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TEVIMBRA® (tislelizumab-jsgr) for Gastric or Gastroesophageal Junction Adenocarcinoma

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PRODUCT PERSPECTIVES

This article was developed by HMP with support from BeOne Medicines.

TEVIMBRA® (tislelizumab-jsgr) for Gastric or Gastroesophageal Junction Adenocarcinoma

An interview with Michael K. Gibson, MD, PhD, FACP
Vanderbilt-Ingram Cancer Center, Nashville, TN

What unmet needs exist in the treatment of gastric cancer?

Gastric cancer is a multifactorial disease that has both genetic and environmental components.[1,2] Globally, gastric cancer is the fifth most diagnosed cancer and the third most common cause of cancer-related death.[1] As gastric cancer can be highly aggressive, there is an increased reliance on early detection and prevention strategies. Over the past several decades, there has been a steady decrease in the incidence and mortality rates due to a better understanding of disease progression.[1,2]

Specific molecular biomarkers, including human epidermal growth factor receptor 2 (HER2), microsatellite instability-high (MSI-H), programmed cell death ligand 1 (PD-L1), and claudin 18.2 (CLDN18.2), have been validated as actionable biomarkers in gastric cancer, and biomarker testing can inform personalized treatment strategies.

What treatment options are available for gastric cancer?

Treatment of gastric cancer often uses endoscopic resection, which may be curative in the early stages of the disease. Given the high rate of relapse, neoadjuvant and adjuvant chemotherapy has become standard practice due to the robust data indicating increased rates of survival post-resection.[1]

Several targeted therapies and immunotherapies that increase patients' overall survival in the first-line metastatic setting have been approved by the US Food & Drug Administration (FDA), including treatments that target HER2, CLDN18.2, and programmed cell death protein 1 (PD-1).[1,3-7]

Trastuzumab is indicated in adults, in combination with cisplatin and capecitabine or 5-fluorouracil, for the treatment of patients with HER2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma who have not received prior treatment for metastatic disease.[3]

Zolbetuximab-clzb is a CLDN18.2-directed antibody indicated in combination with fluoropyrimidine- and platinum-containing chemotherapy for first-line treatment of adults with locally advanced unresectable or metastatic HER2-negative gastric or gastroesophageal junction adenocarcinoma whose tumors are CLDN18.2-positive.[4]

Nivolumab is a PD-1-blocking antibody indicated in combination with fluoropyrimidine- and platinum-containing chemotherapy for treating adults with advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma.[5]

Pembrolizumab is a PD-1-blocking antibody indicated in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy for first-line treatment of adults with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 (CPS ≥1); in combination with fluoropyrimidine- and platinum-containing chemotherapy for first-line treatment of adults with locally advanced unresectable or metastatic HER2-negative gastric or gastroesophageal junction adenocarcinoma.[6]

Tislelizumab-jsgr is a PD-1-blocking antibody indicated in combination with platinum- and fluoropyrimidine-based chemotherapy for the treatment of adult patients with

unresectable or metastatic HER2-negative gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 (≥1).[7]

What is the role of PD-1 in gastric cancer?

PD-1 and its ligands, PD-L1 and PD-L2, maintain immune homeostasis by reducing immune cell targeting to self-tissues via inhibition of T cell activation.[8] In the tumor microenvironment, PD-1, expressed on activated T cells, binds to the PD-L1 ligand expressed on tumor cells, resulting in T cell apoptosis.[9] PD-1 is also expressed by tumor-associated macrophages (TAMs), and overexpression of PD-1 in TAMs results in an increase in tumor growth.[10] The binding of PD-1 to its ligands, therefore, exerts an immunosuppressive effect within the tumor microenvironment, disrupting immune homeostasis and allowing tumor cell immune escape.[8]

What challenges are associated with PD-1 inhibition?

As with many therapeutic targets in oncology, mitigation of resistance to therapy is paramount. Primary resistance to anti–PD-1 therapy may result due to insufficient antigen immunogenicity, dysfunction of antigen presentation, irreversible T cell exhaustion, resistance of IFN-γ signaling, and immunosuppressive tumor microenvironment.[11] All PD-1 blocking antibodies approved for treating gastric cancer, except tislelizumab-jsgr, mimic the function of wild-type human IgG4, which has an intact Fc region that binds to the Fc gamma receptor on type 1 macrophages, resulting in antibody-dependent cell phagocytosis.[12] This process is thought to be a source of resistance to anti–PD-1 therapy.[13]

Acquired resistance after an initial response to anti–PD-1 therapy is also of concern due to dysfunction in tumor-specific T cells and their inability to develop into memory T cells.[11] To overcome resistance, anti–PD-1 antibodies should be paired with additional therapies to enhance T cell priming, reverse T cell exhaustion, increase T cell infiltration, and improve the immunosuppressive microenvironment, thereby increasing the sensitivity of anti–PD-1 therapy.[11]

What is the design of tislelizumab-jsgr?

Tislelizumab-jsgr is engineered to reduce binding to FcγR on macrophages, helping to prevent antibody-dependent cellular phagocytosis, a process that may lead to anti–PD-1 therapy resistance.[12] In preclinical studies, the unique binding orientation of tislelizumab-jsgr to PD-1 resulted in an approximately 30- and 80-fold slower dissociation rate compared with nivolumab and pembrolizumab, respectively. Consequently, tislelizumab-jsgr exhibits increased receptor occupancy at lower concentrations.[14] Additionally, while tislelizumab-jsgr was shown to block PD-L1 binding completely, other anti–PD-1 therapies produced only partial blocking (~80%) at a concentration of 3 µg/mL in a prelinical model.[14] ◆

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PRODUCT MONOGRAPH

This article was developed by HMP with support from BeOne Medicines.

TEVIMBRA®
(tislelizumab-jsgr)
Injection, for intravenous use 10 mg/mL

INDICATION

TEVIMBRA® (tislelizumab-jsgr) is a programmed death receptor-1 (PD-1)-blocking antibody indicated in combination with platinum- and fluoropyrimidine-based chemotherapy for the treatment of adult patients with unresectable or metastatic HER2-negative gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 (≥1).

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Severe and Fatal Immune-Mediated Adverse Reactions

TEVIMBRA is a monoclonal antibody that belongs to a class of drugs that block the PD-1/PD-L1 pathway, thereby removing inhibition of the immune response, potentially breaking peripheral tolerance and inducing immune-mediated adverse reactions. Important immune-mediated adverse reactions listed here may not include all possible severe and fatal immune-mediated reactions.

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. Immune-mediated adverse reactions can occur at any time after starting treatment with a PD-1/PD-L1 blocking antibody. While immune-mediated adverse reactions usually manifest during treatment with PD-1/PD-L1 blocking antibodies, immune-mediated adverse reactions can also manifest after discontinuation of PD-1/PD-L1 blocking antibodies. Immune-mediated adverse reactions observed include immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis, immune-mediated endocrinopathies, immune-mediate nephritis with renal dysfunction, immune-mediated dermatologic adverse reactions, and solid organ transplant rejection.

Please see full Prescribing Information after page 7

PRODUCT INFORMATION

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. Tislelizumab-jsgr decreased tumor growth in xenograft models and a human PD-1 transgenic mouse model.

The binding of the PD-1 ligands PD-L1 and PD-L2 to the PD-1 receptor found on T cells inhibits T-cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors, and signaling through this pathway can contribute to the inhibition of active T-cell immune surveillance of tumors.

PHARMACODYNAMICS/ PHARMACOKINETICS

The tislelizumab-jsgr exposure-response relationship for efficacy and safety and time course of pharmacodynamic response has not been fully characterized.

The peak concentration (C_{max}) and area under the plasma concentration versus time curve (AUC) of tislelizumab-jsgr

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS, CONTINUED

Early identification and management of immune-mediated adverse reactions are essential to ensure the safe use of PD-1/PD-L1 blocking antibodies. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate. Withhold or permanently discontinue TEVIMBRA, depending on the severity of the reaction.

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increased dose proportionally in the dose range of 0.5 (0.2 times the approved recommended dosage in a 70 kg patient) to 10 mg/kg (3.5 times the approved recommended dosage in a 70 kg patient). The steady-state AUC_{tau} of tislelizumab-jsgr is 1,283 mcg/mL day (28.7%) and the C_{max} is 110 mcg/mL (22.2%) following the approved recommended dosage. Steady-state concentration of tislelizumab-jsgr is reached after 12 weeks of repeated dosing with an every 3-week regimen and the systemic accumulation was 2.14-fold. The tislelizumab-jsgr steady-state total volume of distribution is 6.42 L (32.6%). The tislelizumab-jsgr total clearance is 0.153 L/day (29.5%), and the terminal half-life (t½) is 24 days (31%).

No clinically significant differences in the pharmacokinetics of tislelizumab-jsgr were observed based on age (range, 18 to 90 years), weight (range, 32 to 130 kg), race (White, Asian, or Black), mild to moderate renal impairment (CLcr ≥30 mL/min, estimated by Cockcroft-Gault), mild to moderate hepatic impairment (total bilirubin ≤3 times ULN and any AST, estimated by NCI criteria). The effect of severe hepatic impairment (total bilirubin >3 times ULN and any AST), severe renal impairment (CLcr 15-29 mL/min), or end stage renal disease (CLcr <15 mL/min) on the pharmacokinetics of tislelizumab-jsgr is unknown.

In patients who received tislelizumab-jsgr in RATIONALE-305 throughout the treatment period and in the ADA analysis set, the incidence of anti-tislelizumab antibodies was 22.7% (108/475). Among the anti-tislelizumab antibody-positive patients, the incidence of neutralizing antibodies was 5.6% (6/108). There was no significant effect of anti-drug antibodies on the pharmacokinetics of tislelizumab-jsgr. The effect of anti-drug antibodies on the pharmacodynamics, safety, or effectiveness of tislelizumab-jsgr has not been fully characterized.

CLINICAL STUDIES IN PATIENTS WITH GASTRIC CANCER

Efficacy

The efficacy of TEVIMBRA in patients with gastric cancer was evaluated in RATIONALE-305, a randomized, multicenter, placebo-controlled, double-blind trial (NCT03777657) in patients with HER2-negative previously untreated unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma. The RATIONALE-305 trial enrolled adults with histologically confirmed, locally advanced unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma and no previous systemic therapy for locally advanced unresectable or metastatic gastric or gastroesophageal junction cancer.

Patients were randomized to receive either TEVIMBRA 200 mg every 3 weeks or placebo in combination with investigator's choice of chemotherapy on a 21-day cycle. TEVIMBRA (or placebo) was administered until disease progression or unacceptable toxicity. The chemotherapy regimens consisted of:

CAPOX: Oxaliplatin 130 mg/m^2 IV on Day 1 for up to 6 cycles and capecitabine 1000 mg/m^2 orally twice daily for 14 consecutive days. Capecitabine treatment could be continued beyond 6 cycles, or

FP: Cisplatin 80 mg/m^2 IV, Day 1, and 5-FU 800 mg/m^2/day IV continuous infusion over 24 hours daily Day 1-5. Cisplatin and 5-FU were given for up to 6 cycles.

The primary efficacy outcome measures were OS in the PD-L1 TAP score ≥5% population and in the Intent-to-Treat (ITT) population. Secondary outcome measures included progression-free survival (PFS), objective response rate (ORR), and duration of response (DoR) as assessed by the investigator per RECIST v1.1. Additional analyses of efficacy outcome measures were also conducted based on PD-L1 TAP ≥1% and CPS ≥1.

A total of 997 patients were randomized. The trial population characteristics were median age 61 years (range, 23 to 86 years), 35% ≥65 years of age, 69% male; 75% Asian, 22% White, and 0% Black or African American. Eighty percent had primary stomach tumor; 89% had PD-L1 TAP ≥1% and 86% had PD-L1 CPS ≥1, and 99% of patients had metastatic disease at baseline. Baseline ECOG performance status was 0 (32%) or 1 (68%). Ninety-three percent of patients received CAPOX and 7% received FP.

RATIONALE-305 demonstrated a statistically significant improvement in OS for patients randomized to TEVIMBRA in combination with chemotherapy compared with placebo plus chemotherapy in the PD-L1 TAP ≥5% population and in the ITT population. Exploratory analyses of OS in the TAP <1% population and in the CPS <1 population showed hazard ratios of 0.98 (95% CI: 0.64, 1.50) and 1.01 (95% CI: 0.66, 1.52) respectively, indicating that the improvement in the ITT population

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS, CONTINUED

Infusion-Related Reactions

TEVIMBRA can cause severe or life-threatening infusion-related reactions. Infusion-related reactions occurred in 5% (99/1972) patients receiving TEVIMBRA, including Grade 3 or higher (0.2%) reactions. Monitor patients for signs and symptoms of infusion-related reactions.

Slow the rate of infusion for mild (Grade 1) and interrupt the infusion for moderate (Grade 2) infusion-related reactions. For severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions, stop infusion and permanently discontinue TEVIMBRA.

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Table 1. Efficacy Results in RATIONALE-305

Endpoint	TEVIMBRA + Chemotherapy (N=432)	Placebo + Chemotherapy (N=453)	TEVIMBRA + Chemotherapy (N=420)	Placebo + Chemotherapy (N=434)
	PD-L1 TAP ≥1%		PD-L1 CPS ≥1	
Overall Survival				
Deaths n (%)	318 (74)	370 (82)	308 (73)	356 (82)
Median (months)[a] (95% CI)	15.0 (13.3, 16.7)	12.8 (12.1, 14.1)	15.1 (13.6, 17.2)	12.9 (12.1, 14.1)
HRb (95% CI)	0.78 (0.67, 0.90)		0.78 (0.67, 0.91)	
Progression-Free Survival				
Events, n (%)	316 (73)	364 (80)	303 (72)	348 (80)
Median[c] (months) (95% CI)	6.9 (5.7, 7.2)	5.9 (5.6, 6.9)	7.0 (5.7, 7.7)	6.4 (5.6, 6.9)
HRb (95% CI)	0.78 (0.67, 0.91)		0.77 (0.66, 0.90)	
Objective Response Rate[c]				
ORR, n	206	186	204	183
ORR, %	48	41	49	42
95% CI (%)[d]	(43, 53)	(37, 46)	(44, 53)	(37, 47)
Complete response, n (%)	15 (3.5)	15 (3.3)	16 (3.8)	16 (3.7)
Partial response, n (%)	191 (44)	171 (38)	188 (45)	167 (38)
Duration of Response				
Median (months)a (95% CI)	8.6 (7.8, 10.4)	7.2 (5.8, 8.3)	8.6 (7.8, 10.4)	7.2 (5.8, 8.5)

Abbreviations: CI, confidence interval; HR, hazard ratio; ORR, objective response rate.
[a]Medians were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley.
[b]Estimated by Cox proportional hazards model.
[c]Based on confirmed response.
[d]Exact Clopper-Pearson 2-sided confidence interval.

was primarily attributed to the results observed in the subgroup of patients with PD-L1 ≥1 (**Table 1**). An exploratory subgroup analysis of OS in 40 patients with MSI-H tumors irrespective of PD-L1 status showed a HR of 0.66 (0.3, 1.43).

Safety

The safety of TEVIMBRA in combination with chemotherapy was evaluated in RATIONALE-305. Serious adverse reactions occurred in 42% of patients receiving TEVIMBRA in combination with chemotherapy. The most frequent serious adverse drug reactions (≥2%) were pneumonia (3.6%), decreased platelet count (3.2%), gastrointestinal hemorrhage (3%), and colitis (2.2%). Fatal adverse reactions occurred in 4.2% of patients who received TEVIMBRA in combination with chemotherapy; events occurring in 2 or more patients were death, sepsis, pneumonia, pulmonary embolism, and respiratory failure.

Permanent discontinuation of TEVIMBRA due to an adverse reaction occurred in 16% of patients. Adverse drug reactions which resulted in permanent discontinuation in ≥1% of patients were death, fatigue, and pneumonitis.

Dosage interruption of TEVIMBRA due to an adverse drug reaction occurred in 49% of patients. Adverse drug reactions

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Table 2. Adverse Reactions (≥10%) in Patients with G/GEJ Receiving TEVIMBRA + Chemotherapy with a Difference Between Arms of ≥5% for All Grades or ≥2% for Grades 3 and 4 vs Placebo + Chemotherapy in RATIONALE-305

Adverse Drug Reaction	TEVIMBRA + Chemotherapy (N=498)		Placebo + Chemotherapy (N=494)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
General Disorders and Administration Site Conditions				
Pyrexia	20	1.6	14	0.6
Skin and Subcutaneous Tissue Disorders				
Rash[a]	16	1.6	7	0
Pruritus	10	0.2	3.2	0
Endocrine Disorders				
Hypothyroidism	13	0.2	2.8	0

[a]Represents a composite of multiple, related preferred terms.

which required dosage interruption in ≥2% of patients were decreased platelet count (12%), decreased neutrophil count (10%), neutropenia (6%), decreased white blood cell count (6%), increased AST (4.8%), increased ALT (3.8%), increased blood bilirubin (3%), COVID-19 (3%), thrombocytopenia (2.8%), leukopenia (2.6%), pneumonitis (2.2%), and pneumonia (2%).

The most common (≥20%) adverse reactions, including laboratory abnormalities, for TEVIMBRA in combination with chemotherapy were nausea, fatigue, decreased appetite, anemia, peripheral sensory neuropathy, vomiting, decreased platelet count, decreased neutrophil count, increased aspartate aminotransferase, diarrhea, abdominal pain, increased alanine aminotransferase, white blood cell count decreased, decreased weight, and pyrexia. See **Table 2** for additional data on adverse reactions and **Table 3** for laboratory abnormality data from RATIONALE-305.

DOSAGE AND ADMINISTRATION

TEVIMBRA is available as a 100 mg/10 mL solution in a single-dose vial. TEVIMBRA should be stored in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. The recommended dosage of TEVIMBRA administered intravenously as a single agent or in combination with platinum and fluoropyrimidine-containing chemotherapy is 150 mg every 2 weeks or 200 mg every 3 weeks or 300 mg every 4 weeks until disease progression or unacceptable toxicity.

Prepare the solution for infusion as follows:

- Withdraw the required volume of TEVIMBRA from the vial(s).
- Transfer solution into an intravenous infusion bag containing 0.9% Sodium Chloride Injection, USP to prepare an infusion solution with a final concentration of 2 mg/mL to 5 mg/mL.
- Mix diluted solution by gentle inversion to avoid foaming or excessive shearing of the solution. Do not shake.
- TEVIMBRA is for single use only. Discard any unused portion left in the vial.

As TEVIMBRA does not contain any preservatives, if not used immediately, store the TEVIMBRA diluted solution either:

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS, CONTINUED

Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with a PD-1/PD-L1 blocking antibody prior to or after an allogeneic HSCT.

Embryo-Fetal Toxicity

Based on its mechanism of action, TEVIMBRA 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. Advise women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TEVIMBRA and for 4 months after the last dose.

Please see full Prescribing Information after page 7

Table 3. Select Laboratory Abnormalities Worsening from Baseline Occurring in ≥10% of Patients Receiving TEVIMBRA+ Chemotherapy with a Difference Between Arms of ≥5% for All Grades or ≥2% for Grades 3 and 4 vs Placebo + Chemotherapy in RATIONALE-305

Laboratory Abnormality	TEVIMBRA + Chemotherapy[a] (N=498)		Placebo + Chemotherapy[a] (N=494)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Chemistry				
AST increased	58	6	56	3
Sodium decreased	42	7	36	5
ALT increased	41	4.8	36	2
Potassium decreased	33	9	28	6
Hematology				
Lymphocytes decreased	53	12	46	9

Abbreviations: ALT, alanine aminotransferase; AST, aspartate amino transferase.
[a]The denominator used to calculate the rate varied from 480 to 494 based on the number of patients with a baseline value and at least one post-treatment value.

- At room temperature at 20°C to 25°C (68°F to 77°F) for no more than 4 hours, including preparation and infusion duration. Discard after 4 hours.
- Under refrigeration at 2°C to 8°C (36°F to 46°F) for up to 20 hours, including preparation and infusion duration. Allow the diluted solution to come to room temperature prior to administration. Discard after 20 hours.

Do not freeze the diluted solution.

No dose reduction of TEVIMBRA is recommended. In general, withhold TEVIMBRA for severe (Grade 3) immune-mediated adverse reactions. Permanently discontinue TEVIMBRA for life-threatening (Grade 4) immune-mediated adverse reactions, recurrent severe (Grade 3) immune-mediated reactions that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone equivalent per day within 12 weeks of initiating steroids.

SUMMARY

Tislelizumab-jsgr is a unique anti–PD-1 antibody that demonstrates improved PD-1 binding characteristics compared with previously approved anti–PD-1 antibodies in gastric cancer. In patients with previously untreated unresectable or metastatic gastric or gastroesophageal junction cancer, tislelizumab-jsgr in combination with chemotherapy demonstrated a clinically meaningful improvement compared with placebo in combination with chemotherapy in overall survival, progression-free survival, objective response rate, and duration of response. This indicates that tislelizumab-jsgr may be an effective addition to the treatment arsenal for patients with gastric or gastroesophageal junction cancer whose tumors express PD-L1 (≥1). ◆

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS, CONTINUED

Adverse Reactions

The most common adverse reactions (≥20%), including laboratory abnormalities of TEVIMBRA in combination with platinum and fluoropyrimidine-based chemotherapy, were nausea, fatigue, decreased appetite, anemia, peripheral sensory neuropathy, vomiting, decreased platelet count, decreased neutrophil count, increased aspartate aminotransferase, diarrhea, abdominal pain, increased alanine aminotransferase, decreased white blood cell count, decreased weight, and pyrexia.

SPECIAL POPULATIONS

Lactation

Advise not to breastfeed.

Please see full Prescribing Information after page 7

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TEVIMBRA safely and effectively. See full prescribing information for TEVIMBRA.

TEVIMBRA® (tislelizumab-jsgr) injection, for intravenous use
Initial U.S. Approval: 2024

----------RECENT MAJOR CHANGES----------

Indications and Usage (1.1, 1.2)	3/2025
Dosage and Administration (2.1)	3/2025
Dosage and Administration (2.2)	4/2025

----------INDICATIONS AND USAGE----------

TEVIMBRA is a programmed death receptor-1 (PD-1)-blocking antibody indicated for:

Esophageal Cancer

- in combination with platinum-containing chemotherapy for the first-line treatment of adults with unresectable or metastatic esophageal squamous cell carcinoma (ESCC) whose tumors express PD-L1 (≥1). (1.1)
- as a single agent in adults with unresectable or metastatic esophageal squamous cell carcinoma (ESCC) after prior systemic chemotherapy that did not include a PD-(L)1 inhibitor. (1.1)

Gastric Cancer

- in combination with platinum and fluoropyrimidine-based chemotherapy in adults for the first line treatment of unresectable or metastatic HER2-negative gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 (≥1). (1.2)

----------DOSAGE AND ADMINISTRATION----------

Recommended Dosage:
Esophageal Cancer:

- 150 mg every 2 weeks or 200 mg every 3 weeks or 300 mg every 4 weeks in combination with platinum-containing chemotherapy for first-line treatment of unresectable or metastatic ESCC. (2.2)
- 150 mg every 2 weeks or 200 mg every 3 weeks or 300 mg every 4 weeks as a single agent for treatment of unresectable or metastatic ESCC. (2.2)

Gastric Cancer:

- 150 mg every 2 weeks or 200 mg every 3 weeks or 300 mg every 4 weeks in combination with platinum and fluoropyrimidine-based chemotherapy. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

Injection: 100 mg/10 mL (10 mg/mL) solution in a single-dose vial. (3)

----------CONTRAINDICATIONS ----------

None. (4)

----------WARNINGS AND PRECAUTIONS----------

- Immune-Mediated Adverse Reactions: (5.1)
  - Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue, including the following: immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis, immune-mediated endocrinopathies, immune-mediated nephritis with renal dysfunction, immune-mediated dermatologic adverse reactions, and solid organ transplant rejection.
  - Monitor for early identification and management. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment.
  - Withhold or permanently discontinue TEVIMBRA based on the severity of reaction.
- Infusion-Related Reactions: Slow the rate of infusion, interrupt, or permanently discontinue based on severity of infusion reaction. (5.2)
- Complications of Allogeneic Hematopoietic Stem Cell Transplantation (HSCT): Fatal and other serious complications can occur in patients who receive allogeneic HSCT before or after being treated with a PD-1/PD-L1 blocking antibody. (5.3)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception. (5.4, 8.1, 8.3)

----------ADVERSE REACTIONS----------

Most common adverse reactions (≥20%), including laboratory abnormalities, were:

- TEVIMBRA in combination with platinum-containing chemotherapy: decreased neutrophil count, decreased sodium, increased glucose, anemia, fatigue, decreased appetite, increased AST, decreased potassium, increased serum creatinine, decreased calcium, increased ALT, diarrhea, stomatitis, and vomiting. (6.1)
- TEVIMBRA as a single agent: increased glucose, decreased hemoglobin, decreased lymphocytes, decreased sodium, decreased albumin, increased alkaline phosphatase, anemia, fatigue, increased AST, musculoskeletal pain, decreased weight, increased ALT, and cough. (6.1)
- TEVIMBRA in combination with platinum and fluoropyrimidine-based chemotherapy: nausea, fatigue, decreased appetite, anemia, peripheral sensory neuropathy, vomiting, decreased platelet count, decreased neutrophil count, increased aspartate aminotransferase, diarrhea, abdominal pain, increased alanine aminotransferase, decreased white blood cell count, decreased weight, and pyrexia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact BeiGene at 1-877-828-5596 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------

Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 5/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Esophageal Cancer

- First-Line Treatment of Esophageal Squamous Cell Carcinoma

  TEVIMBRA, in combination with platinum-containing chemotherapy, is indicated for the first-line treatment of adults with unresectable or metastatic esophageal squamous cell carcinoma (ESCC) whose tumors express PD-L1 (≥1).

- Previously Treated Esophageal Squamous Cell Carcinoma

  TEVIMBRA, as a single agent, is indicated for the treatment of adults with unresectable or metastatic esophageal squamous cell carcinoma (ESCC) after prior systemic chemotherapy that did not include a PD-(L)1 inhibitor.

1.2 Gastric Cancer

TEVIMBRA, in combination with platinum and fluoropyrimidine-based chemotherapy, is indicated for the first-line treatment of adults with unresectable or metastatic HER2-negative gastric or gastroesophageal junction adenocarcinoma (G/GEJ) whose tumors express PD-L1 (≥1).

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients for the first-line treatment of unresectable or metastatic esophageal squamous cell carcinoma based on the presence of PD-L1 in tumor specimens *[see Clinical Studies (14.1)]*. An FDA-approved companion diagnostic for the detection of PD-L1 in patients with unresectable or metastatic esophageal squamous cell carcinoma is not available.

Select patients for the first-line treatment of unresectable or metastatic HER2-negative gastric or gastroesophageal junction adenocarcinoma (G/GEJ) based on the presence of PD-L1 in tumor specimens *[see Clinical Studies (14.2)]*. An FDA-approved companion diagnostic for the detection of PD-L1 in patients with unresectable or metastatic HER2-negative gastric or gastroesophageal junction adenocarcinoma (G/GEJ) is not available.

2.2 Recommended Dosage

The recommended dosages of TEVIMBRA administered intravenously as a single agent or in combination with other therapeutic agents are presented in Table 1.

Table 1: Recommended Dosages for TEVIMBRA as a Single Agent or in Combination with Other Therapeutic Agents

Indication	Recommended Dosage of TEVIMBRA	Duration/Timing of Treatment
ESCC OR	150 mg every 2 weeks OR 200 mg every 3 weeks	Until disease progression or unacceptable toxicity.

Indication	Recommended Dosage of TEVIMBRA	Duration/Timing of Treatment
First-Line Gastric Cancer	OR 300 mg every 4 weeks	

Refer to the respective Prescribing Information for each therapeutic agent administered in combination with TEVIMBRA for the recommended dosage information, as appropriate.

2.3 Dosage Modifications for Adverse Reactions

No dose reduction of TEVIMBRA is recommended. In general, withhold TEVIMBRA for severe (Grade 3) immune-mediated adverse reactions. Permanently discontinue TEVIMBRA for life-threatening (Grade 4) immune-mediated adverse reactions, recurrent severe (Grade 3) immune-mediated reactions that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone equivalent per day within 12 weeks of initiating steroids *[see Warnings and Precautions (5.1)]*.

Dosage modifications for TEVIMBRA for adverse reactions that require management different from these general guidelines are summarized in Table 2.

Refer to the respective Prescribing Information for dosage modifications for the platinum and fluoropyrimidine agent administered in combination with TEVIMBRA.

Table 2: Recommended Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity of Adverse Reaction[a]	Dosage Modifications
Immune-Mediated Adverse Reactions *[see Warnings and Precautions (5.1)]*		
Pneumonitis	Grade 2	Withhold[b]
	Grade 3 or 4 or recurrent Grade 2	Permanently discontinue
Colitis	Grade 2 or 3	Withhold[b]
	Grade 4	Permanently discontinue
Hepatitis with no tumor involvement of the liver	AST or ALT increases to more than 3 and up to 8 times ULN or Total bilirubin increases to more than 1.5 and up to 3 times ULN	Withhold[b]
	AST or ALT increases to more than 8 times ULN or Total bilirubin increases to more than 3 times ULN	Permanently discontinue
Hepatitis with tumor involvement of the liver[c]	Baseline AST or ALT is more than 1 and up to 3 times ULN and increases to more than 5 and up to 10 times ULN or Baseline AST or ALT is more than 3 and up to 5 times ULN and	Withhold[b]

Adverse Reaction	Severity of Adverse Reaction[a]	Dosage Modifications
Immune-Mediated Adverse Reactions *[see Warnings and Precautions (5.1)]*		
	increases to more than 8 and up to 10 times ULN	
	ALT or AST increases to more than 10 times ULN or Total bilirubin increases to more than 3 times ULN	Permanently discontinue
Endocrinopathies	Grade 3 or 4	Withhold until clinically stable or permanently discontinue depending on severity
Nephritis with renal dysfunction	Grade 2 or 3 increased blood creatinine	Withhold[b]
	Grade 4 increased blood creatinine	Permanently discontinue
Exfoliative dermatologic conditions	Grade 3, or suspected SJS, TEN, or DRESS	Withhold[b]
	Grade 4, or confirmed SJS, TEN, or DRESS	Permanently discontinue
Myocarditis	Grade 2, 3, or 4	Permanently discontinue
Neurological toxicities	Grade 2	Withhold[b]
	Grade 3 or 4	Permanently discontinue
Other Adverse Reactions		
Infusion-related reactions *[see Warnings and Precautions (5.2)]*	Grade 1	Slow infusion rate by 50%
	Grade 2	Interrupt infusion[d]
	Grade 3 or 4	Permanently discontinue

ALT = alanine aminotransferase, AST = aspartate aminotransferase, ULN = upper limit of normal, SJS = Stevens-Johnson syndrome, TEN = toxic epidermal necrolysis, DRESS = drug rash with eosinophilia and systemic symptoms.

[a] Based on Common Terminology Criteria for Adverse Events (CTCAE) Version 4.

[b] Resume in patients with complete or partial resolution (Grades 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to 10 mg per day or less (or equivalent) within 12 weeks of initiating steroids.

[c] If AST and ALT are less than or equal to ULN at baseline, withhold or permanently discontinue TEVIMBRA based on recommendations for hepatitis with no liver involvement.

[d] Resume infusion if resolved or decreased to Grade 1, and slow rate of infusion by 50% of the previous rate.

2.4 Preparation and Administration

Preparation

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. TEVIMBRA is a clear to slightly opalescent, colorless to slightly yellow solution. Discard the vial if the solution is cloudy, discolored, or contains visible particles. Do not shake the vial.

Prepare the solution for infusion as follows:

- Withdraw the required volume of TEVIMBRA from the vial(s).
- Transfer solution into an intravenous infusion bag containing 0.9% Sodium Chloride Injection, USP to prepare an infusion solution with a final concentration of 2 mg/mL to 5 mg/mL.
- Mix diluted solution by gentle inversion to avoid foaming or excessive shearing of the solution. Do not shake.
- TEVIMBRA is for single use only. Discard any unused portion left in the vial.

Storage of Diluted Solution

This product does not contain any preservatives. If not used immediately, store the TEVIMBRA diluted solution either:

- At room temperature at 20°C to 25°C (68°F to 77°F) for up to 4 hours, including preparation and infusion duration. Discard after 4 hours.
- Under refrigeration at 2°C to 8°C (36°F to 46°F) for up to 20 hours, including preparation and infusion duration. Allow the diluted solution to come to room temperature prior to administration. Discard after 20 hours.

Do not freeze the diluted solution.

Administration

- Administer diluted solution by intravenous infusion through an intravenous line with a sterile, nonpyrogenic, low protein binding 0.2 micron or 0.22 micron in-line or add-on filter.
- For 150 mg and 200 mg doses, administer the initial infusion over 60 minutes. If tolerated, all subsequent infusions may be administered over 30 minutes.

  For 300 mg doses, administer the initial infusion over 90 minutes. If tolerated, administer the second infusion over 60 minutes. If the second infusion is tolerated, administer subsequent infusions over 30 minutes.
- Do NOT coadminister other drugs through the same infusion line.
- Do NOT administer TEVIMBRA as an intravenous push or single bolus injection.
- Flush the intravenous line at the end of infusion.

3 DOSAGE FORMS AND STRENGTHS

Injection: 100 mg/10 mL (10 mg/mL) clear to slightly opalescent, colorless to slightly yellow solution in a single-dose vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Severe and Fatal Immune-Mediated Adverse Reactions

TEVIMBRA is a monoclonal antibody that belongs to a class of drugs that bind to either the

programmed death receptor-1 (PD-1) or PD-ligand 1 (PD-L1), blocking the PD-1/PD-L1 pathway, thereby removing inhibition of the immune response, potentially breaking peripheral tolerance and inducing immune-mediated adverse reactions. Important immune-mediated adverse reactions listed under WARNINGS AND PRECAUTIONS may not include all possible severe and fatal immune-mediated reactions.

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. Immune-mediated adverse reactions can occur at any time after starting treatment with a PD-1/PD-L1 blocking antibody. While immune-mediated adverse reactions usually manifest during treatment with PD-1/PD-L1 blocking antibodies, immune-mediated adverse reactions can also manifest after discontinuation of PD-1/PD-L1 blocking antibodies.

Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue TEVIMBRA depending on severity *[see Dosage and Administration (2.2)]*. In general, if TEVIMBRA requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroids.

Toxicity management guidelines for adverse reactions that do not necessarily require systemic steroids (e.g., endocrinopathies and dermatologic reactions) are discussed below.

Immune-Mediated Pneumonitis

TEVIMBRA can cause immune-mediated pneumonitis, which can be fatal. In patients treated with other PD-1/PD-L1 blocking antibodies, the incidence of pneumonitis is higher in patients who have received prior thoracic radiation.

Immune-mediated pneumonitis occurred in 4.7% (113/2390) of patients receiving TEVIMBRA, including fatal (0.1%), Grade 4 (0.3%), Grade 3 (1.4%), and Grade 2 (1.9%) adverse reactions. Pneumonitis led to permanent discontinuation of TEVIMBRA in 44 (1.8%) patients and withholding of TEVIMBRA in 40 (1.7%) patients.

Eighty-one (71.7%) of the 113 patients received systemic corticosteroids. Seventy-four (65.5%) of the 113 patients received high-dose systemic corticosteroids. Immune-mediated pneumonitis resolved in 48.7% of the 113 patients. Of the 40 patients in whom TEVIMBRA was withheld for pneumonitis, 26 (65%) reinitiated TEVIMBRA after symptom improvement; of these, 5 (19%) patients had recurrence of pneumonitis.

Immune-Mediated Colitis

TEVIMBRA can cause immune-mediated colitis, which can be fatal. Cytomegalovirus infection/reactivation has been reported in patients with corticosteroid-refractory immune-

mediated colitis treated with PD-1/PD-L1 blocking antibodies. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies.

Immune-mediated colitis occurred in 0.8% (19/2390) of patients receiving TEVIMBRA, including Grade 3 (0.3%) and Grade 2 (0.4%) adverse reactions. Colitis led to permanent discontinuation of TEVIMBRA in 5 (0.2%) patients and withholding of TEVIMBRA in 10 (0.4%) patients. Seventeen (89.5%) of the 19 patients received systemic corticosteroids. Twelve (63.2%) of the 19 patients received high-dose systemic corticosteroids. Two (10.5%) of the 19 patients received immunosuppressive treatment. Immune-mediated colitis resolved in 89.5% of the 19 patients. Of the 10 patients in whom TEVIMBRA was withheld for colitis, 9 (90%) reinitiated TEVIMBRA after symptom improvement; of these, 2 (22%) patients had recurrence of colitis.

Immune-Mediated Hepatitis

TEVIMBRA can cause immune-mediated hepatitis, which can be fatal.

Immune-mediated hepatitis occurred in 1.3% (30/2390) of patients receiving TEVIMBRA, including Grade 4 (0.3%), Grade 3 (0.6%), and Grade 2 (0.3%) adverse reactions. Immune-mediated hepatitis led to permanent discontinuation in 6 (0.3%) patients and withholding of TEVIMBRA in 19 (0.8%) patients. Twenty-five (83.3%) of the 30 patients received systemic corticosteroids. Twenty-four (80%) of the 30 patients received high-dose systemic corticosteroids. Two (6.7%) of the 30 patients received immunosuppressive treatment. Immune-mediated hepatitis resolved in 66.7% of the 30 patients. Of the 19 patients in whom TEVIMBRA was withheld for hepatitis, 7 (37%) reinitiated TEVIMBRA after symptom improvement; of these, 1 (14%) patient had recurrence of hepatitis.

Immune-Mediated Endocrinopathies

Adrenal Insufficiency

TEVIMBRA can cause immune-mediated adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold TEVIMBRA depending on severity *[see Dosage and Administration (2.2)]*.

Immune-mediated adrenal insufficiency occurred in 0.5% (12/2390) of patients receiving TEVIMBRA, including Grade 4 (0.04%), Grade 3 (0.2%), and Grade 2 (0.3%) adverse reactions. Adrenal insufficiency did not lead to permanent discontinuation of TEVIMBRA. TEVIMBRA was withheld in 10 (0.4%) patients. All 12 patients received systemic corticosteroids. Three (25%) of the 12 patients received high-dose systemic corticosteroids. Adrenal insufficiency resolved in 25% of the 12 patients. Of the 10 patients in whom TEVIMBRA was withheld for adrenal insufficiency, 8 (80%) reinitiated TEVIMBRA after symptom improvement; of these, none of the patients had recurrence of adrenal insufficiency.

Hypophysitis

TEVIMBRA can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism. Initiate hormone replacement as clinically indicated. Withhold or permanently discontinue TEVIMBRA depending on severity *[see Dosage and Administration (2.2)]*.

Hypophysitis/hypopituitarism occurred in 0.3% (6/2390) of patients receiving TEVIMBRA; all

were Grade 2 (0.3%). Hypophysitis did not lead to permanent discontinuation of TEVIMBRA. TEVIMBRA was withheld in 1 (0.04%) patient. Five (83.3%) of the 6 patients received systemic corticosteroids. One (17%) of the 6 patients received high-dose systemic corticosteroids. Hypophysitis/hypopituitarism resolved in 17% of the 6 patients. For the 1 patient where TEVIMBRA was withheld for hypophysitis/hypopituitarism, there was no recurrence of hypophysitis/hypopituitarism.

Thyroid Disorders

TEVIMBRA can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement for hypothyroidism or institute medical management of hyperthyroidism as clinically indicated. Withhold or permanently discontinue TEVIMBRA depending on severity *[see Dosage and Administration (2.2)]*.

Thyroiditis: Immune-mediated thyroiditis occurred in 1% (25/2390) of patients receiving TEVIMBRA, including Grade 2 (0.5%) adverse reactions. Thyroiditis did not lead to permanent discontinuation of TEVIMBRA. TEVIMBRA was withheld in 5 (0.2%) patients. Two (8%) of the 25 patients received systemic corticosteroids. Thyroiditis resolved in 36% of the 25 patients. All 5 patients in whom TEVIMBRA was withheld for thyroiditis reinitiated TEVIMBRA after symptom improvement; of these, 1 (20%) patient had recurrence of thyroiditis.

Hyperthyroidism: Immune-mediated hyperthyroidism occurred in 4.9% (118/2390) of patients receiving TEVIMBRA, including Grade 3 (0.04%) and Grade 2 (0.9%) adverse reactions. Hyperthyroidism led to the permanent discontinuation of TEVIMBRA in 1 (0.04%) patient and withholding of TEVIMBRA in 7 (0.3%) patients. Three (2.5%) of the 118 patients received systemic corticosteroids. Hyperthyroidism resolved in 76.3% of the 118 patients. Of the 7 patients in whom TEVIMBRA was withheld for hyperthyroidism, 5 (71.4%) reinitiated TEVIMBRA after symptom improvement; of these, none of the patients had recurrence of hyperthyroidism.

Hypothyroidism: Immune-mediated hypothyroidism occurred in 12.5% (299/2390) of patients receiving TEVIMBRA, including Grade 4 (0.04%), Grade 3 (0.04%), and Grade 2 (6.7%) adverse reactions. TEVIMBRA was permanently discontinued in 2 (0.1%) patients and treatment was withheld in 12 (0.5%) patients. Two (0.7%) of the 299 patients received systemic corticosteroids. One hundred ninety-five patients received hormone replacement therapy. Hypothyroidism resolved in 34.4% of the 299 patients. The majority (83.6%) of patients with hypothyroidism required long-term thyroid hormone replacement. Of the 12 patients in whom TEVIMBRA was withheld for hypothyroidism, 11 (91.7%) reinitiated TEVIMBRA after symptom improvement; of these, 2 (18.2%) patients had recurrence of hypothyroidism.

Type 1 Diabetes Mellitus, which can present with Diabetic Ketoacidosis

Diabetes mellitus has been reported with PD-1/PD-L1 blocking antibodies. Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold or permanently discontinue TEVIMBRA depending on severity *[see Dosage and Administration (2.2)]*.

Diabetes mellitus occurred in 0.7% (16/2390) of patients receiving TEVIMBRA, including Grade 4 (0.1%), Grade 3 (0.3%), and Grade 2 (0.3%) adverse reactions. TEVIMBRA was permanently discontinued in 4 (0.2%) patients, and TEVIMBRA treatment was withheld in 4

(0.2%) patients. Fourteen of the 16 patients received insulin therapy for diabetes mellitus. Diabetes mellitus resolved in 12.5% of the 16 patients. Of the 4 patients in whom TEVIMBRA was withheld for diabetes mellitus, 1 (25%) patient reinitiated TEVIMBRA after symptom improvement.

Immune-Mediated Nephritis with Renal Dysfunction

TEVIMBRA can cause immune-mediated nephritis, which can be fatal.

Immune-mediated nephritis with renal dysfunction occurred in 0.2% (5/2390) of patients receiving TEVIMBRA, including Grade 3 (0.04%) and Grade 2 (0.1%) adverse reactions. TEVIMBRA was permanently discontinued in 1 (0.04%) patient and treatment was withheld in 3 (0.1%) patients. Three (60%) out of 5 patients received systemic corticosteroids. Three (60%) of the 5 patients received high-dose systemic corticosteroids. Nephritis with renal dysfunction resolved in 40% of the 5 patients. Of the 3 patients in whom TEVIMBRA was withheld for nephritis, 2 (66.7%) reinitiated TEVIMBRA after symptom improvement and no patients had recurrence of nephritis.

Immune-Mediated Dermatologic Adverse Reactions

TEVIMBRA can cause immune-mediated rash or dermatitis. Cases of severe cutaneous adverse reactions (SCARs), including exfoliative dermatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), have been reported, some with fatal outcome. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes. Withhold or permanently discontinue TEVIMBRA depending on severity *[see Dosage and Administration (2.2)]*.

Immune-mediated dermatologic adverse reactions occurred in 13% (311/2390) of patients receiving TEVIMBRA, including Grade 4 (0.1%), Grade 3 (1.1%), and Grade 2 (3.4%) adverse reactions. Stevens-Johnson syndrome occurred in 1 (0.04%) patient. Dermatologic adverse reactions led to permanent discontinuation of TEVIMBRA in 3 (0.1%) patients and withholding of TEVIMBRA in 30 (1.3%) patients. Forty-four (14.1%) of the 311 patients received systemic corticosteroids. Nineteen (6.1%) of the 311 patients received high-dose systemic corticosteroids. Immune-mediated skin reactions resolved in 66.9% of the 311 patients. Of the 30 patients in whom TEVIMBRA was withheld for dermatologic adverse reactions, 26 (86.7%) reinitiated TEVIMBRA after symptom improvement; of these, 3 (12%) patients had recurrence of immune-mediated dermatologic adverse reactions.

Other Immune-Mediated Adverse Reactions

The following clinically significant immune-mediated adverse reactions occurred at an incidence of less than 1% in 2390 patients who received TEVIMBRA or were reported with the use of other PD-1/PD-L1 blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions.

Cardiac/Vascular: Myocarditis, pericarditis, vasculitis.

Nervous System: Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barre syndrome, nerve paresis, autoimmune neuropathy.

Ocular: Uveitis, iritis, and other ocular inflammatory toxicities. Some cases can be associated with retinal detachment. Various grades of visual impairment, including blindness, can occur. If

uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada–like syndrome, as this may require treatment with systemic steroids to reduce the risk of permanent vision loss.

Gastrointestinal: Pancreatitis including increases in serum amylase and lipase levels, gastritis, duodenitis, stomatitis.

Musculoskeletal and Connective Tissue: Myositis/polymyositis/dermatomyositis, rhabdomyolysis and associated sequelae including renal failure, arthritis, polymyalgia rheumatica.

Endocrine: Hypoparathyroidism.

Other (Hematologic/Immune): Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenia, solid organ transplant rejection, other transplant (including corneal graft) rejection.

5.2 Infusion-Related Reactions

TEVIMBRA can cause severe or life-threatening infusion-related reactions. Infusion-related reactions occurred in 5% (99/1972) patients receiving TEVIMBRA, including Grade 3 or higher (0.2%) reactions. Monitor patients for signs and symptoms of infusion-related reactions.

Slow the rate of infusion for mild (Grade 1) and interrupt the infusion for moderate (Grade 2) infusion-related reactions. For severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions, stop infusion and permanently discontinue TEVIMBRA *[see Dosage and Administration (2.2)]*.

5.3 Complications of Allogeneic HSCT

Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with a PD-1/PD-L1 blocking antibody. Transplant-related complications include hyperacute graft-versus-host disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between PD-1/PD-L1 blockade and allogeneic HSCT.

Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with a PD-1/PD-L1 blocking antibody prior to or after an allogeneic HSCT.

5.4 Embryo-Fetal Toxicity

Based on its mechanism of action, TEVIMBRA 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. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TEVIMBRA and for 4 months after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in more detail in other sections of the label:

- Severe and fatal immune-mediated adverse reactions *[see Warnings and Precautions (5.1)]*
- Infusion-related reactions *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The pooled safety population described in WARNINGS AND PRECAUTIONS reflect exposure to TEVIMBRA as a single agent in 2390 patients enrolled in three randomized open-label, active-controlled studies (BGB-A317-301, RATIONALE-302, BGB-A317-303) and six open-label, single-arm studies (BGB-A317-209, BGB-A317-208, BGB-A317-204, BGB-A317-203, BGB-A317-102, BGB-A317_Study_001), which enrolled 307 patients with esophageal squamous cell carcinoma and 2083 patients with advanced or recurrent tumors. TEVIMBRA was administered at a dose of 200 mg intravenously once every 3 weeks, except in study BGB-A317_Study_001 where patients also received other dosage regimens. Among the 2390 patients, 38% were exposed for longer than 6 months, and 23% were exposed for longer than 12 months.

First-line Treatment of Unresectable or Metastatic Esophageal Carcinoma (ESCC)

The safety of TEVIMBRA in combination with chemotherapy was evaluated in RATIONALE-306, a randomized, placebo-controlled, multicenter, double-blind trial in patients with unresectable, advanced, or metastatic ESCC *[see Clinical Studies (14.1)]*.

Patients were randomized (1:1) to receive either TEVIMBRA 200 mg by intravenous infusion over 30-60 minutes every 3 weeks or placebo plus a chemotherapy doublet regimen. The chemotherapy doublet regimens consisted of:

- Platinum (cisplatin [60 to 80 mg/m^2 IV, on Day 1] or oxaliplatin [130 mg/m^2 IV, on Day 1]) and a fluoropyrimidine (5-FU [750 to 800 mg/m^2 IV, on Day 1 to 5] or capecitabine [1000 mg/m^2 orally twice daily, on Day 1 to 14])

or

- Platinum (cisplatin [60 to 80 mg/m^2 IV, on Day 1 or 2] or oxaliplatin [130 mg/m^2 IV, on Day 1 or 2]) and (paclitaxel 175 mg/m^2 IV, on Day 1)

Patients were treated until disease progression or unacceptable toxicity. The median duration of exposure was 6.4 months (range: 0.1 to 38.3 months) in TEVIMBRA-treated patients.

Serious adverse reactions occurred in 48% of patients receiving TEVIMBRA in combination with chemotherapy. The most frequent serious adverse reactions (≥2%) were pneumonia (5.2%), dysphagia (5.2%), diarrhea (2.2%), fatigue (2.2%), and esophageal stenosis (2.2%). Fatal adverse reactions occurred in 8% of patients who received TEVIMBRA in combination with chemotherapy.

Permanent discontinuation of TEVIMBRA due to adverse reactions occurred in 13% of patients. The adverse reaction which resulted in discontinuation in ≥2% of patients was pneumonitis (2.2%).

Dosage interruptions of TEVIMBRA due to adverse reactions occurred in 52% of patients. Adverse reactions which required dosage interruption in ≥2% of patients were neutrophil count decreased (7%), fatigue (6%), pneumonia (6%), anemia (4.3%), neutropenia (4.3%), white blood cell count decreased (4.3%), rash (3.7%), dysphagia (2.8%), platelet count decreased (2.8%), pyrexia (2.8%), and diarrhea (2.2%).

The most common (≥20%) adverse reactions including laboratory abnormalities were decreased neutrophil count, decreased sodium, increased glucose, anemia, fatigue, decreased appetite, increased AST, decreased potassium, increased serum creatinine, decreased calcium, increased ALT, diarrhea, stomatitis, and vomiting.

Adverse reactions and laboratory abnormalities are listed in Table 3 and Table 4, respectively.

Table 3: Adverse Reactions (≥10%) in Patients with ESCC Receiving TEVIMBRA + Chemotherapy with a Difference Between Arms of ≥5% for All Grades or ≥2% for Grades 3 and 4 vs Placebo + Chemotherapy in RATIONALE-306

Adverse Reaction	TEVIMBRA + Chemotherapy N=324		Placebo + Chemotherapy N=321	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Blood and Lymphatic System Disorders				
Anemia	61	17	56	16
Neutropenia	16	7	15	10
General Disorders and Administration Site Conditions				
Fatigue[a]	45	9	45	4.7
Metabolism and Nutrition Disorders				
Decreased Appetite	44	6	39	2.2
Gastrointestinal Disorders				
Diarrhea	28	4.3	24	1.9
Stomatitis[a]	22	4	16	2.2
Vomiting	22	1.5	27	2.5
Dysphagia	14	6	11	4
Skin and Subcutaneous Tissue Disorders				
Rash[a]	19	4	9	0.3
Pruritus	13	0.3	7	0
Endocrine Disorders				
Hypothyroidism[a]	11	0	6	0

[a] Represents a composite of multiple, related preferred terms.

Table 4: Select Laboratory Abnormalities Worsening From Baseline Occurring in ≥10% of Patients Receiving TEVIMBRA in Combination with Chemotherapy in RATIONALE-306 with a Difference Between Arms of ≥5% for All Grades or ≥2% for Grades 3 and 4 vs Placebo + Chemotherapy in RATIONALE-306

Laboratory Abnormality	TEVIMBRA + Chemotherapy[a] (N=324)		Placebo + Chemotherapy[a] (N=321)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hematology				
Neutrophils decreased	75	41	75	46
Chemistry				
Sodium decreased	67	19	62	11
Glucose increased	65	7	61	5
AST increased	36	3.4	27	1.3
Potassium decreased	33	10	29	2.8
Creatinine increased	33	2.5	25	1.6
Calcium decreased	29	6	24	4.4
ALT increased	28	3.1	22	1.6

[a] The denominator used to calculate the rate varied from 132 to 323 based on the number of patients with a baseline value and at least one post-treatment value.

Previously Treated Unresectable Advanced or Metastatic Esophageal Squamous Cell Carcinoma (ESCC)

The safety of TEVIMBRA was evaluated in RATIONALE-302, a randomized, active-controlled, open-label, multicenter study in 255 patients with unresectable advanced, recurrent or metastatic ESCC *[see Clinical Studies (14.1)]*. The trial excluded patients who 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 site.

Patients received TEVIMBRA 200 mg by intravenous infusion over 30-60 minutes every 3 weeks or investigator's choice: 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 or unacceptable toxicity. The median duration of exposure was 2.8 months (range: 0.2 to 28.3 months) in TEVIMBRA-treated patients and 1.5 months (range: 0.2 to 19.2 months) in paclitaxel, docetaxel, or irinotecan-treated patients.

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. Fatal adverse reactions occurred in 7% of patients who received TEVIMBRA, including 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).

Permanent discontinuation of TEVIMBRA 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 TEVIMBRA 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.

The most common (≥20%) adverse reactions were anemia, fatigue, musculoskeletal pain, decreased weight, and cough.

Adverse reactions and laboratory abnormalities are listed in Table 5 and Table 6, respectively.

Table 5: Adverse Reactions (≥10%) in Patients With ESCC Receiving TEVIMBRA in RATIONALE-302

Adverse Reaction	TEVIMBRA (N=255)		ICC (N=240)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Blood Disorders				
Anemia	31	6	45	11
General Disorders				
Fatigue[a]	28	2	46	6
Pyrexia	16	0.4	14	0
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain[b]	24	1	25	1
Investigations				
Weight decreased	23	1	19	0
Respiratory, Thoracic and Mediastinal Disorders				
Cough[c]	22	0.4	16	0.4
Metabolism and Nutrition Disorders				
Decreased appetite	16	0.4	35	4
Infections and Infestations				
Pneumonia[d]	16	6	12	7
Gastrointestinal Disorders				
Constipation	15	0	19	0.4
Nausea	14	0.4	30	3
Diarrhea[e]	13	1	32	7
Dysphagia	11	6	8	3
Abdominal pain[f]	11	0.8	16	2
Vomiting	11	0.8	20	4
Endocrine Disorders				
Hypothyroidism[g]	13	0.4	0.8	0
Skin and Subcutaneous Tissue Disorders				
Rash[h]	13	0.4	6	0
Vascular Disorders				

Adverse Reaction	TEVIMBRA (N=255)		ICC (N=240)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hemorrhage[i]	12	2	10	3

ICC = investigator's choice of chemotherapy
[a] Fatigue includes asthenia, fatigue, malaise.
[b] Musculoskeletal pain includes musculoskeletal pain, spinal pain, arthralgia, back pain, neck pain, musculoskeletal chest pain, myalgia, pain in extremity, non-cardiac chest pain, bone pain, arthritis.
[c] Cough includes productive cough, cough.
[d] Pneumonia includes pneumonia aspiration, pneumonia, pneumonia bacterial, lower respiratory tract infection.
[e] Diarrhea includes diarrhea, colitis.
[f] Abdominal pain includes abdominal pain upper, abdominal pain, abdominal discomfort, abdominal pain lower, gastrointestinal pain.
[g] Hypothyroidism includes hypothyroidism, blood thyroid stimulating hormone increased.
[h] Rash includes dermatitis, dermatitis acneiform, dermatitis allergic, eczema, erythema, psoriasis, rash, rash follicular, rash maculo-papular, rash pruritic.
[i] Hemorrhage includes tumor hemorrhage, upper gastrointestinal hemorrhage, gastrointestinal hemorrhage, hemoptysis, esophageal hemorrhage, hematuria, gastric hemorrhage, epistaxis, tracheal hemorrhage, gingival bleeding, pulmonary hemorrhage, procedural hemorrhage, rectal hemorrhage, stoma site hemorrhage.

Table 6: Laboratory Abnormalities Worsening From Baseline Occurring in ≥10% of Patients Receiving TEVIMBRA in RATIONALE-302

Laboratory Abnormality	TEVIMBRA[a]		ICC[a]	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Chemistry				
Glucose increased	46	4	40	2
Sodium decreased	34	9	36	8
Albumin decreased	33	0.8	37	1
Alkaline phosphatase increased	32	3	15	0.5
AST increased	27	0.8	12	0.5
ALT increased	23	0.8	15	1
Phosphate decreased	15	4	20	3
Creatine kinase increased	13	1	2	0
Potassium decreased	13	1	15	3
Bilirubin increased	11	2	8	0.5
Glucose decreased	10	0.4	10	0.5
Hematology				
Hemoglobin decreased	45	6	61	10
Lymphocytes decreased	43	11	60	28
Platelets decreased	11	1	11	0.9
Leukocytes decreased	10	0.8	66	31

[a] The denominator used to calculate the rate varied from 136 to 240 based on the number of patients with a baseline value and at least one post-treatment value.

Treatment of Previously Untreated Unresectable or Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma (G/GEJ)

The safety of TEVIMBRA in combination with chemotherapy was evaluated in RATIONALE-305, a randomized, multicenter, double-blind, placebo-controlled trial in patients with previously

untreated unresectable or metastatic G/GEJ adenocarcinoma *[see Clinical Studies (14.2)]*.

Patients were randomized (1:1) to receive either TEVIMBRA 200 mg by intravenous infusion over 30-60 minutes every 3 weeks or placebo plus a platinum and fluoropyrimidine-based chemotherapy. The chemotherapy regimens consisted of:

- Oxaliplatin 130 mg/m^2 IV on Day 1 for up to 6 cycles and capecitabine 1000 mg/m^2 orally twice daily for 14 consecutive days of every 3-week cycle

or

- Cisplatin 80 mg/m^2 IV, Day 1, and 5-FU (5-fluorouracil) 800 mg/m^2/day IV continuous infusion over 24 hours daily Day 1-5, every 3 weeks for up to 6 cycles

Patients were treated until disease progression or unacceptable toxicity. The median duration of exposure was 5.91 months (range: 0.1 to 47 months) in TEVIMBRA-treated patients.

Serious adverse reactions occurred in 42% of patients receiving TEVIMBRA in combination with chemotherapy. The most frequent serious adverse drug reactions (≥2%) were pneumonia (3.6%), decreased platelet count (3.2%), gastrointestinal hemorrhage (3%), and colitis (2.2%). Fatal adverse reactions occurred in 4.2% of patients who received TEVIMBRA in combination with chemotherapy; events occurring in 2 or more patients were death, sepsis, pneumonia, pulmonary embolism, and respiratory failure.

Permanent discontinuation of TEVIMBRA due to an adverse reaction occurred in 16% of patients. Adverse drug reactions which resulted in permanent discontinuation in ≥1% of patients were death, fatigue, and pneumonitis.

Dosage interruption of TEVIMBRA due to an adverse drug reaction occurred in 49% of patients. Adverse drug reactions which required dosage interruption in ≥2% of patients were decreased platelet count (12%), decreased neutrophil count (10%), neutropenia (6%), decreased white blood cell count (6%), increased AST (4.8%), increased ALT (3.8%), increased blood bilirubin (3%), COVID-19 (3%), thrombocytopenia (2.8%), leukopenia (2.6%), pneumonitis (2.2%), and pneumonia (2%).

The most common (≥20%) adverse reactions, including laboratory abnormalities, for TEVIMBRA in combination with chemotherapy were nausea, fatigue, decreased appetite, anemia, peripheral sensory neuropathy, vomiting, decreased platelet count, decreased neutrophil count, increased aspartate aminotransferase, diarrhea, abdominal pain, increased alanine aminotransferase, white blood cell count decreased, decreased weight, and pyrexia.

Adverse reactions and laboratory abnormalities are listed in Table 7 and Table 8, respectively.

Table 7: Adverse Reactions (≥10%) in Patients with G/GEJ Receiving TEVIMBRA + Chemotherapy with a Difference Between Arms of ≥5% for All Grades or ≥2% for Grades 3 and 4 vs Placebo + Chemotherapy in RATIONALE-305

Adverse Drug Reaction	TEVIMBRA + Chemotherapy (N=498)		Placebo + Chemotherapy (N=494)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
General Disorders and Administration Site Conditions				
Pyrexia	20	1.6	14	0.6

Skin and Subcutaneous Tissue Disorders				
Rash[a]	16	1.6	7	0
Pruritus	10	0.2	3.2	0
Endocrine Disorders				
Hypothyroidism[a]	13	0.2	2.8	0

[a] Represents a composite of multiple, related preferred terms.

Other Clinically Important Adverse Reactions Occurring in Less Than 10% include:

Stomatitis, infusion-related reaction, dyspnea, hepatitis, hyperthyroidism, pneumonitis, hyperglycemia, myalgia, diabetes mellitus, pancreatitis, arthritis, Sjogren's syndrome, thyroiditis, adrenal insufficiency, hypophysitis, myasthenia gravis, uveitis, myocarditis, pericarditis, colitis, vitiligo, myositis, and nephritis.

Table 8: Select Laboratory Abnormalities Worsening from Baseline Occurring in ≥10% of Patients Receiving TEVIMBRA + Chemotherapy with a Difference Between Arms of ≥5% for All Grades or ≥2% for Grades 3 and 4 vs Placebo + Chemotherapy in RATIONALE-305

Laboratory Abnormality	TEVIMBRA + Chemotherapy[a] (N=498)		Placebo + Chemotherapy[a] (N=494)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Chemistry				
AST increased	58	6	56	3
Sodium decreased	42	7	36	5
ALT increased	41	4.8	36	2
Potassium decreased	33	9	28	6
Hematology				
Lymphocytes decreased	53	12	46	9

Abbreviations: ALT = alanine aminotransferase, AST = aspartate amino transferase.

[a] The denominator used to calculate the rate varied from 480 to 494 based on the number of patients with a baseline value and at least one post-treatment value.

Other Clinically Important Laboratory Abnormalities Occurring in <20% include:

Creatinine increased, potassium increased, glucose decreased, sodium increased, lymphocytes increased, hemoglobin increased.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of TEVIMBRA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome, toxic epidermal necrolysis (including fatal cases).

Immune system disorders: Immune-mediated cystitis.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, TEVIMBRA can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. There are no available data on the use of TEVIMBRA in pregnant women.

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 (*see Data*). Human IgG4 immunoglobulins (IgG4) are known to cross the placental barrier; therefore, tislelizumab-jsgr has the potential to be transmitted from the mother to the developing fetus. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

Animal reproduction studies have not been conducted with TEVIMBRA to evaluate its effect on reproduction and fetal development. A central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the fetus. In murine models of pregnancy, blockade of PD-L1 signaling has been shown to disrupt tolerance to the fetus and to result in an increase in fetal loss; therefore, potential risks of administering TEVIMBRA during pregnancy include increased rates of abortion or stillbirth. As reported in the literature, there were no malformations related to the blockade of PD-1 signaling in the offspring of these animals; however, immune-mediated disorders occurred in PD-1 and PD-L1 knockout mice. Based on its mechanism of action, fetal exposure to tislelizumab-jsgr may increase the risk of developing immune-mediated disorders or altering the normal immune response.

8.2 Lactation

Risk Summary

There is no information regarding the presence of tislelizumab-jsgr in human milk, or its effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment and for 4 months after the last dose of TEVIMBRA.

8.3 Females and Males of Reproductive Potential

TEVIMBRA can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating TEVIMBRA *[see Use in Specific Populations (8.1)]*.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with TEVIMBRA and for 4 months after the last dose of TEVIMBRA.

8.4 Pediatric Use

The safety and effectiveness of TEVIMBRA have not been established in pediatric patients.

8.5 Geriatric Use

TEVIMBRA as a Single Agent

Of the 255 patients who were treated with TEVIMBRA for previously treated unresectable or metastatic ESCC in the clinical study RATIONALE-302, 98 (38%) were 65 years and older and 13 (5%) were 75 years and older. No overall differences in safety or effectiveness were observed between elderly patients and younger patients.

TEVIMBRA in Combination with Chemotherapy

Of the 324 patients who were treated with TEVIMBRA and platinum-containing chemotherapy as first-line treatment for unresectable advanced or metastatic ESCC in the clinical study RATIONALE-306, 149 (46%) were 65 years and older and 13 (4%) were 75 years and older. No overall differences in safety or effectiveness were observed between elderly patients and younger patients.

Of the 498 patients who were treated with TEVIMBRA in combination with platinum-containing chemotherapy for G/GEJ adenocarcinoma in the clinical study RATIONALE-305, 161 (32%) were 65 years and older, and 28 (6%) were 75 years and older. No overall differences in safety or effectiveness were observed between elderly patients and younger patients.

11 DESCRIPTION

Tislelizumab-jsgr is a programmed death receptor-1 (PD-1)–blocking antibody. Tislelizumab-jsgr is an Fc-engineered humanized monoclonal IgG4 kappa antibody with an approximate molecular weight of 147 kDa. Tislelizumab-jsgr is produced in recombinant Chinese hamster ovary (CHO) cells.

TEVIMBRA (tislelizumab-jsgr) injection is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution for intravenous use, supplied in single-dose vials. Each vial contains 100 mg of tislelizumab-jsgr monoclonal antibody in 10 mL of solution, with a concentration of 10 mg/mL, and is formulated in: citric acid monohydrate (4.2 mg), histidine (17.2 mg), L-histidine hydrochloride monohydrate (8.2 mg), polysorbate 20 (2 mg), sodium citrate (59.3 mg), trehalose (650.4 mg), and Water for Injection, USP. The pH is 6.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Binding of the PD-1 ligands PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T-cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors.

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. Tislelizumab-jsgr decreased tumor growth in xenograft models and a human PD-1 transgenic mouse model.

12.2 Pharmacodynamics

The tislelizumab-jsgr exposure-response relationship for efficacy and safety and time course of pharmacodynamic response has not been fully characterized.

12.3 Pharmacokinetics

Pharmacokinetic parameters are presented as geometric mean (% CV) unless otherwise specified.

The peak concentration (C_{max}) and area under the plasma concentration versus time curve (AUC) of tislelizumab-jsgr increased dose proportionally in the dose range of 0.5 (0.2 times the approved recommended dosage in a 70 kg patient) to 10 mg/kg (3.5 times the approved recommended dosage in a 70 kg patient).

The steady-state AUC_{tau} of tislelizumab-jsgr is 1,283 mcg/mL·day (28.7%) and the C_{max} is 110 mcg/mL (22.2%) following the approved recommended dosage. Steady-state concentration of tislelizumab-jsgr is reached after 12 weeks of repeated dosing with an every 3-week regimen and the systemic accumulation was 2.14-fold.

Distribution

The tislelizumab-jsgr steady-state total volume of distribution is 6.42 L (32.6%).

Elimination

The tislelizumab-jsgr total clearance is 0.153 L/day (29.5%) and the terminal half-life ($t_{½}$) is 24 days (31%).

Specific Populations

No clinically significant differences in the pharmacokinetics of tislelizumab-jsgr were observed based on age (range: 18 to 90 years), weight (range: 32 to 130 kg), race (White, Asian, or Black), mild to moderate renal impairment (CLcr ≥30 mL/min, estimated by Cockcroft-Gault), mild to moderate hepatic impairment (total bilirubin ≤3 times ULN and any AST, estimated by NCI criteria). The effect of severe hepatic impairment (total bilirubin >3 times ULN and any AST), severe renal impairment (CLcr 15-29 mL/min), or end-stage renal disease (CLcr <15 mL/min) on the pharmacokinetics of tislelizumab-jsgr is unknown.

12.6 Immunogenicity

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, including those of tislelizumab-jsgr products.

In patients who received tislelizumab-jsgr in RATIONALE-306 for up to 26 months, the incidence of anti-tislelizumab antibodies was 22% (66/300). Among the anti-tislelizumab antibody-positive patients, the incidence of neutralizing antibodies was 1.5% (1/66).

In patients who received tislelizumab-jsgr in RATIONALE-302 for up to 22 months, the incidence of anti-tislelizumab antibodies was 14.5% (32/221). Among the anti-tislelizumab antibody-positive patients, the incidence of neutralizing antibodies was 3.1% (1/32).

In patients who received tislelizumab-jsgr in RATIONALE-305 throughout the treatment period and in the ADA analysis set, the incidence of anti-tislelizumab antibodies was 22.7% (108/475).

Among the anti-tislelizumab antibody-positive patients, the incidence of neutralizing antibodies was 5.6% (6/108).

There was no significant effect of anti-drug antibodies on the pharmacokinetics of tislelizumab-jsgr. The effect of anti-drug antibodies on pharmacodynamics, safety, or effectiveness of tislelizumab-jsgr has not been fully characterized.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been performed to assess the potential of tislelizumab-jsgr for carcinogenicity or genotoxicity.

In a 3-month repeat-dose toxicology study in cynomolgus monkeys, there were no notable effects in the male and female reproductive organs; however, most animals in the study were not sexually mature.

13.2 Animal Toxicology and/or Pharmacology

In animal models, inhibition of PD-L1/PD-1 signaling resulted in an increased severity of some infections and enhanced inflammatory responses. *Mycobacterium tuberculosis*–infected PD-1 knockout mice exhibit markedly decreased survival compared with wild-type controls, which correlated with increased bacterial proliferation and inflammatory responses in these animals. PD-1 blockade using a primate anti–PD-1 antibody was also shown to exacerbate *M. tuberculosis* infection in rhesus macaques. PD-L1 and PD-1 knockout mice have also shown decreased survival following infection with lymphocytic choriomeningitis virus.

14 CLINICAL STUDIES

14.1 Esophageal Squamous Cell Carcinoma

First-line Treatment of Unresectable or Metastatic Esophageal Carcinoma (ESCC) in Patients Whose Tumors Express PD-L1 (≥1)

The efficacy of TEVIMBRA, in combination with chemotherapy, was evaluated in RATIONALE-306 (NCT03783442), a global, randomized, placebo-controlled, double-blind study in patients with unresectable, recurrent, or metastatic esophageal squamous cell carcinoma (ESCC).

Patients were enrolled regardless of their 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 (Tumor Area Positivity or TAP). A retrospective scoring of tumor PD-L1 status using Combined Positive Score (CPS) was also conducted using the PD-L1–stained tumor specimens used for randomization.

Patients should not have received prior systemic therapy for advanced or metastatic disease. A treatment-free interval of at least 6 months was required if there was prior neoadjuvant/adjuvant therapy with platinum-based chemotherapy. The trial excluded patients who had active leptomeningeal disease or uncontrolled brain metastasis, active autoimmune disease, a medical condition requiring systemic corticosteroids or immunosuppressants, or evidence of fistula or complete esophageal obstruction not amenable to treatment.

Patients were randomized (1:1) to receive either TEVIMBRA 200 mg every 3 weeks or placebo in combination with investigator's choice of chemotherapy (ICC) on a 21-day cycle. Patients received TEVIMBRA until disease progression assessed by the investigator per RECIST v1.1, or until unacceptable toxicity. The chemotherapy doublet regimen consists of:

- Platinum (cisplatin [60 to 80 mg/m^2 IV, on Day 1] or oxaliplatin [130 mg/m^2 IV, on Day 1]) and a fluoropyrimidine (fluorouracil [750 to 800 mg/m^2 IV, on Days 1 to 5] or capecitabine [1000 mg/m^2 orally twice daily, on Days 1 to 14])

or

- Platinum (cisplatin [60 to 80 mg/m^2 IV, on Day 1 or 2] or oxaliplatin [130 mg/m^2 IV, on Day 1 or 2]) and (paclitaxel 175 mg/m^2 IV, on Day 1)

Cross-over between treatment arms or between fluoropyrimidine and paclitaxel during the study treatment period was not allowed.

Patient randomization was stratified by geographic region (Asia [excluding Japan] versus Japan versus Rest of World), prior definitive therapy (yes versus no), and investigator choice of chemotherapy (ICC; platinum with fluoropyrimidine versus platinum with paclitaxel).

Tumor assessments were performed every 6 weeks for the first 48 weeks, then every 9 weeks thereafter.

The primary efficacy outcome measure was overall survival (OS) in the Intent-to-Treat (ITT) population. Secondary outcome measures included progression-free survival (PFS), objective response rate (ORR), and duration of response (DoR) as assessed by the investigator per RECIST v1.1. Additional analyses of efficacy outcome measures were also conducted based on PD-L1 TAP ≥1% and CPS ≥1.

A total of 649 patients were randomized. The trial population characteristics were median age 64 years (range: 26 to 84 years), 48% were ≥65 years of age, 87% were male, 75% were Asian, and 24% were White. Eighty-six percent had metastatic disease and 14% had locally advanced disease; 99.8% of patients had histological confirmation of squamous cell carcinoma. Baseline ECOG performance status was 0 (33%) or 1 (67%). Thirty-four percent of patients had tumors that expressed PD-L1 TAP ≥10%, 74% had PD-L1 TAP ≥1%, and 74% had PD-L1 CPS ≥1. Fifty-five percent of patients received platinum (cisplatin or oxaliplatin) and paclitaxel-containing regimens, and 45% received platinum (cisplatin or oxaliplatin) and fluoropyrimidine-containing regimens.

RATIONALE-306 demonstrated a statistically significant improvement in OS for patients randomized to TEVIMBRA in combination with chemotherapy compared to placebo in combination with chemotherapy. Exploratory analysis of OS in the population with TAP <1% population and in the CPS <1 population showed hazard ratios of 1.34 (95% CI 0.73, 2.46) and 1.52 (95% CI 0.81, 2.84), respectively, indicating that the improvement in the ITT population was primarily attributed to the results observed in the subgroup of patients with PD-L1 ≥1.

Efficacy results are shown in Table 9, Figure 1, and Figure 2.

Table 9: Efficacy results in RATIONALE-306

Endpoint	TEVIMBRA + Chemotherapy (N=231)	Placebo + Chemotherapy (N=250)	TEVIMBRA + Chemotherapy (N=233)	Placebo + Chemotherapy (N=247)
	PD-L1 TAP ≥1%		PD-L1 CPS ≥1	
Overall Survival (OS)				
Deaths n (%)	141 (61)	177 (70.8)	141 (61)	175 (71)
Median (months)[a] (95% CI)	16.8 (15.3, 20.8)	9.6 (8.9, 11.8)	16.8 (15.3, 20.8)	9.6 (8.9, 11.8)
HR[b] (95% CI)	0.66 (0.53, 0.82)		0.65 (0.52,0.81)	
Progression-Free Survival (PFS)				
Events, n (%)	152 (66)	199 (80)	153 (66)	195 (79)
Median (months)[a] (95% CI)	7.2 (6.8, 8.5)	5.5 (4.5, 5.8)	7.1 (6.8, 8.3)	5.5 (4.5, 5.8)
HR[b] (95% CI)	0.56 (0.45, 0.70)		0.57 (0.46, 0.71)	
Objective Response Rate (ORR)[c]				
Responders, n	134	90	134	89
ORR, %	58	36	58	36
95% CI[d]	(51, 65)	(30, 42)	(51, 64)	(30, 42)
Complete response (CR), n (%)	11 (4.8)	5 (2)	11 (4.7)	5 (2)
Partial response, n (%)	123 (53)	85 (34)	123 (53)	84 (34)
Duration of Response (DoR)				
Median DoR (months)[a] (95% CI)	7.2 (6.2, 9.6)	5.7 (4.4, 7.3)	7.6 (6.6, 9.7)	5.6 (4.4, 7.3)

CI = confidence interval; HR = hazard ratio.

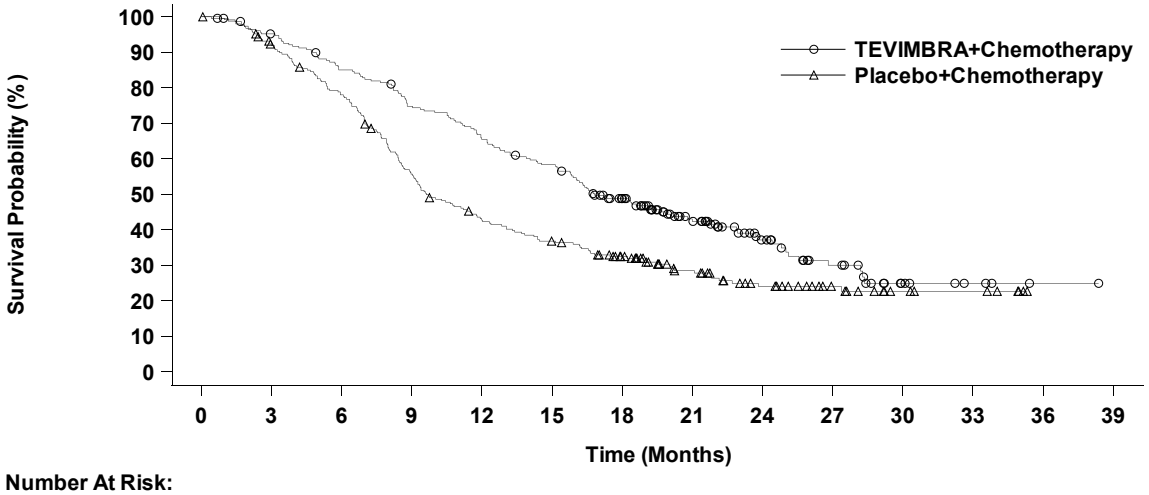
[a] Medians were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley.

[b] Estimated by Cox proportional hazards model.

[c] Confirmed responses.

[d] Exact Clopper-Person-2-sided CI.

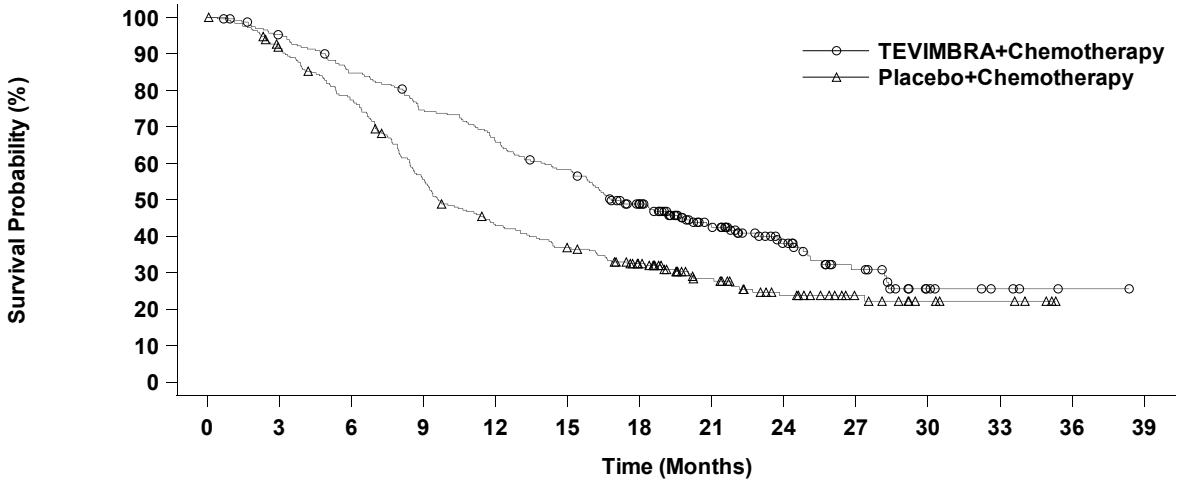
Figure 1: Kaplan-Meier Curve for Overall Survival in RATIONALE-306 (PD-L1 TAP ≥1%)



Number At Risk:

TEVIMBRA+ Chemotherapy	231	216	192	168	147	130	98	61	36	22	8	4	1	0
Placebo+ Chemotherapy	250	225	190	134	101	86	68	44	29	17	9	6	0	0

Figure 2: Kaplan-Meier Curve for Overall Survival in RATIONALE-306 (PD-L1 CPS ≥1)



Number At Risk:

TEVIMBRA+ Chemotherapy	233	218	193	169	149	131	99	61	37	22	8	4	1	0
Placebo+ Chemotherapy	247	221	186	132	100	85	67	42	27	15	8	5	0	0

Efficacy results from the exploratory retrospective analysis with CPS scoring were generally consistent with the efficacy results for TAP subgroups detailed in Table 9 and Figure 1.

Previously Treated Unresectable or Metastatic Esophageal Squamous Cell Carcinoma (ESCC)

RATIONALE-302 (NCT03430843) was a multicenter, randomized (1:1), open-label trial 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 (TAP). 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 TEVIMBRA 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 to 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.

Randomization was stratified by geographic region (Asia [excluding Japan] vs Japan vs US/EU), ECOG performance status (0 vs 1), and ICC option. Tumor assessments were conducted every 6 weeks for the first 6 months, then every 9 weeks until disease progression.

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.

A total of 512 patients were enrolled and randomized to TEVIMBRA (n=256) or ICC (n=256) (irinotecan [46%], paclitaxel [33%], or docetaxel [21%]). Of the 512 patients, 142 (28%) had PD-L1 ≥10%, 222 (43%) had PD-L1 <10%, and 148 (29%) had unknown baseline PD-L1 status.

The trial population characteristics were: median age of 62 years (range: 35 to 86), 38% age ≥65; 84% male; 19% White and 80% Asian; 95% had metastatic disease. All patients had received at least one prior anti-cancer systemic therapy. Baseline ECOG performance status was 0 (25%) or 1 (75%).

RATIONALE-302 demonstrated a statistically significant improvement in OS for patients randomized to TEVIMBRA as compared with ICC. OS results by PD-L1 CPS level (<1 and ≥1) were not studied.

Efficacy results are shown in Table 10 and Figure 3.

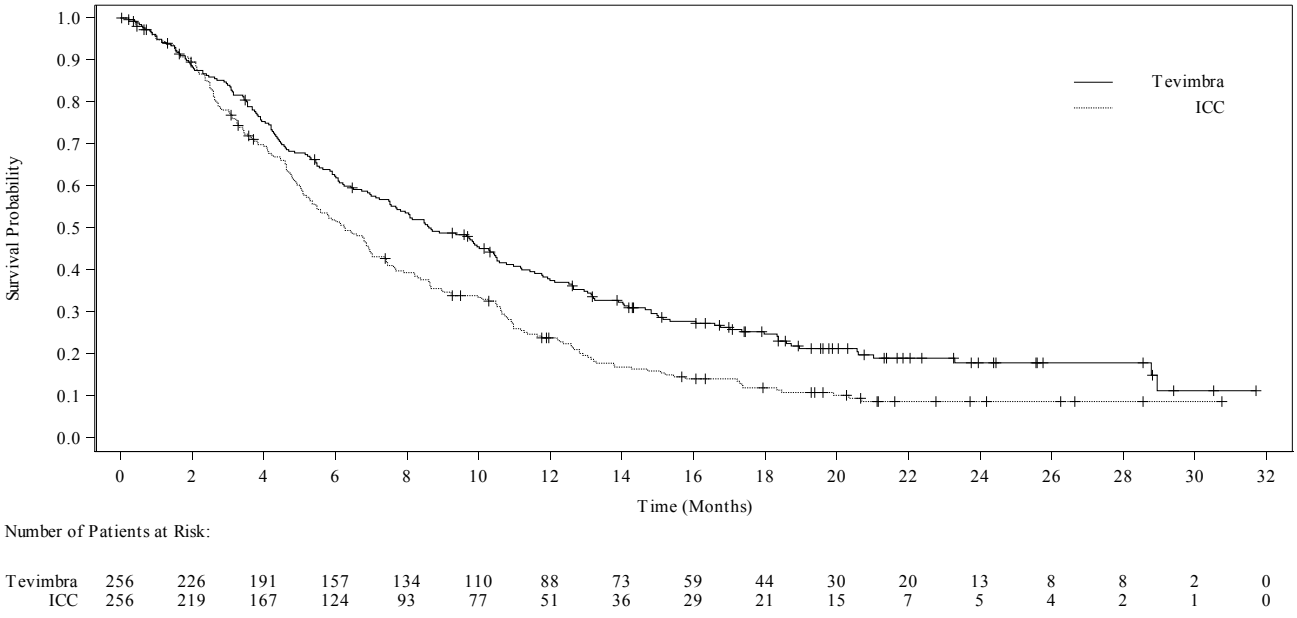
Table 10: Efficacy Results in RATIONALE-302 in ITT Population

Endpoint	**TEVIMBRA (N=256)**	**ICC (N=256)**
Overall Survival		
Deaths n (%)	197 (77)	213 (83.2)
Median (months)[a] (95% CI)	8.6 (7.5, 10.4)	6.3 (5.3, 7)
Hazard ratio[b] (95% CI)	0.7 (0.57, 0.85)	
p-value[c]	0.0001	
Progression-Free Survival		
Disease progression or death (%)	223 (87.1)	180 (70.3)

Endpoint	TEVIMBRA (N=256)	ICC (N=256)
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)	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.

Figure 3: Kaplan-Meier Curve for Overall Survival in RATIONALE-302 (ITT)



14.2 Gastric Cancer

Previously Untreated, Unresectable, or Metastatic HER2-Negative Gastric or Gastroesophageal Junction (G/GEJ) Adenocarcinoma in Patients Whose Tumors Express PD-L1 (≥1)

RATIONALE-305 (NCT03777657) was a randomized, multicenter, placebo-controlled, double-blind trial in patients with HER2-negative previously untreated unresectable or metastatic G/GEJ adenocarcinoma.

Patients were enrolled regardless of their tumor PD-L1 expression level, which was evaluated prospectively at a central laboratory using the VENTANA PD-L1 (SP263) assay that identified PD-L1 staining on both tumor and tumor-associated immune cells (TAP). A retrospective scoring of tumor PD-L1 status using Combined Positive Score (CPS) was also conducted using

the PD-L1-stained tumor specimens used for randomization.

The trial excluded patients who had active leptomeningeal disease or uncontrolled brain metastasis, and patients with active autoimmune disease or history of autoimmune diseases, or a medical condition requiring systemic corticosteroids or immunosuppressants.

Patients were randomized to receive either TEVIMBRA 200 mg every 3 weeks or placebo in combination with investigator's choice of chemotherapy on a 21-day cycle. TEVIMBRA (or placebo) was administered until disease progression or unacceptable toxicity.

The chemotherapy doublets regimen consisted of:

- CAPOX: Oxaliplatin 130 mg/m^2 IV on Day 1 for up to 6 cycles and capecitabine 1000 mg/m^2 orally twice daily for 14 consecutive days. Capecitabine treatment could be continued beyond 6 cycles

or

- FP: Cisplatin 80 mg/m^2 IV, Day 1, and 5-FU 800 mg/m^2/day IV continuous infusion over 24 hours daily Day 1-5. Cisplatin and 5-FU were given for up to 6 cycles

Cross-over between treatment arms was not allowed.

Patient randomization was stratified by geographic region (China [including Taiwan], vs Japan and South Korea vs rest of the world, including US and Europe); PD-L1 expression (PD-L1 TAP score ≥5% vs PD-L1 TAP score <5%); presence of peritoneal metastasis (yes vs no); and ICC option (oxaliplatin plus capecitabine vs cisplatin plus 5-FU).

Tumor assessments were performed every 6 weeks for the first 48 weeks and thereafter approximately every 9 weeks.

The primary efficacy outcome measures were OS in the PD-L1 TAP score ≥5% population and in the Intent-to-Treat (ITT) population. Secondary outcome measures included progression-free survival (PFS), objective response rate (ORR), and duration of response (DoR) as assessed by the investigator per RECIST v1.1. Additional analyses of efficacy outcome measures were also conducted based on PD-L1 TAP ≥1% and CPS ≥1.

A total of 997 patients were randomized. The trial population characteristics were median age 61 years (range: 23 to 86 years), 35% ≥65 years of age, 69% male; 75% Asian, 22% White, and 0% Black or African American. Eighty percent had primary stomach tumor; 89% had PD-L1 TAP ≥1% and 86% had PD-L1 CPS ≥1, and 99% of patients had metastatic disease at baseline. Baseline ECOG performance status was 0 (32%) or 1 (68%). Ninety-three percent of patients received CAPOX and 7% received FP.

RATIONALE-305 demonstrated a statistically significant improvement in OS for patients randomized to TEVIMBRA in combination with chemotherapy compared with placebo plus chemotherapy in the PD-L1 TAP ≥5% population and in the ITT population. Exploratory analyses of OS in the TAP <1% population and in the CPS <1 population showed hazard ratios of 0.98 (95% CI: 0.64, 1.50) and 1.01 (95% CI: 0.66, 1.52) respectively, indicating that the improvement in the ITT population was primarily attributed to the results observed in the subgroup of patients with PD-L1 ≥1.

Efficacy results are summarized in Table 11, Figure 4, and Figure 5.

Table 11: Efficacy Results in RATIONALE-305

Endpoint	TEVIMBRA + Chemotherapy (N=432)	Placebo + Chemotherapy (N=453)	TEVIMBRA + Chemotherapy (N=420)	Placebo + Chemotherapy (N=434)
	PD-L1 TAP ≥1%		PD-L1 CPS ≥1	
Overall Survival				
Deaths n (%)	318 (74)	370 (82)	308 (73)	356 (82)
Median (months)[a] (95% CI)	15.0 (13.3, 16.7)	12.8 (12.1, 14.1)	15.1 (13.6, 17.2)	12.9 (12.1, 14.1)
HR[b] (95% CI)	0.78 (0.67, 0.90)		0.78 (0.67, 0.91)	
Progression-Free Survival				
Events, n (%)	316 (73)	364 (80)	303 (72)	348 (80)
Median[c] (months) (95% CI)	6.9 (5.7, 7.2)	5.9 (5.6, 6.9)	7.0 (5.7, 7.7)	6.4 (5.6, 6.9)
HR[b] (95% CI)	0.78 (0.67, 0.91)		0.77 (0.66, 0.90)	
Objective Response Rate[c]				
ORR, n	206	186	204	183
ORR, %	48	41	49	42
95% CI (%)[d]	(43, 53)	(37, 46)	(44, 53)	(37, 47)
Complete response, n (%)	15 (3.5)	15 (3.3)	16 (3.8)	16 (3.7)
Partial response, n (%)	191 (44)	171 (38)	188 (45)	167 (38)
Duration of Response				
Median (months)[a] (95% CI)	8.6 (7.8, 10.4)	7.2 (5.8, 8.3)	8.6 (7.8, 10.4)	7.2 (5.8, 8.5)

Abbreviations: CI = confidence interval, HR = hazard ratio, ORR = objective response rate.

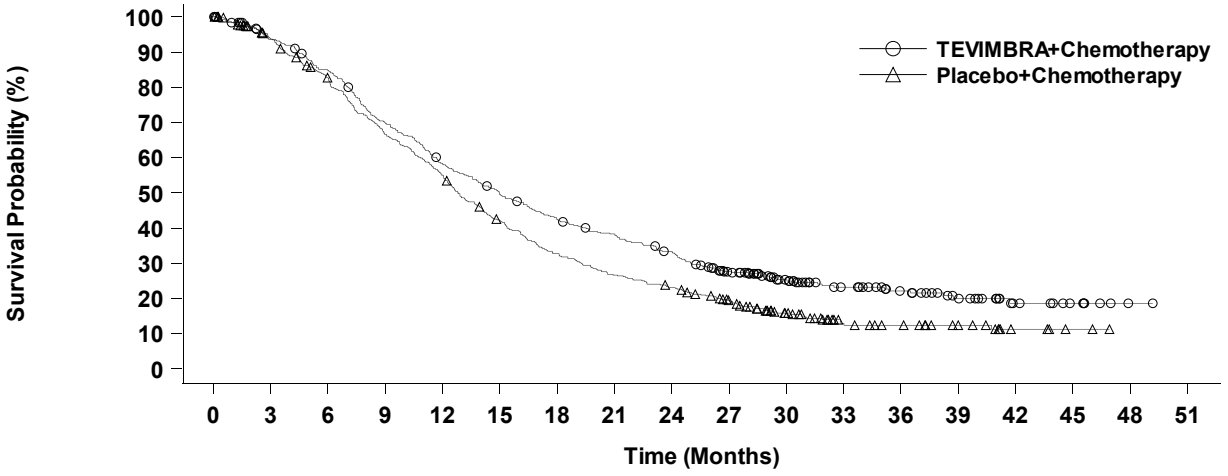
[a] Medians were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley.

[b] Estimated by Cox proportional hazards model.

[c] Based on confirmed response.

[d] Exact Clopper-Pearson 2-sided confidence interval.

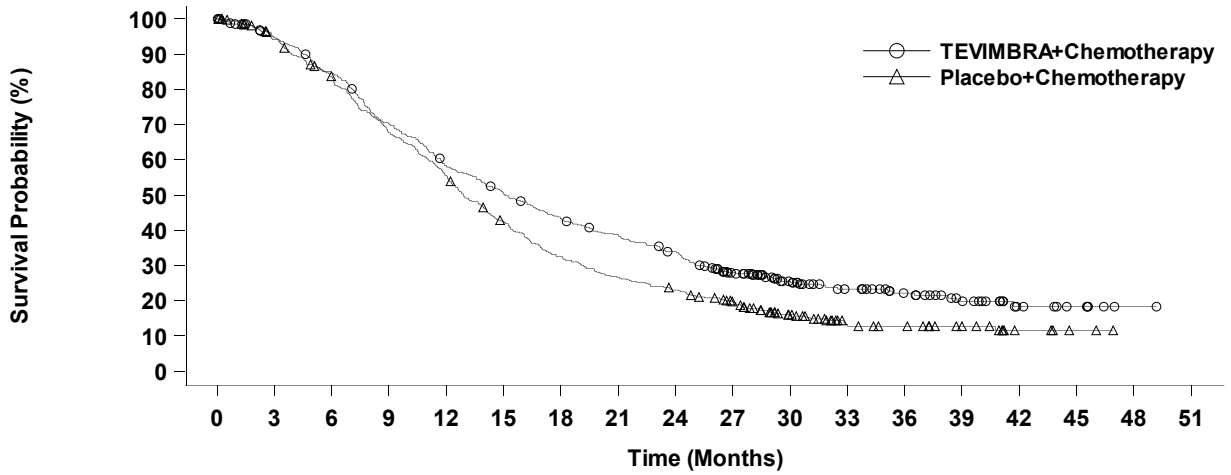
Figure 4: Kaplan-Meier Curve for Overall Survival in RATIONALE-305 (PD-L1 TAP ≥1%)



Number At Risk:

TEVIMBRA+ Chemotherapy	432	394	355	292	242	205	175	156	134	100	68	50	39	24	12	7	1	0
Placebo+ Chemotherapy	453	412	359	289	239	180	140	114	98	75	46	25	20	13	5	2	0	0

Figure 5: Kaplan-Meier Curve for Overall Survival in RATIONALE-305 (PD-L1 CPS ≥1)



Number At Risk:

TEVIMBRA+ Chemotherapy	**420**	**384**	**345**	**285**	**235**	**202**	**173**	**153**	**132**	**96**	**64**	**48**	**37**	**22**	**10**	**6**	**1**	**0**
Placebo+ Chemotherapy	**434**	**401**	**351**	**284**	**233**	**175**	**134**	**110**	**94**	**74**	**44**	**24**	**20**	**13**	**5**	**2**	**0**	**0**

An exploratory subgroup analysis of OS in 40 patients with MSI-H tumors irrespective of PD-L1 status showed a HR of 0.66 (0.3, 1.43).

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

TEVIMBRA injection is a clear to slightly opalescent, colorless to slightly yellow solution supplied in a carton containing one 100 mg/10 mL (10 mg/mL) single-dose vial (NDC 72579-121-01).

Storage

Store in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light.

Do not freeze. Do not shake.

17 PATIENT COUNSELING INFORMATION

Advise patients to read the FDA-approved patient labeling (Medication Guide).

Immune-Mediated Adverse Reactions

Inform patients of the risk of immune-mediated adverse reactions that may be severe or fatal, may occur after discontinuation of treatment, and may require corticosteroid treatment and interruption or discontinuation of TEVIMBRA. These reactions may include:

- *Pneumonitis:* Advise patients to contact their healthcare provider immediately for new or worsening cough, chest pain, or shortness of breath *[see Warnings and Precautions (5.1)]*.
- *Colitis:* Advise patients to contact their healthcare provider immediately for diarrhea, or severe abdominal pain *[see Warnings and Precautions (5.1)]*.

- *Hepatitis:* Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, pain on the right side of the abdomen, or easy bruising or bleeding *[see Warnings and Precautions (5.1)]*.
- *Endocrinopathies:* Advise patients to contact their healthcare provider immediately for signs or symptoms of hypophysitis, adrenal insufficiency, hypothyroidism, hyperthyroidism, thyroiditis, or Type 1 diabetes mellitus *[see Warnings and Precautions (5.1)]*.
- *Nephritis:* Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis *[see Warnings and Precautions (5.1)]*.
- *Dermatologic Adverse Reactions:* Advise patients to contact their healthcare provider immediately for any signs or symptoms of severe skin reactions, SJS, TEN, or DRESS *[see Warnings and Precautions (5.1)]*.
- *Other Immune-Mediated Adverse Reactions:*
    - Advise patients that immune-mediated adverse reactions can occur and may involve any organ system, and to contact their healthcare provider immediately for any new or worsening signs or symptoms *[see Warnings and Precautions (5.1)]*.
    - Advise patients of the risk of solid organ transplant rejection and other transplant (including corneal graft) rejection and to contact their healthcare provider immediately for signs or symptoms of organ transplant rejection *[see Warnings and Precautions (5.1)]*.

Infusion-Related Reactions

Advise patients to contact their healthcare provider immediately for signs or symptoms of infusion-related reactions *[see Warnings and Precautions (5.2)]*.

Complications of Allogeneic Hematopoietic Stem Cell Transplantation Complications

Advise patients of potential risk of post-allogeneic hematopoietic stem cell transplantation complications (HSCT) *[see Warnings and Precautions (5.3)]*.

Embryo-Fetal Toxicity

Advise females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.4), Use in Specific Populations (8.1, 8.3)]*.

Advise females of reproductive potential to use effective contraception during treatment with TEVIMBRA and for 4 months after the last dose *[see Warnings and Precautions (5.4)*, *Use in Specific Populations (8.1, 8.3)]*.

Lactation

Advise women not to breastfeed during treatment with TEVIMBRA and for 4 months after the last dose *[see Use in Specific Populations (8.2)]*.

Manufactured by:
BeiGene USA, Inc.
San Mateo, CA 94404
U.S. License No. 2232

Notes

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