-jsgr.

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

Esophageal cancer (EC) is a type of malignant tumor in the digestive system and is one of the leading causes of cancer-related death, seriously affecting human health worldwide. EC is the eighth most diagnosed cancer and is the sixth leading cause of cancer-related deaths worldwide.[3] In the United States, EC is the 6th most commonly diagnosed gastrointestinal malignancy but contributes to the 4th highest number of deaths. Over three-quarters of EC affect men.[4] Cancer of the esophagus occurs in several forms: squamous cell carcinoma (SCC), adenocarcinoma (AC), sarcomas, small cell carcinomas and rare types such as lymphomas and melanomas.[3] In patients with esophageal cancer, ESCC accounts for the majority of cases, approximately 90%, worldwide.[3,5] Many of the patients with esophageal squamous cell carcinoma present in late adult life mainly in the seventh decade. Patients with esophageal squamous cell carcinoma often present with symptoms related to difficulty in swallowing as well as weight loss.[5] In 2020, there were an estimated 0.6 million new cases of EC and 0.54 million deaths occurred as a result of this disease based on GLOBOCAN 2020.[6,3] The estimated number of new

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

cases of EC in the United States in 2023 is 21,560[c], with 16,120 estimated deaths due to the disease[d]. The prognosis of patients with cancer remains poor; five-year survival for patients diagnosed with EC is approximately 21.7%.[7]

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Patients with early ESCC should undergo an endoscopic resection. If histological margins are infiltrated with tumor cells or other risk factors for lymph node metastasis are present, further resective surgery should be offered. In a locally advanced setting, radiochemotherapy with or without resection remains the standard of care.[8] ESCC is most often seen in the mid third of the esophagus. Approximately half of the squamous cell carcinoma is moderately differentiated, and most of the cases present at stage III; more than 30% of patients with ESCC are diagnosed at an advanced or metastatic stage.[5,9] Patients are characterized as advanced when the cancer is metastatic or cannot be resected or treated with definitive radiochemotherapy. In the first-line setting, platin/fluoropyrimidine-based chemotherapy with or without checkpoint inhibitors presents the current treatment standard. Accumulated evidence has shown that the PD-1/PD-L1 pathway is a promising therapeutic target for cancer immunotherapy. The meta-analysis by Guo W, Wang P, Li N, et al. indicated that high PD-L1 expression in ESCC was associated with distant metastasis and reduced overall survival (OS).[10] Recently, pembrolizumab[11] and nivolumab[12], two immune checkpoint inhibitors (CPIs) targeting PD-1, have received approval from the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), both as combination therapy for advanced or metastatic ESCC in the 1L setting. In July 2019, the FDA approved pembrolizumab for patients with recurrent, locally advanced or metastatic, ESCC whose tumors express PD-L1 Combined Positive Score (CPS) ≥10 with disease progression after one or more prior lines of systemic therapy. In June 2020, the US FDA approved nivolumab for patients with unresectable advanced, recurrent or metastatic ESCC after prior fluoropyrimidine- and platinum-based chemotherapy. On May 27th, 2022, FDA approved nivolumab in combination with fluoropyrimidine- and platinum-based chemotherapy, or in combination with ipilimumab[13] for the first-line treatment of patients with advanced or metastatic ESCC.[14] Despite these new treatment strategies in ESCC, both in localized and advanced settings, as immunotherapy showed promising trial results, the prognosis in advanced disease remains poor. There is a clear need for therapeutic strategies with new alternative modalities that encompass a better tolerated treatment option.

4 Benefit Assessment

The efficacy of tislelizumab-jsgr was evaluated in multicenter, randomized (1:1), open-label trial, RATIONALE-302 (NCT03430843), in 512 adult patients with unresectable advanced or metastatic ESCC who progressed on or after prior systemic chemotherapy. Patients were enrolled regardless of their tumor PD-L1 expression level. PD-L1 expression was evaluated at a central laboratory using the Ventana PD-L1 (SP263) assay that identified PD-L1 staining on both tumor and tumor-associated immune cells.

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

[d] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

The trial excluded patients who received a prior immune checkpoint inhibitor, had brain or leptomeningeal metastases that were symptomatic or required treatment, active autoimmune disease, a medical condition requiring systemic corticosteroids or immunosuppressants, or apparent tumor invasion of organs adjacent to the esophageal tumor. Patients were randomized (1:1) to receive either tislelizumab-jsgr 200 mg every 3 weeks or investigator's choice of chemotherapy (ICC), all given intravenously: paclitaxel 135-175 mg/m^2 every 3 weeks or 80-100 mg/m^2 weekly, docetaxel 75 mg/m^2 every 3 weeks, or irinotecan 125 mg/m^2 on Days 1 and 8 of every 3-week cycle. Patients were treated until disease progression assessed by the investigator or unacceptable toxicity. The median duration of exposure was 2.8 months (range: 0.2 to 28.3 months) in tislelizumab-jsgr -treated patients and 1.5 months (range: 0.2 to 19.2 months) in paclitaxel, docetaxel, or irinotecan-treated patients. A total of 512 patients were enrolled and randomized to tislelizumab-jsgr (n=256) or ICC (n=256) [irinotecan (46%), paclitaxel (33%), or docetaxel (21%)]. The major efficacy outcome measure was overall survival (OS) in the Intent-to-Treat (ITT) population. Additional efficacy outcome measures were investigator-assessed progression-free survival (PFS), overall response rate (ORR), and duration of response (DOR) per RECIST v1.1. The efficacy results are summarized in Table 1.[1,14,e]

Table 1: Efficacy Results in RATIONALE-302 in ITT Population [1,14,e]

Endpoint	**tislelizumab-jsgr (N=256)**	**ICC (N=256)**
Overall Survival		
Deaths n (%)	197 (77.0)	213 (83.2)
Median (months) [a] (95% CI)	8.6 (7.5, 10.4)	6.3 (5.3, 7.0)
Hazard ratio [b] (95% CI)	0.70 (0.57, 0.85)	
p-value [c]	0.0001	
Progression-Free Survival		
Disease progression or death (%)	223 (87.1)	180 (70.3)
Median (months) [a] (95% CI)	1.6 (1.4, 2.7)	2.1 (1.5, 2.7)
Hazard ratio [b] (95% CI)	0.83 (0.67, 1.01)	
Objective Response Rate [d]		
ORR (%) (95% CI)	15.2 (11.1, 20.2)	6.6 (3.9, 10.4)
Complete response n (%)	5 (2.0)	1 (0.4)
Partial response n (%)	34 (13.3)	16 (6.3)
Duration of Response		
Median (months) [a] (95% CI)	10.3 (6.5, 13.2)	6.3 (2.8, 8.5)

CI = confidence interval, ORR = objective response rate
[a] Estimated using Kaplan-Meier method.
[b] Based on Cox regression model stratified by baseline ECOG status and ICC option.
[c] One-sided p-value based on log rank test stratified by ECOG performance status and ICC option.
[d] Confirmed response.

[e] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition*

The clinical reviewer stated that in RATIONALE-302, tislelizumab-jsgr provided a statistically significant and clinically meaningful improvement in OS compared with chemotherapy. The OS HR in the ITT was 0.70 (95% CI 0.57, 0.85; one-sided p-value = 0.0001) with a median OS of 8.6 months (95% CI 7.5, 10.4) in the tislelizumab arm and 6.3 months (95% CI 5.3, 7) in the ICC arm. The ORR was 15.2% (95% CI 11.1, 20.2) in the tislelizumab arm and 6.6% (95% CI 3.9, 10.4) in the ICC arm. Duration of response was prolonged in the tislelizumab arm when compared to the ICC arm (10.3 vs. 6.3 months). The HR for PFS in the ITT was 0.83 (95% CI 0.67, 1.01). These results are supportive of the primary outcomes and consistent with immune checkpoint inhibitors effects (modest effect on PFS and ORR) in ESCC.

5 Risk Assessment & Safe-Use Conditions

The following section is a summary of relevant safety information to date for tislelizumab-jsgr. The safety of tislelizumab-jsgr was evaluated in Study RATIONALE-302 (see Section 4: Benefit Assessment). [1]

The pooled safety population included data from 1972 patients exposed to tislelizumab-jsgr as a single agent in two randomized open-label, active-controlled studies (RATIONALE-302, and BGB-A317-303 which evaluated patients with locally advanced or metastatic non-small cell lung cancer) and five open-label, single-arm studies (BGB-A317-208 evaluating patients with previously treated, unresectable hepatocellular carcinoma, BGB-A317-204 evaluating locally advanced or metastatic urothelial bladder cancer, BGB-A317-203 evaluating relapsed or refractory classical Hodgkin lymphoma, and BGB-A317-102 and BGB-A317_Study_001 evaluating advanced solid tumors). The pooled safety population includes 307 patients with ESCC and 1665 patients with other advanced or recurrent tumors. Tislelizumab-jsgr was administered at a dose of 200 mg intravenously once every 3 weeks, except in studies BGB-A317 Study 001 where patients also received other dosage regimens. Among the 1972 patients, 37% were exposed for longer than 6 months, and 20% were exposed for longer than 12 months.[1]

Deaths

In FDA's analysis, 196 (77%) of all deaths in Study RATIONALE-302 are categorized as follows: 157 (62%) disease under study/progression of disease, 21 (8%) indeterminate, or 18 (7%) adverse event where tislelizumab-jsgr may have contributed to the event, however, causality is difficult to determine in all cases. Fatal adverse events in patients receiving tislelizumab-jsgr included the following which occurred in more than one patient: pneumonia/pneumonitis (5 patients), hemorrhage (3 patients), and death due to an unknown cause (3 patients).[1] One patient on the tislelizumab arm died from hepatic failure on Day 45 of the study. Based on the narrative, immune-mediated hepatitis could not be ruled out.[14] Examination of the specific AEs resulting in death does not indicate a notable imbalance between the study arms and the events leading to death do not appear differ from what is expected in this patient population undergoing treatment.

Serious Adverse Events (SAE)

Serious adverse reactions occurred in 41% of patients. The most frequent serious adverse reactions (≥ 2%) were pneumonia, dysphagia, hemorrhage, pneumonitis (including pneumonitis and immune-mediated pneumonitis), and esophageal obstruction. Permanent discontinuation of tislelizumab-jsgr due to an adverse reaction occurred in 19% of patients. Adverse reactions which resulted in permanent discontinuation in ≥ 1% of patients were hemorrhage, pneumonitis (including pneumonitis and immune-

mediated pneumonitis), and pneumonia. Dosage interruptions of tislelizumab-jsgr due to an adverse reaction occurred in 23% of patients. Adverse reactions which required dosage interruptions in ≥ 2% of patients were pneumonia, pneumonitis, and fatigue.[1]

The most common (≥ 20%) adverse reactions, including laboratory abnormalities, were increased glucose (46%), decreased hemoglobin (45%), decreased lymphocytes (43%), decreased sodium (34%), decreased albumin (33%), increased alkaline phosphatase (32%), anemia (31%), fatigue (28%), increased AST (27%), musculoskeletal pain (24%), decreased weight (23%), increased ALT (23%), and cough (22%).[1]

Similar to other PD-1 blocking antibodies such as pembrolizumab (Keytruda)[11] and nivolumab (Opdivo)[12], if approved, labeling will include descriptions and management for the following risks in the Warnings and Precautions: severe and fatal immune-mediated adverse reactions, infusion-related reactions, complications of allogeneic hematopoietic stem cell transplantation (HSCT) and embryo-fetal toxicity. These risks are further described below.

5.1 SEVERE AND FATAL IMMUNE-MEDIATED ADVERSE REACTIONS

Immune-mediated adverse reactions can occur at any time after starting treatment with a PD-1/PD- L1 blocking antibody. Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Similar to other PD-1 blocking antibodies such as pembrolizumab (Keytruda)[11] and nivolumab (Opdivo)[12], labeling instructs healthcare providers to monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions, and evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, labeling instructs healthcare providers to initiate appropriate workup to exclude alternative etiologies, including infection. Labeling also instructs healthcare providers to withhold or permanently discontinue tislelizumab-jsgr depending on severity, and in general, if tislelizumab-jsgr requires interruption or discontinuation, similar to other PD-1/PD-L1 blocking antibodies, recommendations for initiating systemic corticosteroid therapy will be communicated in the Warnings and Precautions section of the label for the management of immune-mediated adverse reactions. To increase the prominence of this information and promote mitigation of immune-mediated adverse reactions, a Medication Guide as part of labeling will be included to inform patients regarding the potential risks of immune-mediated adverse reactions. Monitoring and dosage modifications for toxicities to address the safety issues with tislelizumab-jsgr will be included in the Dosage and Administration section of the label.[1]

Section 5.1 of the draft labeling describes the risk of immune-mediated adverse reactions which include immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis, immune-mediated endocrinopathies, immune-mediated nephritis with renal dysfunction, immune-mediated dermatologic adverse reactions, and other immune-mediated adverse reactions. These immune-mediated adverse reactions are summarized below[1]:

Immune-mediated pneumonitis:

In clinical studies, immune-mediated pneumonitis occurred in 3.8% (75/1972) of patients receiving tislelizumab-jsgr, including fatal (0.2%), Grade 4 (0.3%), Grade 3 (1.4%), and Grade 2 (1.7%) adverse reactions. Pneumonitis led to permanent discontinuation of tislelizumab-jsgr in 35 (1.8%) patients and withholding of tislelizumab-jsgr in 27 (1.4%) patients. Systemic corticosteroids were required in all patients with pneumonitis. Immune-mediated pneumonitis resolved in 47% of the 75 patients. Of the 27

patients in whom tislelizumab-jsgr was withheld for pneumonitis, 18 reinitiated tislelizumab-jsgr after symptom improvement; of these, 3 (17%) patients had recurrence of pneumonitis.[1]

Immune-mediated colitis:

In clinical studies, 0.9% (17/1972) of patients receiving tislelizumab-jsgr was reported with immune-mediated colitis, including Grade 3 (0.4%), and Grade 2 (0.5%) adverse reactions. Colitis led to permanent discontinuation of tislelizumab-jsgr in 2 (0.1%) patients and withholding of tislelizumab-jsgr in 10 (0.5%) patients. All patients received systemic corticosteroids. Twelve (71%) of the 17 patients received high-dose systemic corticosteroids. Two (12%) of the 17 patients received immunosuppressive treatment. Immune-mediated colitis resolved in 88% of the 17 patients. Of the 10 patients in whom tislelizumab-jsgr was withheld for colitis, 8 reinitiated tislelizumab-jsgr after symptom improvement; of these, 1 (13%) patient had recurrence of colitis.[1]

Immune-Mediated Hepatitis:

In clinical studies, 1.7% (34/1972) of patients receiving tislelizumab-jsgr was reported with immune-mediated hepatitis, including fatal (0.1%), Grade 4 (0.1%), Grade 3 (1%), and Grade 2 (0.6%) adverse reactions. Immune-mediated hepatitis led to permanent discontinuation in 9 (0.5%) patients and withholding of tislelizumab-jsgr in 20 (1%) patients. All patients received systemic corticosteroids. Twenty-nine (85%) of the 34 patients received high-dose systemic corticosteroids. One patient (2.9%) of the 34 patients received immunosuppressive treatment. Immune-mediated hepatitis resolved in 59% of the 34 patients. Of the 20 patients in whom tislelizumab-jsgr was withheld for hepatitis, 12 reinitiated tislelizumab-jsgr after symptom improvement; of these, 2 (17%) patients had recurrence of hepatitis.

Immune-mediated endocrinopathies:

In clinical studies, 0.3% (6/1972) of patients receiving tislelizumab-jsgr were reported with adrenal insufficiency, which includes Grade 4 (0.1%), Grade 3 (0.1%), and Grade 2 (0.2%) adverse reactions. Adrenal insufficiency did not lead to permanent discontinuation of tislelizumab-jsgr. Tislelizumab-jsgr was withheld in 5 out of the 6 patients. All 6 patients received systemic corticosteroids. Two (33%) of the 6 patients received high-dose systemic corticosteroids. Adrenal insufficiency resolved in 17% of the 6 patients.[1]

In clinical studies, 0.1% (1/1972) of patients receiving tislelizumab-jsgr were reported with hypophysitis/hypopituitarism, including a Grade 2 (0.1%) adverse reaction. No tislelizumab-jsgr treatment discontinuation or withholding was required.[1]

Immune-mediated thyroiditis occurred in 0.4% (7/1972) of patients receiving tislelizumab-jsgr, including Grade 2 (0.3%) adverse reactions. Thyroiditis did not lead to permanent discontinuation of tislelizumab-jsgr. Tislelizumab-jsgr was withheld in 1 (0.1%) patient. One (14%) of the 7 patients received systemic corticosteroids. Thyroiditis resolved in 29% of the 7 patients.[1]

In clinical studies, 0.6% (12/1972) of patients receiving tislelizumab-jsgr were reported with immune-mediated hyperthyroidism, including Grade 3 (0.1%), and Grade 2 (0.5%) adverse reactions. Hyperthyroidism led to the permanent discontinuation of tislelizumab-jsgr in 1 (0.1%) patient and

withholding of tislelizumab-jsgr in 1 (0.1%) patient. One (8%) of the 12 patients received systemic corticosteroids. Hyperthyroidism resolved in 92% of the 12 patients. Immune-mediated hypothyroidism occurred in 7% (132/1972) of patients receiving tislelizumab-jsgr, including Grade 4 (0.1%) and Grade 2 (5%) adverse reactions. Tislelizumab-jsgr was not permanently discontinued in any patient, while treatment was withheld in 6 (0.3%) patients. Two (1.5%) of the 132 patients received systemic corticosteroids. All 132 patients received hormone replacement therapy. Hypothyroidism resolved in 27% of the 132 patients. The majority (86%) of patients with hypothyroidism required long-term thyroid hormone replacement.[1]

Immune-mediated dermatologic adverse reactions

In clinical studies, 1.2% (24/1972) of patients receiving tislelizumab-jsgr were reported with immune-mediated dermatologic adverse reactions, which includes Grade 4 (0.2%), Grade 3 (0.4%), and Grade 2 (0.4%) adverse reactions. Dermatologic adverse reactions led to permanent discontinuation of tislelizumab-jsgr in 3 (0.2%) patients and withholding of tislelizumab-jsgr in 9 (0.5%) patients. Twenty-three (96%) of the 24 patients received systemic corticosteroids. Immune-mediated skin reactions resolved in 58% of the 24 patients. Of the 9 patients in whom tislelizumab-jsgr was withheld for dermatologic adverse reactions, 8 reinitiated tislelizumab-jsgr after symptom improvement; of these, 2 (25%) patients had recurrence of immune-mediated rash.[1]

Other immune-mediated adverse reactions.

Section 5.1 of the draft labeling also describes other immune-mediated adverse reactions, including myocarditis, meningitis, uveitis, autoimmune hemolytic anemia that were reported in < 1% of patients receiving tislelizumab-jsgr .[1]

5.2 INFUSION-RELATED REACTIONS

In clinical studies, 4.2% (83/1972) of patients receiving tislelizumab-jsgr experienced infusion related reactions, including Grade 3 or higher (0.3%) reactions. If tislelizumab-jsgr is approved, the labeling instructs healthcare providers to monitor patients for signs and symptoms of infusion-related reactions, interrupt or slow the rate of infusion or permanently discontinue tislelizumab-jsgr based on severity of reaction.[1]

5.3 COMPLICATIONS OF ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT)

Transplant-related complications include hyperacute graft-versus-host-disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease (VOD) after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause), have been reported in allogeneic HSCT patients treated with PD-1/L-1 blocking antibody. If approved, this risk will be communicated in the warnings and precautions section of the label.[1]

5.4 EMBRYO-FETAL TOXICITY

Based on its mechanism of action and findings from animal data, tislelizumab-jsgr can cause fetal harm when administered to a pregnant woman. Animal studies have demonstrated that inhibition of the PD-

1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus resulting in fetal death. The proposed label states to advise pregnant women of the potential risk to a fetus. If approved, healthcare providers should advise females of reproductive potential to use effective contraception during treatment with tislelizumab-jsgr and for 4 months after the last dose.[1]

6 Expected Postmarket Use

According to the currently proposed indication, if approved, tislelizumab-jsgr will be used in both inpatient and outpatient settings (such as infusion centers). It is expected that oncologists, familiar with the management of toxicities such as immune-mediated adverse reactions, infusion-related reactions, complications of allogeneic HSCT and embryo-fetal toxicity, will be the likely prescribers of tislelizumab-jsgr.

7 Risk Management Activities Proposed by the Applicant

The applicant did not propose any risk management activities for tislelizumab-jsgr beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS

When evaluating factors of whether a REMS is necessary to ensure that the benefits outweigh the risks for tislelizumab-jsgr, this reviewer considered the patient population, seriousness of the disease, expected benefit of the drug, seriousness of known or potential adverse events, and the likely prescribing population.

Tislelizumab-jsgr is a PD-1 blocking antibody, with the proposed indication for the treatment of adult patients with unresectable or metastatic ESCC after prior systemic chemotherapy that did not include a PD-(L)1 inhibitor. EC is the eighth most commonly diagnosed cancer and is the sixth leading cause of cancer death worldwide. ESCC accounts for most cases, approximately 90%, worldwide. The prognosis of patients with EC remains poor; five-year survival for patients diagnosed with EC is approximately 21.7%. Despite new treatment strategies in ESCC, both in localized and advanced settings, the prognosis in advanced disease remains poor. Based on the efficacy and safety information currently available, the clinical reviewer stated that tislelizumab-jsgr shows clinically meaningful benefit and recommends approval of tislelizumab-jsgr for the treatment of adult patients with unresectable or metastatic ESCC after prior systemic chemotherapy that did not include a PD-(L)1 inhibitor.[1,14]

DRM and DO3 have determined that if approved, a REMS is not necessary to ensure the benefits of tislelizumab-jsgr outweigh its risks. Tislelizumab-jsgr appeared efficacious in its primary outcome of OS and secondary outcomes of PFS, ORR and DOR, and its risks can be communicated and managed through labeling.[1,14] The review team concluded that in RATIONALE-302, tislelizumab-jsgr provided a statistically significant and clinically meaningful improvement in OS compared with chemotherapy.[14] The most concerning adverse reactions observed with the use of tislelizumab-jsgr are risks for severe and fatal immune-mediated adverse reactions, infusion-related reactions, complications of allogeneic HSCT and embryo-fetal toxicity, which are the same as in the currently approved PD-1 blocking antibodies such as pembrolizumab (Keytruda)[11] and nivolumab (Opdivo)[12]. It is expected that oncologists, familiar with the management of these toxicities, will be the likely prescribers of tislelizumab-jsgr. The review

team concluded the observed safety profile of tislelizumab-jsgr in patients with metastatic or unresectable ESCC was consistent with the established safety profile of checkpoint inhibitors in patients with ESCC and other types of cancer.[14] None of the PD-1 blocking antibody products have a boxed warning in their labels, nor was a REMS required for approval. At the time of this review, none of these risks will receive a boxed warning in the label.[1] If tislelizumab-jsgr is approved, similar to approved PD-1 blocking antibodies such as pembrolizumab and nivolumab, Warnings and Precautions in the labeling will be used to communicate the safety issues and management of toxicities associated with tislelizumab-jsgr, as well as information to be included in Patient Counseling Information, and a Medication Guide as part of labeling to inform patients regarding the potential risks.

9 Conclusion & Recommendations

Based on the available data, a REMS is not necessary to ensure the benefits outweigh the risks of tislelizumab-jsgr for the treatment of adult patients with unresectable or metastatic ESCC after prior systemic chemotherapy that did not include a PD-(L)1 inhibitor. The management of the risks associated with tislelizumab-jsgr treatment will be communicated through labeling. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 References

[1] Draft Prescribing Information for tislelizumab-jsgr as currently edited by the FDA, last updated November 2, 2022.

[2] BeiGene USA, Inc. Summary of Clinical Safety of tislelizumab-jsgr, BLA 761232, dated July 12, 2021.

[3] Liu CQ, Ma YL, Qin Q, et al. Epidemiology of esophageal cancer in 2020 and projections to 2030 and 2040. Thorac Cancer. Jan 2023;14(1):3-11.

[4] Codipilly DC, Wang KK. Squamous Cell Carcinoma of the Esophagus. Gastroenterol Clin North Am. Sep 2022;51(3):457-484.

[5] Lam AK. Introduction: Esophageal Squamous Cell Carcinoma-Current Status and Future Advances. Methods Mol Biol. 2020;2129:1-6.

[6] Ferlay J, Colombet M, Soerjomataram I, et al. Cancer statistics for the year 2020: An overview. Int J Cancer. Apr 5 2021.

[7] National Institutes of Health (NIH). The Surveillance, Epidemiology and End Results (SEER) program of the National Cancer Institute (NCI). Cancer Stat Facts: Esophageal Cancer. https://seer.cancer.gov/statfacts/html/esoph.html. Accessed January 5, 2024.

[8] Puhr HC, Prager GW, Ilhan-Mutlu A. How we treat esophageal squamous cell carcinoma. ESMO Open. Feb 2023;8(1):100789.

[9] Abraham P, Gricar J, Zhang Y, Shankaran V. Real-World Treatment Patterns and Outcomes in Patients Receiving Second-Line Therapy for Advanced/Metastatic Esophageal Squamous Cell Carcinoma. Adv Ther. Jul 2020;37(7):3392-3403.

[10] Guo W, Wang P, Li N, et al. Prognostic value of PD-L1 in esophageal squamous cell carcinoma: a meta-analysis. Oncotarget. Mar 2 2018;9(17):13920-13933.

[11] Keytruda. Prescribing Information (last updated 12/2023).

[12] Opdivo. Prescribing Information (last updated 10/2023).

[13] Yervoy. Prescribing Information (last updated 2/2023).

[14] Division of Oncology 3 (DO3). Multi-disciplinary Review and Evaluation (draft) for tislelizumab-jsgr, BLA 761232, dated February 28, 2023.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

TILL OLICKAL
01/12/2024 01:02:45 PM

NAOMI S BOSTON
01/12/2024 01:05:36 PM

LAURA A ZENDEL
01/12/2024 01:40:41 PM