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APPLICATION NUMBER:

761232Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review

Office Director

Cross Discipline Team Leader Review

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

BLA Multi-disciplinary Review and Evaluation

Disclaimer: In this document, the sections labeled as “Data” and “The Applicant’s Position” are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

Application Type	BLA
Application Number(s)	761232
Priority or Standard	Standard
Submit Date(s)	July 10, 2021
Received Date(s)	July 12, 2021
PDUFA Goal Date	July 12, 2022
Division/Office	Division of Oncology 3/ Office of New Drugs
Review Completion Date	See electronic stamp date
Established Name	Tislelizumab-jsgr
(Proposed) Trade Name	Tevimbra
Pharmacologic Class	Programmed death receptor-1 (PD-1) blocking antibody
Code name	BGB-A317
Applicant	BeiGene U.S.A., Inc.
Formulation(s)	100 mg/mL (10 mg/mL) for injection
Dosing Regimen	200 mg once every 3 weeks
Applicant Proposed Indication(s)/Population(s)	Treatment of patients with unresectable recurrent locally advanced or metastatic esophageal squamous cell carcinoma after prior systemic therapy.
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	Treatment of adult patients with unresectable or metastatic esophageal squamous cell carcinoma (ESCC) after prior systemic chemotherapy that did not include a PD-(L)1 inhibitor

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OPQ=Office of Pharmaceutical Quality
 OPDP=Office of Prescription Drug Promotion
 OSI=Office of Scientific Investigations
 OSE= Office of Surveillance and Epidemiology
 DEPI= Division of Epidemiology
 DMEPA=Division of Medication Error Prevention and Analysis
 DRISK=Division of Risk Management

Glossary

AC	advisory committee
ADA	anti-drug antibody
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AUC	area under the curve
BLA	biologics license application
BOR	best overall response
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
C _{max}	maximum serum concentration
CBER	Center for Biologics Evaluation and Research
CDC	Complement-dependent cytotoxicity
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	confidence interval
CL	clearance
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CPS	combined positive score
vCPS	visually-estimated combined positive score
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DCR	disease control rate
DMC	data monitoring committee
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCTD	electronic common technical document
E-R	exposure-response
ESCC	esophageal squamous cell carcinoma
ETASU	elements to assure safe use
FACS	fluorescence-activated cell sorting
Fc	fragment crystallizable
FDA	Food and Drug Administration

BLA Multi-disciplinary Review and Evaluation – BLA 761232
TEVIMBRA (tisnelizumab)

FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act first-in-human
GCP	good clinical practice
GHS	global health status
GLP	good laboratory practice
GRMP	good review management practice
HCC	hepatocellular carcinoma
HR	hazard ratio
HRQoL	health-related quality of life
ICC	Investigator's Choice of Chemotherapy
ICH	International Conference on Harmonization
imAE	immune-mediated adverse event
IND	Investigational New Drug
IRR	infusion-related reactions
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MSI	microsatellite instability
MTD	maximum tolerated dose
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
NSCLC	non-small-cell lung carcinoma
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
ORR	Overall Rate Response
OS	Overall Survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD-L1	programmed death-ligand 1
PFS	progression-free survival
PI	prescribing information
PK	pharmacokinetics
PMC	post-marketing commitment
PMR	post-marketing requirement
PP	per protocol
PPI	patient package insert
PR	partial response
PREA	Pediatric Research Equity Act
PRO	patient reported outcome

BLA Multi-disciplinary Review and Evaluation – BLA 761232
TEVIMBRA (tislelizumab)

PS	performance status
PTs	preferred terms
PSUR	Periodic Safety Update report
Q2W	once every 2 weeks
Q3W	once every 3 weeks
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SGE	special government employee
SOC	MedDRA System Organ Class
t _{1/2}	terminal half-life
TEAE	treatment emergent adverse event
TrAE	treatment-related adverse event
UK	United Kingdom
US	United States
V _d	volume of distribution
WRO	written response only

1. Executive Summary

1.1. Product Introduction

Tislelizumab-jsgr (tislelizumab) is a recombinant humanized immunoglobulin G4 (IgG4) monoclonal antibody that binds to the programmed death 1 (PD-1) receptor and blocks the interaction between PD-1 with its ligands PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the antitumor immune response. Tislelizumab is supplied in single vials of 100 mg/mL (10 mg/mL) clear to slightly opalescent, colorless to slightly yellow solution. Tislelizumab is not currently approved in the U.S. In China, it is approved for the treatment of:

- patients with relapsed or refractory classical Hodgkin's lymphoma who received at least 2 prior lines of systemic chemotherapy regimens.
- patients with locally advanced or metastatic urothelial carcinoma with PD-L1 high expression and whose disease progressed during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.
- in combination with two chemotherapy regimens as a first-line treatment for patients with advanced squamous non-small cell lung cancer

1.2. Conclusions on the Substantial Evidence of Effectiveness

Substantial Evidence of Effectiveness (SEE) was established with one adequate and well-controlled clinical investigation and confirmatory evidence.

The Applicant submitted the results of a single adequate and well-controlled study to support the claims of effectiveness for the proposed indication. RATIONALE-302 (NCT03430843) is a randomized, international, open-label trial in patients with locally advanced unresectable or metastatic esophageal squamous cell carcinoma (ESCC) with disease progression on/after previous therapy. Patients were eligible if they had histologically confirmed predominant squamous cell histology, irrespective of PD-L1 status, and ECOG PS of 0 or 1. Prior chemotherapy in the neoadjuvant/adjuvant setting was permitted if completed before enrollment and patients had a recurrence-free period of less than 6 months. Patients with prior therapy with PD-1 or PD-L1 monoclonal antibodies were not eligible for the trial. Tumor cell PD-L1 was determined by a central lab using the Ventana SP263 assay (vCPS).

Patients were randomized (1:1) to receive

- Tislelizumab 200 mg intravenously (IV) every 3 weeks (Q3W)
- Investigator's choice of chemotherapy (ICC): paclitaxel (135 mg/m² IV Q3W), docetaxel (75 mg/m² IV Q3W), or irinotecan (125 mg/m² IV on Days 1 and 8 of every 3-week cycle). Regional variations on dosing regimen for taxanes were allowed.

Patients were treated until disease progression, unacceptable toxicity, or 2 years of tislelizumab treatment. The stratification factors for randomization were geographic region (Asia [excluding Japan] vs. Japan vs. US/EU), ECOG performance status (0 vs. 1) and ICC choice (paclitaxel vs. docetaxel vs. irinotecan). PD-L1 expression was not a stratification factor. The primary endpoint of the trial was overall survival (OS) in all patients; the key secondary endpoint was OS in patients with PD-L1 $\geq 10\%$. Additional efficacy outcome measures (no alpha allocated) included objective response rate (ORR), duration of response, and progression-free survival (PFS) in all patients and in the subpopulation with PD-L1 $\geq 10\%$.

In RATIONALE-302, tislelizumab provided a modest but statistically significant improvement in OS compared with chemotherapy. The OS HR in the ITT analysis was 0.70 (95% CI 0.57, 0.85; one-sided p-value = 0.0001) with a median OS of 8.6 months (95% CI 7.5, 10.4) in the tislelizumab arm and 6.3 months (95% CI 5.3, 7) in the ICC arm. Although the secondary endpoint of OS in the PD-L1 $\geq 10\%$ subpopulation (n: 157 patients, 31% of the overall population) was statistically significant at the prespecified alpha level (stratified HR 0.53, 95% CI: 0.37, 0.77; one-sided p-value = 0.006), ascertainment of PD-L1 status was missing in 19% of patients, less than a third of patients had PD-L1 $\geq 10\%$, and PD-L1 status was not a stratification factor for this study. Therefore, although supportive of the primary efficacy outcome, the positive results in the PD-L1 $\geq 10\%$ should be interpreted with caution in the context of these limitations. The ORR was 20.3% (95% CI 15.6, 25.8) in the tislelizumab arm and 9.8% (95% CI 6.4, 14.1) in the ICC arm. Duration of response was prolonged in the tislelizumab arm when compared to the ICC arm (7.1 vs. 4 months). The HR for PFS in the ITT was 0.83 (95% CI 0.67, 1.01). These results are supportive of the primary outcomes and consistent with immune checkpoint inhibitors effects (modest effect on PFS and ORR) in ESCC.

Although worldwide ESCC is the dominant histological subtype (~ 90%) of esophageal cancer, approximately 35% of patients in the US present with this histology (~5000 new patients/year). The study was conducted in several geographic regions; however, only 21% of patients in RATIONALE-302 were enrolled in non-Asian countries. Although only exploratory in nature, subgroup analyses of demographic subgroups of the ITT efficacy population do not indicate differential activity based on race/ethnicity (of those explored) or for patients in Europe/North America. Importantly, based on the SEER database analysis, there are no differences in outcomes for patients with ESCC based on race or ethnicity (Then EO, 2020). Although minorities have not been adequately represented in the study, based on the epidemiological data, tislelizumab mechanism of action, known safety profile of the drug class, and the clinical pharmacology conclusions, the review team agrees that the study results are applicable to the US population.

The submitted evidence meets the statutory evidentiary standard for the approval of tislelizumab for the treatment of patients with locally advanced unresectable or metastatic esophageal squamous cell carcinoma with disease progression on or after prior chemotherapy. The observed improvement in overall survival with a HR of 0.70 is statistically robust. This finding is supported by consistent results on prespecified exploratory subgroup analyses and secondary and exploratory endpoints. Approval of the Application was delayed pending inspections of the clinical sites and manufacturing facilities, which could not be conducted because of the COVID-

19 pandemic. Uncertainty exists regarding whether efficacy would be optimized based on selection using one or more PD-L1 cut-offs.

BLA Multi-disciplinary Review and Evaluation – BLA 761232
TEVIMBRA (tislelizumab)

Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Tislelizumab is a monoclonal antibody that binds to programmed-death receptor 1 (PD-1) and blocks its interactions with both its ligands. This releases the PD-1/PD-L1-mediated inhibition of the immune response, including activation of the anti-tumor immune response. There is extensive clinical experience with immune checkpoint inhibitors, which are approved by the FDA for multiple indications, either alone or in combination with other drugs.

The safety and effectiveness of tislelizumab for the treatment of patients with metastatic or locally advanced unresectable esophageal squamous cell carcinoma (ESCC) with disease progression after prior chemotherapy therapy is demonstrated by the results of a single multicenter, international, open-label, randomized trial, RATIONALE-302 (NCT03430843). The study evaluated tislelizumab as a single agent versus chemotherapy (investigator's choice between irinotecan, paclitaxel, or docetaxel). Patients were eligible if they had histologically confirmed predominant squamous cell histology, irrespective of PD-L1 status, and ECOG PS of 0 or 1. Prior chemotherapy in the neoadjuvant/adjuvant setting was considered prior therapy if patients had a recurrence-free period of less than 6 months. Patients with prior therapy with PD-1 or PD-L1 monoclonal antibodies were not eligible for the trial. Tumor cell PD-L1 was determined by a central lab using the Ventana SP263 assay (vCPS).

Patients were randomized (1:1) to receive

- Tislelizumab 200 mg intravenously (IV) every 3 weeks (Q3W)
- Investigator's choice of chemotherapy: paclitaxel (135 mg/m² IV Q3W), docetaxel (75 mg/m² IV Q3W), or irinotecan (125 mg/m² IV on Days 1 and 8 of every 3-week cycle). Regional variations on dosing regimen for taxanes were allowed.

Patients were treated until disease progression, unacceptable toxicity, or 2 years of tislelizumab treatment. The stratification factors for randomization were geographic region (Asia [excluding Japan] vs. Japan vs. US/EU), ECOG performance status (0 vs. 1), and ICC choice (paclitaxel vs. docetaxel vs. irinotecan). PD-L1 expression was not a stratification factor. The primary endpoint of the trial was overall survival (OS) in all patients; the key secondary endpoint was OS in patients with PD-L1 $\geq$ 10%. Additional efficacy outcome measures (no alpha allocated) included were objective response rate (ORR), duration of response, and progression-free survival (PFS) in all patients and in the subpopulation with PD-L1 $\geq$ 10%.

In RATIONALE-302, tislelizumab provided a modest but statistically significant improvement in OS compared with chemotherapy. The OS HR in the ITT was 0.70 (95% CI 0.57, 0.85; one-sided p-value = 0.0001) with a median OS of 8.6 months (95% CI 7.5, 10.4) in the tislelizumab arm

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TEVIMBRA (tislelizumab)

and 6.3 months (95% CI 5.3, 7) in the ICC arm. Although the secondary endpoint of OS in the PD-L1 $\geq 10\%$ subpopulation (n: 157 patients, 31% of the overall population) was statistically significant at the prespecified alpha level (stratified HR 0.53, 95% CI: 0.37, 0.77; one-sided p-value = 0.006), ascertainment of PD-L1 status was missing in 19% of patients, less than a third of patients had PD-L1 $\geq 10\%$, and PD-L1 status was not a stratification factor for this study. Therefore, although supportive of the primary efficacy outcome, the positive results in the PD-L1 $\geq 10\%$ should be interpreted with caution in the context of these limitations. The ORR was 20.3% (95% CI 15.6, 25.8) in the tislelizumab arm and 9.8% (95% CI 6.4, 14.1) in the ICC arm. Duration of response was prolonged in the tislelizumab arm when compared to the ICC arm (7.1 vs. 4 months). The HR for PFS in the ITT was 0.83 (95% CI 0.67, 1.01). These results are supportive of the primary outcomes and consistent with immune checkpoint inhibitors effects (modest effect on PFS and ORR) in ESCC.

The observed safety profile of tislelizumab in patients with metastatic or unresectable ESCC was consistent with the established safety profile of checkpoint inhibitors in patients with ESCC and other types of cancer. The primary risks of tislelizumab are immune-mediated adverse events (imAEs), which were reported in 21% patients receiving tislelizumab. Most of the imAEs were Grade 1-2, and the incidence of Grade ≥ 3 imAEs was 4%. Grade 3-4 imAEs was less than 1% except for pneumonitis (1.2%). The most frequently reported imAEs were hypothyroidism (9%) and pneumonitis (7%). Overall, patients in the tislelizumab arm experienced less Grade ≥ 3 adverse events (46%) compared with patients receiving chemotherapy (68%). The most frequently reported Grade ≥ 3 adverse events in the tislelizumab arm were dysphagia, anemia, and hyponatremia; incidence of anemia and hyponatremia were either similar or lower than the ICC arm. In the ICC arm, the most frequently reported Grade ≥ 3 adverse events were predominantly hematologic events, consistent with known toxicities of chemotherapy. Permanent discontinuation of tislelizumab due to an adverse reaction occurred in 19% of patients. Adverse reactions which resulted in permanent discontinuation in $\geq 1\%$ of patients were hemorrhage, pneumonitis (including pneumonitis and immune-mediated pneumonitis), and pneumonia.

The review team concluded that the overall risk:benefit assessment favored approval of tislelizumab as a single agent for the treatment of patients with metastatic or locally advanced unresectable esophageal squamous cell carcinoma with disease progression on or after first line chemotherapy. The demonstrated improvement in survival for patients randomized to tislelizumab compared to patients randomized to chemotherapy is clinically meaningful, statistically significant, and supported by subgroup analyses in Study RATIONALE-302. The adverse reaction profile observed in patients receiving tislelizumab is consistent with the adverse reaction profiles observed with other immune checkpoints in ESCC and other disease settings. The risks of tislelizumab are largely manageable with patient surveillance, treatment delays, and supportive care in most patients. The risks of tislelizumab are acceptable considering the life-threatening nature of relapsed or refractory metastatic or locally advanced esophageal squamous cell carcinoma.

Of note, in current practice, approvals have been granted in the US for PD-1 inhibitors in the first-line setting for patients with ESCC (e.g., in combination with chemotherapy). RATIONALE-302 did not investigate the use of tislelizumab in patients who received prior anti-PD-1 therapy;

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therefore, it is expected that the approval of this application will only be applicable to a minority of patients who did not receive first-line anti-PD-1 therapy.

1.3. Benefit- Risk Assessment

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	In the US in 2020, there were an estimated 18,440 new esophageal cancer cases (1% of new cancer cases), with an estimated 16,170 deaths (2.7% of all cancer deaths) (ASCO website); the 5-year (2010-2016) relative survival rate for patients with metastatic disease was 19.9% (SEER website). In the US, it is estimated that 35% of patients will have squamous cell histology (ESCC); however, ex-US ESCC is the most common histology (up to 88% of all esophageal carcinomas) (Then EO, 2020). The median overall survival for patients with unresectable or metastatic ESCC is less than one year; for patients with disease progression after first-line therapy treated with chemotherapy, median overall survival is estimated in less than 8 months.	Locally advanced unresectable or metastatic esophageal squamous cell carcinoma is serious, life-threatening disease with poor prognosis, and dismal outcomes in patients with disease progression after first-line therapy. This histology is relatively uncommon in the US (estimated ~5000 patients per year).
Current Treatment Options	For patients with unresectable or metastatic disease, treatment options are limited to palliative chemotherapy. Chemotherapy combination regimens are generally used and some of the standard combinations most frequently used in the US include fluoropyrimidine and platinum agents. On May 27, 2022, after submission of this application, nivolumab (a PD-1 monoclonal antibody) was approved in combination with chemotherapy and in combination with	Other checkpoint inhibitors have been approved in the proposed patient population (or subsets) based on similar effects as the one reported in RATIONALE-302. The data in this application are not applicable to the treatment of ESCC in patients who received a prior PD-

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	ipilimumab (another checkpoint inhibitor that targets CTLA-4) for the first-line treatment of patients with unresectable or metastatic ESCC. Nivolumab as a single agent is approved for the second line treatment after disease progression on chemotherapy. Pembrolizumab (a PD-1 targeting monoclonal antibody) is approved in combination with platinum- and fluoropyrimidine-based chemotherapy for the treatment of patients with locally advanced or metastatic esophageal or gastroesophageal junction (GEJ) carcinoma (both adenocarcinoma and squamous cell histologies) that is not amenable to surgical resection or definitive chemoradiation and as a single agent for the second line treatment of patients with ESCC whose tumor PD-L1 CPS is $\geq 10\%$.	L1 containing regimen.
Benefit	The approval is supported by a single study, RATIONALE-302 (NCT03430843). RATIONALE-302 is a randomized, international, open-label trial in patients with locally advanced unresectable or metastatic ESCC with disease progression on/after previous therapy. Patients were eligible if they had histologically confirmed predominant squamous cell histology, irrespective of PD-L1 status, and ECOG PS of 0 or 1. Prior chemotherapy in the neoadjuvant/adjuvant setting was permitted if completed before enrollment and patients had a recurrence-free period of less than 6 months. Patients with prior therapy with PD-1 or PD-L1 monoclonal antibodies were not eligible for the trial. Patients were randomized (1:1) to receive tislelizumab 200 mg intravenously every 3 weeks, or investigator's choice chemotherapy (ICC) (paclitaxel, docetaxel, or irinotecan). Patients were treated until disease progression or unacceptable toxicity. The stratification factors for randomization were geographic region	The submitted evidence meets the statutory evidentiary standard for the approval of tislelizumab for the treatment of patients with locally advanced unresectable or metastatic esophageal squamous cell carcinoma with disease progression on or after prior chemotherapy. The modest observed improvement in overall survival with a HR of 0.70 is statistically robust. This finding is supported by consistent results on prespecified exploratory subgroup analyses.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	(Asia [excluding Japan] vs. Japan vs. US/EU), ECOG performance status (0 vs. 1), and ICC choice (paclitaxel vs. docetaxel vs. irinotecan). PD-L1 expression was not a stratification factor. The primary endpoint of the trial was overall survival (OS) in the overall population (ITT). The additional efficacy outcome with alpha allocation was OS in the PD-L1-positive subpopulation, defined as patients whose tumors PD=L1 vCPS expression was $\geq 10\%$ as assessed by Ventana SP263 assay. Exploratory endpoints were overall response rate (ORR) as assessed by investigators in the ITT and PD-L1-positive populations, progression-free survival (PFS) in the ITT and PD-L1-positive populations, duration of response, quality of life assessments, and safety parameters. The study enrolled 512 patients (256 in each arm). Upon randomization, investigator's choice of chemotherapy in the ICC arm was irinotecan in 118 (46%) patients, paclitaxel in 85 (33%) patients, and docetaxel in 53 (21%) patients. Baseline characteristics in all randomized subjects were balanced between the tislelizumab and the ICC arms. In Study RATIONALE-302, tislelizumab provided a modest but statistically significant improvement in OS compared with chemotherapy. The OS HR in the ITT was 0.70 (95% CI 0.57, 0.85; one-sided p-value = 0.0001) with a median OS of 8.6 months (95% CI 7.5, 10.4) in the tislelizumab arm and 6.3 months (95% CI 5.3, 7) in the ICC arm. Although the secondary endpoint of OS in the PD-L1 vCPS $\geq 10\%$ subpopulation (n: 157 patients, 31% of the overall population) was statistically significant at the prespecified alpha level (stratified HR 0.53, 95% CI: 0.37, 0.77; one-sided p-value = 0.006), ascertainment of PD-L1 status was missing in 19% of patients, less than a third of patients had PD-L1 $\geq 10\%$, and PD-L1 status was not a stratification factor for this study. Therefore,	

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	although supportive of the primary efficacy outcome, the positive results in the PD-L1 $\geq 10\%$ should be interpreted with caution in the context of these limitations. The ORR was 20.3% (95% CI 15.6, 25.8) in the tislelizumab arm and 9.8% (95% CI 6.4, 14.1) in the ICC arm. Duration of response was prolonged in the tislelizumab arm when compared to the ICC arm (7.1 vs. 4 months). The HR for PFS in the ITT was 0.83 (95% CI 0.67, 1.01). These results are supportive of the primary outcomes and consistent with immune checkpoint inhibitors effects (modest effect on PFS and ORR) in ESCC.	
Risk and Risk Management	The observed safety profile of tislelizumab in patients with metastatic or unresectable ESCC was consistent with the established safety profile of checkpoint inhibitors in patients with ESCC and other types of cancer. The primary risks of tislelizumab are immune-mediated adverse events (imAEs), which were reported in 21% patients receiving tislelizumab. Most of the imAEs were Grade 1-2, and the incidence of Grade ≥ 3 imAEs was 4%. Grade 3-4 imAEs was less than 1% except for pneumonitis (1.2%). The most frequently reported imMAEs were hypothyroidism (9%) and pneumonitis (7%). Overall, patients in the tislelizumab arm experienced less Grade ≥ 3 adverse events (46%) compared with patients receiving chemotherapy (68%). The most frequently reported Grade ≥ 3 adverse events in the tislelizumab arm were dysphagia, anemia, and hyponatremia; incidence of anemia and hyponatremia were either similar or lower than the ICC arm. In the ICC arm, the most frequently reported Grade ≥ 3 adverse	No unexpected significant safety concerns were identified during review of this application that would require a new risk management plan, including a Risk Evaluation and Mitigation Strategy (REMS) to ensure safe use of tislelizumab. Significant and serious adverse reactions for tislelizumab are predictable based on the antibody mechanism of action. These risks are adequately addressed in product labeling, and oncologists who treat patients with gastroesophageal cancer are well-trained in the monitoring and treatment of these adverse reactions. The review team determined that standard postmarketing surveillance would be sufficient

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	events were predominantly hematologic events, consistent with known toxicities of chemotherapy.	for continued assessment of the safety of tislelizumab in patients with advanced, unresectable or metastatic ESCC with disease progression after prior chemotherapy treatment.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	The patient experience data that was submitted as part of the application, include:	Section where discussed, if applicable
☐	Clinical outcome assessment (COA) data, such as	[e.g., Section 6.1 Study endpoints]
☒	Patient reported outcome (PRO)	Sections 8.2, 9.1, 9.5.1.1.2, 9.7.1.2.2.5, 11.4.1.3.4, 14.2
☐	Observer reported outcome (ObsRO)	
☒	Clinician reported outcome (ClinRO)	Sections 8.2, 9.1, 9.5.1.1.2, 9.7.1.2.2.5, 11.4.1.3.4, 14.2
☐	Performance outcome (PerfO)	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
☐	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Section 2.1 Analysis of Condition]
☐	Observational survey studies designed to capture patient experience data	

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☐	Natural history studies	
☐	Patient preference studies (e.g., submitted studies or scientific publications)	
☐	Other: (Please specify)	
☐	Patient experience data that was not submitted in the application, but was considered in this review.	

X

Cross-Disciplinary Team Leader

Disclaimer: In this document, the sections labeled as “Data” and “The Applicant’s Position” are completed by the Applicant and do not necessarily reflect the positions of the FDA.

2. Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

Esophageal squamous cell carcinoma (ESCC) is the dominant histological subtype (approximately 90%) of esophageal cancer (EC) worldwide (Abnet et al 2018). Regions of high incidence include Eastern to Central Asia, along the Rift Valley in East Africa, and into South Africa. ESCC is more common in the elderly (aged ≥ 60 years) and has a mean male to female ratio of 3:1 to 4:1 (Lagergren et al 2017). Epidemiologic factors associated with higher ESCC prevalence include prolonged consumption of tobacco and alcohol, poor nutrition and diet, and low socioeconomic status that can complicate its treatment (Uhlenhopp et al 2020; Tran et al 2005; Engel et al 2003). Certain histopathologic and anatomic features of ESCC (e.g., high-grade dysplasia, early submucosal invasion, location in mid-to-low esophagus) can render the ESCC difficult to detect, prone to rapid lymph node infiltration and distant metastases, and challenging to treat (Gibson et al 2021).

The prevalence of ESCC has decreased in Western regions due to changes in lifestyle and improvements in general health. In North America, ESCC has become less prevalent than esophageal adenocarcinoma, which is twice as common and has a different etiology (e.g., Barrett's esophagus, obesity, reflux), management, and prognosis. Despite this decrease in prevalence, EC remains the 10th leading cause of cancer-related death in the United States (US) overall, and the 7th among males (Patel 2018; Siegel 2020; American Cancer Society 2021).

Diagnosis of ESCC is often made after symptoms appear later in the course of the disease. One-third of US patients present with ESCC that has already spread to regional lymph nodes, and 39% have distant metastases at the time of diagnosis (SEER 2021). The 5-year survival for localized disease is 47.1% but drops to 25.2% for regional disease and 4.9% for patients with distant metastases.

Advanced (metastatic, non-resectable, or recurrent) ESCC is aggressive with frequent recurrence and limited survival. Lymphatic spread of ESCC to internal jugular, cervical, supraclavicular, mediastinal, and celiac nodes is common. Metastases to lung, liver, and distant lymph nodes are most common, but metastases to the adrenal gland, pleura, bone, peritoneum, kidney, and heart also occur (Verstegen et al 2020). Patients with advanced ESCC experience several debilitating symptoms including dysphagia, cough, tracheo-esophageal fistulas, anemia, weight loss, and aspiration pneumonia that complicate care, diminish underlying health, and worsen quality of life. Advanced ESCC is a rapidly progressing and symptomatic disease with poor clinical outcomes.

The FDA's Assessment:

FDA agrees that esophageal cancer is a serious and life-threatening illness and acknowledges the differences discussed by the Applicant with respect to esophageal cancer histologies (esophageal adenocarcinoma [EAC] and ESCC) in high-risk regions of the world compared to in lower-risk regions of the world (including the U.S). In the U.S., approximately 20,640 new cases of esophageal cancer are expected in 2022, and approximately 16,410 deaths are expected. The male:female ratio is 4:1 for both diagnoses and deaths (American Cancer Society 2022). The estimated 5-year survival rate for U.S. patients with esophageal cancer is only approximately 20% (Siegel 2020; American Cancer Society). EAC is more common in Western populations (Torre 2016) and ESCC accounts for less than 30% of all esophageal cancers in the U.S. (American Cancer Society).

In a retrospective analysis of the Surveillance Epidemiology and End Results (SEER) database data from the years 2004 – 2015, in the US 23,804 patients with EAC and 13,919 patients with ESCC were diagnosed. The most common stage of presentation for both adenocarcinoma (36.9%) and squamous cell (26.8%) carcinoma was Stage IV. In this analysis, 66% of patients with ESCC were men, 56% were White, 26% were Black, 8% were Hispanic and 9% were Asian or Pacific islanders. Important for this BLA, as per the analysis of the SEER database, there are no differences in outcomes for patients with ESCC based on race or ethnicity (Then EO, 2020).

2.2. Analysis of Current Treatment Options

Prior to the use of checkpoint inhibitors (CPIs), the therapeutic approach for unresectable recurrent locally advanced or metastatic ESCC after prior systemic therapy was based on the single-agent chemotherapy regimens (second-line treatment), such as docetaxel, paclitaxel, or irinotecan (NCCN 2017). These regimens were generally recommended for patients with good performance status, Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) score of 0 or 1 and were often associated with key toxicities that led to treatment interruptions or delays, dose reductions, and/or treatment discontinuations. Fewer than 20% of patients receiving second-line chemotherapy respond to treatment, with median overall survival (OS) ranging from 5 to 7 months (Abraham et al 2020). Hence, an improvement in the second-line setting was needed that provided a longer survival time, with fewer high-grade adverse events.

Phase 3 study results demonstrating benefit over standard chemotherapy coupled with a more tolerable safety profile are available for 3 immune CPIs including Study 302 for tislelizumab (also known as BGB-A317), the most recently completed study, and 2 previously completed studies, ATTRACTION-3 for nivolumab and KEYNOTE-181 for pembrolizumab. Results of ATTRACTION-3 or KEYNOTE-181 were not available at the time of initiation of Study 302.

In ATTRACTION-3, nivolumab demonstrated a 23% reduction in risk of death (OS HR of 0.77 [95% CI: 0.62 to 0.96, p-value = 0.019; median OS: 10.9 months compared with chemotherapy median OS: 8.4 months) in previously treated patients with advanced ESCC (Kato et al 2019).

In KEYNOTE-181, although pembrolizumab failed to demonstrate a statistically significant improvement in OS over chemotherapy in patients with previously treated ESCC (OS HR of 0.78 [95% CI: 0.63 to 0.96], $p = 0.0095$; median OS: 8.2 months versus 7.1 months), it showed an improvement in OS compared with chemotherapy (OS HR of 0.64 [95% CI: 0.46 to 0.90]; median OS: 10.3 months versus 6.7 months) in patients with previously treated ESCC with tumor Combined Positive Score (CPS) ≥ 10 (Kojima et al 2020).

Both pembrolizumab and nivolumab were approved for use in advanced ESCC based on the above Phase 3 study results. In July 2019, the US Food and Drug Administration (FDA) approved pembrolizumab for patients with recurrent, locally advanced or metastatic, ESCC whose tumors express programmed death-ligand 1 (PD-L1) CPS ≥ 10 with disease progression after one or more prior lines of systemic therapy. In June 2020, the US FDA approved nivolumab for patients with unresectable advanced, recurrent or metastatic ESCC after prior fluoropyrimidine- and platinum-based chemotherapy.

The survival benefit of cytotoxic chemotherapies, as standard of care second-line palliative systemic treatment for recurrent advanced or metastatic ESCC, is marginal. Moreover, they are associated with significant toxicity with substantial morbidity and mortality for patients and frequent treatment interruptions, delays, and dose reductions that increases the risk of disease progression. More recently, immune checkpoint inhibitors targeting the PD-1/PD-L1 axis have further shaped the treatment landscape for patients with ESCC. PD-1 inhibitors, including tislelizumab, have demonstrated survival improvement over chemotherapy in advanced or metastatic ESCC patients with disease progression after prior systemic therapies.

The FDA's Assessment:

The major efficacy outcome measure in KEYNOTE-181 was OS evaluated in patients with ESCC, patients with tumors expressing PD-L1 CPS ≥ 10 , and all randomized patients. The observed OS hazard ratio was 0.77 (95% CI: 0.63, 0.96) in patients with ESCC (not 0.78 as stated above), 0.70 (95% CI: 0.52, 0.94) in patients with tumors expressing PD-L1 CPS ≥ 10 , and 0.89 (95% CI: 0.75, 1.05) in all randomized patients (Keytruda UPSI). Based on the results in patients whose ESCC tumors expressed PD-L1 (CPS ≥ 10), an improvement in OS was observed among patients randomized to pembrolizumab as compared with chemotherapy with an observed OS hazard ratio of 0.64 (95% CI: 0.46, 0.90).

Per the current USPI, pembrolizumab is approved, in combination with platinum and fluoropyrimidine for the treatment of patients with locally advanced or metastatic esophageal or GEJ (tumors with epicenter 1 to 5 centimeters above the GEJ) carcinoma that is not amenable to surgical resection or definitive chemoradiation, and as a single agent after one or more prior lines of systemic therapy for patients with tumors of squamous cell histology that express PD-L1 (CPS ≥ 10) as determined by an FDA-approved test. Nivolumab is approved for unresectable advanced, recurrent or metastatic ESCC after prior fluoropyrimidine- and platinum-based chemotherapy. After submission of this application, on May 27th, 2022, FDA approved nivolumab in combination with fluoropyrimidine- and platinum-based chemotherapy, or in

combination with ipilimumab for the first-line treatment of patients with advanced or metastatic ESCC. Therefore, it is likely that most patients will be treated with immune checkpoint inhibitors in the front-line setting. *Given the prior approvals of alternative PD-1 inhibitors in the second-line setting and combination PD-L1 regimens in the first-line setting, this application is not addressing an unmet medical need.*

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:

Currently, tislelizumab is not approved or marketed in the US. Tislelizumab has received the following marketing authorization approvals in China:

- | | |
|--------------|---|
| 27 Dec 2019: | Treatment of patients with relapsed or refractory classical Hodgkin's lymphoma who received at least two prior lines of systemic chemotherapy regimens. |
| 10 Apr 2020: | Treatment of patients with locally advanced or metastatic urothelial carcinoma with PD-L1 high expression and whose disease progressed during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. |
| 13 Jan 2021: | Treatment in combination with two chemotherapy regimens as a first-line treatment for patients with advanced squamous non-small cell lung cancer (NSCLC). |
| 23 Jun 2021: | First-line treatment of patients with advanced non-squamous NSCLC in combination with chemotherapy. |
| 23 Jun 2021: | Conditional approval for the treatment of patients with hepatocellular carcinoma (HCC) who have received at least one systemic therapy. |

The clinical development program for tislelizumab is being conducted under Investigational New Drug (IND) 126875 with Division of Oncology Products 2, and the relevant regulatory history is included in Section 1.

The FDA's Assessment:

In addition to the parent IND 126875, the clinical development for tislelizumab for the treatment of ESCC is under IND 135699 with the Division of Oncology 3.

3.2. Summary of Pre-submission/Submission Regulatory Activity

The Applicant's Position:

An overview of the key events related to the development of tislelizumab for the treatment of ESCC is summarized in [Table 1](#).

Table 1: BeiGene - Summary of Key Events Related to the Development of Tislelizumab for the Treatment of ESCC of ESCC Under IND 135699

Description	Correspondence Date	Reference #, SN
IND 135699 Study May Proceed for Study A317-302	12 Dec 2017	Reference 4194168
Orphan Drug Designation for EC	06 Nov 2019	2019-7089
Agreed Amended Initial Pediatric Study Plan for		
(b) (4)		

A list of key FDA meetings related to the development of tislelizumab for the treatment of ESCC are summarized in [Table 2](#).

Table 2: BeiGene - Summary of Key FDA Meetings Related to the Development of Tislelizumab for the Treatment of ESCC

Meeting Description	IND	Meeting Format	Correspondence Date	Correspondence Reference No.
Type B Pre-IND/Pre-Phase 3	135699	Preliminary comments only	20 Sep 2017	4155475
Type C CMC Development	126875	WRO	15 Nov 2017	4181710
Type B CMC	126875	Face-to-Face Meeting	14 Jan 2020	4561020
Type C BLA Format-Content	135699	WRO	03 Sep 2020	4666046

Meeting Description	IND	Meeting Format	Correspondence Date	Correspondence Reference No.
Type C AESI Proposal	135699	WRO	24 Nov 2020	4706494
Type B Pre-BLA CMC-Only	126875	WRO	24 Nov 2020	4707250
Type B Pre-BLA	135699	WRO	30 Apr 2021	4783397

The FDA's Assessment:

In addition to the summary for meetings under IND135699 listed above, pertinent regulatory history for Study 302 is summarized below.

In the letter issued September 20, 2017 for the Type B Pre-IND/Pre-Phase 3 meeting, FDA:

- encouraged the incorporation of an additional stratification factor for investigator's choice of chemotherapy.
- recommended that BeiGene consider including ECOG performance status (0 versus 1) as a stratification factor in place of gender.
- stated that FDA has no objections to the anticipated geographic distribution provided that the BLA contains adequate justification that the results observed in a predominantly Asian population can be extrapolated to the U.S. population, as discussed in the International Conference on Harmonization (ICH) E5 Ethnic Factors in the Acceptability of Foreign Clinical Data, and the FDA Guidance for Industry ICH E5 Ethnic Factors in the Acceptability of Foreign Clinical Data, Questions and Answers.
- stated that FDA has no objections to the chemotherapy options proposed for use in the investigator's choice control arm; however, the protocol should require investigators to choose the control chemotherapy prior to patient randomization, so that this can be used as a stratification factor for randomization.
- stated that the primary endpoint of OS is acceptable but that a decision regarding whether the proposed magnitude of OS benefit, corresponding to an approximately 2.3-month improvement in median OS, is sufficient to support approval will depend on the totality of the data, including the overall benefit-risk assessment of the application.
- stated that the quality of the safety data and its applicability to the U.S. patient population will be assessed upon submission of the data.
- asked BeiGene to provide case definitions for immune-mediated AEs (imAEs), include more frequent laboratory monitoring, provide management guidelines for all Grade 2-4 imAEs, provide a monitoring plan for potential ocular toxicities, and revise the protocol and consent forms regarding treatment beyond radiologic progression.

On December 12, 2017, FDA issued a Study May Proceed letter for Study 302.

In a letter issued on September 3, 2020, FDA:

- stated that for an agreement of the content of an application, top-line results of Study 302 must be submitted. Regarding the proposed format of the BLA, FDA does not consider necessary submission of efficacy data from a non-ESCC population. The proposed format and pooling of safety data appeared adequate.
- stated that BeiGene should submit narratives of AEs leading to death, AEs leading to discontinuation, and Grade 3-4 AEs of special interest regardless of attribution.

In the letter issued on November 24, 2020, FDA:

- stated that “Although the proposed list of preferred terms for the “Lookup List” appears acceptable, BeiGene did not provide a list of terms or a query for events that could be defined as infusion-related reactions (IRRs). FDA requested that BeiGene provide the search strategy and definition of IRRs in a pre BLA meeting.
- stated that all imAEs should be reported, regardless of the need for systemic steroids or pharmacological treatment.

In the letter issued on April 21, 2021 (preliminary comments issued April 21 and meeting cancellation requested by BeiGene), FDA stated that the results of Study BGB-A317-302 and the proposed clinical package may support a regulatory submission; however, the relevance of the proposed indication is not clear given the March 22, 2021, approval of pembrolizumab and April 16, 2021, approval of nivolumab in the first line esophageal cancer setting (both in combination with a platinum and fluoropyrimidine). If approved, the indication statement may need to identify that the treatment would be for patients in the second-line setting who are PD-1 inhibitor naïve.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The Office of Scientific Investigations (OSI) conducted inspections of the study sponsor (BeiGene (Shanghai) Co., Ltd) and three clinical sites:

BeiGene USA, Inc. was inspected October 18, 2021, through October 22, 2021, and had a regulatory classification as No Action Indicated (NAI). Regarding BeiGene USA’s role, OSI stated the following: “BeiGene USA is the sponsor for this regulatory submission in the US. BeiGene, Ltd., is located in the Cayman Islands and oversees all global BeiGene operations. The study data is produced by and the clinical sites work under global BeiGene, Ltd. All vendors and CROs have contracts with BeiGene, Ltd. BeiGene, Ltd. has an agreement in place with BeiGene

USA to act as sponsor for all USA regulatory submissions and with BeiGene China to act as sponsor for all China regulatory submissions.” This October 2021 inspection of BeiGene USA was the fourth FDA inspection of this firm and the previous 3 inspections had regulatory classifications of NAI as well.

Inspections of two clinical sites in China were delayed due to travel restrictions during the COVID pandemic. The 3 clinical sites inspected were:

- Dr. Lin Shen (Site 086001 in Beijing which enrolled 24 patients) was inspected November 16, 2021 through November 24, 2021 and had a regulatory classification as Voluntary Action Indicated (VAI). This was the first FDA inspection of this site.
- Dr. Xinmin Yu (Site 086027, Hangzhou, 15 patients enrolled) was inspected September 11 through November 15, 2023. The inspection found that the data generated in the site appear acceptable in support of the proposed BLA.
- Dr. Kuaile Zhao (Site 086003, Shanghai, 41 patients enrolled) was inspected October 31, 2023 through November 3, 2023. The inspection found that the data generated in the site appear acceptable in support of the proposed BLA

The OSI team concluded that inspections of the clinical investigators in these sites (Drs. Shen, Yu, and Zhao as well as BeiGene US) revealed no discrepancies or regulatory violations and that RATIONALE-302 appears to have been conducted adequately, with acceptable data in support of the proposed indication.

4.2. Product Quality

The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761232 for tislelizumab-jsgr manufactured by BeiGene USA, Inc. Based on OPQ’s evaluation of the submission, the Applicant provided adequate information on the proposed drug product to ensure the identity, strength, purity, and quality of the proposed drug product. The overall manufacturing inspection recommendation is approval for all the facilities associated with this application. The proposed labeling and labels include adequate information to meet the regulatory requirements. Refer to the OPQ’s review of this application for additional information.

4.3. Clinical Microbiology

This BLA was reviewed by OPQ’s Division of Microbiology Assessment. The microbiology reviewers did not identify issues that would preclude approval of tislelizumab-jsgr; however, two post-marketing commitments (PMCs) will be included in the approval letter for BeiGene to 1) develop a reliable endotoxin detection method that can overcome the LER phenomenon for the tislelizumab drug product and 2) to implement an in-line pressure monitoring of sterile filtration for the tislelizumab drug product.

4.4. Devices and Companion Diagnostic Issues

There is no companion diagnostic for this indication. Patients were enrolled regardless of PD-L1 expression. PD-L1 status was centrally determined using the Ventana PD-L1 (SP263) CDx assay and the algorithm of vCPS, which measures the total percentage of the tumor area covered by tumor cells with PD-L1 membrane staining and tumor-associated immune cells with PD-L1 staining at any intensity. PD-L1 assessment was added in study amendment 4, dated March 20, 2020. FDA considered all analyses based on PD-L1 expression exploratory.

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Tislelizumab is an IgG4κ monoclonal antibody that recognizes PD-1 and blocks its interaction with PD-L1 and PD-L2. Tislelizumab has an approximate molecular weight of 148 kDa. 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. Based on the nonclinical data submitted in the BLA, the established pharmacological class (EPC) of “programmed death receptor-1 (PD-1) blocking antibody” is scientifically valid.

In vitro studies showed tislelizumab bound to human and cynomolgus monkey PD-1 with nanomolar affinity and absence of cross reaction with mouse PD-1, supporting the use of cynomolgus monkeys as a pharmacologically relevant species for toxicity assessment. Tislelizumab blocked the binding of human PD-1 to human PD-L1 and PD-L2 in a cell-based assay and promoted T-cell activation measured by IL-2 secretion by a PD-1 expressing cell line. Tislelizumab did not have in vitro complement-dependent cytotoxicity (CDC) activity or antibody-dependent cellular cytotoxicity (ADCC) activity. Anti-tumor activity was observed in three xenograft models (A431 human epidermoid carcinoma, BCCO-028 colon cancer, and BCLU-054 non-small cell lung cancer). Anti-tumor activity was observed in human PD-1 transgenic mice with B16/F10 mouse melanoma cells.

Tislelizumab was evaluated in a 13-week repeat-dose toxicology study in cynomolgus monkeys. Monkeys received once weekly intravenous administration of tislelizumab at doses up to 30 mg/kg. There was no mortality. Findings included an increase in lymphoid aggregates and immune cell infiltration in various tissues.

Embryo-fetal developmental toxicology studies were not conducted with tislelizumab. The Applicant provided a literature-based assessment of the potential reproductive toxicity of tislelizumab. Data from the literature indicates the PD-1/PD-L1 pathway plays a critical role in maintaining maternal immunological tolerance to the fetus during pregnancy. In allogeneic mouse models of pregnancy, blockade of PD-1/PD-L1 signaling resulted in an increased incidence of fetal loss but no fetal malformations. There are no reports of fetal malformations associated with PD-1 deficiency in mice; however, late onset autoimmunity can occur. Based on these findings, potential risks of administering the product during pregnancy include increased rates of abortion or stillbirth and an increased risk in offspring developing immune-related disorders or altered immune response. Labeling states the product can cause fetal harm if administered during pregnancy based on its mechanism of action. Effective contraception for 4 months after the last dose is recommended based on 5 half-lives. The Applicant did not evaluate transfer of tislelizumab to the fetus or into animal or human milk; however, IgG antibodies can be present in milk. Based on the potential for serious adverse reactions in a breastfed child,

women are advised not to breastfeed during treatment with tislelizumab-jsgs and for 4 months after the last dose.

Genetic toxicology and carcinogenicity studies were not warranted.

Based on data from the literature and its mechanism of action, treatment with tislelizumab has the potential for enhanced immune responses to infection or impaired microbial immune responses. The absence of PD-1 pathway signaling in mouse models of lymphocytic choriomeningitis virus (LCMV) infection led to fatal CD8⁺ T cell-mediated killing of virally infected vascular endothelial cells, systemic vascular leakage, and cardiovascular collapse (Frebel et al., 2012; Mueller et al., 2010). In PD-1 deficient mice (C57BL/6), infection with *M. tuberculosis* resulted in decreased survival that correlated with uncontrolled bacterial proliferation in the lungs. It is unclear whether decreased survival in this model resulted from an inability to mount an appropriate antibacterial response or a failure to control the immune response leading to normal tissue destruction and organ failure (Lazar-Molnar, et al., 2010). As this data represents a potential mechanistic risk associated with the use of a PD-1 signaling inhibitor, a brief description of this data is included in the proposed label under Section 13.2.

5.2. Referenced NDAs, BLAs, DMFs

DMF
DMF
DMF

(b) (4)

The Applicant's Position:

The referenced Drug Master Files (DMFs) support the use of pharmaceutical packaging material.

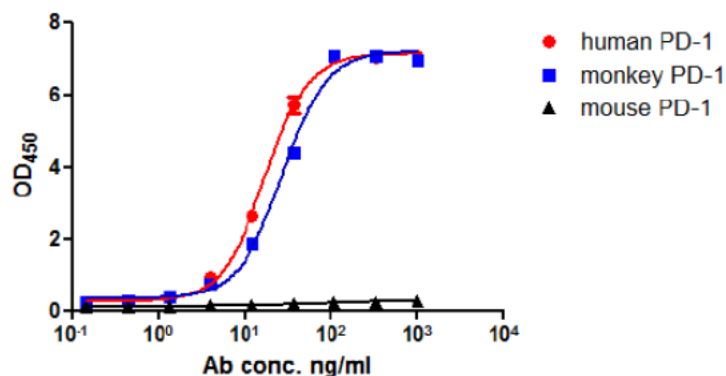
5.3. Pharmacology

Primary pharmacology

The Applicant determined the binding affinity of tislelizumab for human PD-1 using surface plasmon resonance (Study BLGC-004). The binding affinity (K_d) of tislelizumab for human PD-1 was 0.15 nM.

Cynomolgus monkeys were a pharmacologically relevant species for toxicity assessment based on sequence homology and binding. As assessed by ELISA, tislelizumab bound to human and monkey PD-1 in a dose-dependent manner (EC₅₀ of 17.3 ng/mL and EC₅₀ of 27.4 ng/mL, respectively). Tislelizumab did not bind to mouse PD-1 (see Figure 1; Study BLGC-003).

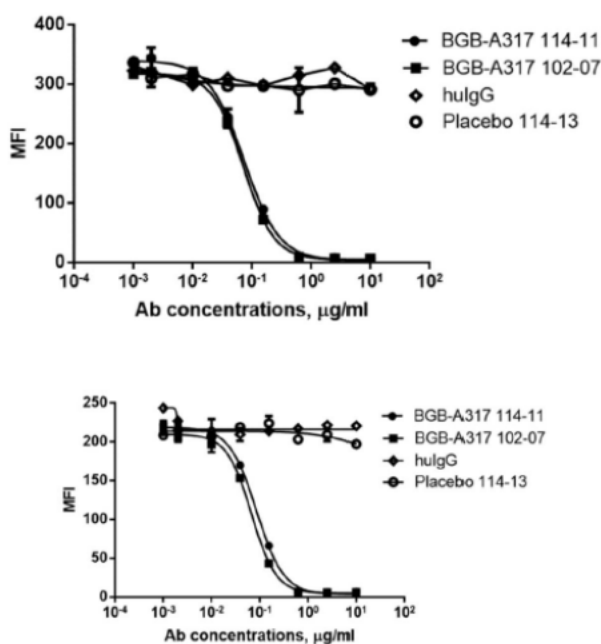
Figure 1. Binding of Tislelizumab in Nonclinical Species



(Applicant Figure Reproduced from Study BLGC-003)

Tislelizumab blocked the binding of human PD-1 to human PD-L1 and PD-L2 in a HuT78/PD-1 cell based assay with IC₅₀s of 72 to 74 ng/mL and 67 to 86 ng/mL, respectively.

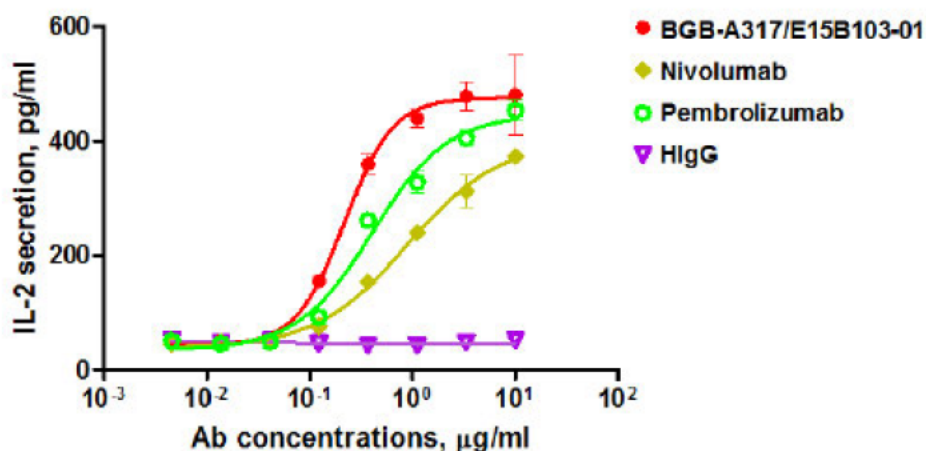
Figure 2. Tislelizumab Blocking of PD-1 Binding to /PD-L1 (top) and PD-L2 (bottom) Assessed by FACS



(Applicant Figure Reproduced from Study BLGC-006)

In a cell-based assay, incubation with tislelizumab blocked PD-1/PD-L1 interaction, promoting T-cell activation and IL-2 secretion with a PD-1 expressing cell line.

Figure 3. Tislelizumab (BGB-A317) Enhances IL-2 Signaling in a PD-1 transgene-expressing human T-cell line (HuT78/PD-1) using target cells expressing a T cell engager protein and PD-L1 (HEK293/OS8-PD-L1)



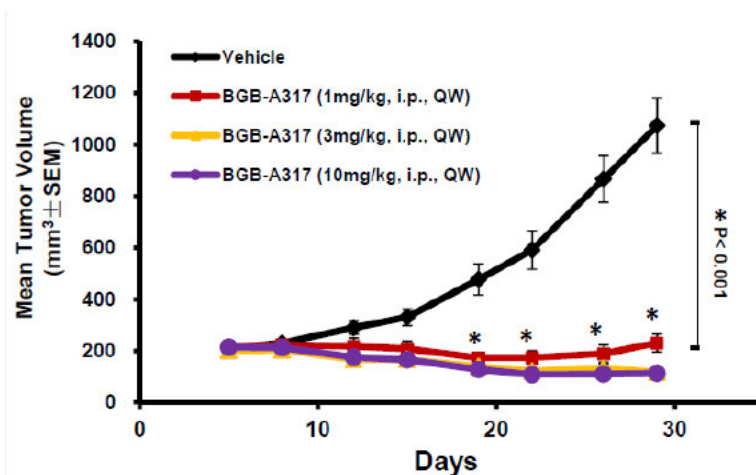
(Applicant Figure Reproduced from Study BLGC-008)

To determine whether BGB-A317 can functionally block PD-L1-mediated inhibitory signaling and activate cytokine release in human T cells, a PD-1-expressing human T-cell line HuT78/PD-1 and a target cell HEK293/OS8-PDL1 were generated. In HEK293/OS8-PD-L1 cells, a membrane-bound form of anti-CD3 scFv (OS8) and a PD-1 ligand, PD-L1 were stably transfected. The resulting signal-sending cell is capable of engaging TCR and PD-1 simultaneously. The assay was carried out by co-culture of HuT78/PD-1 and HEK293/OS8-PDL1 cells in the presence of BGB-A317. Secretion of IL-2 in media was analyzed by ELISA.

Anti-tumor activity was measured in three human cancer xenograft models (A431 human epidermoid carcinoma, Study R01-VIVO-126; BCCO-028 colon cancer, Study R01-VIVO-127); and BCLU-054 NSCLC models, Study R01-VIVO-128) and in a human PD-1 transgenic mouse model with B16/F10 mouse melanoma cells overexpressing murine granulocyte macrophage colony-stimulation factor (mGM-CSF) (Study R01-VIVO-135).

Tislelizumab (1, 3, or 10 mg/kg, once per week) had anti-tumor activity in an A431 xenograft model in non-obese diabetic (NOD)/severe combined immune deficient (SCID) mice.

Figure 4. Anti-Tumor Activity of Tisnelizumab (BGB-A317) in A431 Xenograft Model



A431 tumor cells (2.5×10^6) and freshly prepared human PBMCs (5×10^6) from healthy donor were co-implanted subcutaneously in NOD/SCID mice. On the day of implantation, mice were randomly allocated into 4 groups and treated with PBS (vehicle) or BGB-A317 i.p. for 5 weeks (on day 1, 8, 15, 22 and 29) as indicated. Tumor volume was measured twice weekly. Data are presented as mean tumor volume + standard error of the mean (SEM) of 10-12 animals in each group. P value was calculated using Student's t-test.

(Applicant Figure Reproduced from Study R01-VIVO-126)

Table 3. Tumor Growth Inhibition of Tisnelizumab (BGB-A317) in an A431 Xenograft Model

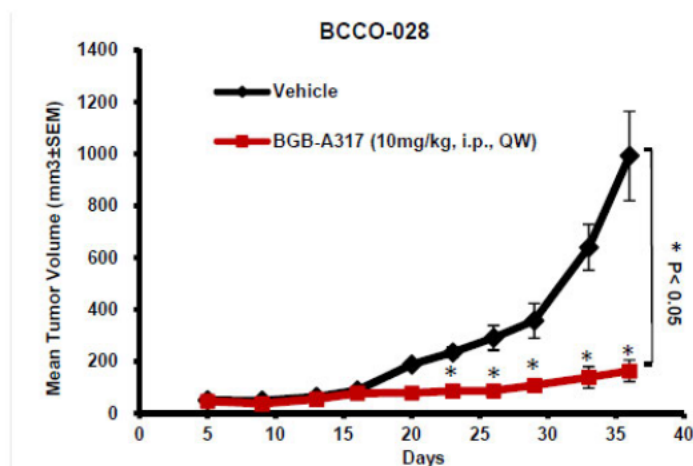
Test Article	Dose (QW)	N	TGI (Day 29)	Mean Tumor Volume on Day 29 (mm ³)	Single dose (Day 1)		Steady-State (Day 29)	
					C _{max} (µg/mL)	AUC _{0-168h} (µg·h/mL)	C _{max} (µg/mL)	AUC _{0-168h} (µg·h/mL)
Vehicle	-	12	-	1074	-	-	-	-
BGB-A317	1 mg/kg	11	78%	231	8.2	998	19.2	2468
	3 mg/kg	11	89%	117	25.0	3115	45.1	5593
	10 mg/kg	10	89%	113	84.1	11009	157.7	18437

Abbreviations: C_{max}, maximum concentration; N, number of animals; QW, once every week; TGI, tumor growth inhibition; AUC_{0-168h}, area under the concentration-time curve from 0 to 168 hours.

(Applicant Table Reproduced from Study R01-VIVO-126)

Tisnelizumab (10 mg/kg, once per week) had anti-tumor activity in a BCCO-028 colon cancer xenograft model with tumor fragments and human PBMCs implanted subcutaneously in NOD/SCID mice.

Figure 5. Anti-Tumor Activity of Tislelizumab (BGB-A317) in BCCO-028 Xenograft Model



BCCO-028 tumor fragments ($3 \times 3 \times 3 \text{ mm}^3$) and freshly prepared human PBMCs (5×10^6) were implanted subcutaneously in NOD/SCID mice. On the day of implantation, mice were randomly allocated into 2 groups and treated for 5 weeks (on Days 1, 8, 15, 22 and 29) with either vehicle (PBS) or BGB-A317 i.p. as indicated. Tumor volume was measured twice weekly. Data are presented as mean tumor volume + standard error of the mean (SEM) of 8 animals in each group. P value was calculated using Student's t-test.

(Applicant Figure Reproduced from Study R01-VIVO-127)

Table 4. Tumor Growth Inhibition of Tislelizumab (BGB-A317) in BCCO-028 Xenograft Model

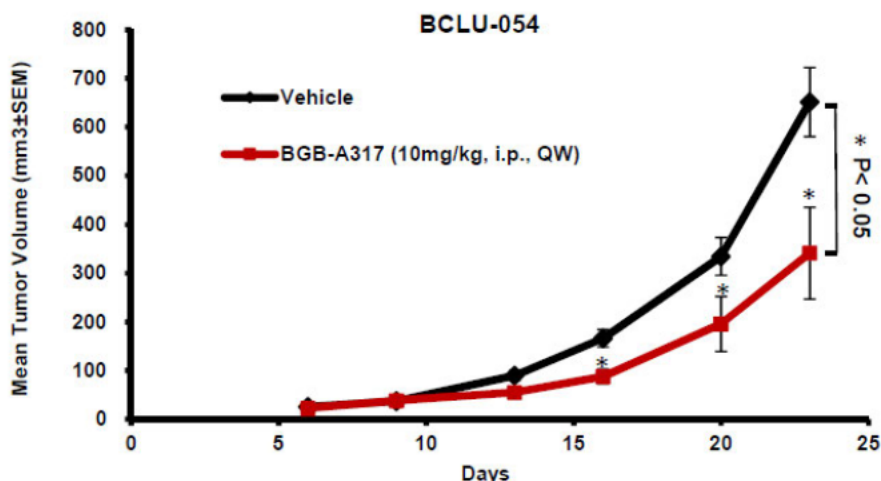
Test Article	Dose (QW)	N	TGI (Day 36)	Mean Tumor Volume on Day 36 (mm ³)
Vehicle	-	8	-	992
BGB-A317	10 mg/kg	8	83%	164

Abbreviations: N, number of animals; QW, once every week; TGI, tumor growth inhibition.

(Applicant Table Reproduced from Study R01-VIVO-127)

Tislelizumab (10 mg/kg, once per week) had anti-tumor activity in a BCLU-054 NSCLC xenograft model with tumor fragments and human PBMCs implanted subcutaneously in NOD/SCID mice.

Figure 6. Anti-Tumor Activity of Tislelizumab (BGB-A317) in BCLU-054 Xenograft Model



BCLU-054 tumor fragments ($3 \times 3 \times 3 \text{ mm}^3$) and freshly prepared human PBMCs (4×10^6) were implanted subcutaneously in NOD/SCID mice. On the day of implantation, mice were randomly allocated into 2 groups and treated for 3 weeks (on day 1, 8, 15 and 22) with either vehicle (PBS) or BGB-A317 i.p. as indicated. Tumor volume was measured twice weekly. Data are presented as mean tumor volume + standard error of the mean (SEM) of 10 animals in each group. P value was calculated using Student's t-test.

(Applicant Figure Reproduced from Study R01-VIVO-128)

Table 5. Tumor Growth Inhibition of Tislelizumab (BGB-A317) in BCLU-054 Xenograft Model

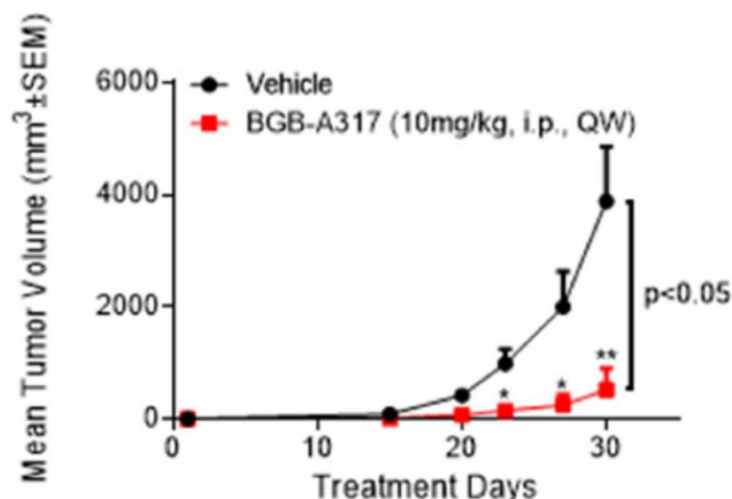
Test Article	Dose (QW)	N	TGI (Day 23)	Mean Tumor Volume on Day23 (mm ³)
Vehicle	-	10	-	652
BGB-A317	10 mg/kg	10	45%	357

Abbreviations: N, number of animals; QW, once every week; TGI, tumor growth inhibition.

(Applicant Table Reproduced from Study R01-VIVO-128)

Tislelizumab (10 mg/kg, once per week) had anti-tumor activity observed in a human PD-1 transgenic mouse model with B16F10/GMCSF mouse melanoma syngeneic tumors.

Figure 7. Anti-Tumor Activity of Tislelizumab (BGB-A317) in a PD-1 Transgenic Mouse Model



B16F10/GMCSF tumor cells (5×10^4) were implanted subcutaneously in B-hPD-1 C57BL/6J mice. On the day of implantation, mice were randomly allocated into 2 groups and treated with PBS (vehicle) or BGB-A317 i.p. for 5 weeks as indicated. Tumor volume was measured twice weekly. Data are presented as mean tumor volume + standard error of the mean (SEM) of 8 animals in each group. P value was calculated using Student's t-test.

(Applicant Figure Reproduced from Study R01-VIVO-135)

Table 6. Tumor Growth Inhibition by Tislelizumab (BGB-A317) in a PD-1 Transgenic Mouse Model

Test Article	Dose (QW)	N	TGI (Day 30)	Mean Tumor Volume on Day 30 (mm ³)
Vehicle	-	8	-	3885
BGB-A317	10 mg/kg	8	86.7%	518

Abbreviations: N, number of animals; QW, once every week; TGI, tumor growth inhibition. The indicated parameters are summarized for all treatment groups. TGI on day 30 was calculated.

(Applicant Table Reproduced from Study R01-VIVO-135)

Secondary Pharmacology

The Applicant's Position:

Tislelizumab uses a form of human Immunoglobulin G4 (IgG4) in the fragment crystallizable region (Fc) which limits IgG4 Fc-mediated effector protein binding. This characteristic was

verified in binding assays by enzyme-linked immunosorbent assay (ELISA) and fluorescence-activated cell sorting (FACS).

Unlike many other human IgG antibodies, tislelizumab has diminished binding capacity to human Fc gamma receptors, including FcγRI, FcγRIIA_{H131}, FcγRIIA_{R131}, FcγRIIB, FcγRIIIA_{V158}, FcγRIIIA_{F158}, and FcγRIIIB, which may result in diminished Fc gamma receptor mediated effector functions. In addition, tislelizumab has diminished binding to C1q, the initiating component of complement complex formation, involved in complement-dependent cytotoxicity (CDC) induction.

Cell-based functional assays were conducted to assess whether tislelizumab could induce antibody-dependent cellular cytotoxicity (ADCC) or CDC. Results showed that tislelizumab had no detectable ADCC or CDC activity.

The FDA's Assessment:
The FDA generally agrees.

Safety Pharmacology

Stand-alone safety pharmacology studies were not conducted nor required for this product in accordance with International Conference on Harmonization (ICH) S9 Nonclinical Evaluation for Anticancer Pharmaceuticals. The effects of tislelizumab on vital organ functions (including cardiovascular, respiratory and central nervous systems) were evaluated as part of single-dose and 13-week repeat dose toxicity studies in monkeys under Good Laboratory Practice (GLP) conditions.

In the single dose study, there were no treatment-related changes in electrocardiogram parameters at doses up to 100 mg/kg, administered via intravenous infusion. Similarly, there were no changes in electrocardiogram parameters after 13 weeks of bi-weekly dosing at doses up to 30 mg/kg. There were also no clinical signs or histopathological changes indicative of any cardiac, respiratory, or central nervous system toxicity.

The Applicant's Position:

No effect was observed on electrocardiogram (ECG), heart rate, blood pressure, or respiratory or central nervous system safety pharmacology parameters evaluated as part of the general toxicology studies.

The FDA's Assessment:
The FDA generally agrees; however, See FDA's Assessment under 5.5.1.

5.4. ADME/PK

The Applicant's Position:

Absorption

A series of in vivo studies were conducted to characterize the pharmacokinetic (PK) and/or toxicokinetic (TK) properties of tislelizumab in cynomolgus monkeys. A PK study was conducted at single and repeated doses via intravenous infusion (IV). TK studies were conducted in single, and 13-week repeat dose toxicity studies. In addition, two single dose studies were conducted to evaluate the comparability of PK profiles among batches produced by different manufacturing sites during the clinical development of tislelizumab.

The results demonstrated that tislelizumab mean terminal half-life ($t_{1/2}$) was approximately 3 to 8 days (74 to 183 hours); maximum serum concentration (C_{max}) ranged from 90 to 999 $\mu\text{g/mL}$; area under the concentration-time curve from 0 to 1008 hours ($AUC_{0-1008h}$) ranged from 12,322 to 163,755 $\text{h}\cdot\mu\text{g}/\text{mL}$; the volume of distribution (V_d) was approximately 22 to 52 mL/kg ; and the clearance (CL) was approximately 0.18 to 0.31 mL/h/kg in monkeys at a single dose of 3, 10, or 30 mg/kg . The half-life of tislelizumab in cynomolgus monkeys supported biweekly dosing in the repeat dose toxicology study.

The systemic exposure (C_{max} and AUC) increased dose proportionally from 3 to 30 mg/kg without apparent sex differences. No apparent drug accumulation or changes in systemic exposure were noted after repeated doses weekly for 5 doses or every two weeks for 6 doses.

Two single dose PK studies were conducted in cynomolgus monkeys to compare the PK profiles among batches produced by 3 different manufacturing sites during the clinical development. The PK profiles of these batches were comparable.

Anti-drug antibodies (ADAs) were detected in most monkeys at each dose level in all studies but did not have apparent effects on the systemic exposure.

Distribution, metabolism, and excretion studies were not conducted per ICH S6 (R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals.

The FDA's Assessment:

The FDA generally agrees.

5.5. Toxicology

5.5.1. General Toxicology

The Applicant's Position:

The nonclinical toxicity and toxicokinetic profile of tislelizumab was characterized in single dose toxicity studies in both mice and cynomolgus monkeys and in a 13-week repeat dose study in cynomolgus monkeys. In addition, studies were conducted to evaluate tislelizumab tissue cross reactivity, neutralizing ADA activity, and cytokine release responses.

No mortality or treatment related toxicities were noted in mice or cynomolgus monkeys at a single dose up to 100 mg/kg via intravenous infusion.

No treatment related toxicity, including inflammation and immunotoxicity, was identified in monkeys at repeated doses up to 30 mg/kg every two weeks for 13 weeks (total 7 doses).

No specific safety concerns were identified in the vital functions of the cardiovascular, respiratory, or central nervous systems in monkeys. No specific cross reactivity between tissue cell surface epitopes and tislelizumab was noted in monkey or human tissues. No apparent cytokine releases were noted in assays conducted with human whole blood cells or peripheral blood mononuclear cells (PBMCs). The dose of 30 mg/kg in monkeys is approximately 10-fold of the recommended human dose (200 mg) based on body weight and resulted in exposures (AUC) approximately 5-fold to 8-fold higher than those in patients receiving the recommended human dose of 200 mg.

Neutralizing ADA were detected in most of monkeys in all studies, however, there was no immune related toxicity or apparent effect on systemic exposure.

The systemic exposure appeared to increase dose proportionally without apparent sex difference. No drug accumulation or changes in systemic exposure were noted after repeated doses every two weeks for 13 weeks.

The toxicology studies and resulting data are considered adequate to support the clinical development and marketing authorization application of tislelizumab.

The FDA's Assessment:

The FDA generally agrees. Immune cell infiltration was observed in various tissues including the heart and skin. One high dose female has mild myocardial degeneration.

Study title/ number: A 13-week Intravenous Infusion Toxicity Study of A Monoclonal Antibody BGB-A317 with A 6-Week Recovery Period in Cynomolgus Monkeys/P14-057-CD

GLP compliance: Stated compliance with US GLP (21 CFR Part 58).

FDA considers this to be a non-GLP study based on results of study inspection. A follow-up GLP-compliant 13-week repeat-dose toxicology study in cynomolgus with intravenous (IV) injection every 2 weeks (Q2W) did not further inform the safety profile. Considering the toxicology profile observed in Study No. P14-057-CD and the pharmacology data are consistent with the class, the totality of the data supports the nonclinical safety of tislelizumab.

Methods

Dose and frequency of dosing:	0, 3, 10, or 30 mg/kg once every two weeks for 13 weeks
Route of administration:	Intravenous infusion
Formulation/Vehicle:	0.9% sodium chloride injection
Species/Strain:	Cynomolgus monkeys

Number/Sex/Group:	6/sex/group
Age:	2.5 to 4.5 years
Satellite groups/ unique design:	No
Deviation from study protocol affecting interpretation of results:	No

Table 7. 13-week Intravenous Toxicity in Cynomolgus Monkeys

Parameters	Major findings
Mortality	There were no deaths during the study.
Clinical Signs	Unremarkable
Body Weights	Unremarkable
Ophthalmoscopy	Unremarkable
ECG	Unremarkable
Hematology	Unremarkable
Clinical Chemistry	Unremarkable
Urinalysis	Unremarkable
Gross Pathology	Unremarkable
Organ Weights	Unremarkable
Histopathology Adequate battery: Yes	Minimal to mild myocardial inflammatory cell infiltrate was noted. One high dose female has mild myocardial degeneration. Minimal to moderate inflammatory cell infiltrate was noted in various tissues including the skin. Minimal to moderate lymphoid aggregates were noted in various tissues. Tails in one high dose male and one high dose female had scabs, ulceration, and moderate to marked inflammatory cell infiltrate.
Toxicokinetics	

Dose Level (mg/kg)	0		3		10		30	
Sex: Number of Animals	M:6	F: 6	M:6	F: 6	M:6	F: 6	M:6	F: 6
Toxicokinetics: C_{max} (µg/mL)								
Day 1 (1 st dose)	-	-	86.34±9.91	75.47±4.44	251.59±19.07	257.36±14.64	849.18±131.52	846.97±75.78
Day 29 (3 rd dose)	-	-	66.73±39.18	66.59±36.33	344.54±100.85	332.38±71.77	1025.81±123.79	1059.39±249.31
Day 71 (6 th dose)	-	-	62.76±47.04	61.85±53.43	403.54±243.93	518.54±201.36	1238.80±470.89	908.50±365.03
Toxicokinetics: AUC_{0-336h} (h·µg/mL)								
Day 1 (1 st dose)	-	-	11869.38±1881.50	11924.35±1182.00	36425.96±3747.51	37188.03±4451.16	125871.33±24410.37	117736.34±15311.26
Day 29 (3 rd dose)	-	-	5400.11±6159.03	6297.68±9046.09	28803.27±21191.19	36961.88±23153.79	144696.29±70376.6	113969.77±61780.56
Day 71 (6 th dose)	-	-	7287.91±8694.95	9114.64±12565.02	44584.56±53138.74	69396.93±46563.00	218887.91±135667.77	138577.5±109970.46

5.5.2. Genetic Toxicology

The Applicant's Position:

Tislelizumab, as a monoclonal antibody, is not expected to interact directly with deoxyribonucleic acid (DNA) or other chromosomal material. No genotoxicity studies were conducted as they are not recommended for a monoclonal antibody per ICH S6(R1) Preclinical Safety Evaluation of Biotechnology Derived Pharmaceuticals.

The FDA's Assessment:

The FDA agrees that genotoxicity studies were not warranted.

5.5.3. Carcinogenicity

The Applicant's Position:

No carcinogenicity studies were conducted as they are not recommended per ICH S9 Nonclinical Evaluation for Anticancer Pharmaceuticals.

The FDA's Assessment:

The FDA agrees that carcinogenicity studies were not warranted.

5.5.4. Reproductive and Developmental Toxicology

The Applicant's Position:

Fertility and Early Embryonic Development Study

No gross lesions or histopathologic changes were noted in the reproductive organs of male or female cynomolgus monkeys in the 13-week repeat dose study.

No fertility or early embryonic development study was conducted per ICH S9 Nonclinical Evaluation for Anticancer Pharmaceuticals, as observation that fetal exposure to tislelizumab may increase risk of developing immune-mediated disorders or altering the normal immune response.

Embryo-Fetal Development Toxicity Study

A dedicated embryo-fetal development toxicity study was not conducted or recommended per ICH S9 Nonclinical Evaluation for Anticancer Pharmaceuticals. A weight-of-evidence literature-based assessment of the effects of PD-1/PD-L1 on embryo-fetal toxicity in animals, on normal and abnormal pregnancy in women, and on immune-related response in transgenic mice and patients has been performed.

Review of published literature and information on the well-recognized mechanism of action revealed that blocking the PD-1/PD-L1 pathway resulted in fetal loss in animal models and that PD-1/PD-L1 expression plays an indispensable role in maintaining a normal and successful pregnancy. This literature-based assessment provides evidence of that tislelizumab may cause fetal harm, increase rates of abortion or stillbirth and increase risk of developing immune-mediated disorders or altering the normal immune response in fetuses if administered to a pregnant woman.

Therefore, no embryo-fetal toxicity studies in animals were conducted for this risk assessment.

Prenatal and Postnatal Development Toxicity Study

No study was conducted or recommended per ICH S9 guideline Nonclinical Evaluation for Anticancer Pharmaceuticals.

Based on the literature, PD-1 plays an important role in suppressing aberrant immune responses by inhibiting the activation of autoreactive lymphocytes. It is reported that PD-1 and PD-L1 knockout mice develop a late-onset autoimmune phenotype, including lupus-like glomerulonephritis, arthritis, and cardiomyopathy. A meta-analysis suggests PD-1 polymorphisms are associated with susceptibility to rheumatoid arthritis, ankylosing spondylitis and type 1 diabetes. These studies suggest that inhibition of the PD-1/PD-L pathway during pregnancy may cause or potentiate autoimmune diseases in infants.

The FDA's Assessment:

The FDA generally agrees.

Studies in the literature demonstrate that the PD-1/PD-L1 pathway plays a critical role in maintaining maternal immunological tolerance to the fetus during pregnancy.

- PD-L1 is expressed in the human placenta throughout pregnancy (Petroff, et al. 2003).
- Fetomaternal tolerance was studied in a mouse abortion-prone allogeneic pregnancy model (CBA x C57BL/6) where PD-L1 expression was detected at the uteroplacental interface of the placenta as early as 10.5 days post-conception (Guleria, et al. 2005).
 - administration of a murine anti-PD-L1 monoclonal antibody to allogeneic

- pregnant mice resulted in increased resorptions compared to isotype control
 - allogeneic fetal rejection was T-cell dependent
 - increased rates of resorptions occurred in female PD-L1 deficient mice
- Adoptive transfer of Tregs from wild-type mice to PD-L1 ^{-/-} mice improved fetal survival, suggesting that PD-L1-expressing Tregs are responsible for tolerance to fetal alloantigens (Habicht, et al. 2007).
- Blockade of PD-1 reduced the protective effects of Tregs in an abortion-prone mouse pregnancy model resulting in a higher rate of abortion (Wafula, et al. 2009).
- Mice deficient in PD-1 develop autoimmune phenotypes, and therefore fetal exposure may increase the risk of developing immune-related disorders or alterations in the immune response (Wang, et al. 2005).

Administration of a murine anti-PD-L1 monoclonal antibody to allogeneic pregnant mice resulted in increased resorptions compared to isotype control allogeneic fetal rejection was T-cell dependent increased rates of resorptions occurred in female PD-L1 deficient mice.

Administration of a murine anti-PD-L1 monoclonal antibody to allogeneic pregnant mice resulted in increased resorptions compared to isotype control allogeneic fetal rejection was T-cell dependent increased rates of resorptions occurred in female PD-L1 deficient mice

Based on its mechanism of action, the labeling includes a warning for embryo-fetal toxicity, administration of PD-1 blocking antibody is likely to disrupt the maintenance of normal pregnancy (e.g., increased rates of abortion and stillbirth). The labeling also advises females of reproductive potential to use contraception during treatment with tisnelizumab and for at least four months after the last dose.

5.5.5. Other Toxicology Studies

The Applicant's Position:

- There was no specific staining observed in the human or cynomolgus tissue cross reactivity studies with tisnelizumab.
- Tisnelizumab had no hemolytic or aggregatory effects in rabbit red blood cells (RBCs) in the in vitro hemolysis test.
- Tisnelizumab did not induce cytokine release in the peripheral blood cells from healthy donors or in human whole blood cells study. The results suggested that tisnelizumab has low risk of causing acute cytokine release syndrome (CRS) arising from PBMCs.
- The potential of enhanced immune recall responses was observed in an in vitro immunologic recall response assay using human PBMC cells, but not in a T-cell dependent antibody response to keyhole limpet hemocyanin (KLH) antigen in a human PD-1 transgenic mouse study.

The FDA's Assessment:

The FDA generally agrees.

- The T-cell dependent antibody response to keyhole limpet hemocyanin (KLH) antigen was assessed in a human PD-1 transgenic mouse model. All mice produced a primary and secondary humoral anti-KLH IgG response after immunization with KLH on Days 2 and 23. Tisnelizumab (10 mg/kg) was intraperitoneally administered on Days 1, 8, and 15 to assess the effect on the primary TDAR, and on Days 22, 29, and 36 to assess the effect on the recall TDAR. Tisnelizumab did not induce significant changes in the primary or secondary anti-KLH responses relative to control (Study BGB-A317-IVP-Tox-OT-0001).
- Cytokine release responses in human whole blood cells did not identify a safety signal (Studies: CRAA317- 1; CRA-A317-2)

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Emily Place
Primary Reviewer

Matthew Thompson
Team Leader

6. Clinical Pharmacology

6.1. Executive Summary

The FDA's Assessment:

Tislelizumab is a humanized immunoglobulin G4 (IgG4) variant monoclonal antibody against the programmed cell death-1 receptor (PD-1). The Applicant is seeking full approval of tislelizumab for the treatment of patients with unresectable recurrent locally advanced or metastatic esophageal squamous cell carcinoma (ESCC) after prior systemic therapy. The proposed dosing regimen is 200 mg as IV infusion (60 min for first cycle and 30 min for subsequent cycles if tolerable) once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity.

The clinical pharmacology review focused on dose selection, exposure-response analyses, and immunogenicity.

Recommendations: The Office of Clinical Pharmacology has reviewed the information submitted in BLA 761232. This BLA is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations/comments are summarized below in Table 8.

Table 8. Key Clinical Pharmacology Review Issues by FDA

Review Issue	Recommendations and Comments
Pivotal and Supportive evidence of effectiveness	The primary evidence of effectiveness comes from Study BGB-A317-302. The proposed dosing regimen is supported by a favorable overall survival of tislelizumab monotherapy against investigator-chosen chemotherapy (ICC) with a stratified hazard ratio (HR) of 0.70 (95% CI 0.57, 0.85) and a 1-sided p-value of 0.0001. In addition, the safety profile of tislelizumab was comparable to that of ICC.
General dosing instructions	The proposed tislelizumab dosing regimen of 200 mg Q3W is supported by the following: Favorable anti-tumor activity: In Study BGB-A317-302, a favorable effect on overall survival was reported with tislelizumab monotherapy against ICC, with a stratified HR of 0.70 (95% CI 0.57, 0.85). Flat exposure-response for safety in patients with ESCC at PK exposure (i.e., $C_{avg,dose1}$ and steady state C_{avg}, C_{max}, C_{min}) observed with 200 mg Q3W. Limitations Lower dose levels not tested: There is insufficient activity and safety information at lower dose levels (< 200 mg Q3W). Exposure-response for efficacy was inconclusive because the effect of tislelizumab exposure on survival and potential effects of exposure on ORR may have been confounded by an imbalance in baseline factors of patients in different quartiles of tislelizumab exposure.

Review Issue	Recommendations and Comments
Dosing in patient subgroups (intrinsic and extrinsic factors)	Based on PopPK analyses using pooled PK data across clinical trials, no clinically significant differences in the pharmacokinetics of tislelizumab were observed based on age (18 to 90 years), weight (32 to 130 kg), race (White, Asian, or Black), mild to moderate renal impairment ($CL_{Cr} \geq 30$ 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 (CL_{Cr} 15-29 mL/min), or end stage renal disease ($CL_{Cr} < 15$ mL/min) on the pharmacokinetics of tislelizumab is unknown. In patients who received tislelizumab-jsgr in Study 302 for up to 22 months, the incidence of anti-tislelizumab antibodies (ADA) was 14.5% (32/221). Among the ADA positive patients, the incidence of neutralizing antibodies (NAb) was 3.1% (1/32). Tislelizumab ADA development has no clinically meaningful impact on the PK of tislelizumab. The effect of ADA on the efficacy and safety of tislelizumab in patients with unresectable or metastatic esophageal squamous cell carcinoma (ESCC) could not be fully characterized as the number of patients with positive ADA and neutralizing ADA were small.
Labeling	Overall, the proposed labeling recommendations are acceptable upon the Applicant's agreement to the FDA revisions to the labeling. Clinical pharmacology labeling recommendations are detailed in Section 12.2, 12.3 and 12.6.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Data:

The clinical pharmacology information in this submission includes characterization of pharmacokinetics, exposure-response (E-R) analyses, and immunogenicity profile of tislelizumab.

The PK profile of tislelizumab was characterized using noncompartmental analysis and population PK (popPK) analysis. Exposure-response (E-R) analyses were performed to understand the relationships between PK and efficacy, as well as safety parameters. These analyses support the proposed dosing regimen of 200 mg once every 3 weeks and demonstrated that no dose modifications are needed based on age, weight, race, sex, hepatic impairment (mild to moderate), renal impairment (mild to moderate), and other intrinsic or extrinsic factors. The immunogenicity profile of tislelizumab has been characterized and its lack of clinically relevant impact on PK, safety, and efficacy in the ESCC population is also discussed in this section.

Additional information are reported in section 6.3.1.

The Applicant's Position:

The clinical pharmacology of tislelizumab has been well characterized, and the outcomes of the exposure – efficacy and exposure – safety analyses for tislelizumab support the use of the recommended dose in the target indication.

The FDA's Assessment:

FDA generally agrees with the Applicant's position. Clinical data in Study 302 were limited with respect to the conduct of analyses on efficacy and safety based on race/ethnicity as the trial enrolled only Asian and White patients. Limited data were available in other racial or ethnic groups to assess the potential for differences in PK or PD.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

Data:

The recommended dose of 200 mg administered intravenously once every 3 weeks was selected based on safety, efficacy, and PK assessments in the first-in-human (FIH) dose escalation Study 001. In this study, dose ranges of 0.5 mg/kg through 10 mg/kg (once every 2 or 3 weeks) were studied in patients with advanced solid tumors and comparable safety and efficacy profiles were observed between the 2 mg/kg and 5 mg/kg levels. Also, no significant E-R relationships were observed between exposure and efficacy (ie, ORR), or safety endpoints across the dose range tested in this study. Based on this observation, a flat dose of 200 mg (corresponding to a dose between 2 mg/kg and 5 mg/kg) once every 3 weeks was chosen as the clinical dose because tislelizumab concentrations with this dose largely overlapped with those observed with the 2 mg/kg and 5 mg/kg once every 3 weeks. The less frequent regimen of once every 3 weeks regimen had similar efficacy and safety events compared with once every 2 weeks. The efficacy and safety with the 200 mg once every 3 weeks dose regimen has been subsequently studied in clinical studies including the pivotal study 302 that forms the basis of this Biologics License Application (BLA) submission.

The E-R analyses using data from ESCC patients from the tislelizumab cohort in Study 302 demonstrated that there were no clinically meaningful relationships between exposure and efficacy endpoints (ORR and OS), and exposure and safety endpoints (imAE, IRR, AE with Grade ≥ 3 , AE leading to dose modification, and AE leading to drug discontinuation). Comparable efficacy and safety response were observed across White and Asian ESCC patients. Similarly, no clinically relevant E-R relationships were observed for efficacy endpoint of ORR and safety endpoints, which include the same endpoints as above, based on tislelizumab-treated patients in Supportive studies (001, 102, 203 and 204). Taken together, the recommended dose of 200 mg Q3W demonstrated a favorable risk-benefit profile in 2L ESCC patients.

The Applicant's Position:

The recommended dose of tislelizumab is 200 mg administered as an intravenous infusion once every 3 weeks until disease progression or unacceptable toxicity. Deciding whether to keep a patient on tislelizumab beyond initial signs of disease progression should be based on factors such as the extent of disease progression and the clinician's assessment of the patient's clinical status.

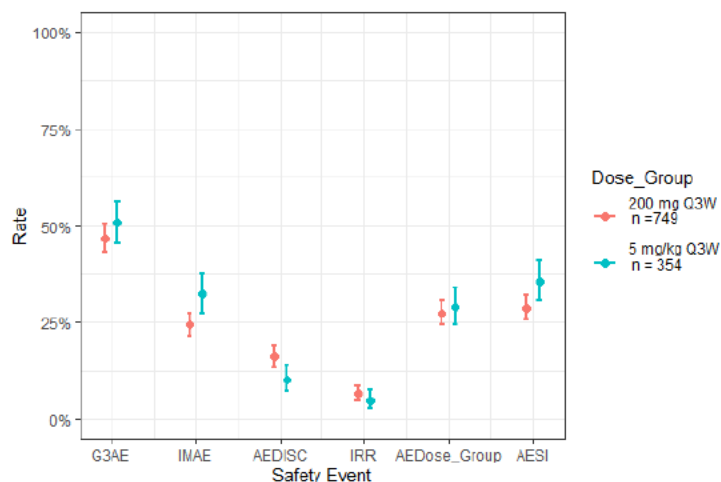
The FDA's Assessment:

FDA generally agrees with the Applicant's assessment that the recommended dosage of 200 mg every 3 weeks (Q3W) is acceptable from a clinical pharmacology perspective. However, FDA does not agree that there is sufficient data to evaluate differences in efficacy and safety for dose levels between 2 mg/kg and 5 mg/kg and dosing regimens between once every 2 weeks (Q2W) and Q3W.

In the clinical development program of tislelizumab, 280 patients with ESCC received 200 mg Q3W and 26 patients with ESCC received 5 mg/kg Q3W. Body weight is a significant covariate to tislelizumab clearance though the exposure change is small. The exposure of 200 mg Q3W is slightly lower than that of 5 mg/kg Q3W and slightly higher than 2 mg/kg Q3W. In addition, there is no efficacy data in patients with ESCC who received tislelizumab Q2W. Overall, there are limited data to evaluate efficacy of tislelizumab in patients with ESCC between 2 and 5 mg/kg doses and Q2W and Q3W dosing regimens.

In addition, a slight trend of higher incidence of imAE and adverse events of special interest (AESI) was observed in patients with advanced solid tumors receiving 5 mg/kg Q3W as compared with those receiving 200 mg Q3W (Figure 8). Due to limited number of patients with solid tumors (n=21) evaluated at the 2 mg/kg dose, a formal comparison of safety between 2 mg/kg and 5 mg/kg is limited. There are also limited safety data for comparison between the Q2W and Q3W dosing regimens because only a small portion of patients with solid tumors received tislelizumab at the Q2W dosing regimens (n=26 for 2 mg/kg Q2W; n=26 for 5 mg/kg Q2W). Furthermore, there are limited data to rule out any potential differences in safety across different tumors as final safety analyses of other supportive clinical trials for other cancers are pending. Thus, there is limited data to compare safety between 2 and 5 mg/kg doses and dosing regimens (Q2W and Q3W) for patients with ESCC.

Figure 8. Key safety event rates in different dose groups (Q3W)



Source: FDA Analysis

Although the tislelizumab exposure-response relationship for efficacy was inconclusive, the finding of effectiveness of tislelizumab was supported by an improvement in overall survival of tislelizumab monotherapy against ICC with a stratified HR of 0.70 (95% CI 0.57, 0.85). In addition, a flat exposure-response for safety was observed in patients with ESCC with PK exposure (i.e., $C_{avg,dose1}$ and steady state C_{avg} , C_{max} , C_{min}) observed at 200 mg Q3W. Thus, the recommended dosage of 200 mg Q3W is acceptable from a clinical pharmacology perspective.

Reported in vitro binding activities are generally comparable among tislelizumab, nivolumab, and pembrolizumab.

6.2.2.2. Therapeutic Individualization

Data:

Please see Section 6.3.1.- Sub-paragraph “Clinical Pharmacokinetics”.

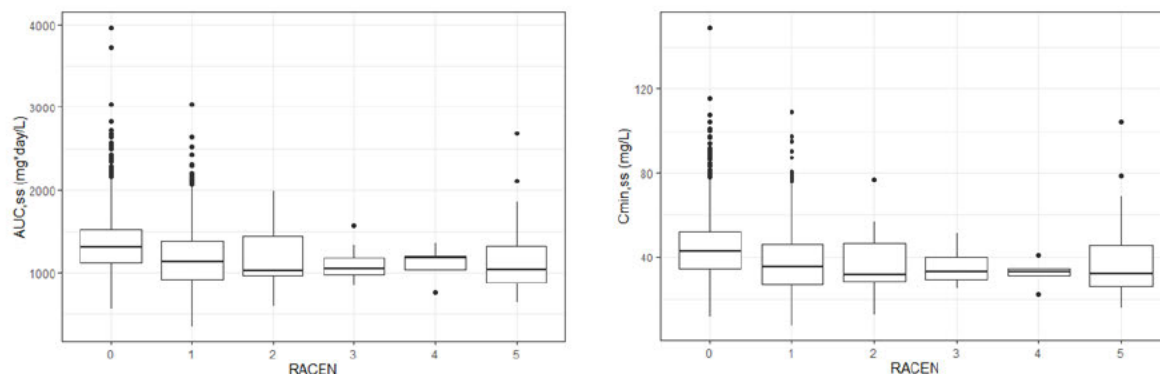
The Applicant’s Position:

No therapeutic individualization is needed in the proposed indication based on demographic factors (body weight, age, gender, race) or in special populations (hepatic or renal impairment).

The FDA’s Assessment:

FDA generally agrees with the Applicant’s position. In addition, FDA’s PopPK analyses using PK data from all clinical trials (n=1,995) suggests that race is not a significant covariate on the CL and V_c of tislelizumab and has no clinically meaningful effect on tislelizumab PK exposure (i.e. steady state AUC and C_{min}). Asian, White, and Black patients administered 200 mg Q3W tislelizumab had comparable PK exposure (Figure 9).

Figure 9. PK exposure across race using population PK approach

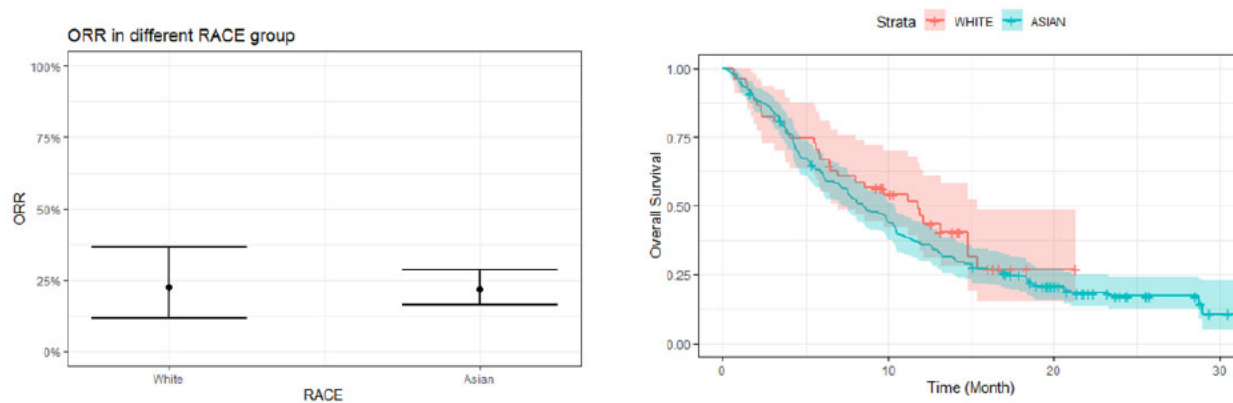


RACEN	0	1	2	3	4	5
RACE	Asian	White	American Indian or Alaska native	Black or African American	Hawaiian or other pacific islanders	Other or missing
# Patients	1995	529	13	10	5	49

Source: FDA's analysis

In Study BGB-A317-302, 78.5% patients were (n=201) Asian and 20.7% patients were White (n=53). There are no observable differences between Asian and White for ORR and OS (Figure 10). In addition, a flat exposure-response for safety was observed in patients with ESCC with PK exposure (i.e., $C_{avg,dose1}$ and steady state C_{avg} , C_{max} , C_{min}) observed at 200 mg Q3W (see Appendix 19.4.4). Thus, there appear to be no clinically meaningful differences in efficacy or safety between Asian and White patients.

Figure 10. Exploratory analysis of ORR and OS for White and Asian patients



6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Data:

An overview of the clinical pharmacokinetics and immunogenicity is provided below.

Absorption: Tisnelizumab is administered intravenously. Maximum serum concentrations are observed immediately after the end of the infusion.

Distribution: Consistent with the volume of distribution of endogenous IgG antibodies, tisnelizumab has low volume of distribution (6.42 L).

Metabolism: The metabolic pathway for tisnelizumab is expected to be non-specific degradation to peptides and amino acids by lysosome through fluid-phase or target-mediated endocytosis.

Excretion: Clearance of tisnelizumab is 0.153 L/day and does not appear to be time varying. The $t_{1/2}$ was estimated to be approximately 23.8 days.

Clinical Pharmacokinetics: A population PK (popPK) analysis was conducted to evaluate the PK of tisnelizumab and to identify factors contributing to between-patient variability in PK using pooled PK data from 2596 patients enrolled in 12 clinical studies (Studies 001, 102, 203, 204, 205, 206, 208, 209, 302, 303, 304 and 307).

Tisnelizumab exhibited a dose proportional increase in exposure over the entire dose range/dose regimens tested (0.5 mg/kg to 10 mg/kg Q2W or Q3W, including the 200 mg Q3W flat dose). The PK of tisnelizumab was best characterized using a 3 compartmental model with linear clearance mechanism. No time-varying clearance was observed in tisnelizumab PK. The typical estimates of CL, central volume of distribution (V_c), and peripheral volumes 2 and 3 (V_2 and V_3 , respectively), were 0.153 L/day, 3.05 L, 1.27 L, and 2.10 L, respectively, with interindividual variability in CL (26.3%), V_c (16.7%), V_2 (74.7%), and V_3 (99.9%). The terminal half-life ($t_{1/2}$) was estimated to be approximately 23.8 days. Steady state is expected to be reached in approximately 12 weeks. The accumulation ratios are estimated to be 2.14 and 2.49 for area under the serum concentration-time curve at steady state (AUC_{ss}) and minimum concentration at steady-state ($C_{min,ss}$), respectively.

PopPK analysis demonstrated that race, baseline alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, lactate dehydrogenase (LDH), estimated glomerular filtration rate (eGFR) and ECOG PS score did not have a statistically significant influence on tisnelizumab PK. Baseline body weight, tumor size of solid tumors, albumin level, immunogenicity, sex, age, and tumor type were found to be statistically significant covariates on the PK of tisnelizumab. However, none of them are considered to result in clinically relevant changes in exposure of tisnelizumab because the CL and V_c derived based on the extremes (10th and 90th percentiles) of covariate distribution were still within $\pm 20\%$ of the typical estimates. As the impact of these covariates on tisnelizumab exposure metrics is relatively small compared to the overall variability of exposure in the population, dose adjustment is not warranted based on these covariates. This is

further supported by the relatively flat exposure-response relationship on efficacy and safety between 2 mg/kg and 5 mg/kg Q3W.

Immunogenicity: The immunogenicity profile of tislelizumab has been characterized in all clinical studies using validated assays. Overall, a 16.5% incidence of treatment-emergent ADA was observed (295 of 1785 evaluable patients). Neutralizing antibodies (Nabs) were detected in 11 (0.6%) patients. At the recommended dose of 200 mg once every three weeks, 16.3% (232 of 1424 evaluable patients) tested positive for treatment-emergent ADA. Nabs were detected in 0.8% (11 of 1424 evaluable patients). PopPK analysis showed that ADA status was a significant covariate; however, based on the flat exposure-response relationships and the assessment of overall clinical response and safety events, the presence of treatment-emergent ADA did not impact PK, efficacy, or safety to a clinically meaningful extent.

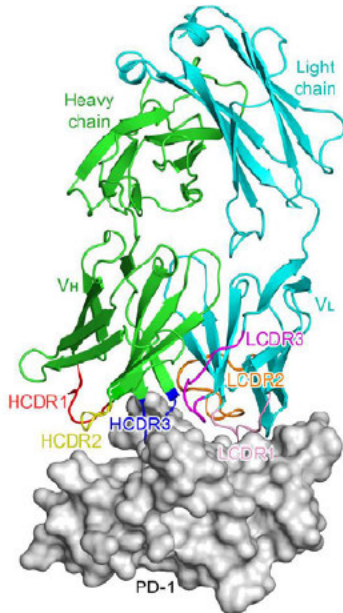
The Applicant's Position:

The clinical pharmacokinetics and immunogenicity profile of tislelizumab have been sufficiently characterized and demonstrated that no dose modifications are needed based on age, weight, race, sex, hepatic impairment (mild to moderate), renal impairment (mild to moderate), and other intrinsic or extrinsic factors.

The FDA's Assessment:

FDA generally agrees with the Applicant's assessment. In the FDA's assessment, analysis of immunogenicity was limited to patients with ESCC because of the potential for differences in immunogenicity across differences in tumor types. See Table 9 for highlights of FDA's assessment of the clinical pharmacology information.

Table 9. Highlights of Clinical Pharmacology for tislelizumab

Physiochemical properties	
Chemical structure and molecular weight	 Chemical Structure of Tislelizumab Molecular weight of Tislelizumab: 144,080 Da with 1318 amino acid residues
Pharmacology	
Mechanism of Action	Tislelizumab is an IgG4 monoclonal antibody that binds to PD-1 and blocks the binding of both PD-L1 and PD-L2, inhibiting PD-1-mediated signaling and enhancing activity in T-cells.
Active Moieties	Tislelizumab
QT/QTc Prolongation	Not applicable as tislelizumab is a large monoclonal antibody, which is unlikely to block ion channels.
General Information	
Bioanalysis	In Study BGB-A317-001 and BGB-A317-302, serum tislelizumab concentrations were measured using a validated antigen-binding enzyme-linked immunosorbent assay (ELISA) method. A summary of the method validation reports is included in Appendix 19.4.1.

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Healthy Volunteers vs. Patients	All studies are conducted in patients with cancer.
Drug exposure at steady state following the therapeutic dosing regimen	In adult patients with cancer, geometric mean steady-state AUC _{tau} of tislelizumab was 1,283 µg/mL*day and the C _{max} was 110 µg/mL following a dosage of 200 mg Q3W.
Minimal effective dose or exposure	Not determined. There is insufficient anticancer activity and safety information at doses < 200 mg Q3W to determine the minimal effective dose.
Maximal tolerated dose or exposure	In Study BGB-A317-001, the highest dose explored was 10 mg/kg and the MTD of tislelizumab was identified.
Dose Proportionality	The dose proportionality analysis was assessed using a power model with PK parameters obtained following a single dose on Cycle 1 Day 1 in Study BGB-A317-001. The estimation of the slope of the dose proportionality analysis was approximately 0.98 [0.91, 1.07] for doses 0.5 to 10 mg/kg group for AUC_{0-14days} and 0.98 [0.91, 1.06] for doses 0.5 to 10 mg/kg group for C_{max} in 108 patients with cancer.
Accumulation	Steady-state concentrations of tislelizumab are reached after 12 weeks following administration every 3-weeks and the systemic accumulation was 2.1-fold based on PopPK analysis.
Variability	Based on PopPK analysis, the inter-subject variability (CV%) of steady state tislelizumab AUC _{tau} and C _{max} was 28.7% and 22.2%, respectively.

Immunogenicity

In patients who received tislelizumab-jsgf in RATIONALE-302 (Study 302) for up to 22 months, the incidence of anti-tislelizumab antibodies (ADA) was 14.5% (32/221). Among the ADA positive patients, the incidence of neutralizing antibodies (NAb) was 3.1% (1/32) as shown in Table 10.

Table 10. Summary of Immunogenicity by Study

Dose Regimen	Study	Evaluable Patients: n	Treatment Emergent: n (%)	Treatment Boosted: n (%)	Treatment Induced: n (%)	Persistent: n (%)	Transient: n (%)	NAb Positive: n (%)
0.5 mg/kg Q2W	001	3	1 (33.3)	0 (0.0)	1 (33.3)	0 (0.0)	1 (33.3)	0 (0.0)
2.0 mg/kg Q2W		21	6 (28.6)	0 (0.0)	6 (28.6)	2 (9.5)	4 (19.0)	0 (0.0)
5.0 mg/kg Q2W		25	5 (20.0)	0 (0.0)	5 (20.0)	4 (16.0)	1 (4.0)	0 (0.0)
10.0 mg/kg Q2W		6	1 (16.7)	0 (0.0)	1 (16.7)	1 (16.7)	0 (0.0)	0 (0.0)
2.0 mg/kg Q3W		19	6 (31.6)	0 (0.0)	6 (31.6)	3 (15.8)	3 (15.8)	0 (0.0)
5.0 mg/kg Q3W		287	44 (15.3)	1 (0.3)	43 (15.0)	21 (7.3)	22 (7.7)	0 (0.0)
200 mg Q3W		11	3 (27.3)	0 (0.0)	3 (27.3)	1 (9.1)	2 (18.2)	1 (9.1)
Subtotal of Study 001		372	66 (17.7)	1 (0.3)	65 (17.5)	32 (8.6)	33 (8.9)	1 (0.3)
200 mg Q3W	102	280	43 (15.4)	2 (0.7)	41 (14.6)	26 (9.3)	15 (5.4)	2 (0.7)
200 mg Q3W	203	70	6 (8.6)	0 (0.0)	6 (8.6)	4 (5.7)	2 (2.9)	1 (1.4)
200 mg Q3W	204	104	18 (17.3)	1 (1.0)	17 (16.3)	13 (12.5)	4 (3.8)	0 (0.0)
200 mg Q3W	208	231	50 (21.6)	0 (0.0)	50 (21.6)	33 (14.3)	17 (7.4)	4 (1.7)
200 mg Q3W	302	221	32 (14.5)	2 (0.9)	30 (13.6)	20 (9.0)	10 (4.5)	1 (0.5)
200 mg Q3W	303	507	80 (15.8)	3 (0.6)	77 (15.2)	40 (7.9)	37 (7.3)	2 (0.4)
Subtotal of 200 mg without Study 302		1203	200 (16.6)	6 (0.5)	194 (16.1)	117 (9.7)	77 (6.4)	10 (0.8)
Subtotal of all doses without Study 302		1564	263 (16.8)	7 (0.4)	256 (16.4)	148 (9.5)	108 (6.9)	10 (0.6)
Subtotal of 200 mg Q3W		1424	232 (16.3)	8 (0.6)	224 (15.7)	137 (9.6)	87 (6.1)	11 (0.8)
Total		1785	295 (16.5)	9 (0.5)	286 (16.0)	168 (9.4)	118 (6.6)	11 (0.6)

Source: Module 5.3.5.3, ISI Report 2, Table 2.

Based on PopPK analysis, tislelizumab ADA had no clinically significant effect on its PK. The effect of ADA on the efficacy and safety of tislelizumab in the patients with ESCC has not been fully characterized will limited patients with positive ADA.

Absorption

Bioavailability

Not applicable.

T_{max}

Since tislelizumab is given as an intravenous infusion, the expected T_{max} is around end of infusion.

Distribution

Volume of distribution

The mean (%CV) steady-state total volume of distribution is 6.4 L (32.6%) based on PopPK analysis.

Plasma protein binding

Not applicable.

Blood to plasma ratio	Not applicable.
Elimination	
Half-life	The mean (%CV) terminal half-life ($t_{1/2}$) is 24 days (26%) based on PopPK analysis.
Clearance	The mean (%CV) total clearance is 0.15 L/day (29.5%) based on PopPK analysis.
Metabolism	
Primary metabolic pathway(s)	Tislelizumab is expected to be catabolized by non-hepatic pathways.
Excretion	
Primary excretion pathways (% dose) $\pm$SD	Not applicable.

6.3.2. Clinical Pharmacology Questions

6.3.2.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?

Data:

Refer to section 8 for efficacy results from Study 302.

The exposure-efficacy relationships were evaluated in previously treated advanced or metastatic ESCC patients receiving tislelizumab monotherapy in the pivotal Study 302. In the intention-to-treat (ITT) Population in Study 302, a longer OS was observed in patients in the highest exposure quartile compared with those in the lower three quartiles. However, the lack of a consistent trend in OS by exposure quartiles, the confounding effects of baseline characteristics like tumor size and albumin on OS and tislelizumab clearance, and the imbalance in distribution of these baseline characteristics across exposure quartiles suggest there is not a meaningful association of exposure with efficacy.

In addition, no exposure-safety relationships were observed for immune-mediated adverse events (imAEs), infusion-related reactions (IRRs), any adverse event (AE) $\geq$ Grade 3, AE of special interest (AESI, imAE + IRR), and AE leading to dose modification or drug discontinuation within the exposure range at tislelizumab 200 mg once every 3 weeks dosing regimen as monotherapy in ESCC patients in the pivotal Study 302.

The Applicant's position:

The results from the Study 302 and the supportive studies provide evidence of the positive benefit-risk supporting the efficacy claim of tislelizumab 200 mg Q3W in 2L ESCC patients. While clinical pharmacology evaluation does not include a direct assessment of benefit-risk, the exposure-response models in safety and efficacy highlight a flat dose – response relationship between 2 mg/kg and 5 mg/kg Q3W from earlier studies, as well as in patients who received 200 mg Q3W tislelizumab from the 302 study. Taken together, these results support tislelizumab 200 mg Q3W to be an appropriate dosage regimen for this population.

The FDA's Assessment:

FDA generally agrees with the Applicant's assessment.

6.3.2.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Data:

Refer to section 6.2.2.

The Applicant's Position:

The totality of clinical efficacy and safety data in patients with advanced or metastatic ESCC along with a lack of clinically relevant E-R relationships between PK, efficacy, and safety support the proposed tislelizumab dose of 200 mg administered intravenously once every 3 weeks.

FDA's Assessment:

FDA generally agrees with the Applicant's position.

6.3.2.3 Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Data:

Refer to section 6.2.2.2.

The Applicant's Position:

In the population pharmacokinetic analysis, potential covariates influencing the pharmacokinetics of tislelizumab have been evaluated. No dose adjustment is required for race, hepatic and renal function-related covariates (eg, ALT, AST, bilirubin, eGFR), and disease-related covariates (eg, LDH, ECOG PS score).

The FDA's Assessment:

FDA generally agrees with the Applicant's position.

6.3.2.4 Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Data:

No dedicated DDI study was conducted.

The Applicant's Position:

A PK based drug-drug interaction of tislelizumab with other therapeutics is not anticipated given that the primary elimination pathways are protein catabolism via the reticuloendothelial system or target-mediated disposition. Tislelizumab is not expected to induce or inhibit the major drug metabolizing CYP pathways (Evers et al 2013), as tislelizumab is neither a proinflammatory cytokine nor a cytokine modulator. Therefore, no dedicated drug-drug interaction studies have been conducted with tislelizumab as of the data cutoff date of the Study 302 clinical study report.

Tislelizumab is intended for intravenous infusion administration; therefore, food-drug interactions are not expected.

The FDA's Assessment:

FDA generally agrees with the Applicant's position.

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Team Leader

7. Sources of Clinical Data

7.1. Table of Clinical Studies

Data:

A summary of the key design features, including patient population, treatment regimen, and efficacy endpoints for the Phase 3 study (Study 302) and the 6 supporting studies (Studies 001, 102, 203, 204, 208, and 303) is provided in [Table 11](#).

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Table 11: BeiGene - Clinical Studies Contributing Efficacy and/or Safety Data in the tislelizumab Submission in Esophageal Squamous Cell Carcinoma

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
<i>Primary Study to Support Efficacy and Safety</i>								
BGB-A317-302	NCT03430843	Phase 3, randomized, controlled, open label, multicenter study	Tislelizumab Arm: 200 mg Q3W; IV ICC Arm: One of: Paclitaxel 135-175 mg/m ² IV Q3W starting Day 1) ^b Docetaxel (75 mg/m ² IV Q3W starting Day 1) ^c Irinotecan (125 mg/m ² IV on Days 1 and 8, and then Q3W)	Primary: OS in the ITT Analysis Set Secondary: - OS in the PD-L1-Positive Analysis Set (Key secondary) - ORR - PFS - DOR - HRQoL - Adverse events	until disease progression, intolerable toxicity, or withdrawal for other reasons	512 (256 randomized to each treatment arm; 255 received tislelizumab and 240 received ICC)	Patients with histologically confirmed advanced or metastatic ESCC and tumor progression during or after first-line systemic treatment	132 centers 11 countries/ regions
<i>Additional Studies to Support Safety and Efficacy</i>								

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BGB-A317-Study_001	NCT02407990	Phase 1A/1B, open label, multicenter, 2part, dose-escalation and indication expansion ^d study	Tislelizumab: 0.5, 2, 5, 10 mg/kg Q2W; 2, 5 mg/kg Q3W; 200 mg Q3W; IV	Primary: Phase 1A - Safety and tolerability Phase 1B - ORR in different tumor types Secondary: - PK evaluations: AUC0-14 day, Cmax and Tmax, Ctough, t _{1/2} , Cl and Vd. - Anti-BGB-A317 antibody: immunogenic responses - Efficacy evaluations: ORR (CR+PR), rates of CR, PR, and SD, PFS, OS, and DOR and duration of SD - MTD and RP2D and regimen - PD biomarkers:	until confirmed disease progression, intolerable toxicity, patient discontinuation/ withdrawal or at the discretion of the sponsor/investigator.	451 (26 with ESCC)	Patients with advanced solid tumors ^e	27 centers 5 countries
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				changes in immune cell subpopulations and cytokine/chemokine levels in peripheral blood; changes in tumor microenvironment (eg, PD-L1 expression and TILs); and relationship to BGB-A317 efficacy				
BGB-A317-102	NCT04068519	Phase 1/2 open label, single arm, multicenter, 2 part, dose-verification and indication-expansion ^c study	Tislelizumab: 200 mg Q3W; IV or 200 mg W1D1, W5+D1 Q3W ^d (PK substudy); IV	Primary: Phase 1A - Safety and tolerability - MTD (if any) and/or RP2D (s) Phase 1B - ORR in different tumor types Secondary: Phase 1A - PK evaluations: AUC0-21 day, Cmax and	until no evidence of continued clinical benefit, had unacceptable toxicity, or withdrew informed consent	300 (26 with ESCC)	Patients with advanced solid tumors ^f	16 centers 1 country (China)

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				Tmax, Ctrough, t½, CI and Vz. - Efficacy evaluations: ORR, rates of CR, PR, and SD, PFS, OS and DOR and duration of SD				
<i>Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)</i>								
BGB-A317-203	NCT03209973	Phase 2, open-label, single-arm, multicenter study	Tislelizumab: 200 mg Q3W; IV	Primary: ORR Secondary: - PFS - DOR - Rate of CR - TTR - Steady state Ctrough	until the patient had progressive disease (PD), unacceptable toxicity, died, or until study withdrawal for other reasons	70	Patients with R/R cHL	11 centers 1 country (China)
BGB-A317-204	NCT04004221	Phase 2, open-label, single-arm, multicenter study	Tislelizumab: 200 mg Q3W; IV	Primary: ORR Secondary: - PFS - DOR - DCR - OS - ORR, DOR, PFS and DCR assessed by Investigators per RECIST v1.1 and	until disease progression, intolerable toxicity, or withdrawal for other reasons	113	Patients with previously treated high PD-L1 expression, locally advanced or metastatic UC	30 centers 2 countries

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				irRECIST respectively				
BGB-A317-208	NCT03419897	Phase 2, open-label, single-arm, multicenter study	Tislelizumab: 200 mg Q3W; IV	Primary: ORR (CR + PR) Secondary: - DOR, PFS, DCR and CBR assessed by IRC, and OS - ORR, DOR, PFS, DCR and CBR assessed by investigators - Safety and tolerability assessment of AEs, SAEs, physical examination, vital signs, ECG, and laboratory measurements - HRQoL	intolerable toxicity, withdrawal of informed consent, or the timepoint at which, in the opinion of the investigator, the patient is no longer benefiting from study therapy, whichever should occur first	249	Patients with previously treated, unresectable HCC	73 centers 8 countries
BGB-A317-303	NCT03358875	Phase 3, open-label, multicenter, randomized study	Tislelizumab: 200 mg Q3W; IV versus Docetaxel 75 mg/m ² Q3W	Primary: OS Secondary: - ORR - DOR -PFS -HRQoL Incidence and	until disease progression, unacceptable toxicity, or withdrawal for other reasons	805 (535 randomized to tislelizumab and 270 randomized	Patients with locally advanced or metastatic NSCLC who had disease progression	109 centers 10 countries

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				severity of TEAEs		to Docetaxel; 534 received tislelizumab and 258 received Docetaxel)	on or after at least 1 prior chemotherapy (Global)	
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Undefined Abbreviations: Q2W, once every 2 weeks; Q3W, once every 3 weeks; RP2D, recommended Phase 2 dose; R/R, relapsed or refractory; W1D1, Week 1 Day 1; W5+D1 Q3W, every 3 weeks from Week 5 Day 1.

^a Includes enrolled and randomized patients (as applicable). Key criteria for end of treatment in each study are listed in this table; for more details, please refer to the CSRs.

^b Paclitaxel could also be given at doses of 80 to 100 mg/m² on a weekly schedule according to local and/or country specific guidelines for standard of care; in Japan, paclitaxel was given at doses of 100 mg/m² on Days 1, 8, 15, 22, 29, and 36, followed by 1 week of rest.

^c The docetaxel dose that was used in Japan was 70 mg/m² on Day 1, and then every 3 weeks.

^d In Study 001, the disease types included: colorectal cancer (MSI-H or dMMR); esophageal cancer; gastric cancer; head and neck squamous cell carcinoma; hepatocellular carcinoma; melanoma; nasopharyngeal carcinoma; non-small cell lung cancer; renal cell carcinoma; small cell neuroendocrine carcinoma; triple negative breast cancer; urothelial carcinoma; or other tumors with MSI-H or dMMR

^e In Study 102, the disease types included: bladder cancer, cholangiocarcinoma, cutaneous squamous cell carcinoma, esophageal carcinoma, gastric cancer, gastrointestinal stromal tumor, hepatocellular carcinoma, head and neck squamous cell carcinoma, melanoma, Merkel-cell carcinoma, non-small cell lung cancer, ovarian cancer, renal cell carcinoma, sarcoma, solid tumors with MSI-H or dMMR such as colorectal carcinoma or pancreatic cancer, and triple-negative breast cancer

^f In Study 102, the dose of 200 mg in W1D1, W5+D1 Q3W equates to dosing with 200 mg on Day 1 with an interval of 4 weeks for Cycle 1 and once every 3 weeks for cycles thereafter.

The Applicant's Position:

The primary evidence supporting the efficacy and safety of tislelizumab in patients with advanced or metastatic ESCC is based on pivotal study 302 (RATIONALE-302). Study 302 is a randomized, controlled, open-label, global study assessing the efficacy and safety of tislelizumab in patients with advanced or metastatic ESCC after prior systemic treatment. Study 302 was designed in accordance with international treatment guidelines.

Supportive efficacy evidence for tislelizumab in the treatment of advanced or metastatic ESCC comes from patients enrolled in Studies 001 and 102.

The remaining studies (BGB-A317-203, BGB-A317-204, BGB-A317-208, and BGB-A317-303; hereafter referred to as Studies 203, 204, 208, and 303, respectively) investigated tislelizumab monotherapy in patients with other advanced cancers and provide additional safety and PK data to support this BLA.

The FDA's Assessment:

FDA agrees with Applicant's general description of the clinical trials considered in this review.

8. Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. BGB-A317-302

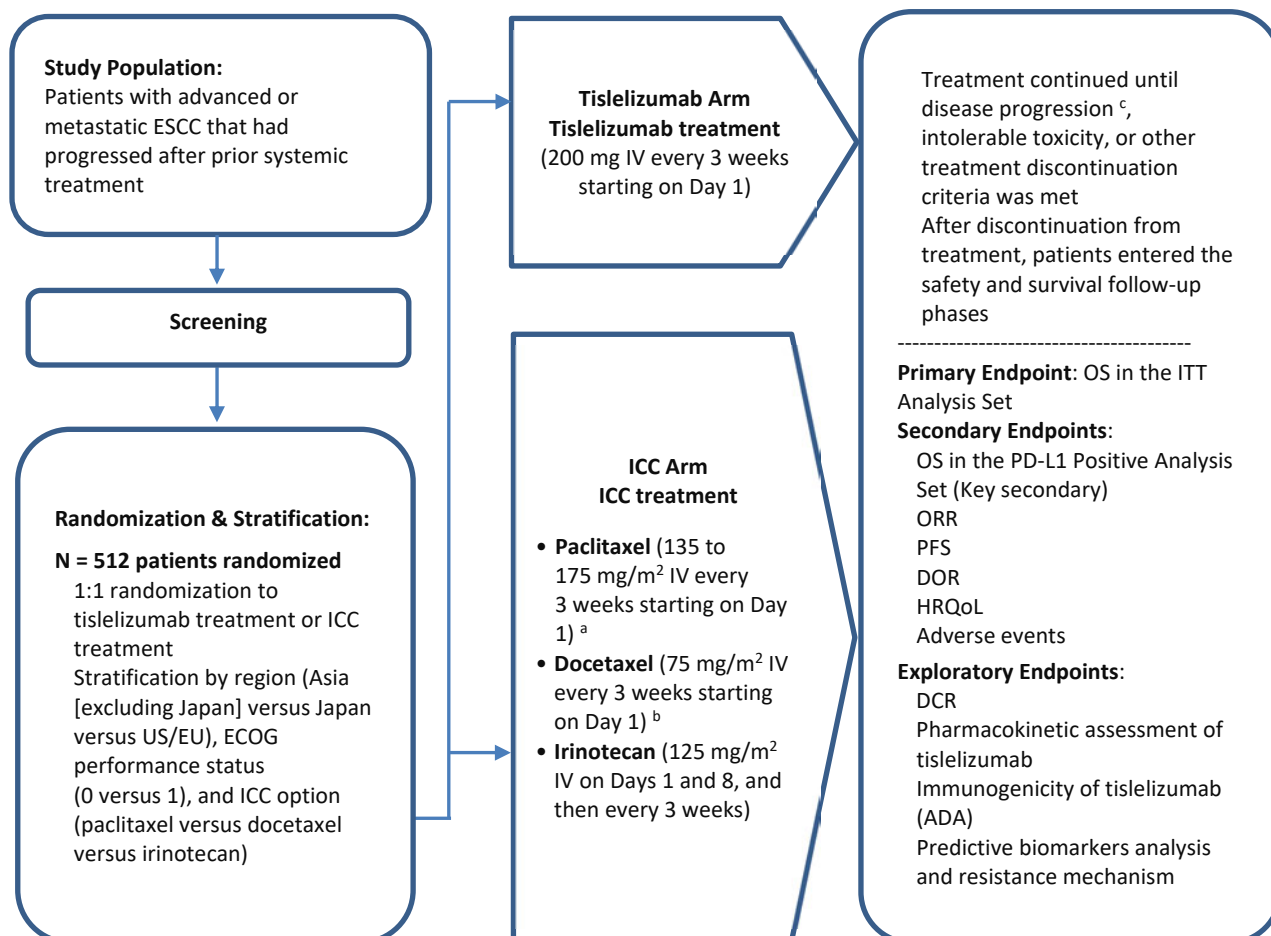
Trial Design

The Applicant's Description:

Study 302 is an open-label, multicenter, randomized Phase 3 study comparing the efficacy and safety of tislelizumab versus ICC (paclitaxel, docetaxel, or irinotecan) in patients with advanced or metastatic ESCC after prior systemic treatment. The study design schematic is presented in Figure 11.

As of the data cutoff date of 01 December 2020, a total of 512 patients were randomized to the Tislelizumab Arm (256 patients) and the ICC Arm (256 patients), with the last patient randomized on 04 March 2020.

Figure 11. BeiGene: Study Schema of Study 302



^a Paclitaxel could also be given at doses of 80 to 100 mg/m² on a weekly schedule according to local and/or country-specific guidelines for standard of care; in Japan, paclitaxel was given at doses of 100 mg/m² on Days 1, 8, 15, 22, 29, and 36, followed by 1 week of rest.

^b The docetaxel dose that was used in Japan was 70 mg/m² on Day 1, and then every 3 weeks.

Trial locations

Belgium, France, Germany, Italy, Japan, Korea, Mainland China, Spain, Taiwan, China, the United Kingdom, and US.

Choice of control group

The regimen of ICC was selected according to international and/or country-specific guidelines (NCCN 2017; Lordick et al 2016) and advice from health authorities to accommodate differences in treatment management among regions. At the time the study was

designed and was initiated, PD-1 antibodies were not approved for ESCC, making ICC, which was standard of care at the time, an acceptable active comparator.

Diagnostic criteria:

Subjects with histologically confirmed diagnosis of advanced or metastatic ESCC that had progressed after prior systemic treatment were enrolled.

Key inclusion criteria included:

- Male or female, aged ≥ 18 years
- Histologically confirmed diagnosis of ESCC.
- Tumor progression during or after first-line systemic treatment for advanced unresectable or metastatic ESCC. NOTE: Patients with disease progression that occurs during treatment or within ≤ 6 months (180 days) of cessation of neoadjuvant/adjuvant treatment (chemotherapy or chemoradiotherapy) are eligible provided all other criteria are met.
- At least 1 measurable/evaluable lesion by RECIST v1.1
- ECOG PS score of 0 or 1 before randomization.
- Adequate organ function

Key exclusion criteria included:

- Prior treatment with ≥ 2 prior lines of systemic treatment for advanced or metastatic ESCC
- Prior therapies targeting PD-1 or PD-L1
- Brain or leptomeningeal metastases that were symptomatic or required treatment
- Apparent tumor invasion of organs adjacent to the esophageal site
- Active autoimmune disease
- A medical condition requiring systemic corticosteroids (> 10 mg daily prednisone or equivalents) or other immunosuppressive medications ≤ 14 days before randomization.

Dose selection:

The adopted dosing regimen of 200 mg once every 3 weeks is supported by the PK profile of tislelizumab characterized using noncompartmental analysis, popPK analysis and E-R analyses.

Details are provided in section [6.2.2.1](#).

Study treatments: Tislelizumab: 200 mg IV on Day 1, given every 21 days

ICC:

- Paclitaxel: 135-175 mg/m² IV on Day 1, given every 21 days. NOTE: Paclitaxel may also be given in doses of 80-100 mg/m² IV on a weekly schedule according to local and/or

country specific guidelines for standard of care. Japan: 100 mg/m² IV on Day 1, 8, 15, 22, 29, and 36, followed by one week of rest

- Docetaxel: 75 mg/m² IV on Day 1, given every 21 days. Japan: 70 mg/m² IV on Day 1, given every 21 days.
- Irinotecan: 125 mg/m² IV on Days 1 and 8, given every 21 days.

Treatment assignment

Patients were enrolled and randomized in a 1:1 ratio stratified by region (Asia [excluding Japan] versus Japan versus US/Europe), ECOG PS score (0 versus 1), and ICC options (paclitaxel, docetaxel or irinotecan). Site personnel accessed the IRT system to randomize patients to treatment arms and to enable study drug dispensation. A block size of four was used in the stratified randomization.

Blinding:

N/A. This was an open-label study

Dose modification, dose discontinuation:

Dose Delay or Modification for Tislelizumab

Dose reduction of tislelizumab was not allowed in this study. Dose delay or interruption of < 12 weeks was permitted. If the administration delay was ≤ 10 days, the delayed dose was administered. If the delay was > 10 days, the delayed dose was omitted in the affected cycle. If a patient was benefiting from study treatment while meeting the discontinuation criteria, continuation of study treatment was permitted upon discussion and agreement with the medical monitor.

Dose Delay or Modification for Chemotherapy

Study treatment-related toxicities were required to be resolved to baseline or Grade 0 to 1 before administering the next dose, except for alopecia or Grade 2 fatigue. A maximum of 2 dose reductions for each chemotherapeutic agent was permitted. Once the dose had been decreased, it remained reduced for all subsequent administrations or was further reduced if necessary. There were no dose escalations in this study. Chemotherapy treatment may have been delayed up to 21 days if the reason for the delay was toxicity/adverse event. All subsequent chemotherapy doses were rescheduled according to the last chemotherapy dose administration date. If considered in the best interest of the patient and consistent with local practice, investigators could have used supportive measures or treatment and/or secondary prophylaxis instead of dose reductions for the next treatment cycle. If any chemotherapy agent was held for > 6 weeks from the anticipated

treatment date, or the dose level -2 was not tolerated, chemotherapy was permanently discontinued.

Administrative structure:

BeiGene, Ltd is the developer of tislelizumab. Study 302 is a global, multicenter study sponsored by BeiGene, Ltd. c/o BeiGene USA, Inc. (San Mateo, CA, USA) and conducted under US IND (b) (4) BeiGene, Ltd. is the holder of this IND, (b) (4) provides CRO services for clinical operations and medical monitoring in Europe, South Korea, Japan and China. BeiGene, Ltd developed the statistical analysis plan (SAP), performed the statistical analyses, and prepared the clinical study report (CSR), which presents the efficacy, safety, and PK data for the planned final analysis, with a data cutoff date of 01 December 2020.

This study included an Independent Data Monitoring Committee (IDMC) that periodically monitored safety data. The IDMC could have also recommended modifications to the study procedures or conduct based on available data. The IDMC consisted of members with pertinent expertise who provided oversight of the study in compliance with applicable regulations, legislation, and associated guidance for the nature of the study.

Procedures and schedule:

Table 12 describes the schedule of events.

Table 12: BeiGene – Study BGB-A317-302 - Schedule of Assessments

Study Phase or Visit	Screening ^a	All Treatment Cycles ^b				End of Treatment ^c	Safety Follow-up ^d	Survival Follow-up
		Cycles 1 to 2			Cycle 3 and Subsequent Cycles			
Assessment Window (Days)	Day -28 to Day -1	Day 1 (± 3)	Day 8 (± 2)	Day 15 (± 2)	Day 1 (± 3)	0 to 7 days	30 ± 7 days after last dose	Every month
Informed consent ^a	x							
Inclusion/exclusion criteria	x							
Randomization	x							
Demographic/medical history/prior medications	x							
Cancer diagnosis and treatment history ^e	x							

Study Phase or Visit	Screening ^a	All Treatment Cycles ^b				End of Treatment ^c	Safety Follow-up ^d	Survival Follow-up
		Cycles 1 to 2			Cycle 3 and Subsequent Cycles			
Assessment Window (Days)	Day -28 to Day -1	Day 1 (± 3)	Day 8 (± 2)	Day 15 (± 2)	Day 1 (± 3)	0 to 7 days	30 ± 7 days after last dose	Every month
Concomitant medications ^f	x	x	x	x	x	x	x	x
Adverse events	x	x	x	x	x	x	x	
Physical examination	x	x			x	x	x	
ECOG performance status	x	x			x	x	x	
Vital signs/weight	x	x	x	x	x	x	x	
12-lead ECG	x	As clinically indicated				x		
HBV and HCV serology	x	As clinically indicated						
Hematology	x	x	x	x	x	x	x	
Serum chemistry	x	x	x	x	x	x	x	
Total CK and CK-MB	x	x	x	x	x	x	x	
Coagulation parameters	x	As clinically indicated				x	x	
Urinalysis	x	As clinically indicated				x	x	
Pregnancy test	x	x			x	x	x	
Thyroid function	x	x			x		x	
Pharmacokinetics		x			x		x	
Anti-tislelizumab antibodies		x			x		x	
Tumor assessment	x (≤ 28 days)	Every 6 weeks for 6 months, then every 9 weeks ⁱ				x		
Tislelizumab administration ^g		x			x			
Chemotherapy administration ^h		x			x			
Archive/fresh tumor tissue collection	x					x (optional)		
Optional blood sample for biomarker analysis		x						
HRQoL assessments		x			Cycles 3 to	x	x	

Study Phase or Visit	Screening ^a	All Treatment Cycles ^b				End of Treatment ^c	Safety Follow-up ^d	Survival Follow-up
		Cycles 1 to 2			Cycle 3 and Subsequent Cycles			
Assessment Window (Days)	Day -28 to Day -1	Day 1 (± 3)	Day 8 (± 2)	Day 15 (± 2)	Day 1 (± 3)	0 to 7 days	30 ± 7 days after last dose	Every month
					6 only			
Survival status								x
Pulmonary function tests	x							
Optical coherence tomography (or equivalent diagnostic test) and visual acuity tests	x	Every 15 weeks ± 7 days				x	x	

- ^a Results of standard-of-care laboratory tests and physical examinations performed before obtaining informed consent and ≤ 7 days before randomization could be used for screening assessments rather than repeating such tests. A fresh tumor biopsy was permitted if no archival tumor tissue was available.
- ^b Cycle 1 treatment was required to be given ≤ 3 business days before randomization. From Cycle 2, there was a 3-day window for all study treatment given on a 21-day cycle unless otherwise noted. There was a 2-day window for treatments given on a weekly schedule.
- ^c If routine laboratory tests (eg, hematology, serum chemistry) were completed ≤ 7 days before the End-of-Treatment Visit, the tests were not required to be repeated. Tumor assessment was not required at the End-of-Treatment Visit, provided that fewer than 6 weeks had passed since the last assessment.
- ^d The End-of-Treatment Visit could be combined with the Safety Follow-up Visit, provided that the end of treatment occurred 30 days (± 7 days) after the last study treatment; the assessments for both visits were required to be performed.
- ^e Included history of treatment for the primary diagnosis, including prior systemic, radiation treatment, and surgical treatment. Radiographic imaging that was performed before study entry could be collected for review by the investigator, as clinically appropriate.
- ^f Concomitant medications included any prescription medications, over-the-counter medications, herbal supplements, and intravenous medications and fluids. All concomitant medications received ≤ 30 days before the first dose of study treatment and 30 days after the last infusion of study treatment were required to be recorded. At subsequent visits, changes to current medications or medications that were used since the last documentation of medications were recorded. Only new anticancer treatment was collected at the Survival Follow-up Visits.

Dietary restrictions/instructions:

N/A. No dietary restrictions.

Concurrent medications:

Please refer to section 8.1.2, subsection “Concurrent medications”.

Treatment compliance:

Please refer to section 8.1.2, subsection “Treatment compliance”.

Rescue medication:

N/A

Subject completion, discontinuation, or withdrawal:

Subjects were considered to have completed the study when they were no longer actively being followed for survival. Subject completion could occur for the following reasons: patient withdrawal of consent, lost to follow-up, death, or study termination by BeiGene, Ltd. After patients had completed the study, no further study procedures or assessments were performed. No patients were replaced, regardless of the reason for study discontinuation or withdrawal.

The FDA’s Assessment:

FDA agrees with the general trial description above. Additional important eligibility criteria were:

- Organ function
 - Absolute neutrophil count ≥ 1500 cells/mm³
 - Platelet count $\geq 100,000$ cells/mm³
 - Hemoglobin ≥ 9 g/dL or ≥ 5.6 mmol/L
 - Estimated glomerular filtration rate ≥ 30 mL/min/1.73 m²
 - Serum total bilirubin ≤ 1.5 x ULN (or < 3 x ULN in patients with Gilbert’s syndrome)
 - Prothrombin time/international normalized ratio ≤ 1.5 x ULN unless the patient was receiving anticoagulant therapy
 - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x ULN (or ≤ 5.0 x ULN in patients with liver metastases)
- Patients with Hepatitis B or infection were eligible if
 - HBV that is inactive/asymptomatic carrier, chronic, or active: HBV DNA < 500 IU/mL (or 2500 copies/mL) at screening. Patients receiving antivirals at screening should have

been treated for > 2 weeks and HBV < 500 IU/mL before randomization and should have continued treatment for ≥ 6 months after study drug treatment discontinuation.

- Patients with detectable HCV RNA and who were receiving treatment at screening were required to remain on continuous, effective antiviral therapy during the study.

Additional exclusion criteria were

- history of gastrointestinal perforation and/or fistula or aorto-esophageal fistula ≤ 6 months before randomization;
- tumor invasion into organs located adjacent to the esophageal disease site (eg, aorta or respiratory tract) at an increased risk of fistula in the study treatment assessed by investigator;
- uncontrollable pleural effusion, pericardial effusion, or ascites requiring frequent drainage (recurrence ≤ 2 weeks of intervention);
- HIV infection;
- standard comorbidities (cardiovascular risk factors, infection, history of pneumonitis, etc) for checkpoint inhibitors therapy.

While AEs reporting continued for up to 30 days after treatment completion, serious imAEs were reported for 90 days after the last dose of tislelizumab.

Study Endpoints

The Applicant's Description:

Primary Endpoint

- OS in the ITT analysis set - defined as the time from the date of randomization until the date of death due to any cause in all randomized patients.

The primary efficacy endpoint was designed according to regulatory guidelines (FDA Guidance on Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, December 2018) and in consultation with the US Food and Drug Administration (FDA), European Medicines Agency (EMA), Center for Drug Evaluation of National Medical Products Administration (NMPA), and Pharmaceuticals and Medical Devices Agency (PMDA). In an advanced or metastatic solid malignancy with a poor prognosis, improvement of overall survival is the most clinically meaningful and robust primary endpoint. As a direct measure of clinical benefit, it provides evidence relevant to patients in each region and country. Adequate sensitivity analyses were predefined in the statistical analysis plan to explore and address the effect of subsequent anticancer treatment and the robustness of overall survival in the study (please refer to the below section "Statistical Analysis Plan and Amendments").

Key Secondary Endpoint:

- OS in the PD-L1 positive analysis set - defined as the time from the date of randomization until the date of death due to any cause in PD-L1 positive population

Overall survival in patients with PD-L1 vCPS $\geq 10\%$ was selected as the key secondary endpoint to explore the predictive role of PD-L1 expression in ESCC. PD-L1 is expressed in tumor and tumor-infiltrating immune cells in ESCC at a prevalence of 18.4% to 82.8% (Guo et al 2017), which may vary by different detecting antibodies, scoring methods, and cutoffs chosen. PD-L1 expression level showed a trend of correlation with the clinical efficacy of anti-PD-1 treatment in multiple studies, including KEYNOTE-181, ATTRACTION-3, and ESCORT (Kojima et al 2020; Kato et al 2019; Huang et al 2020). In these studies, PD-L1 prevalence ranged from 40% to 50%. However, the association between PD-L1 expression and clinical outcomes of tislelizumab treatment in ESCC is not fully understood and therefore further investigated in this study.

Other Secondary Endpoints:

- Overall response rate (ORR) in both the ITT analysis set and the PD-L1 positive analysis set - defined as the proportion of patients who had complete response (CR) or partial response (PR) assessed by the investigator per RECIST v1.1.
- Progression-free survival (PFS) in both the ITT analysis set and the PD-L1 positive analysis set - defined as the time from the date of randomization to the date of first documentation of disease progression assessed by the investigator per RECIST v1.1 or death, whichever occurs first
- Duration of response (DOR) in both the ITT analysis set and the PD-L1 positive analysis set - defined as the time from the first determination of an overall response (first recorded CR or PR) until the first documentation of progression as assessed by the investigator per RECIST v1.1, or death, whichever comes first.
- Health-related quality of life (HRQoL) in both the ITT analysis set and the PD-L1 positive analysis set – defined as changes in the key patient reported outcomes (PROs) endpoints measured by the European Organization for Research on Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C-30) and EORTC Quality of Life Questionnaire-Oesophageal Cancer Module (EORTC QLQ-OES18), and by European Quality of Life 5-Dimension 5-Level Questionnaire (EQ-5D-5L).
- The incidence and severity of adverse events according to NCI-CTCAE v4.03

Exploratory Endpoints

- Disease control rate (DCR) in both the ITT analysis set and the PD-L1 positive analysis set - defined as the proportion of patients who have CR, PR and SD assessed by the investigator per RECIST v1.1
- Pharmacokinetic endpoints: summary of serum concentration of tislelizumab to include but not limited to Ctrough
- Assessments of immunogenicity of tislelizumab to determine the incidence of ADA

The FDA's Assessment:

FDA agrees with the description of the study endpoints above and that an improvement in OS represents a direct measure of clinical benefit.

Statistical Analysis Plan and Amendments

The Applicant's Description:

Analysis Sets

ITT Analysis Set included all randomized patients and was the primary analysis set for all efficacy analyses. Patients were analyzed according to their randomized arms. Patients who died before the randomization but who were inadvertently randomized into the study were excluded from the ITT Analysis Set.

PD-L1-Positive Analysis Set included all randomized patients whose tumor PD-L1 vCPS was $\geq 10\%$ as assessed by Ventana PD-L1 (SP263) CDx Assay.

Per-Protocol (PP) Analysis Set included all randomized patients who received ≥ 1 dose of their assigned study treatment and had no critical protocol deviations that significantly impacted efficacy or safety evaluation.

Safety Analysis Set included all randomized patients who received ≥ 1 dose of study treatment and was the primary analysis set for all safety analyses. Patients were analyzed by actual treatment received.

PK Analysis Set included all patients who received ≥ 1 dose of tislelizumab per the protocol, for whom any postdose PK data were available.

ADA Analysis Set included all patients who received ≥ 1 dose of tislelizumab, had non-missing baseline ADA result, and ≥ 1 postbaseline ADA result.

Efficacy Analyses

The primary and key secondary endpoints were tested sequentially at a 1-sided alpha of 0.025. No statistical inference was planned for the other efficacy and safety analyses; the p-values presented for these analyses were calculated for descriptive purpose only.

Primary Efficacy Endpoint

The primary efficacy endpoint for this study was overall survival in the ITT Analysis Set, defined as the time from the date of randomization to the date of death from any cause. In the absence of death on or before data cutoff date, overall survival was censored either at the date that the patient was last known to be alive or the date of data cutoff, whichever occurred earlier.

Overall survival was compared between the Tislelizumab Arm and the ICC Arm. The null and alternative hypotheses were set as follows:

H_0 : overall survival in the Tislelizumab Arm $\leq$ overall survival in the ICC Arm

H_a : overall survival in the Tislelizumab Arm $>$ overall survival in the ICC Arm

The primary analysis of overall survival was to be performed in the ITT Analysis Set once the targeted number of deaths (approximately 400) was reached. The p-value was obtained from 1-sided log-rank test stratified by selected stratification factors at randomization: ECOG PS score (0 versus 1) and ICC option (paclitaxel versus docetaxel versus irinotecan). The region as the third stratification factor was not included in the analysis due to the potential sparse number of events, in particular, with the small number of patients enrolled from Japan.

The median overall survival with 95% confidence interval (CI), if estimable, was constructed using a generalized Brookmeyer and Crowley method. The cumulative probability of overall survival at 6 and 12 months, if estimable, was calculated and presented with 2-sided 95% CI by using Greenwood's formula.

The treatment effect was estimated by fitting a Cox regression model to the overall survival times including treatment arm as a covariate and was stratified by ICC option and ECOG PS score. From this model, the hazard ratio (HR) of overall survival was estimated and presented with a 2-sided 95% CI.

Secondary Efficacy Endpoints

- Overall Survival (OS) in patients with PD-L1 vCPS $\geq 10\%$: The same statistical methods described in the primary efficacy analysis were applied for the analysis of this key secondary efficacy endpoint.
- Objective Response Rate (ORR): ORR per RECIST v1.1 was tested using Cochran-Mantel-Haenszel (CMH) test adjusting for ECOG PS score, and ICC option in the ITT analysis set and PD-L1 positive analysis set. The common odds ratio for ORR adjusted for strata and its two-sided 95% CIs will be calculated. ORR and difference in ORR as well as Clopper-Pearson 95% CI were calculated.

- Progression-Free Survival (PFS): Similar statistical methods described in the primary efficacy analysis of OS were applied to the PFS analysis. According to the primary censoring rule, PFS were censored in patients with 1) no baseline or any post-baseline tumor assessments and without death within two tumor assessments from randomization; 2) no progression at the time of data cutoff or withdrawal from study; 3) new anticancer treatment started before disease progression; and 4) death or progression after more than one missed tumor assessment.
- Duration of response (DOR): The same censoring rule for PFS primary analysis was applied to DOR. Median of DOR per treatment arm with 95% confidence interval was constructed with a generalized Brookmeyer and Crowley method.
- Health-Related Quality of Life (HRQoL): PRO key endpoints included the global health status/QoL (GHS) and physical function as measured by the EORTC QLQ-C30 and esophageal cancer main symptoms of pain, eating, dysphagia and reflux as measured by EORTC QLQ-OES18. Descriptive analysis (mean [standard deviation], median, range and change of mean scores) for the EORTC QLQ-C30 and the EORTC QLQ-OES18 scales and the EQ-5D-5L VAS were summarized by treatment arm. Time to clinically meaningful worsening for key PRO endpoints were evaluated by treatment arm. All HRQoL measures were summarized in the ITT Analysis Set and the patients with PD-L1 vCPS $\geq 10\%$.

The FDA's Assessment:

FDA agrees with the applicant's presentation of the statistical analysis plan for efficacy analyses. The overall type I error rate of 0.025 (one-sided) was controlled by testing the primary endpoint of OS in the ITT population and the key secondary endpoint of OS in the PDL1 vCPS $\geq 10\%$ patient subpopulation sequentially. According to the study protocol there was no formal interim analysis planned for the primary and key secondary endpoint. Other secondary endpoints of PFS, ORR, DOR and HRQoL were not formally tested with alpha allocation and are considered descriptive only.

Protocol Amendments

The Applicant's Description:

The original global protocol for this study was dated 13 July 2017. All patients were enrolled after the implementation of Protocol Amendment Version 1.0. Key changes to the protocol are summarized below.

Amendment Version 1.0 (07 November 2017)

Evaluation of overall response rate, PFS, and duration of response using immune-related RECIST was removed because the tool had not been validated.

The stratification factors were modified (gender was replaced with ECOG PS score and ICC option) per the request from the US FDA.

Alternative paclitaxel and docetaxel treatment regimens were added to provide Japan-specific regimens per the request from the PMDA.

Clarified that patient who had received ≥ 2 prior systemic treatments for advanced unresectable or metastatic ESCC were excluded.

Management guidance for infusion-related reactions, severe hypersensitivity reactions, flu-like symptoms, and renal function abnormalities were added.

The guidance for the immune-mediated adverse event management was modified and updated.

Amendment Version 2.0 (06 December 2017)

The requirement of treatment beyond radiographic progression was further clarified per the request from the US FDA.

Criteria for dose modification of paclitaxel, docetaxel and irinotecan and permanent discontinuation of chemotherapy regimens were clarified, and dose modifications guidelines for specific adverse events and other toxicities were provided, per the request from the US FDA.

Amendment Version 3.0 (08 November 2018)

CK (creatin kinase) and CK-MB (creatin kinase cardiac muscle isoenzyme) tests and management guidance were added to monitor the risk of myocarditis more closely.

Incorporated the US FDA request of implementing measures to further decrease the potential for viral reactivation: continuous treatment for 6 months after treatment discontinuation was required for patients with detectable HBsAg or HBV DNA; continuous effective antiviral therapy was required for patients who had detectable HCV and were receiving treatment at screening.

The criterion to exclude patients who had a history of anterior organ transplant, including stem cell allograft, was added per the request from the French National Agency for the Safety of Medicines and Health Products (ANSM).

Immune-mediated adverse event management guidelines were updated: “tislelizumab must be permanently discontinued for any onset of Grade 4 or recurrent Grade 3 immune-mediated adverse events.”

A new appendix of “Determining Line of Therapy in ESCC” was added to further clarify the definition of first-line systemic treatment in inclusion criteria, and first line or front-line systemic treatment was defined as “platinum-based regimen.”

Amendment Version 4.0 (20 March 2020)

Updated the statistical estimation of the sample size to increase the sample size from 450 to 500 and increase target number of death events from 336 to 400, with the following consideration: (1) overall survival HR assumption was adjusted from 0.73 to 0.75 based on recently published results of anti-PD-1 therapies in second-line treatment of ESCC and (2) addition of a dropout rate of 5%.

The predefined interim analysis was removed due to differences in survival data maturity among regions leading to the lack of geographically representative population for the analysis, which resulted from the disparity in global enrollment rates.

The overall survival in patients with PD-L1 vCPS $\geq 10\%$ was added as the key secondary endpoint of this study to reflect the clinical relevance and importance of PD-L1 biomarker in ESCC observed in competitors' published data. (NOTE: PD-L1 assessment [by Ventana PD-L1 SP263 CDx Assay] at a central laboratory was not initiated before the key secondary endpoint was added in this protocol amendment, and PD-L1 status of each patient was unknown.)

The FDA's Assessment:

FDA agrees with the summary of significant global protocol amendments. Of note, all but 3 patients were enrolled before Amendment 4.

8.1.2. Study Results

Compliance with Good Clinical Practices

Data:

The protocol, any amendments, and informed consent form were reviewed and approved by the Institutional Review Boards/Independent Ethics Committees in conformance with the Good Clinical Practice (GCP) and applicable regulatory requirements. To ensure compliance with GCP and all applicable regulatory requirements, BeiGene, Ltd or designee conducted quality assurance audit(s).

The Applicant's Position:

A total of 07 sites were audited by independent quality assurance (QA) team from (b) (4) with BeiGene involvement in the audit plan and report review. No critical findings, which had a direct and significant impact on patient safety and/or data integrity, were noted. This study was conducted in accordance with BeiGene, Ltd procedures, which comply with the principles of GCP, ICH guidelines, the Declaration of Helsinki, and applicable local regulatory requirements.

The FDA's Assessment:

FDA notes BeiGene's statement in Section 9.6 of the study report that the study was conducted

according to principles of Good Clinical Practice as described in the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use guidelines. BeiGene states that to ensure compliance with Good Clinical Practice and all applicable regulatory requirements, BeiGene or designee conducted quality assurance audits. Audit certificates are provided in Appendix 16.1.8 of the CSR.

Financial Disclosure

Data:

Financial Interest was not disclosed by 12 investigators who did not complete the Financial Disclosure Form. Attempts were made to contact the investigators to obtain the financial disclosure information, and the applicant will provide the missing forms to FDA as soon as they will come available. The 12 investigators with no Financial Disclosure Forms enrolled a total of (b) (6) patients across 5 different sites; no single investigator enrolled more than (b) (6) patients.

Financial interest was disclosed by 3 investigators who enrolled patients in Study 302. Two of the three investigators with disclosed financial interest were sub-investigators (each one for a different clinical site) involved in the screening and recruiting of a total of (b) (6) patients each; (b) (6) patients in the Tislelizumab Arm and (b) (6) patients in ICC Arm at this site. For both sub-investigators, the site first patient dose was on (b) (6), and last patient last dose was on (b) (6). All (b) (6) patients experienced the end of study before (b) (6). All (b) (6) patients provided fewer than 2 months of clinical and laboratory data, all of which was source verified.

The third investigator with disclosed financial interest was a principal investigator who screened (b) (6) patients and enrolled (b) (6) patients: (b) (6) patients in the Tislelizumab Arm and (b) (6) patients in ICC Arm. The first patient dose was (b) (6), and last patient last dose was (b) (6). (b) (6) patients completed the end of study in (b) (6) and (b) (6) patients completed the end of study in (b) (6). One site audit was performed in (b) (6) and all data were source verified.

The Applicant's Position:

BeiGene has determined that the disclosed financial interest had minimal potential to bias the outcome of the study.

The FDA's Assessment:

In accordance with 21 CFR 54, the Applicant submitted information for all but 12 Principal Investigators and Sub-investigators who participated in Study 302 (b) (6) in Spain and 11 in the United Kingdom) and did not complete financial disclosure forms. In many of these cases, the investigator had left the institution and attempts to reach them were unsuccessful. As noted above, 3 investigators for Study 302 did disclose financial interests (provided in Module 1.3.4)

which were reviewed. Of these, 2 were sub-investigators at the same site (not at different sites, as stated by the Applicant, above).

- One investigator (principal investigator for site (b) (6)) received \$32,663 from BeiGene for conference/meetings and travel reimbursements. This site enrolled (b) (6) patients ((b) (6) randomized to the tislelizumab arm).
- One investigator (sub-investigator at site (b) (6)) received \$29,025 from BeiGene for conference/meetings and travel reimbursements. This site enrolled (b) (6) patients.
- One investigator (sub-investigator at site (b) (6)) received \$24,768 from BeiGene for conference/meetings and travel reimbursements. This site enrolled (b) (6) patients.

Regardless, upon review of the information provided about these investigators and in the context of this study that randomized 512 patients and had a primary endpoint of overall survival, FDA concluded that these disclosed financial interests (concerning (b) (6) of the studied population) are not likely to have had a material impact on the conduct of Study 302 and conclusions derived from this clinical study. Sensitivity analysis removing the (b) (6) patients from sites (b) (6) and (b) (6) did not decrease the magnitude of treatment effect between the arms (the stratified OS HR excluding these (b) (6) patients was 0.68 [95% CI: 0.56, 0.83]).

Patient Disposition

Data:

A total of 512 patients were randomized 1:1 to receive tislelizumab or ICC (256 patients each) in the ITT Analysis Set (Table 13). More patients were randomized but not treated in the ICC Arm (16 patients) than in the Tislelizumab Arm (1 patient), possibly due to the open-label nature of the study.

Over 90% of patients discontinued treatment by the data cutoff date, most frequently due to radiographic progression (Table 13). More patients in the ICC Arm discontinued treatment due to adverse events or withdrawal by the patient.

Overall, approximately 80% of patients discontinued the study due to death. Withdrew by patient and lost to follow-up were more common from the ICC Arm (6.3%) than the Tislelizumab Arm (2.0%). Approximately 20% of patients in the Tislelizumab Arm and 10% of patients in the ICC Arm remained on study as of the data cutoff date.

The median duration of study follow-up was 8.5 months in the Tislelizumab Arm (range: 0.2 to 31.7 months) and 5.8 months in the ICC Arm (range: 0.0 to 30.8 months).

Table 13. BeiGene: Patient Disposition and Reasons for Discontinuation (Study 302) (ITT Analysis Set)

	Tislelizumab (N = 256) n (%)	ICC (N = 256) n (%)	Total (N = 512) n (%)
Number of Patients Randomized	256 (100.0)	256 (100.0)	512 (100.0)
Patients Randomized, but Not Treated	1 (0.4)	16 (6.3)	17 (3.3)
Primary Reason for Not Treated			
Adverse Event	0 (0.0)	2 (0.8)	2 (0.4)
Withdrawal by Subject	0 (0.0)	11 (4.3)	11 (2.1)
Other	1 (0.4)	3 (1.2)	4 (0.8)
Number of Patients Treated	255 (99.6)	240 (93.8)	495 (96.7)
Number of Patients Discontinued From Treatment	239 (93.4)	239 (93.4)	478 (93.4)
Primary Reason for Study Drug Discontinuation			
Radiographic Progression	177 (69.1)	133 (52.0)	310 (60.5)
Adverse Event	31 (12.1)	44 (17.2)	75 (14.6)
Clinical Progression	23 (9.0)	25 (9.8)	48 (9.4)
Withdrawal by Subject	6 (2.3)	29 (11.3)	35 (6.8)
Non Compliance With Study Drug	0 (0.0)	1 (0.4)	1 (0.2)
Physician Decision	0 (0.0)	5 (2.0)	5 (1.0)
Other	2 (0.8)	2 (0.8)	4 (0.8)
Number of Patients Remained on Treatment	16 (6.3)	1 (0.4)	17 (3.3)
Number of Patients Discontinued From Study	202 (78.9)	229 (89.5)	431 (84.2)
Primary Reason for Study Discontinuation			
Subject Death	197 (77.0)	213 (83.2)	410 (80.1)
Related to COVID-19	1 (0.4)	1 (0.4)	2 (0.4)
Voluntary Withdrawal by Subject	5 (2.0)	14 (5.5)	19 (3.7)
Subject Lost to Follow-up	0 (0.0)	2 (0.8)	2 (0.4)
Number of Patients Remained on Study	54 (21.1)	27 (10.5)	81 (15.8)
Study Follow-up Duration (months)^a			
n	256	256	512
Mean (SD)	10.09 (7.423)	7.59 (6.154)	8.84 (6.926)
Median	8.49	5.80	6.88
Q1, Q3	3.93, 14.90	2.81, 10.86	3.43, 12.65
Min, Max	0.2, 31.7	0.0, 30.8	0.0, 31.7

Source: ADSL. Data cutoff: 01DEC2020. Data extraction: 15JAN2021.

Percentages were based on N.

^a Study follow-up duration is defined as the duration from the randomization date to the study discontinuation date (due to death, consent withdrawal, lost to follow-up etc.) or to the cutoff

date if a patient is still ongoing.

The Applicant's Position:

Study 302 was conducted in accordance with international clinical research guidelines (NCCN 2017). The data cutoff occurred at the pre-determined point of at least 400 deaths. The study met its accrual target, by accumulating sufficient death events (ie 410) to allow endpoint assessment.

Nearly all patients were no longer receiving treatment as of the data cutoff. A higher proportion of patients in the Tislelizumab Arm discontinued the treatment due to radiographic or clinical progression than in the ICC Arm, due at least in part to the higher proportion of patients in the ICC Arm who discontinued for an AE or voluntarily withdrew from the treatment. The primary reason for study discontinuation in both arms was death, the primary endpoint. More patients on the Tislelizumab Arm remained on study as of the data cutoff, consistent with the treatment effect observed. More patients in the ICC arm discontinued the study before their first dose of study treatment, mainly due to patient decision, suggesting a desire for treatment other than the ICC to which they were assigned.

The FDA's Assessment:

Although FDA generally agrees with the patient disposition summary presented above, FDA's analysis of the ADSL dataset shows slight differences in the reasons for treatment discontinuation, summarized in Table 14.

Table 14. RATIONALE-302: Reasons for treatment discontinuation

Reason for discontinuation	Tislelizumab (n: 256); n (%)	ICC (n: 256); n (%)
Disease progression (radiographic or clinical)	200 (78)	158 (62)
Adverse events	31 (12)	46 (18)
Withdrawal by subject	6 (2)	40 (16)
Other	3 (1)	5 (2)
Physician's decision	0	5 (2)
Non-compliance	0	1 (<1)

Most patients who discontinued treatment discontinued due to progression of disease (69% of the total ITT population when combining radiographic and clinical progression) but there is a 16% difference between arms, which can be explained by an increased incidence of treatment discontinuation and withdrawal by patients in the ICC arm. The specific reasons underlying "withdrawal by subject" (2% vs 11% in the tislelizumab and ICC arms, respectively) were not uniformly captured but, based on the small number documented in the narratives, appear to be

AE-related (e.g. following a series of different AEs in a given patient). Although a similar number of patients (50% and 51% in the tislelizumab and ICC arms respectively) received post-study anticancer treatment, 22% patients in the ICC arm (vs. 4% in the tislelizumab arm) went on to receive monoclonal antibody therapy (mostly other immune checkpoint inhibitors), which may have had an impact on withdrawal of patients from chemotherapy upon toxicity.

Protocol Violations/Deviations

Data:

A total of 60 patients (11.7%) in the ITT Analysis Set, including 33 patients (12.9%) in the Tislelizumab Arm and 27 patients (10.5%) in the ICC Arm, had ≥ 1 important protocol deviation. The percentage of patients with ≥ 1 important protocol deviation was similar in the 2 arms (Table 15).

The most common important protocol deviations were those concerning informed consent (21 patients [4.1%]). A total of 15 patients (2.9%) were not re-consented in a timely manner; among them, 9 patients were re-consented with the updated Informed Consent Form (ICF) after the discontinuation from the treatment (Tislelizumab: 4 patients; ICC: 5 patients). Two patients (0.4%) reported missing signature for ICF protocol deviations at study entry. For both patients, the signatures were signed by the investigator after the patients orally consented to participate in the study. Corrective actions were implemented immediately to obtain re-consent/signature from the patients.

Table 15. BeiGene: Summary of Important Protocol Deviations (ITT Analysis Set)

Classification	Tislelizumab (N = 256) n (%)	ICC (N = 256) n (%)	Total (N = 512) n (%)
Patients With at Least One Important Protocol Deviation	33 (12.9)	27 (10.5)	60 (11.7)
Informed Consent	13 (5.1)	8 (3.1)	21 (4.1)
AE/SAE	11 (4.3)	10 (3.9)	21 (4.1)
Inc or Excl Criteria	5 (2.0)	3 (1.2)	8 (1.6)
Disallowed Medications	3 (1.2)	1 (0.4)	4 (0.8)
Procedures/Tests	2 (0.8)	1 (0.4)	3 (0.6)
Concomitant Therapy	1 (0.4)	2 (0.8)	3 (0.6)
IP Admin/Study Treatment	1 (0.4)	1 (0.4)	2 (0.4)
Withdrawal Criteria	0 (0.0)	3 (1.2)	3 (0.6)

Source: Post-Text Table 14.1.1.4. Data cutoff: 01DEC2020. Data extraction: 15JAN2021.

Percentages were based on N.

A patient was counted only once within each category but may be counted in multiple categories.

Critical protocol deviations are defined as a subset of important protocol deviations that significantly impact efficacy and safety analyses. In the ITT Analysis Set, 11 patients (2.1%)

were identified as having ≥ 1 critical protocol deviation (Table 16). The most common critical protocol deviations were those concerning disallowed medications (Tislelizumab: 3 patients [1.2%]; ICC: 1 patient [0.4%]), inclusion or exclusion criteria (Tislelizumab: 1 patient [0.4%]; ICC: 2 patients [0.8%]) and withdrawal criteria (Tislelizumab: 0 patients; ICC: 3 patients [1.2%]).

Table 16. BeiGene: Summary of Critical Protocol Deviations (ITT Analysis Set)

Classification	Tislelizumab (N = 256) n (%)	ICC (N = 256) n (%)	Total (N = 512) n (%)
Patients With at Least One Critical Protocol Deviation	5 (2.0)	6 (2.3)	11 (2.1)
Disallowed Medications	3 (1.2)	1 (0.4)	4 (0.8)
IP Admin/Study Treatment	1 (0.4)	0 (0.0)	1 (0.2)
Inc or Excl Criteria	1 (0.4)	2 (0.8)	3 (0.6)
Withdrawal Criteria	0 (0.0)	3 (1.2)	3 (0.6)

Source: Post-Text Table 14.1.1.4. Data cutoff: 01DEC2020. Data extraction: 15JAN2021.

Percentages were based on N.

Deviation categories are not mutually exclusive. Multiple deviations within the same category are counted once per patient.

The Applicant's Position:

Only 2.1% of patients enrolled in Study 302 had critical protocol deviations which were balanced across the arms. Data of patients with critical protocol deviations were excluded from a sensitivity analysis of OS based on the PP Analysis Set.

The FDA's Assessment:

FDA agrees with the results as presented in Table 15 and Table 16. Irrespective of small differences between arms, because of the nature of these protocol deviations, they are unlikely to have had an impact on the observed efficacy outcomes or assessment of the safety of tislelizumab for the proposed indication.

Table of Demographic Characteristics

Data:

In the ITT Analysis Set, demographics and baseline characteristics were balanced between the 2 arms, except for the PD-L1 expression status. The median age of all randomized patients was 62.0 years (range: 35 to 86 years), with 194 patients (37.9%) ≥ 65 years of age. Most patients were male (Tislelizumab: 84.8%; ICC: 84.0%) and had a baseline ECOG PS score of 1 (Tislelizumab: 74.2%; ICC: 76.6%). In each arm, 26.6% and 24.6% of (Tislelizumab Arm and the ICC Arm, respectively) had never smoked (Table 17).

Most patients in the study were Asian (79.7% [Tislelizumab: 78.5%; ICC: 80.9%]) or White or Caucasian (18.9% [Tislelizumab: 20.7%; ICC: 17.2%]). Most of the Asian patients were Chinese (63.3%) (Table 17).

A total of 157 patients (30.7% in the ITT Analysis Set; 89 [34.8%] in the Tislelizumab Arm and 68 [26.6%] in the ICC Arm) had a PD-L1 expression status of vCPS $\geq$ 10%. There were some imbalances in baseline PD-L1 expression status between the two arms, and sensitivity analyses were conducted. Results showed that the imbalance in baseline PD-L1 expression status had little impact on the estimate of the treatment effect on the primary analysis of OS (please refer to the below section “Efficacy Results – Primary Endpoint (Including Sensitivity Analyses”).

In addition, 19.3% of patients overall had missing PD-L1 status; this was balanced across the 2 arms.

Table 17. BeiGene: Summary of Demographic and Baseline Characteristics (ITT Analysis Set)*

Parameter	Tislelizumab (N = 256)	ICC (N = 256)	Total (N = 512)
Age (years)			
n	256	256	512
Mean (SD)	61.4 (8.43)	61.6 (8.01)	61.5 (8.21)
Median	62.0	63.0	62.0
Min, Max	40, 86	35, 81	35, 86
Age Group, n (%)			
<65 years	157 (61.3)	161 (62.9)	318 (62.1)
$\geq$ 65 years	99 (38.7)	95 (37.1)	194 (37.9)
Gender, n (%)			
Female	39 (15.2)	41 (16.0)	80 (15.6)
Male	217 (84.8)	215 (84.0)	432 (84.4)
Race, n (%)			
Asian	201 (78.5)	207 (80.9)	408 (79.7)
Chinese	161 (62.9)	163 (63.7)	324 (63.3)
Japanese	25 (9.8)	25 (9.8)	50 (9.8)
Korean	15 (5.9)	16 (6.3)	31 (6.1)
Asian Indian	0 (0.0)	3 (1.2)	3 (0.6)
White or Caucasian	53 (20.7)	44 (17.2)	97 (18.9)
Not Reported ^a	1 (0.4)	0 (0.0)	1 (0.2)
Unknown	1 (0.4)	2 (0.8)	3 (0.6)
Black or African American	0 (0.0)	2 (0.8)	2 (0.4)
Other	0 (0.0)	1 (0.4)	1 (0.2)
Ethnicity, n (%)			
Not Hispanic or Latino	252 (98.4)	252 (98.4)	504 (98.4)
Hispanic or Latino	2 (0.8)	2 (0.8)	4 (0.8)
Not Reported ^b	1 (0.4)	0 (0.0)	1 (0.2)

Parameter	Tislelizumab (N = 256)	ICC (N = 256)	Total (N = 512)
Unknown	1 (0.4)	2 (0.8)	3 (0.6)
ECOG Status, n (%)			
0	66 (25.8)	60 (23.4)	126 (24.6)
1	190 (74.2)	196 (76.6)	386 (75.4)
BMI (kg/m ²)			
n	254	256	510
Mean (SD)	21.27 (3.4)	21.62 (3.6)	21.45 (3.5)
Median	21.06	21.15	21.10
Min, Max	14.0, 37.7	14.3, 33.1	14.0, 37.7
PD-L1 Status, n (%)			
vCPS $\geq$ 10%	89 (34.8)	68 (26.6)	157 (30.7)
vCPS $<$ 10%	116 (45.3)	140 (54.7)	256 (50.0)
Missing	51 (19.9)	48 (18.8)	99 (19.3)
Smoking Status, n (%)			
Never	68 (26.6)	63 (24.6)	131 (25.6)
Former	162 (63.3)	159 (62.1)	321 (62.7)
Current	26 (10.2)	33 (12.9)	59 (11.5)
Missing	0 (0.0)	1 (0.4)	1 (0.2)
Alcohol Consumption, n (%)			
Never	75 (29.3)	73 (28.5)	148 (28.9)
Former	146 (57.0)	151 (59.0)	297 (58.0)
Current	34 (13.3)	31 (12.1)	65 (12.7)
Missing	1 (0.4)	1 (0.4)	2 (0.4)

Source: Post-Text Table 14.1.2.1. Data cutoff: 01DEC2020. Data extraction: 15JAN2021.

Percentages were based on N.

PD-L1 positive is defined as vCPS $\geq$ 10%, PD-L1 negative is defined as vCPS $<$ 10%, Missing refers to the patients without sample collection or not evaluable at baseline.

^a 3 patients refused to report race and were entered with race of “unknown” by the site.

^b 3 patients refused to report ethnicity and were entered with ethnicity of “unknown” by the site.

The Applicant’s Position:

Demographics and baseline characteristics were similar between the tislelizumab and ICC treated patients, which represent characteristics of the broader ESCC patient population (SEER 2021). Sensitivity analyses found little impact of the slight imbalance in PD-L1 expression status between arms on the estimate of treatment effect. Demographic and baseline characteristics were generally balanced between the two arms in the Asian and Europe/North America subgroup and were similar between the Asian and Europe/North America subgroups with some regional variations.

The FDA's Assessment:

FDA agrees with Applicant's general demographics summary, above. The two arms were balanced overall with the exception of a higher percentage of patients in the tislelizumab arm having PD-L1 expression $\geq 10\%$ (which could favor the tislelizumab arm), as noted above. The age of patients enrolled in Study 302 was slightly younger than the overall population of patients with esophageal cancer in the US. The BMI of patients appeared lower than the general BMI of adults in the US; however, mean/median BMI data for US patients with esophageal cancer are not available. Of note, although a key secondary endpoint, ascertainment of PD-L1 expression status is missing in 19% of patients. As the trial was enrolled mostly in Asia, race and ethnicity differ from the US population suffering from ESCC. However (see conclusions on effectiveness), race and ethnicity do not appear to have an impact on prognostic factors in ESCC.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Data:

Comorbidities at Baseline:

Most patients (468 patients [91.4%]) in the ITT Analysis Set had multiple comorbidities at baseline. The most frequently comorbidities (by MedDRA System Organ Class (SOC)) were comparable in the 2 arms and included gastrointestinal disorders (Tislelizumab and ICC: 35.5% each), vascular disorders (Tislelizumab: 35.2%; ICC: 34.0%), and metabolism and nutrition disorders (Tislelizumab: 26.6%; ICC: 29.7%).

Disease History and Characteristics:

Overall, disease history of patients was similar between the 2 arms, except for metastatic diagnosis at study entry (Table 18). Over 95% of patients had metastatic disease at study entry (Tislelizumab: 98.0%; ICC: 92.2%), the remaining patients (4.9%) had locally advanced disease at study entry (Tislelizumab: 2.0%; ICC: 7.8%). The median sum of diameters of the target lesions, as assessed by the investigator, were similar in the 2 arms; 42.0 mm (range: 10.0 to 261.0 mm) for the tislelizumab Arm and 42.00 mm (range: 10.0 to 238.0 mm) for the ICC Arm. The location of target and nontarget lesions at study entry in the 2 arms was similar, and the most commonly reported distant metastatic visceral organs were lung (Tislelizumab: 116 [45.3%]; ICC: 119 [46.5%]), liver (Tislelizumab: 76 [29.7%]; ICC: 69 [27.0%]), and bone (Tislelizumab: 30 [11.7%]; ICC: 32 [12.5%]).

Table 18. BeiGene: Disease History and Characteristics at Study Entry (ITT Analysis Set)

Description	Tislelizumab (N = 256)	ICC (N = 256)	Total (N = 512)
Number of Patient With Metastatic Diagnosis at Study Entry, n (%)			
Yes	251 (98.0)	236 (92.2)	487 (95.1)
No	5 (2.0)	20 (7.8)	25 (4.9)
Time from Metastatic Diagnosis to Study Entry (months)			
n	251	236	487
Mean (SD)	6.7 (6.6)	7.1 (6.8)	6.9 (6.7)
Median	5.3	5.4	5.4
Min, Max	0.2, 43.5	0.2, 53.0	0.2, 53.0
Prior Systemic Therapy, n (%)			
Chemotherapy	94 (36.7)	101 (39.5)	195 (38.1)
Chemo-Radiotherapy	161 (62.9)	155 (60.5)	316 (61.7)
Other	1 (0.4)	0 (0.0)	1 (0.2)
Primary Site of Esophageal Cancer at Diagnosis, n (%)			
Cervical	6 (2.3)	4 (1.6)	10 (2.0)
Upper	42 (16.4)	49 (19.1)	91 (17.8)
Middle	107 (41.8)	86 (33.6)	193 (37.7)
Lower	68 (26.6)	86 (33.6)	154 (30.1)
Overlapping Lesions	11 (4.3)	9 (3.5)	20 (3.9)
Esophagus NOS	22 (8.6)	22 (8.6)	44 (8.6)
Histologic Grade at Diagnosis, n (%)			
Gx - Grade cannot be assessed	19 (7.4)	14 (5.5)	33 (6.4)
G1 - Well differentiated	23 (9.0)	16 (6.3)	39 (7.6)
G2 - Moderately differentiated	86 (33.6)	97 (37.9)	183 (35.7)
G3 - Poorly differentiated	49 (19.1)	58 (22.7)	107 (20.9)
Not Done	79 (30.9)	71 (27.7)	150 (29.3)
Target Lesions Sum of Diameter by Investigator (mm)			
n	237	246	483
Mean (SD)	49.3 (32.3)	49.3 (32.3)	49.3 (32.3)
Median	42.0	42.0	42.0
Min, Max	10.0, 261.0	10.0, 238.0	10.0, 261.0
Target/Non-Target Lesion Location at Study Entry, n (%) ^a			
Lymph nodes	186 (72.7)	192 (75.0)	378 (73.8)
Lung	116 (45.3)	119 (46.5)	235 (45.9)
Esophagus	109 (42.6)	107 (41.8)	216 (42.2)
Liver	76 (29.7)	69 (27.0)	145 (28.3)
Bone	30 (11.7)	32 (12.5)	62 (12.1)

Source: Post-Text Table 14.1.3.1. Data cutoff: 01DEC2020. Data extraction: 15JAN2021.

Percentages were based on N.

Study Entry date referred to randomization date in this study.

^a A patient was counted only once within each category but may be counted in multiple categories.

In the 3 PD-L1 subgroups, patient-reported disease history was similar between all 3 subgroups and between the 2 arms within each PD-L1 subgroup. The disease history profile was balanced between the Asia and the Europe/North America subgroups, and between the 2 arms within each region.

Prior Anticancer Systemic Therapies:

Nearly all patients had received 1 prior line of systemic therapy, with 2 patients (1 patient in each arm) whose prior systemic anticancer therapy did not meet the definition of a line of systemic therapy per protocol. Both cases were identified as important protocol deviations. .

Among the 510 patients who received 1 prior line of systemic treatment per protocol, 16.2% received neoadjuvant/adjuvant treatment as first-line systemic therapy (tislelizumab: 19.9%; ICC: 12.5%) and 11.3% received definitive chemoradiotherapy (tislelizumab: 10.2%; ICC: 12.5%) as first-line systemic therapy.

The Applicant's Position:

Overall, comorbidities at baseline, disease history, and prior anticancer systemic therapies were similar between the 2 arms, and representative of the target population. Together with the demographic characteristics, patients characteristics in study 302 were similar to those of patients in recently completed studies, that enrolled patients with ESCC for second-line treatment ([Kojima et al 2020](#); [Kato et al 2019](#); [Huang et al 2020](#)), with a few minor variations due to the difference in the regional distribution and the composition of histological types of tumors in the enrolled populations.

Baseline characteristics (including prior anticancer therapies) had few regional variations. Compared with patients in the Asia subgroup, the Europe/North America subgroup had a lower proportion of patients who had undergone prior surgery for ESCC, and a higher proportion of patients who had received prior definitive chemoradiotherapy. The regional variations were similar with that observed in a retrospective study comparing clinicopathologic features of Eastern and Western populations ([Zhang et al 2015](#)).

The FDA's Assessment:

FDA notes the disease characteristics described above and agrees that the 2 arms were generally

balanced with the exception of a higher percentage of patients in the tislelizumab arm having metastatic disease at study entry (which could favor the ICC arm). Regarding prior therapy, almost all patients (1 protocol deviation per arm) received prior systemic therapy.

Although the chemotherapy regimens received were generally comparable between study regions, there were regional differences. Based on the clinical study report (CSR), the prior systemic therapy included the following drugs based on region:

- Asia:
 - 97% platinum (58% cisplatin; 30% nedaplatin)
 - 62% taxane
 - 45% fluoropyrimidine
- North America/Europe
 - 98% platinum (40% oxaliplatin; 37% cisplatin; 26% carboplatin)
 - 81% fluoropyrimidine
 - 28% taxane

Although there were regional differences in the chemotherapy regimen used, almost all patients (97%) patients received a platinum doublet prior to enrolling in Study 302 and, thus, results from the Study 302 population are relevant to the patient populations in North America and Europe.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data:

Treatment Compliance:

All study drugs were administered at the study site under the supervision of the study staff. Compliance was assessed by periodic reviews of study drug administration data, study drug accountability records, and source documents reflecting the patient's medical care. Summaries of the study treatment exposure and dosing data are presented in Section 8.2.2 Overall Exposure. The results of duration of exposure and number of cycles received were in line with the results of median PFS and anti-tumor response, suggesting a good treatment compliance to the protocol requirement. The median relative dose intensity was 100% and 89.4% for the tislelizumab and the ICC, respectively.

Concomitant Medications:

Permitted Concomitant Therapy

Most concomitant medications and therapies were allowed if deemed necessary in keeping with the local standard of medical care at the discretion of the investigator for the supportive care (eg, antiemetics, antidiarrheals, pain medications, and nutritional support).

Therapies Excluded During Tislelizumab Treatment

The following medications were prohibited or restricted at the time of screening and during the administration of tislelizumab:

- Immunosuppressive agents (except to treat a drug-related adverse event)
- Systemic corticosteroids > 10 mg daily (prednisone or equivalent), except to treat or control a drug-related adverse event or for short-term use as prophylactic treatment
- Live vaccines ≤ 28 days before the first dose of tislelizumab and 60 days after the last dose of tislelizumab
- Herbal remedies with immune-stimulating properties (eg, mistletoe extract) or that were known to potentially interfere with liver or other major organ functions (eg, hypericin). Patients were required to notify the investigator of all herbal remedies used during the study.

Therapies Excluded During Investigator-Chosen Chemotherapy Treatment

- Caution was exercised for patients receiving paclitaxel concomitantly with substrates, inhibitors, or inducers of CYP2C8 or CYP3A4. The metabolism of paclitaxel is catalyzed by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. Potential interactions between paclitaxel, a substrate of CYP3A4, and protease inhibitors, which were substrates and/or inhibitors of CYP3A4, were not evaluated in clinical studies.
- Patients receiving docetaxel were required to avoid concomitant use of strong inhibitors of CYP3A4; however, if strong inhibitors of CYP3A4 could not be avoided, the docetaxel dose was reduced per the product label.
- Strong CYP3A4 inducers were not allowed to be administered with irinotecan unless there were no therapeutic alternatives. Strong CYP3A4 inhibitors and UGT1A1 inhibitors or both CYP3A4 and UGT1A1 inhibitors were not allowed when patients were treated with irinotecan unless there were no therapeutic alternatives.

Therapies Excluded During All Study Treatment

Concurrent antineoplastic therapy (eg, chemotherapy, hormonal therapy, immunotherapy, or standard or investigational agents [including Chinese herbal medicine and Chinese patent medicines] for the treatment of cancer) and extensive radiation therapy (except for local, palliative radiotherapy) were prohibited or restricted at the time of screening and during the administration of study treatment. Palliative (limited-field) radiation therapy is permitted, but only for pain control or prophylaxis of bone fracture to sites of bone disease present at baseline. During the study, surgical procedures required during study participation were reported as treatments for adverse events and patients were required to avoid abuse of alcohol and other drugs.

A total of 487 patients (98.4%) received concomitant medications on study (Tislelizumab: 97.6%; ICC: 99.2%). The concomitant medications most commonly received by patients in both

arms included proton pump inhibitors (54.1% versus 70.4%), glucocorticoids (36.9% versus 72.5%), unspecified herbal and traditional medicine (32.2% versus 32.1%), and natural opium alkaloids (31.4% versus 31.7%). A total of 90 patients (35.3%) in the tislelizumab Arm and 173 patients (72.1%) in the ICC Arm received concomitant systemic corticosteroids. More patients in the tislelizumab Arm used systemic corticosteroids for adverse events (24.3% versus 15.8%), and more patients in the ICC Arm used systemic corticosteroids for prophylaxis (12.5% versus 63.8%). A total of 35 patients (13.7%) received systemic corticosteroids for the treatment of imAEs. No other immunosuppressive drugs were used by any patient to treat imAEs in this study. A total of 23 patients received thyroid hormone for the treatment of imAEs, and all were in the Tislelizumab Arm.

Rescue Medication

No rescue medications were used or needed in Study 302.

The Applicant's Position:

Overall, the drug exposure results showed a good treatment compliance of both tislelizumab and ICC, and the concomitant treatments administered were representative of those commonly prescribed for patients in the target population and were not expected to have impacted study results.

The FDA's Assessment:

FDA agrees with the Applicant's general assessment above. FDA concurs with the Applicant's data. Although it is stated above that immune suppressive regimens and steroids were restricted or prohibited during tislelizumab treatment, corticosteroids were recommended and used for the management of imAEs in the tislelizumab arm. Other immunosuppressive drugs (e.g. mycophenolate) were not used in Study 302.

Efficacy Results – Primary Endpoint (Including Sensitivity/Supportive Analyses)

Data:

Primary Efficacy Endpoint: Overall Survival in the ITT Analysis Set

Tislelizumab demonstrated a statistically significant and clinically meaningful improvement in OS versus ICC in patients with advanced or metastatic ESCC with disease progression after prior systemic treatment.

With 410 death events (80.1% of all patients randomized) reported, the stratified HR of OS was 0.70 (95% CI: 0.57 to 0.85) with 1-sided p-value of 0.0001, indicating a 30% reduction in the risk of death events in the Tislelizumab Arm compared with the ICC Arm. A 2.3-month improvement in median OS was observed (8.6 months in the Tislelizumab Arm versus 6.3 months in the ICC Arm). The separation of the Kaplan Meier OS plots began at approximately

2.5 months and remained separate throughout the study follow-up period (Figure 12). The estimated 6- and 12-month survival rates were 62.3% (95% CI: 56.0% to 67.9%) versus 51.8% (95% CI: 45.3% to 57.9%), and 37.4% (95% CI: 31.4% to 43.4%) versus 23.7% (95% CI: 18.5% to 29.3%) in the Tislelizumab Arm and the ICC Arm, respectively. The median follow-up times by reverse Kaplan-Meier methodology were 20.8 months (95% CI: 19.5 to 22.4 months) and 21.1 months (95% CI: 19.3 to 22.8 months) for the Tislelizumab Arm and ICC Arm, respectively.

It is important to note that the magnitude of improvement in OS with tislelizumab in Study 302 was observed in the context of a notably higher rate of use of subsequent anti-PD-1 or PD-L1 inhibitors after discontinuing from study treatment in the ICC Arm (21.5%) than in the Tislelizumab Arm (4.3%).

The OS benefit in favor of tislelizumab was observed across all pre-defined subgroups by demographic and baseline characteristics, including by region and PD-L1 status. These analyses are provided and discussed below.

In addition, several sensitivity/supportive analyses were performed to examine the robustness of the primary analysis results. Treatment effect estimates from sensitivity and supportive analyses were similar to the results of the primary analysis, providing evidence that tislelizumab offered a statistically persuasive and clinically meaningful benefit over ICC.

OS in the Per-Protocol Analysis Set: stratified HR of 0.68 (95% CI: 0.56 to 0.83).

Unstratified OS Analysis in the ITT Analysis Set: unstratified HR of 0.69 (95% CI: 0.57 to 0.84).

Stratified OS Analysis by Strata as collected in the electronic case report form: stratified HR of 0.69 (95% CI: 0.57 to 0.84).

Sensitivity analysis by adding region as one of the strata: stratified HR of 0.70 (95% CI: 0.58 to 0.86).

Sensitivity analysis evaluating the impact of patients randomized but not treated by excluding them from the analysis: stratified HR of 0.69 (95% CI: 0.57 to 0.84).

Supportive analysis in patients with nonmissing baseline PD-L1 expression status (N = 413, combining patients with vCPS $\geq 10\%$ and vCPS $< 10\%$): stratified HR of 0.68 (95% CI: 0.55 to 0.85). The consistency of this result with that obtained in the ITT analysis set and in patients with PD-L1 status missing, along with the fact that absence of baseline PD-L1 expression status was random, appears to mitigate concern about potential bias introduced by the missing status subgroup in the interpretation of the primary analysis results in the ITT Analysis Set.

Sensitivity analysis to adjust the treatment effect estimate by adding PD-L1 expression status either as a covariate to the stratified Cox regression model of the primary analysis: stratified HR: 0.72 [95% CI: 0.59 to 0.88]; or as an additional stratification factor: stratified HR: 0.70 [95% CI: 0.57 to 0.87]. Results from these analyses showed that the random imbalance in baseline PD-L1 expression status had little impact on the primary analysis OS treatment effect estimate.

Table 19. BeiGene: Overall Survival (ITT Analysis Set)

	Tislelizumab (N = 256)	ICC (N = 256)
Number of Patients		
Death, n (%)	197 (77.0)	213 (83.2)
Censored, n (%)	59 (23.0)	43 (16.8)
Ongoing Without Event	54 (21.1)	27 (10.5)
Lost to Follow-up	0 (0.0)	2 (0.8)
Withdrew Consent	5 (2.0)	14 (5.5)
One-Sided Stratified Log-Rank Test P-value ^a	0.0001	---
Stratified Hazard Ratio (95% CI) ^b	0.70 (0.57, 0.85)	---
Unstratified Hazard Ratio (95% CI) ^c	0.69 (0.57, 0.84)	---
Overall Survival (months)		
Median (95% CI)	8.6 (7.5, 10.4)	6.3 (5.3, 7.0)
1 st Quartile (95% CI)	4.0 (3.5, 4.6)	3.3 (2.6, 4.0)
3 rd Quartile (95% CI)	18.0 (14.7, 21.0)	11.4 (10.6, 12.9)
Overall Survival Rate at, % (95% CI)		
3 Months (95% CI)	84.0 (78.8, 87.9)	78.0 (72.3, 82.7)
6 Months (95% CI)	62.3 (56.0, 67.9)	51.8 (45.3, 57.9)
9 Months (95% CI)	48.7 (42.4, 54.7)	35.0 (29.0, 41.1)
12 Months (95% CI)	37.4 (31.4, 43.4)	23.7 (18.5, 29.3)
Follow-up Time (months)		
Median (95% CI)	20.8 (19.5, 22.4)	21.1 (19.3, 22.8)

Source: ADTTE. Data cutoff: 01DEC2020. Data extraction: 15JAN2021.

Percentages were based on N.

In absence of death on or before data cutoff, patients will be censored either at the date that the patient was last known to be alive or the date of data cutoff, whichever comes earlier.

Medians and other quartiles were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley.

Overall Survival rates (cumulative probability of OS) were estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula.

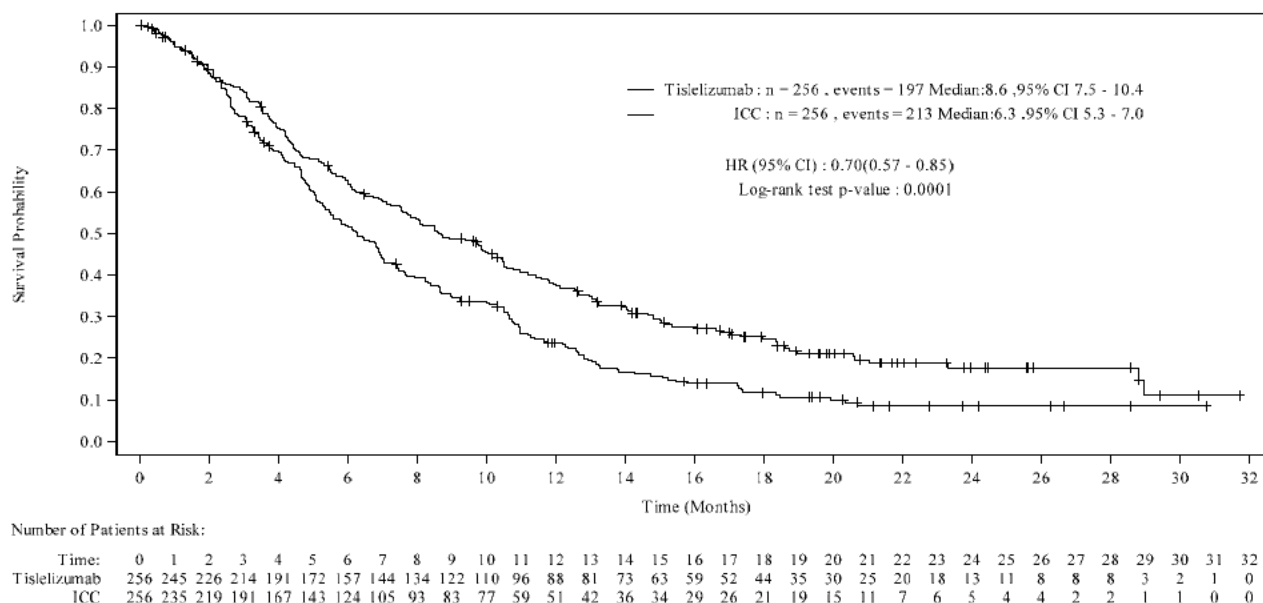
Median follow-up time was estimated by the reverse Kaplan-Meier method.

^a One-sided p-value was estimated from log rank test stratified by ECOG performance status and ICC option.

^b Hazard ratio (tislelizumab vs. ICC) was based on Cox regression model including treatment as covariate, and baseline ECOG status and ICC options as strata.

^c Hazard ratio (tislelizumab vs. ICC) was based on unstratified Cox regression model only including treatment arm as covariate.

Figure 12. BeiGene: Kaplan-Meier Plot of Overall Survival (ITT Analysis Set)



Source: ADTTE. Data cutoff: 01DEC2020. Data extraction: 15JAN2021.

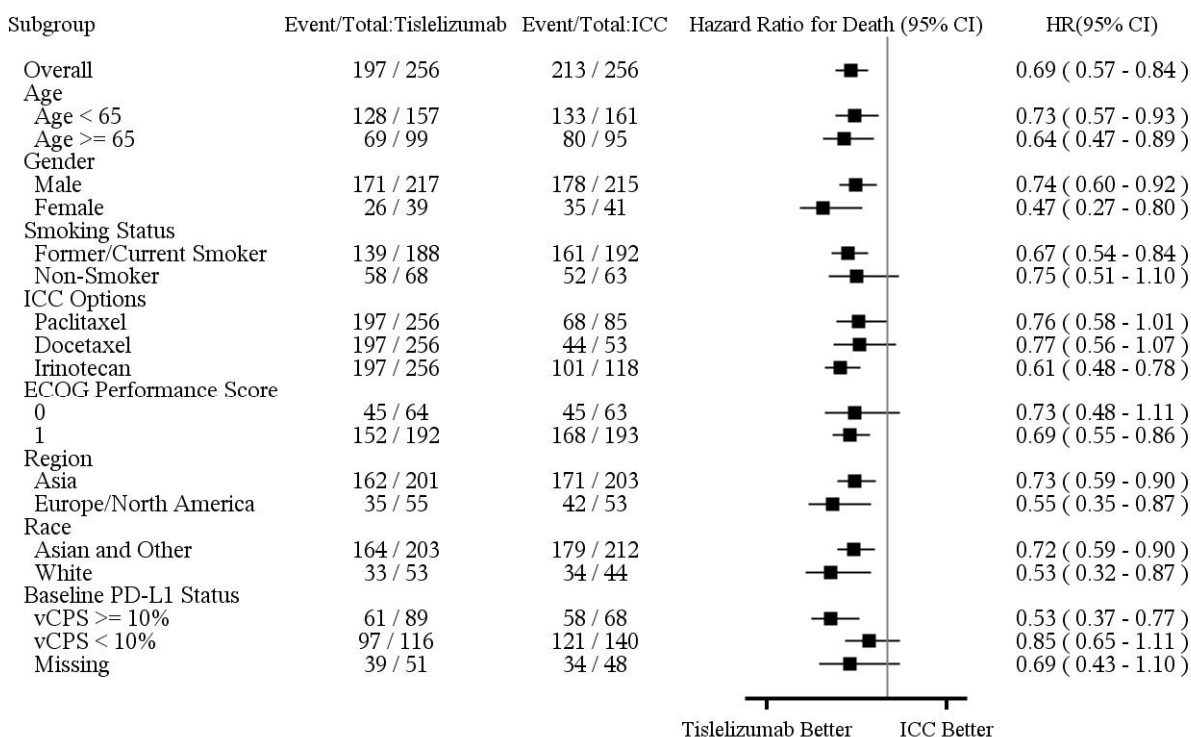
One-sided p-value was estimated from log-rank test stratified on ECOG status and ICC option. Hazard ratio was based on Cox regression model including treatment as covariate stratified by ECOG status and ICC option

Subgroup Analyses for Primary Efficacy Endpoint

Overall, the benefit of tislelizumab in improving OS, when compared with ICC, was observed across all the prespecified subgroups (Figure 13). For all prespecified subgroups, including baseline PD-L1 expression status, age, gender, smoking status, ICC option, ECOG PS score, region, and race, the unstratified HR favored the Tislelizumab Arm (ie, HR < 1).

The OS treatment effect estimated within both the Asia subgroup and Europe/North America subgroup clearly favored the Tislelizumab Arm. In the Asia subgroup, the median OS was 8.5 months (95% CI: 7.1 to 10.3 months) for the Tislelizumab Arm and 6.3 months (95% CI: 5.3 to 7.4 months) for the ICC Arm, and the HR was 0.73 (95% CI: 0.59 to 0.90). In the Europe/North America subgroup, the median OS was 11.2 months (95% CI: 5.9 to 14.8 months) for the Tislelizumab Arm and 6.3 months (95% CI: 4.6 to 7.7 months) for the ICC Arm, and the HR was 0.55 (95% CI: 0.35 to 0.87).

Figure 13. BeiGene: Subgroup Analysis: Forest Plot of Overall Survival (ITT Analysis Set)



Source: ADSL, ADTTE. Data cutoff: 01DEC2020. Data extraction: 15JAN2021.

Hazard ratio was based on unstratified Cox regression model including treatment as covariate
The race subcategory Other includes Black or African American, Not Reported, Unknown and Other.

PD-L1 positive is defined as vCPS >= 10%, PD-L1 negative is defined as vCPS < 10%, Missing refers to the patients without sample collection or not evaluable at baseline.

The Applicant's Position:

Study 302 is the largest global Phase 3 study of PD-1 or PD-L1 inhibitor as a second line treatment for ESCC with a global population. Study 302 met its primary endpoint of OS in the ITT Analysis Set with a statistically significant and clinically meaningful improvement in overall survival demonstrating that tislelizumab treatment decreased the risk of death by 30% and improved median survival by 2.3 months with survival benefits beginning within 3 months of starting treatment and continuing at the 6- and 12-month landmark analyses as shown in Kaplan-Meier curves. Of note, the OS benefit was observed across all pre-defined subgroups by

demographic and baseline characteristics, including by region and PD-L1 status.

The FDA's Assessment:

FDA generally agrees with the Applicant's presentation of the primary efficacy results for OS in the ITT population (N = 512). The primary analysis of OS in the ITT population demonstrated a statistically significant improvement favoring the tislelizumab arm (stratified HR = 0.70; 95% CI: 0.57, 0.85; one-sided p-value = 0.0001). This result was robust across the various sensitivity analyses conducted by the applicant. However, FDA notes that the landmark OS rates at 3, 6, 9, and 12 months by arm presented by the applicant should be considered exploratory. In general, the point estimate of event rates at a fixed time point for a time-to-event endpoint can be misleading because it does not represent the entire effect of the treatment and the chosen landmark time is arbitrary.

Regarding the subgroup analyses presented by the Applicant, FDA notes that all subgroup analyses are considered exploratory except for the subgroup of OS in PDL1 vCPS $\geq 10\%$ which was the key secondary endpoint tested in hierarchy.

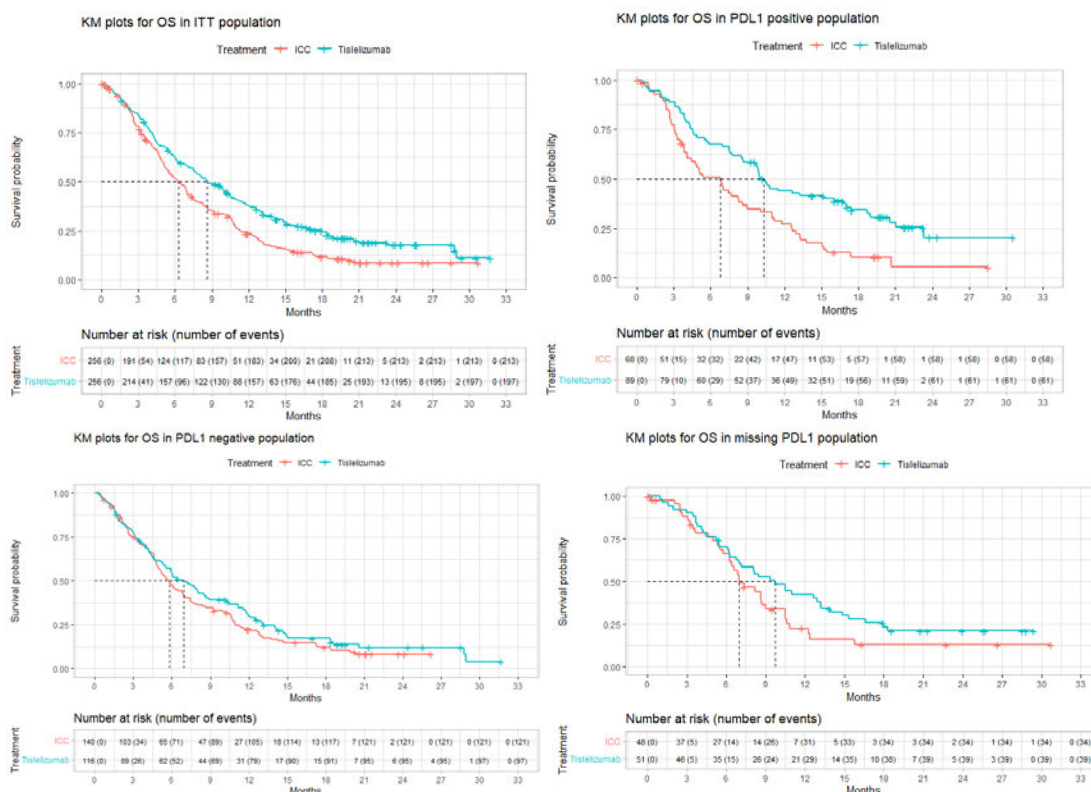
In addition to the results by baseline PD-L1 status presented in Figure 14, the Table 20 summarizes the efficacy results for OS by PD-L1 subgroups, presenting median OS by arm and stratified HRs.

Table 20. RATIONALE-302: Efficacy Results for OS by PDL1 status

	Tislelizumab		ICC		Stratified HR (95% CI)	One-sided p-value (allocated α)
	Events (N)	mOS (95% CI)	Events (N)	mOS (95% CI)		
All randomized patients	197 (256)	8.6 (7.5, 10.4)	213 (256)	6.3 (5.3, 7)	0.7 (0.57, 0.85)	0.0001 ($\alpha=0.025$)
PDL1 Status						
vCPS $\geq 10\%$	61 (89)	10.3 (8.5, 16.1)	58 (68)	6.8 (4.1, 8.3)	0.54 (0.36, 0.79)	0.006 ($\alpha=0.025$)
vCPS < 10%	97 (116)	6.9 (5.3, 8.7)	121 (140)	5.8 (4.9, 6.9)	0.82 (0.62, 1.09)	($\alpha=0$)
Missing	39 (51)	9.8 (6.2, 13.2)	34 (48)	7 (5.8, 9)	0.67 (0.41, 1.12)	($\alpha=0$)

The figure below shows the Kaplan-Meier plots for OS for the ITT population and by baseline PD-L1 status.

Figure 14. RATIONALE-302: KM plots for OS for ITT population and by PDL1 vCPS 10% cutoff



The results for the key secondary endpoint of OS in PD-L1 vCPS $\geq 10\%$ (N = 157) were statistically significant at the prespecified alpha level (stratified HR=0.53, 95% CI: 0.37, 0.77; one-sided p-value=0.006). However, FDA notes that the results in the PD-L1 vCPS $\geq 10\%$ subpopulation should be interpreted with caution given that approximately 19% of patients enrolled had missing PD-L1 vCPS (N = 99). FDA also notes that PD-L1 status was not a stratification factor for this study which could lead to potential imbalances in baseline characteristics between arms and unmeasured confounding in these subgroups.

FDA conducted further sensitivity analyses to evaluate the impact of the missing PDL1 status in the subgroup results for PDL1 (vCPS $\geq 10\%$) positive and PDL1 (vCPS $< 10\%$) negative subpopulations. Two sensitivity analyses were considered with two different scenarios.

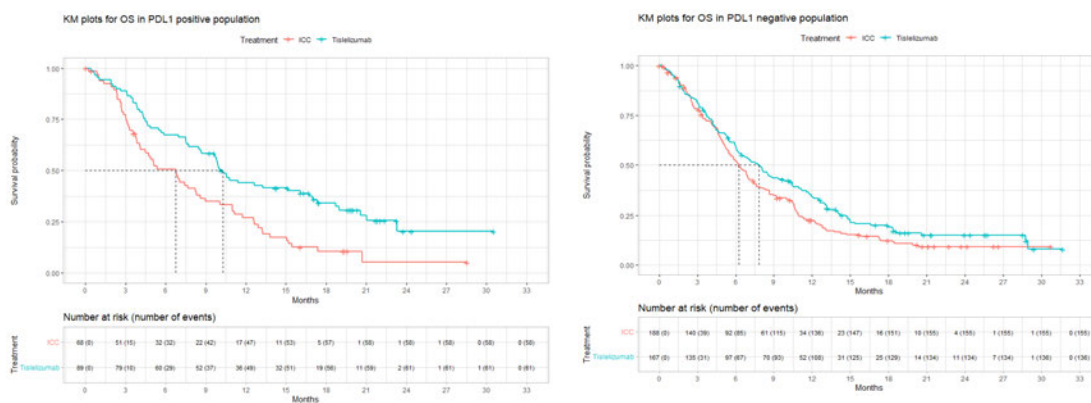
Sensitivity Analysis: Scenario 1.

In scenario 1, patients with missing PDL1 status were classified as PDL1 negative (vCPS < 10%) and subgroup analyses by PDL1 status were performed. The results are shown below.

Table 21. RATIONALE-302: Sensitivity analysis - OS in Scenario 1

	Tislelizumab		ICC		Stratified HR (95% CI)
	Events (N)	mOS (95% CI)	Events (N)	mOS (95% CI)	
PDL1 status					
vCPS ≥10%	61 (89)	10.3 (8.5, 16.1)	58 (68)	6.8 (4.1, 8.3)	0.54 (0.36, 0.79)
vCPS < 10%	136 (155)	7.8 (6.1, 9.8)	155 (188)	6.2 (5.4, 7)	0.78 (0.62, 0.98)

Figure 15. RATIONALE-302: Sensitivity analysis - KM plots for Scenario 1



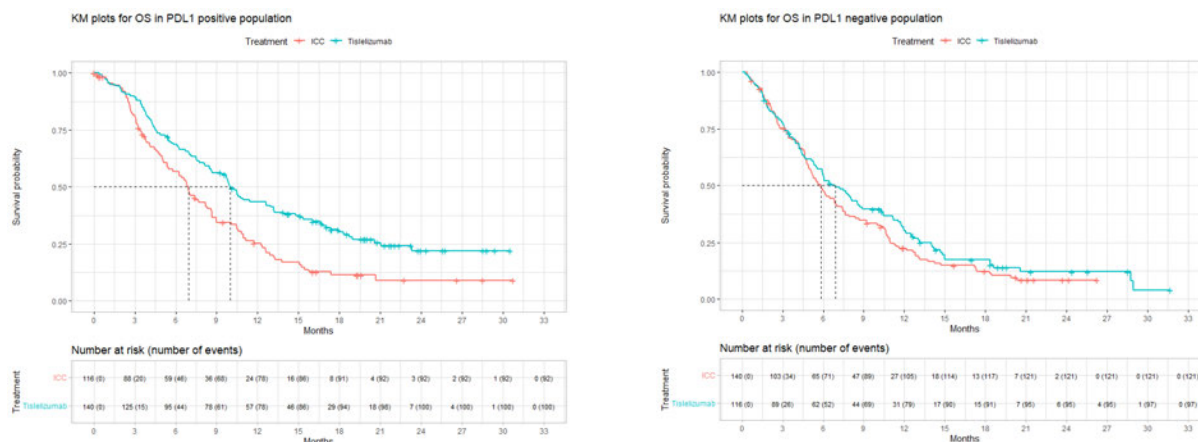
Sensitivity Analysis: Scenario 2

In scenario 2, patients with missing PDL1 status were classified as PDL1 positive (vCPS ≥ 10%) and subgroup analyses by PDL1 status were performed. The results are shown below in Table 22.

Table 22. RATIONALE-302: Sensitivity analysis - OS in Scenario 2

	Tislelizumab		ICC		Stratified HR (95% CI)
	Events (N)	mOS (95% CI)	Events (N)	mOS (95% CI)	
PDL1 status					
vCPS ≥10%	100 (140)	10 (8.5, 12.9)	92 (116)	6.9 (5.4, 8.3)	0.62 (0.46, 0.83)
vCPS < 10%	97 (116)	6.9 (5.3, 8.7)	121 (140)	5.8 (4.9, 6.9)	0.82 (0.62, 1.09)

Figure 16. RATIONALE-302: Sensitivity analysis - KM plots for Scenario 2



Overall, the OS results across PD-L1 subgroups as defined by vCPS $\geq 10\%$ and vCPS <10% appeared consistent when considering sensitivity analyses to assess the impact of missing PD-L1 status. However, results of the sensitivity analyses as well as results in the vCPS <10% patient subgroup should be considered exploratory.

Although RATIONALE-302 was revised (Amendment 4) to include a key secondary endpoint of OS in patients with CPS $\geq 10\%$, which was a predictive factor in Study KEYNOTE-181 in patients with ESCC, ascertainment of PD-L1 expression was missing in 19% of patients and the analysis in this subset of patients was not included in labeling (see below in secondary endpoint

analysis). Approximately 10% of the patients had PD-L1 vCPS < 1% population and few events occur, therefore, the scope of interpretation of any additional analyses based on PD-L1 cutoff is limited and will not be shown.

Data Quality and Integrity

Data:

Not Applicable

The Applicant's Position:

There are no issues regarding the data integrity and submission quality.

The FDA's Assessment:

FDA agrees that Applicant has provided all the datasets and supporting metadata documentation required to validate the results. No issues were found when performing a data quality check.

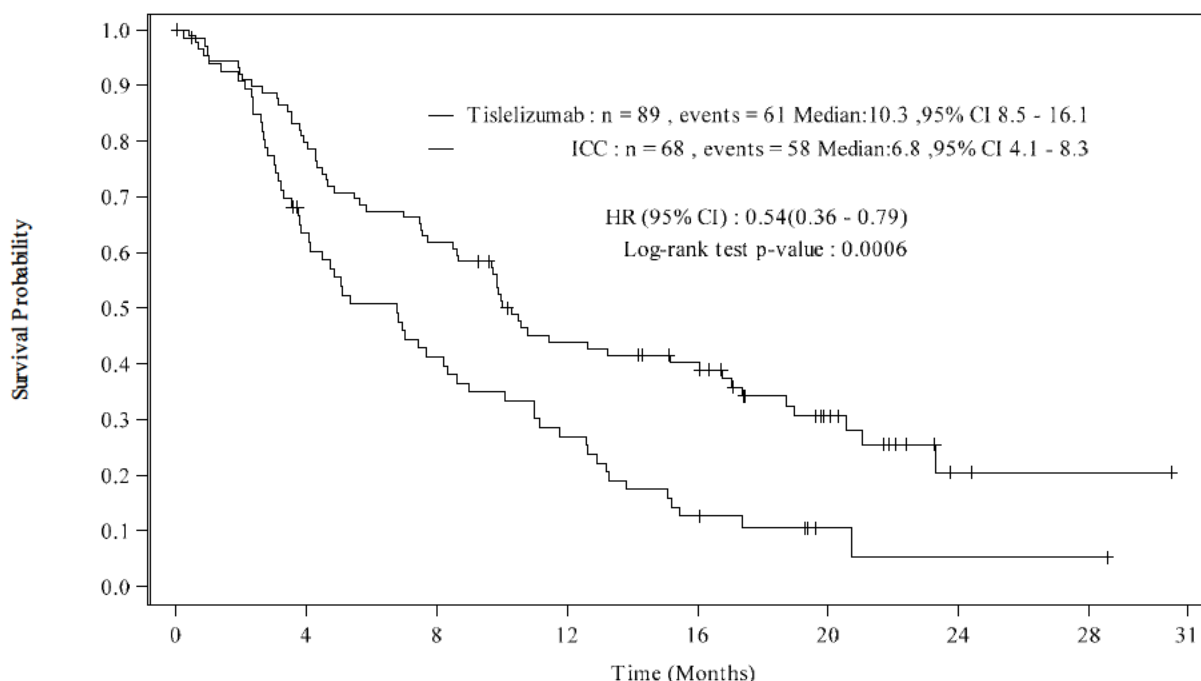
Efficacy Results – Secondary and other relevant endpoints

Data:

Key Secondary Endpoint: Overall Survival in Patients With PD-L1 vCPS $\geq$ 10%

Tislelizumab treatment showed a statistically significant improvement compared to ICC treatment in patients with PD-L1 vCPS $\geq$ 10%, with a stratified HR of 0.54 (95% CI: 0.36 to 0.79) and a 1-sided stratified logrank test p-value of 0.0006. A 3.5-month difference in median OS between the 2 arms was observed and considered clinically meaningful (10.3 months [95% CI: 8.5 to 16.1 months] in the Tislelizumab Arm versus 6.8 months [95% CI: 4.1 to 8.3 months] in the ICC Arm).

Figure 17. BeiGene: Kaplan-Meier Plot of Overall Survival in Patients With PD-L1 vCPS $\geq$ 10% (Study 302) (ITT Analysis Set)



Number of Patients at Risk:

Time:	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
Tislelizumab	89	85	82	79	71	63	60	59	55	52	43	37	36	35	34	32	30	25	19	17	14	11	8	6	2	1	1	1	1	1	1	0
ICC	68	63	60	51	40	35	32	29	26	22	22	19	17	14	11	11	8	6	5	5	2	1	1	1	1	1	1	1	1	0	0	0

Source: ADTTE. Data cutoff: 01DEC2020. Data extraction: 15JAN2021.

One-sided p-value was estimated from log-rank test stratified on ECOG status and ICC option. Hazard ratio was based on Cox regression model including treatment as covariate stratified by ECOG status and ICC option

Progression-Free Survival (ITT Analysis Set)

Results of PFS in the ITT Analysis Set showed a 17% reduction in the risk of disease progression or death in the Tislelizumab Arm compared with the ICC Arm (stratified HR: 0.83 [95% CI: 0.67 to 1.01]) (Table 23).

Although the median PFS was slightly shorter in the Tislelizumab Arm than in the ICC Arm, the Kaplan Meier- plots of PFS began to separate approximately 3 months after randomization in favor of the Tislelizumab Arm and remained separate for the remainder of the study (Figure 18)

with higher landmark PFS rates at 6 months (21.7% versus 14.9%), 9 months (15.8% versus 9.6%), and 12 months (12.7% versus 1.9%) for the Tislelizumab Arm versus the ICC Arm.

Table 23. BeiGene: Progression-Free Survival (Study 302) (ITT Analysis Set)

				Tislelizumab vs ICC	
Treatment	N	Number of Events (%)	Median PFS (Months) (95% CI)	Hazard Ratio (95% CI) ^a	P-Value ^b
Tislelizumab	256	223 (87.1)	1.6 (1.4, 2.7)	0.83 (0.67, 1.01)	0.0292
ICC	256	180 (70.3)	2.1 (1.5, 2.7)	-----	-----

Source: Post-Text Table 14.2.3.1. Data cutoff: 01DEC2020. Data extraction: 15JAN2021.

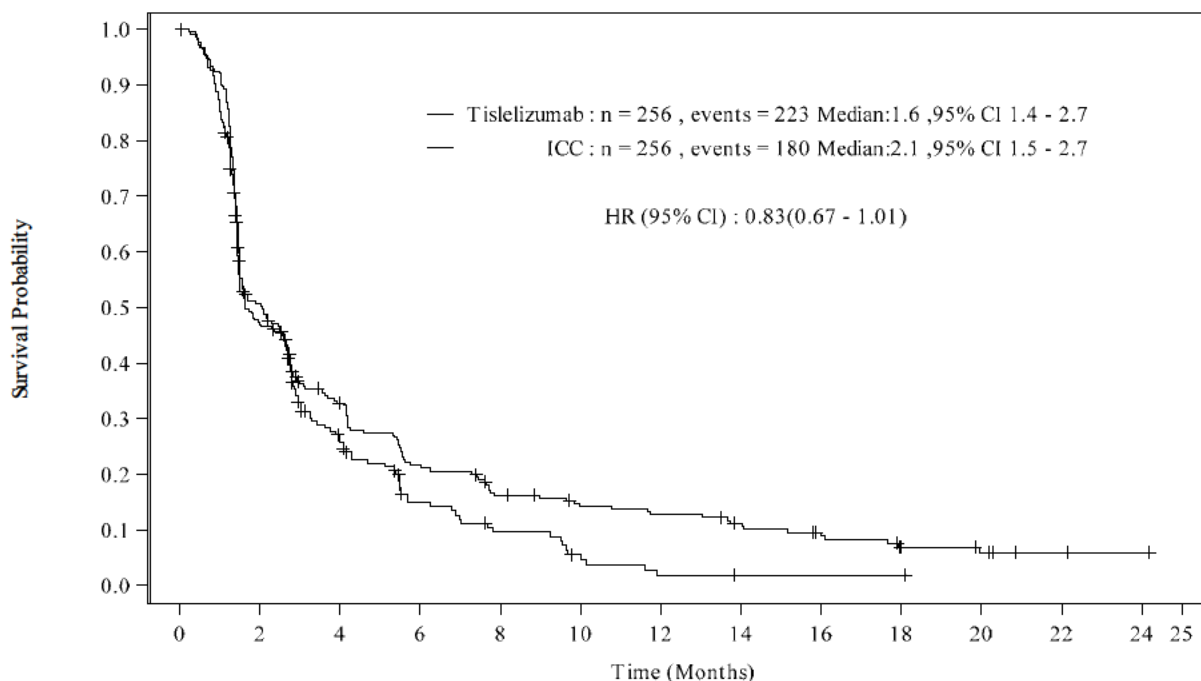
Percentages were based on N.

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

^a Hazard ratio (tislelizumab vs. ICC) was based on Cox regression model including treatment arm as a factor and stratified by ICC and ECOG performance status.

^b One-sided p-value was estimated from log rank test stratified by ECOG performance status and ICC option, for descriptive purpose only.

Figure 18. BeiGene: Kaplan-Meier Plot of Progression Free Survival (Study 302) (ITT Analysis Set)



Number of Patients at Risk:

Time:	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
Tislelizumab	256	233	119	85	74	62	49	46	35	32	28	27	25	25	20	18	15	13	9	8	6	3	3	2	2	0
ICC	256	184	98	57	42	33	20	16	12	12	6	4	2	2	1	1	1	1	1	0	0	0	0	0	0	0

Source: ADTTE. Data cutoff: 01DEC2020. Data extraction: 15JAN2021.

Hazard ratio was based on Cox regression model including treatment as covariate stratified by ECOG status and ICC option

Objective Response and Disease Control Rate (ITT Analysis Set)

Unconfirmed ORR as assessed by the investigators per RECIST v1.1 (secondary endpoint) in the Tislelizumab Arm was more than twice that in the ICC Arm (20.3% [95% CI: 15.6% to 25.8%] versus 9.8% [95% CI: 6.4% to 14.1%]), with an estimated odds ratio of 2.39 (95% CI: 1.42 to 4.01). More patients had a best overall response (BOR) of CR in the Tislelizumab Arm than in the ICC Arm (5 patients [2.0%] versus 1 patient [0.4%]) (Table 24). In a post-hoc sensitivity analysis, confirmed ORR in the Tislelizumab Arm was also more than twice that in the ICC Arm (15.2% versus 6.6%), with 5 CRs in the Tislelizumab Arm and 1 CR in the ICC Arm.

DCR assessed by the investigators (exploratory endpoint) was also numerically higher in the Tislelizumab Arm (46.9%) compared with the ICC Arm (41.8%).

Table 24. BeiGene: Objective Response and Disease Control Rate (Study 302) (ITT Analysis Set)

Response Category	Tislelizumab (N = 256)	ICC (N = 256)
Objective Response Rate (ORR), n	52	25
% (95% CI) ^a	20.3 (15.6, 25.8)	9.8 (6.4, 14.1)
Odds Ratio for ORR, (95% CI) ^b	2.39 (1.42, 4.01)	---
CMH Test P-value ^c	0.0008	---
ORR Difference, % (95% CI) ^b	10.6 (4.5, 16.7)	---
Best Overall Response (BOR), n (%)		
Complete Response (CR)	5 (2.0)	1 (0.4)
Partial Response (PR)	47 (18.4)	24 (9.4)
Stable Disease (SD)	68 (26.6)	82 (32.0)
Progressive Disease (PD)	116 (45.3)	86 (33.6)
Could Not Be Determined ^d	20 (7.8)	63 (24.6)

Source: Post-Text Table 14.2.4.1. Data cutoff: 01DEC2020. Data extraction: 15JAN2021.

Percentages were based on N.

^a Two-sided 95% CI was calculated using Clopper-Pearson method.

^b Objective response rate, overall response rate differences and odds ratios between arms were calculated using the Cochran-Mantel-Haenszel Chi-square test, stratified by ECOG performance status and ICC option.

^c CMH test is stratified by ECOG status and ICC option. P-value for descriptive purpose only.

^d Patients with no post-baseline response assessment (Not Assessable) or assessment as Not Evaluable (NE) per RECIST 1.1.

Duration of Response (ITT Analysis Set)

The tumor response after treatment with tislelizumab was durable and clinically meaningful compared with treatment with chemotherapy. The median DOR was 7.1 months (95% CI: 4.1 to 11.3 months) in the Tislelizumab Arm compared with 4.0 months (95% CI: 2.1 to 8.2 months) in the ICC Arm, with 10 of 52 responders (19.2%) in the Tislelizumab Arm with ongoing overall responses compared with 0 patient in the ICC Arm at the time of data cutoff.

Table 25. BeiGene: Duration of Response (Study 302) (ITT Analysis Set)

Treatment	N	Number of Responders	Number of Events (%)	Median DOR (Months) (95% CI)
Tislelizumab	256	52	35 (67.3)	7.1 (4.1, 11.3)
ICC	256	25	20 (80.0)	4.0 (2.1, 8.2)

Source: Post-Text Table 14.2.5.1. Data cutoff: 01DEC2020. Data extraction: 15JAN2021.

Percentages were based on the number of Patients with CR/PR in relevant treatment arm.

Duration of response analysis included patients with overall response.

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

Health-Related Quality of Life (HRQoL)

Validated and most frequently used PROs instruments in oncology studies, especially in studies of PD-L1 inhibitors, were used to measure and assess HRQoL from the patient's perspective. These included the (EORTC QLQ-C30) to measure general cancer signs and symptoms, its esophageal cancer-specific module, the EORTC QLQ-OES18, and the EQ-5D-5L) to measure general health, were used to further characterize treatment benefits of tislelizumab beyond radiographic measures.

The assessment of HRQoL was based on the comparison of key PRO endpoints relevant to esophageal cancer. The PRO key endpoints in this studies included global health status (GHS) and physical function as measured by the EORTC QLQ-C-30 and esophageal cancer main symptoms of pain, eating, dysphagia and reflux as measured by EORTC QLQ-OES18.

The completion rates defined as number of patients who completed questionnaires total number of patients in relevant treatment arm at the predefined visits) were calculated for all 3 questionnaires in all cycles, and they remained at or above 95% in both ITT and PD-L1 vCPS $\geq$ 10% populations.

Changes from baseline on the scores of scales and index of EORTC QLQ-C30 and EORTC QLQ-OES18, and on the scores of EQ-5D-5L (VAS) were calculated using descriptive analysis. Time to clinically meaningful worsening, defined as ≥ 10 points in direction of worsening in the PRO key endpoints were calculated, using stratified log-lank test with HR at 95% CI. The P

values were nominal. The 10-point threshold was selected based on the EORTC developers' original testing (Osoba et al 1998) and what has been used in the previous clinical studies of PD-L1 inhibitors on HRQoL (Adams et al 2020; Necchi et al 2020; Nishijima et al 2019; Harrington et al 2017).

Treatment with tislelizumab was associated with a better overall HRQoL in Study 302. The better outcomes in HRQoL in the Tislelizumab Arm compared with those in the ICC Arm were related to either a reduction in symptoms (e.g., eating and pain) or slower and milder worsening (e.g., dysphagia and reflux). Improvement in physical functioning was observed in the Tislelizumab Arm compared with the ICC Arm.

Furthermore, in the ITT population, analysis of the time to deterioration showed, patients treated with tislelizumab were at a lower risk for clinically meaningful worsening symptoms of dysphagia (stratified HR of 0.76 [95% CI: 0.53, 1.07]) and reflux (0.50 [95% CI: 0.32, 0.80]) as well as physical function (0.67 [95% CI: 0.45, 1.00]) through the course of treatment. The PD-L1 vCPS $\geq$ 10% patients treated with tislelizumab were at lower risk for pain (0.52 [95% CI: 0.24, 1.13]).

Refer to section 8.2.8 for further details.

The Applicant's Position:

In addition to the statistically significant and clinically meaningful improvement in the primary endpoint of OS in the ITT population, tislelizumab also demonstrated statistically significant improvement in the key secondary endpoint of OS in the PD-L1 vCPS $\geq$ 10% population. The survival benefit of tislelizumab over ICC was accompanied by favorable landmark PFS rates at 6,9 and 12 months, higher ORR, longer DOR and improvements in HRQoL assessment in the key PRO endpoints of eating, pain, and physical functioning and slower and less notable deterioration in dysphagia and reflux.

The FDA's Assessment:

Although FDA confirmed the data as presented above, FDA's interpretation of these results is different. As stated above, given the missing PD-L1 expression data on 19% of patients in RATIONALE-302 and that PD-L1 status was not a stratification factor, FDA notes that the analysis of survival in patients based on PD-L1 expression should be interpreted with caution.

FDA also acknowledges the results of the secondary endpoint of PFS, which are considered exploratory. The p-value for PFS is considered nominal. As noted by the Applicant, median PFS was slightly shorter on the tislelizumab arm compared to the ICC arm but the Kaplan-Meier curves for PFS start to separate in favor of the tislelizumab arm approximately 3 months after randomization. FDA notes that the delayed separation of the PFS curves suggests that the proportional hazards assumption may have been violated.

In regards to the ORR analysis, the review team would like to clarify that following RECIST 1.1,

in randomized trials, the response does not need confirmation with a second scan confirming the findings of the first scan separated by at least 4 weeks. Although the ORR in the tislelizumab arm doubled the ORR in the ICC arm, the RATIONALE-302 ORR showed a modest effect of tislelizumab on ORR, but consistent with the class effect in patients with ESCC. ORR and DOR are considered exploratory results only. The p-value presented for ORR is considered nominal.

FDA reviewed the Applicant's presentation of PRO results in the RATIONALE-302 CSR. FDA did not conduct independent analyses of the PRO endpoints. FDA does not agree with the Applicant's claim that treatment with tislelizumab was associated with a better overall HRQoL. No conclusions can or should be drawn regarding HRQoL given that no alpha was allocated to these endpoints and results are to be considered exploratory only. In addition, while FDA acknowledges that the 10-point threshold used to define clinically meaningful worsening has been cited in the Osoba et al. (1998) publication, FDA does not agree with this threshold as there are several limitations to the approach that was used to derive it, and it has not been justified for this specific disease setting. Results of exploratory time to deterioration endpoints should further be interpreted with caution given these limitations. Comparative claims are unsupported.

Dose/Dose Response

Data:

Not Applicable

The Applicant's Position:

Not Applicable

The FDA's Assessment:

As stated in Section 6, there are limited data to evaluate the efficacy of tislelizumab in patients with ESCC at doses other than the studied in RATIONALE-302. Tislelizumab exposure-response relationship for efficacy was inconclusive. The finding of effectiveness of tislelizumab was supported by a favorable overall survival of tislelizumab monotherapy against ICC with a stratified hazard ratio (HR) of 0.70 (95% CI 0.57, 0.85).

Durability of Response

Data:

Refer to section 8.1.2.

The FDA's Assessment:

FDA's assessment of durability of response is based on the exploratory analysis of DoR in all randomized patients as well as the effect on PFS (secondary endpoint, considered exploratory) and OS (primary endpoint). Refer to FDA's comments above.

Persistence of Effect

Data:

Refer to section [8.1.2](#).

The Applicant's Position:

Refer to section [8.1.2](#).

The FDA's Assessment:

Persistence of effect is a term better suited for continuous variables (e.g., hypertension, biomarker assessments, etc.) and is not intended to characterize or compare treatment effects on selected endpoints. Treatment effect and study outcomes are described elsewhere in this section.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Data:

Refer to section [8.1.2](#).

The Applicant's Position:

Refer to section [8.1.2](#).

The FDA's Assessment:

See FDA review under secondary endpoints.

Additional Analyses Conducted on the Individual Trial (Study 302)

Data:

Data Analysis of Subgroups

Please refer to section [8.1.2](#), subsection “Subgroup Analyses for Primary Efficacy Endpoint”

Sensitivity and Supportive Analyses of OS

Please refer to section [8.1.2](#), subsection Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)”

Post-hoc Analysis of OS

In addition to the above prespecified analysis, the following post-hoc analyses were performed for OS:

- A post-hoc subgroup analysis was performed by excluding patients with baseline PDL1 missing status
- A post-hoc analysis was performed by adding regions as strata in the analysis method.
- A post-hoc analysis was performed by adding a time-dependent variable, defined by treatment and log(time) interaction into the model to assess the potential violation of proportional hazards assumption in the stratified Cox proportional hazards model.

The Applicant's Position:

The OS benefit of Tislelizumab use (ie, HR < 1) was consistent across all prespecified subgroups, including age, gender, smoking status, ICC option, ECOG PS score, region, race, and baseline PD-L1 expression. Imbalances in PD-L1 at baseline and metastatic status at diagnosis or of missing PD-L1 results were demonstrated to have had no impact on the primary endpoint. Thus, the improvement in overall survival with Tislelizumab was observed across all pre-specified and post hoc analyses.

The FDA's Assessment:

FDA notes that results of the post-hoc analysis to assess potential violation of proportional hazards and sensitivity analysis to address imbalances in metastatic status at diagnosis have not been presented by the Applicant in this Multidisciplinary Review and Evaluation. In general, FDA acknowledges that the OS benefit of tislelizumab appeared consistent across various subgroup analyses and sensitivity analyses (both pre-specified and post-hoc) conducted by the Applicant and by FDA but emphasizes that these analyses are all considered exploratory (except for the key secondary endpoint of OS in PD-L1 vCPS $\geq$ 10%, which should also be interpreted with caution for reasons discussed in the Efficacy Results sections).

8.1.3. Integrated Review of Effectiveness

The FDA's Assessment:

Study 302 was designed to compare OS in patients with unresectable/metastatic ESCC that has been previously treated with one prior line of systemic therapy by comparing patients who receive tislelizumab to those who receive ICC of either paclitaxel, docetaxel, or irinotecan. Study 302 demonstrated a statistically significant, clinically meaningful improvement in OS for patients randomized to tislelizumab (n = 256) compared to ICC (n = 256). The median OS of patients in the tislelizumab arm was 8.6 months [95% CI: 7.5, 10.4] and the median OS of patients in the ICC arm was 6.3 months [95% CI: 5.3, 7.0] with an OS HR of 0.70 [95% CI:

0.57, 0.85; one-sided p-value=0.0001]. The pre specified key secondary endpoint of OS in patients with PDL1 vCPS $\geq 10\%$ (N = 157) demonstrated a statistically significant difference between the tislelizumab arm (n = 89) and the ICC arm (n = 68) at the prespecified alpha level (stratified HR=0.53, 95% CI: 0.37, 0.77; one-sided p-value=0.006). As noted above, however, FDA notes that results of OS in patients with PDL1 vCPS $\geq 10\%$ data should be interpreted with caution because approximately 19% of patients enrolled had missing PDL1 vCPS information (N = 99) and because PD-L1 status was not a stratification factor for this study. Other exploratory subgroup analyses of OS (e.g. ECOG performance status, race, region) are consistent with the OS benefit seen in the ITT population.

RATIONALE-302 was an adequate and well-controlled clinical trial and the data submitted meet the statutory evidentiary standard for substantial evidence of the effectiveness of tislelizumab based on an OS benefit.

8.1.4. Assessment of Efficacy Across Trials

The efficacy of tislelizumab from the pivotal Study 302 is supported by efficacy results from 2 early phase clinical studies in previously treated patients with advanced or metastatic solid tumors including ESCC, study 001 and 102 (Table 15). Given the differences in eligibility criteria, study design, tislelizumab dose, and duration of follow up, efficacy results from the 2 supportive studies are presented separately by study.

Primary Endpoints

Data:

Overall Survival

The survival benefits with tislelizumab treatment was also observed in supportive studies 001 and 102. The median OS was 4.7 months (95% CI: 1.5 to 7.9 months) in Study 001 and with estimated 6-month and 12-month OS rates of 47.4% and 21.6%, respectively. In Study 102, the median OS was 4.8 months (95% CI: 3.6 to 8.5 months) with estimated 6-month and 12-month OS rates of 49.2% and 20.5%, respectively. In Study 102, the median OS was 4.8 months (95% CI: 3.6 to 8.5 months) with estimated 6-month and 12-month OS rates of 49.2% and 20.5%, respectively. The survival results in 001 and 102, compared with the historically observed median OS of 3.7 months and a 12-month OS rate < 13% in the second- or third-line treatment setting of ESCC (Dutton et al 2014), supported the use of tislelizumab in patients with advanced or metastatic ESCC who had been treated previously with systemic therapy.

The Applicant's Position:

The OS data from Studies 001 and 102 provided supportive evidence for the efficacy of

tislelizumab monotherapy in patients with advanced or metastatic ESCC who had been heavily treated previously.

The FDA's Assessment:

FDA acknowledges the applicant's presentation of OS results from supportive Studies 101 and 102. FDA did not independently verify the results since the results are supportive and exploratory. Further, OS results from single arm trials are not interpretable.

Secondary Endpoints

Progression-Free Survival (PFS)

The median PFS was 2.0 months (95% CI: 1.3 to 4.2 months) in Study 001 and 2.1 months (95% CI: 2.0 to 4.2 months) in Study 102. The estimated PFS rates at 3 months and at 6 months were 38.5% and 23.1%, respectively, in Study 001, and 32.4% and 18.5%, respectively, in Study 102.

Objective Response and Disease Control Rate

Studies 001 and 102 supported tumor responses observed with tislelizumab in Study 302 with an encouraging ORR in patients with advanced or metastatic ESCC who had been heavily treated previously. The ORRs were 19.2% (95% CI: 6.6% to 39.4%) and 7.7% (95% CI: 0.9% to 25.1%) in Studies 001 and 102, respectively. The DCRs were 42.3% (95% CI: 23.4% to 63.1%) and 34.6% (95% CI: 17.2% to 55.7%) in Studies 001 and 102, respectively. More patients in Study 102 (38.5%) received ≥ 3 lines of treatment than in Study 001 (11.5%), which may have contributed to the lower ORR and DCR in Study 102 compared with Study 001. However, the ORR in Study 102 was considered favorable when compared with the historical ORR of 0.4% to 3% observed in patients in the second- or third-line treatment setting (Dutton et al 2014). In general, the antitumor response observed in Studies 001 and 102 was comparable to the results in the Phase 2 studies with pembrolizumab (the KEYNOTE-180 study) and nivolumab (the ATTRACTION-1 study) in similar heavily pretreated populations.

Duration of Response

Studies 001 and 102 supported the durable antitumor activity of tislelizumab by showing an encouraging 12-month DOR rate in patients with advanced or metastatic ESCC who had been heavily treated previously. In Study 001, the median DOR was 4.2 months (95% CI: 2.8 months to NE) and the 12-month DOR rate was 40.0%. In Study 102, the median DOR was not reached, as 1 of 2 patients who achieved a response continued to respond to treatment as of the cutoff date; both patients achieved a DOR of ≥ 12 months.

The Applicant's Position:

The efficacy results based on secondary endpoints from Studies 001 and 102 provided supportive evidence for the efficacy of tislelizumab monotherapy in patients with advanced or metastatic ESCC who had been heavily treated previously.

The FDA's Assessment:

FDA acknowledges the applicant's presentation of results for secondary endpoints for studies 101 and 102. FDA did not independently verify the results since these are supportive and considered exploratory. Furthermore, time to event endpoints like OS, PFS, and DCR results from single arm trials are not interpretable.

Subpopulations

Data:

Subgroup analyses were not performed across studies as Studies 001 and 102 were single arm studies.

The Applicant's Position:

Not Applicable

The FDA's Assessment:

Not applicable.

Additional Efficacy Considerations

The FDA's Assessment:

Not applicable.

8.1.5. Integrated Assessment of Effectiveness

Data:

As a global multicenter study, Study 302 was designed in accordance with ICH guidelines (including ICH-E17) and international treatment guidelines for patients with ESCC. Key parameters of the study (ie, patient population, stratification factors, choice of comparator, primary endpoint, statistical analysis plan, and safety management plan) were designed in consultation with the US FDA, the European Medicines Agency (EMA), the Center for Drug Evaluation of the National Medical Products Administration (NMPA), and the Pharmaceuticals and Medical Devices Agency (PMDA).

The patients enrolled in Study 302 are representative of patients with advanced or metastatic disease in the US. The control arm received the globally accepted standard of care at the time of

accrual. The results from the pivotal Phase 3 Study 302 and the totality of the supporting clinical data demonstrate that tislelizumab provides benefit to patients with advanced or metastatic ESCC, with clinically and statistically significant improvements in OS as compared with chemotherapy. The improvement in OS with tislelizumab over ICC (ie, HR < 1) was consistently observed across all prespecified subgroups (ie, age, gender, smoking status, baseline ECOG PS score, ICC option, race, region and PD-L1 expression status) and was accompanied by greater and more durable tumor responses, favorable PFS landmark rates after 3 months, and better reported HRQoL.

Specifically, in Study 302, tislelizumab was superior to ICC for the primary endpoint of OS in the ITT population, with a statistically significant 30% reduction (1-sided p-value = 0.0001) in the risk of death and a clinically meaningful improvement in median OS of 2.3 months. tislelizumab also showed superiority to ICC for the key secondary endpoint of OS in the prespecified PD-L1 vCPS $\geq 10\%$ population, with a statistically significant 46% reduction (1-sided p-value = 0.0006) in the risk of death and a clinically meaningful improvement in median OS of 3.5 months.

The improvement in OS with tislelizumab was also observed across prespecified subgroups in Study 302. Two subgroups of interest are summarized below:

- By region: HR of OS was 0.55 (95% CI: 0.35 to 0.87) in patient from Europe/North America and 0.73 (95% CI: 0.59 to 0.90) in patient from Asia
- By baseline PD-L1 expression status: HR of OS was 0.54 (95% CI: 0.36 to 0.79) in patients with PD-L1 vCPS $\geq 10\%$, 0.82 (95% CI: 0.62 to 1.09) in patients with PD-L1 vCPS < 10%, and 0.67 (95% CI: 0.41 to 1.12) in patients with missing PD-L1 status

The efficacy of tislelizumab was also observed across secondary endpoints of PFS, ORR, DOR, and HRQoL in Study 302, supporting the primary endpoint of OS:

- PFS: Treatment with tislelizumab showed a PFS HR of 0.83 (95% CI: 0.67 to 1.01). Separation of the PFS Kaplan-Meier curves began approximately 3 months after randomization and favored tislelizumab for the remainder of the study ([Figure 18](#)) as indicated by PFS landmark analysis at 3, 6, 9 and 12 months.
- ORR: Tislelizumab treatment resulted in a clinically relevant increase in ORR compared with ICC (20.3% [95% CI: 15.6% to 25.8%] versus 9.8% [95% CI: 6.4% to 14.1%]) in Study 302, supported by response rates observed in the supportive studies 001 and 102 where patients were heavily pre-treated
- DOR: The median DOR was 7.1 months (95% CI: 4.1 to 11.3 months) in the Tislelizumab Arm compared with 4.0 months (95% CI: 2.1 to 8.2 months) in the ICC Arm, with 10 of 52 patients (19.2%) having ongoing overall responses at the time of data cutoff

- HRQoL: The risk of worsening of the key esophageal cancer symptoms, particularly reflux, dysphagia, and physical functioning was lower in the Tislelizumab Arm compared with the ICC Arm.

Efficacy results from patients with advanced or metastatic ESCC in Studies 001 and 102 provide supportive evidence of the efficacy of tislelizumab monotherapy in patients with advanced or metastatic ESCC who had been heavily pre-treated, the most patients (65.4% in Study 001 and 76.9% in Study 102) who were enrolled in these 2 studies had received ≥ 2 prior lines of therapy.

The Applicant's Position:

The efficacy results from the pivotal Study 302, together with the results from the 2 supportive Studies 001 and 102, provide evidence that tislelizumab is an effective treatment for patients with advanced or metastatic ESCC after prior systemic treatment in support of the proposed indication.

The FDA's Assessment:

FDA agrees that the primary OS results of RATIONALE-302 provide substantial evidence of the effectiveness of tislelizumab for the treatment of patients with advanced or metastatic ESCC with disease progression after one prior line of treatment. See FDA's assessment in Section 8.1.3 ("Integrated Review of Effectiveness"), above.

8.2. Review of Safety

Data:

8.2.1. Overall Safety Evaluation Plan

The safety analysis for this BLA is based primarily on the pivotal study, Study 302. The Study 302 dataset presents a clear comparison of the safety data of tislelizumab with the standard of care at the time of study initiation, which was single-agent chemotherapy. The safety data from the ESCC population represents the total experience of tislelizumab as treatment for ESCC at the time of BLA submission.

Further details of these populations are provided in section 8.2.2 and safety assessment are listed in Table 26.

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Table 26. BeiGene: Key Study Design Features

Study number	Study design	Patient population	Safety assessments	Number of treated patients	Tislelizumab dose and other treatment as specified ^a	Data cutoff date
Pivotal study						
302	Phase 3, randomized, controlled, open-label, global study to compare the efficacy and safety of tislelizumab versus chemotherapy	Patients with advanced unresectable or metastatic ESCC that has progressed during or after first-line therapy	Incidence and severity of AEs according to NCI-CTCAE v4.03 Changes in vital signs, physical findings, ECG, ECOG Performance Status, ophthalmologic findings, and clinical laboratory results	495	255 patients received tislelizumab 200 mg Q3W 240 patients received ICC	01 Dec 2020
Supportive studies						
102 ^b	Phase 1/2, 2-part, open-label, study investigating the safety, tolerability, PK, and preliminary antitumor activity of tislelizumab	Patients with advanced solid tumors, including ^c : NSCLC (18.7%), MM (11.3%). All other ^d tumor types occurred in < 10% of patients and included 26 ESCC patients ^e (8.7%)	Incidence and severity of AEs according to NCI-CTCAE v4.03 Changes in vital signs, physical findings, ECG, ECOG Performance Status, and clinical laboratory results	300	300 patients received 200 mg Q3W, including 57 patients (PK substudy) who received 200 mg W1D1, W5D1 Q3W	31 May 2020
001	Phase 1A/B, multicenter, open-label, multiple-dose, dose	Patients with advanced tumors, including: GC (12.0%), EC (12.0%), OC (11.3%), HCC	Incidence and severity of AEs according to NCI-CTCAE v4.03	451	3 patients received 0.5 mg/kg Q2W	26 Aug 2020

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Study number	Study design	Patient population	Safety assessments	Number of treated patients	Tislelizumab dose and other treatment as specified ^a	Data cutoff date
	escalation and expansion study to investigate the safety, PK, and antitumor activities of tislelizumab	(11.0%), NSCLC (10.9%), and “Other” (17.7%); all other ^f tumor types occurred in < 4.7% of patients and included 26 ESCC patients ^g (5.8%)	DLTs, deaths, changes in vital signs, physical findings, ECG, ECOG Performance Status, and clinical laboratory results		26 patients received 2 mg/kg Q2W 26 patients received 5 mg/kg Q2W 7 patients received 10 mg/kg Q2W 21 patients received 2 mg/kg Q3W 355 patients received 5 mg/kg Q3W 13 patients received 200 mg Q3W	
303	Phase 3, randomized, open-label, multicenter study	Patients with locally advanced or metastatic NSCLC that progressed on a prior platinum-containing regimen	Incidence and severity of AEs according to NCI-CTCAE v4.03 Changes in vital signs, physical findings, ECG, ECOG Performance Status,	792	534 patients received tislelizumab 200 mg Q3W 258 patients received docetaxel	10 Aug 2020

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Study number	Study design	Patient population	Safety assessments	Number of treated patients	Tislelizumab dose and other treatment as specified ^a	Data cutoff date
			ophthalmologic findings, and clinical laboratory results			
208	Phase 2, single-arm, open-label, multicenter study to evaluate the efficacy, safety, and PK of tislelizumab as monotherapy treatment	Patients with previously treated unresectable HCC who had received ≥ 1 line of prior systemic therapy	Incidence and severity of AEs according to NCI-CTCAE v4.03 Changes in vital signs, physical findings, ECG, ECOG Performance Status, ophthalmologic findings, and clinical laboratory results	249	249 patients received 200 mg Q3W	27 Feb 2020
204	Phase 2, single-arm, multicenter, study to evaluate the efficacy and safety of tislelizumab	Patients with PD-L1 high expression, locally advanced or metastatic UC who have progressed during or following a platinum-containing regimen	Incidence and severity of AEs according to NCI-CTCAE v4.03 Changes in vital signs, physical findings, and clinical laboratory results	113	113 patients received 200 mg Q3W	16 Sep 2019
203	Phase 2, open-label, multicenter, single-arm study to evaluate tislelizumab therapy	Adult patients with relapsed or refractory cHL	Incidence and severity of AEs according to NCI-CTCAE v4.03 Changes in vital signs, physical findings, ECG, ECOG Performance Status, and clinical laboratory results	70	70 patients received 200 mg Q3W	26 Nov 2018

Undefined Abbreviations: W1D1, Week 1 Day 1; W5D1 Q3W, once every 3 weeks from Week 5 Day 1.

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^bThe dose regimen of 200 mg W1D1, W5D1 Q3W means dosing with 200 mg on Day 1 with intervals of 4 weeks for Cycle 1 and once every 3 weeks for cycles thereafter.

^cStudy 102 CSR Table 10

^dOther: CRC, ESCC, GC, HCC, HNSCC, OC, RCC, SCNEC, TNBC, UC, or other tumors with known MSI-H or dMMR, and NPC.

^eThe 26 ESCC patients received tislelizumab 200 mg Q3W.

^fOther: CCC, CRC, ESCC, GIST, HNSCC, MCC, MM, NSCLC, PC, RCC, SCC, UC, UM, and TNBC.

^gThe 26 ESCC patients received tislelizumab 5 mg/kg Q3W.

The Applicant's Position:

The size of the safety database in this submission is adequate to support the use of tislelizumab monotherapy in the treatment of patients with unresectable recurrent locally advanced or metastatic ESCC after prior systemic therapy.

The FDA's Assessment:

FDA agrees with the summary description of the studies used to assess the safety of tislelizumab and agrees that the size of the safety database in this submission is adequate to characterize the safety profile of tislelizumab in this setting.

8.2.2. Safety Review Approach

The safety data package in support of this submission included the following 3 patient populations:

Study 302 population (N = 495) included patients from the global Phase 3 study evaluating tislelizumab monotherapy (Tislelizumab Arm; n = 255) versus ICC of paclitaxel, docetaxel, or irinotecan (ICC Arm; n = 240) as the treatment for patients with ESCC after prior systemic therapy.

The ESCC population (N = 307) included patients with ESCC who received tislelizumab from Study 302 (N = 255), Study 102 (N = 26), and Study 001 (N = 26). The safety results from the ESCC population were similar to that of the Study 302 population.

The All Doses All Indications population (N = 1972) included patients treated with tislelizumab monotherapy from studies evaluating tislelizumab in multiple tumor types with available CSRs. This included the above 3 studies plus Studies 303, 208, 204, and 203. Patients who received comparator agents in these studies are not included in this population.

The goal of this analysis of an integrated safety population is to provide a comprehensive safety profile for tislelizumab and to provide supportive data for the safety profile of tislelizumab in a larger population, as well as to identify possible rare safety signals. The analysis of this population reflects the full experience with tislelizumab in advanced cancers, including ESCC.

This integrated safety population includes patients with different tumor types who received ≥ 1 dose of tislelizumab monotherapy. Of these, 77.8% of patients received tislelizumab 200 mg once every 3 weeks. Patients in the supportive Studies 102, 303, 208, 204, and 203 received 200 mg once every 3 weeks, while patients in Study 001 received a variety of dose regimens, including 200 mg once every 3 weeks.

All patients in Study 102 received 200 mg once every 3 weeks; 57 of the 300 patients (PK substudy) had a first-cycle duration of 28-days instead of 21 days, which was not considered to be a different dose regimen.

Tislelizumab was administered intravenously at a dose of 200 mg once every 3 weeks in all studies, with the exception of Study 001 in which tislelizumab was administered at either 200 mg once every 3 weeks, or after a weight based- regimens including 0.5, 2.0, 5.0, 10.0 mg/kg once every 2 weeks, 2.0 and 5.0 mg/kg once every 3 weeks. Approximately 97% of the patients in the All Doses All Indications population received tislelizumab 200 mg once every 3 weeks or 2.0 and 5.0 mg/kg once every 3 weeks. Key features of all studies are summarized in [Table 26](#).

The Applicant's Position:

The totality of the safety package is sufficient to characterize the safety profile of tislelizumab monotherapy and to guide the management of risks associated with tislelizumab as a treatment for ESCC. The safety review is focused on patients who received the dose of 200 mg once every 3 weeks ([Table 26](#)) as recommended by the proposed label.

The FDA's Assessment:

FDA agrees that the size of the safety database in this submission is adequate to characterize the safety profile of tislelizumab for the treatment of ESCC. For pivotal Study 302, the safety population consists of 255 patients who received tislelizumab 200 mg IV q3 weeks and 240 patients who received ICC. For the ISS, the safety population consists of 1,972 patients who received tislelizumab across seven studies: Study 102, Study 203, Study 204, Study 208, Study 302, Study 303, and Study 001, as described in the Applicant's table above. Although FDA's assessment of the safety of tislelizumab for the proposed indication is based on the overall safety data submitted in this Application, the review is focused on the results of RATIONALE-302.

The Applicant included analyses of relatedness of AEs. Following standard FDA review practices, FDA review did not include relatedness in the safety analyses as the safety profile is best assessed through the comparison with the control arm. Thus, the FDA will not comment on the Applicant's analysis of "drug-related" TEAEs, except for Grade 5 TEAEs.

8.2.3. Review of the Safety Database

Overall Exposure

Data:

In Study 302, a near 2-fold longer median duration of exposure was observed in the Tislelizumab Arm compared with the ICC Arm (2.76 months versus 1.49 months, respectively). The proportion of patients who received ≥ 6 months of exposure was higher in the Tislelizumab Arm (25.5%) compared with the ICC Arm (8.8%). The median relative dose intensity in the Tislelizumab Arm was 100% compared with 89.4% for the ICC Arm. These differences are likely the result of an improvement in efficacy and a better tolerated safety profile for

tislelizumab compared with chemotherapy. With a quarter of the patients receiving tislelizumab for more than 6 months in Study 302 and a median follow-up duration of 8.51 months, the overall exposure for tislelizumab was considered appropriate for an evaluation of safety in patients who were representative of the intended target patient population.

Given the differences in exposure between the two arms described above, exposure-adjusted incidence rates were provided for key adverse event analyses (all grades, serious events, fatal events) of the Study 302 population in addition to overall event incidence.

The exposure for patients in Study 302 was lower than the exposure for patients in the All Doses All Indications population for median duration (2.76 months versus 4.11 months, respectively), and fewer patients in Study 302 received at least 6 months of treatment (25.5% versus 37.3%). This may reflect differences in study population, line of therapy, study timing, and tumor type. For example, Study 302 enrolled more patients with ECOG PS score of 1 (74.5%) and had a population with more comorbidities associated with tobacco and alcohol use (73.3% current or former smoking status, 70.6% current or former alcohol use) than All Doses All Indications population (66.6% ECOG PS score of 1, 56.8% current or former smoking status, 30.8% current or former alcohol use); these are recognized differences between advanced ESCC and other tumor types.

A difference in tislelizumab regimen existed between the Study 302 population and the All Doses All Indications population. The Study 302 population was treated with 200 mg once every 3 weeks regimen; the All Doses All Indications population was treated with 200 mg once every 3 weeks regimen (Studies 302, 102, 303, 208, 204, 203, and 001 [Part 3]) or weight-based regimens including 0.5, 2.0, 5.0, 10.0 mg/kg once every 2 weeks, 2.0 and 5.0 mg/kg once every 3 weeks (Study 001 Parts 1 and 2). Only a small proportion of patients (3.2%) in the All Doses All Indications population were treated with a regimen outside of these 3 dose regimens; hence, the difference in tislelizumab regimen is unlikely to impact the assessment of tislelizumab safety.

The Applicant's Position:

The Tislelizumab Arm had greater treatment exposure than the ICC Arm with longer median duration of exposure, a higher proportion of patients receiving ≥ 6 months of study treatment, and a higher median relative dose intensity. These differences are likely the result of an improvement in efficacy and a better tolerability profile for tislelizumab compared with chemotherapy.

The FDA's Assessment:

FDA verified the results summarized above. Median treatment duration in the tislelizumab arm was 2.8 months compared to the ICC arm (1.5 months) and with the approximately 10% higher median relative dose intensity in the tislelizumab arm compared to the ICC arm in Study 302. FDA would not necessarily agree with the Applicant's conclusions that the tislelizumab is better

tolerated. Although patients receiving anti-PD-1 therapy may have less myelosuppression and short-term GI toxicity than chemotherapy, tislelizumab may cause severe immune related events in a subset of patients, dramatically impacting those patients' quality of life.

Relevant characteristics of the safety population:

Data:

Patient Disposition

A higher proportion of patients remained on study treatment in the Tislelizumab Arm (6.3%) than in the ICC Arm (0.4%), as of the data cutoff date. Disease progression was the primary reason for treatment discontinuation in both arms, and a higher proportion was observed in the Tislelizumab Arm (69.4%) than the ICC Arm (55.4%). Adverse event was the second most common reason for treatment discontinuation in both arms, and a lower proportion of patients reported discontinuation due to adverse event in the Tislelizumab Arm (12.2%) than the ICC Arm (18.3%). These results would suggest that tislelizumab has a better-tolerated safety profile than chemotherapy.

Patients in the ICC Arm discontinued study treatment due to patient withdrawal (12.1%) and investigator decision (2.1%) in higher proportions compared with patients in the Tislelizumab Arm (2.4% patient withdrawal, 0% investigator withdrawal). As described below, the safety profile of tislelizumab in Study 302 was similar to the safety profile of the ESCC population and All Doses All Indications; this similarity suggests no major impact from the open-label design.

Demographic and Baseline Characteristics

The demographic and baseline characteristics were balanced between the 2 arms in the key characteristics (Table 17). The higher proportion of patients in the Tislelizumab Arm (34.9%) compared with patients in the ICC Arm (27.1%) whose tumor had a known PD-L1 expression status of vCPS $\geq 10\%$ is not known to impact clinical safety. The Study 302 population was consistent with the protocol-defined eligibility criteria and was representative of the intended target patient population.

All Doses All Indications Population

The patterns of patient disposition and reason for discontinuation in the All Doses All Indications population were each similar to those in the Study 302 Tislelizumab Arm. Disease progression was the primary reason for study treatment discontinuation, and death was the primary reason for discontinuation from the study. The demographic and baseline characteristics for patients in the All Doses All Indications population were consistent with those in Study 302 Tislelizumab Arm.. The medical history and prior anticancer therapy reflected the differences in tumor types between the Study 302 population and the All Doses All Indications population.

The Applicant's Position:

The demographics and baseline characteristics were balanced between arms, except for PD-L1 expression status, where a higher proportion of patients in the Tislelizumab Arm had a PD-L1 expression status of vCPS $\geq 10\%$. Patients included in the safety datasets are representative of US patients with advanced or metastatic ESCC following prior systemic therapy

The FDA's Assessment:

Table 17 in Section 8 described the demographics of the overall population. However, of the randomized patients, a total of 17 patients (one randomized to receive tislelizumab [0.4%] and 16 [16.3%] randomized to receive ICC) did not receive any study treatment. The most common primary reason for not receiving study treatment in the ICC Arm was "withdrawal by subject" (11 patients [4.3%]) which may be related to patients not wanting to receive standard cytotoxic chemotherapy on this open-label study. The demographics of the safety population were similar to that of the efficacy population and was generally balanced between the 2 arms as shown in FDA's Table 28, below.

Table 28. RATIONALE-302: Demographics of Safety Population

	TISLELIZUMAB N = 255 N (%)	ICC N = 240 N (%)
Gender		
M	216 (85)	204 (85)
F	39 (15)	36 (15)
Age		
Mean (SD)	61 (8)	62 (8)
Median (Min - Max)	62 (40 - 83)	63 (35 - 81)
Age Group		
< 65	157 (62)	149 (62)
≥ 65	98 (38)	91 (38)
ECOG		
1	190 (75)	186 (78)
0	65 (25)	54 (23)
Race		
Asian	201 (79)	194 (81)
White	52 (20)	42 (18)
Unknown	1 (0.4)	2 (0.8)
Not Reported	1 (0.4)	0 (0)

	TISLELIZUMAB N = 255 N (%)	ICC N = 240 N (%)
Black or African American	0 (0)	1 (0.4)
Other	0 (0)	1 (0.4)
Ethnicity		
Not Hispanic or Latino	251 (98)	236 (98)
Hispanic or Latino	2 (0.8)	2 (0.8)
Unknown	1 (0.4)	2 (0.8)
Not Reported	1 (0.4)	0 (0)
Country		
China	146 (57)	140 (58)
Japan	25 (10)	23 (10)
France	20 (8)	9 (3.8)
Korea	15 (6)	16 (7)
Taiwan	15 (6)	12 (5)
Spain	13 (5)	10 (4.2)
Belgium	6 (2.4)	7 (2.9)
Italy	5 (2.0)	5 (2.1)
Great Britain	4 (1.6)	12 (5)
Germany	4 (1.6)	6 (2.5)
USA	2 (0.8)	0 (0)

Source: ADL (Subject-Level Analysis Dataset) - 2021-07-12. Variables used: USUBJID, TRT01A, SAFFL, SEX, AGE, AGEGR1, ECOGBL, RACE, ETHNIC, COUNTRY

Regarding patient disposition, FDA analysis confirms that a higher percentage of patients in the ICC arm compared to the tislelizumab arm had drug interruptions due to any-cause AEs (33% vs 23%) and permanent discontinuations due to any-cause AEs (27% vs 19%).

FDA would not concur with the Applicant's statements regarding the better tolerated safety profile of tislelizumab for the reasons described in the prior section of this review.

8.2.4. Adequacy of the safety database:

Data:

The totality of the safety package is sufficient to characterize the safety profile of tislelizumab and to guide the management of risks associated with tislelizumab as a treatment for recurrent,

locally advanced, metastatic ESCC after prior systemic treatment. The overview of safety focuses on safety data from the Study 302 population and includes safety data from the pooled populations where relevant (see Table 26). For data integration, adverse event preferred terms (PTs) and system organ classes were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0. Adverse event severity grading was based on the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03.

The Applicant's Position:

Study 302 was designed and initiated when single-agent chemotherapy was considered standard of care and the study design enrolled patients with advanced unresectable/metastatic ESCC that has progressed during or after first line therapy.

A potential weakness in the design of Study 302 is the open-label identification of the specific drug, whether tislelizumab or one of the 3 chemotherapeutic agents, assigned to the patient. This element of the study may bias the reporting of adverse events and may have influenced the higher withdrawal rate by patient and by investigator seen in the ICC Arm compared with the Tislelizumab Arm. However, within the analyses of safety data, no obvious impact on the safety results was noted.

Regardless of the limitations noted, the totality of the safety package is sufficient to characterize the safety profile of tislelizumab and to guide the management of risks associated with tislelizumab as a treatment for ESCC.

The FDA's Assessment:

FDA agrees that the safety database is adequate to evaluate the safety of tislelizumab compared to single-agent chemotherapy in this setting. See FDA's comments in Section 8.2.1, above.

8.2.5. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Data:

The clinical sites for the safety analysis groups were monitored by clinical research associates following study-specific monitoring plans for consistency. Data were queried per study-specific data management plans. Additionally, external and internal Safety Monitoring Committee (SMC) reviewed safety data for all studies.

The Applicant's Position:

No issues were identified regarding data integrity or submission quality that had an effect on the safety review.

The FDA's Assessment:

Prior to conducting the safety review, FDA's Office of Computational Science (OCS) generated a CoreDF report of data quality which did not identify any significant or unusual data issues. During the safety review, FDA did not identify any significant data issues that would impact the safety review or overall conclusions.

Categorization of Adverse Event

Data:

All adverse event summaries were based on the Safety Analysis Set. A treatment-emergent adverse event was defined as an adverse event that had an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose of study treatment up to 30 days after study treatment discontinuation or initiation of a new anticancer therapy, whichever occurred first. Treatment-emergent adverse events also included all immune-mediated adverse events (for the Tislelizumab Arm) up to 90 days after the last dose of study treatment regardless of whether a patient started a new anticancer therapy. Only treatment-emergent adverse events were included in the summary tables.

The adverse event verbatim descriptions (investigator's description from the eCRF) were classified into standardized medical terminology using MedDRA. Adverse events were coded to MedDRA (Version 23.0) lower-level term closest to the verbatim term. The linked MedDRA System Organ Class (SOC) and PT were also classified.

The incidence of adverse events was summarized as the number (percentage) of patients with adverse events by SOC, PT, severity, and relationship to study drug. Patients with multiple occurrences of the same adverse event within a specific SOC and PT were counted only once within the SOC and PT, and the maximum grade per NCI-CTCAE (Version 4.03) was used. Serious adverse events, adverse events of $\geq$ Grade 3, adverse events leading to treatment discontinuation or dose modification, and adverse events leading to death were also summarized by SOC, PT, and relationship to study drug.

All deaths and causes of death were summarized, including those that occurred during the study treatment period and those reported during the survival follow-up period after treatment completion/discontinuation.

Immune-mediated adverse events were identified according a 2-step process which included generation of a potential immune-mediated adverse event list and medical evaluation of potential immune-mediated adverse events. The incidence of immune-mediated adverse event (for all grades and $\geq$ Grade 3) was summarized by category and worst grade per NCI-CTCAE (Version 4.03). The immune-mediated adverse events were also summarized by outcome and category. The immune-mediated adverse events leading to treatment discontinuation, dose modification, and death were summarized by category.

Infusion-related reactions were summarized based on the adverse event verbatim terms reported by the investigator and the list of symptoms/signs of infusion-related reactions outlined in the protocol and their association with a tislelizumab infusion in terms of causality and onset time.

If the adverse event term did not include the term infusion-related reactions, but met all of the following criteria:

- one or more of the infusion related reactions-associated symptoms per protocol
- occurred up to 1 day after the onset of the event
- deemed related to tislelizumab by investigator

the terms were firstly reviewed by the medical monitor, and then the investigator was queried to clarify if the event was considered an infusion related reactions, in which case, the adverse event term would have been updated to include the term infusion-related reactions. Infusion-related reactions were summarized by SOC, PT, and worst grade. Infusion related reactions leading to treatment discontinuation or dose modification were summarized by PT level.

The Applicant's Position:

Adverse events were collected and analyzed as described above.

The FDA's Assessment:

National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03 were used to assess the severity of all TEAEs. The MedDRA version 23.0 dictionary was used to code TEAE data. TEAEs were assessed from the time of study treatment initiation and for 30 days after the last dose of study treatment. Because of the long half-life of monoclonal antibodies and the potential for late-onset treatment-emergent imAEs beyond the 30-day period following the last dose of tislelizumab, imAEs were also followed for 90 days after the last dose of study treatment per the study protocol.

Note that FDA, as indicated above, does not consider Applicant's attribution of whether an AE was drug-related or not when reviewing safety data.

Routine Clinical Tests

Data:

Key assessments included routine clinical laboratory tests (hematology, chemistry, thyroid function), ECGs, vital sign assessments, and pregnancy tests ([Table 12](#)).

The Applicant's Position:

Laboratory assessments were carried out as specified in the BGB-A317-302 protocol.

The FDA's Assessment:

Overall, the routine clinical laboratory tests and physical exam elements that were performed in Study 302 are considered adequate for the evaluation of safety of tislelizumab in the target patient population.

8.2.6. Safety Results

Deaths

Data:

Deaths due to adverse events (not due to ESCC) were reported with similar incidence in both arms (5.5% [14 patients] in the Tislelizumab Arm versus 5.8% [14 patients] in the ICC Arm) (Table 28).

Table 27 provides a summary of all fatal adverse events as documented on the Study 302 adverse event case report form, including events in 21 patients in the tislelizumab arm for whom “disease under study” (ie, ESCC) was reported as the primary cause of death. A review of the events indicates no clustering of event types, except for effects typically associated with ESCC disease progression. None of the deaths was associated with an immune-associated adverse event or an infusion related-reaction. Three patients (1.2%) in the Tislelizumab Arm and 1 patient (0.4%) in the ICC Arm died of ‘multiple organ dysfunction syndrome’. These 3 multi-organ events in the Tislelizumab Arm were considered by the Investigator to be due to the underlying ESCC and were unrelated to study drug, whereas the multi-organ failure in the ICC Arm was considered related to study drug (irinotecan). Deaths reported as due to “indeterminate” cause (7.1% in each treatment arm) or “other” (2.7% Tislelizumab Arm; 2.9% ICC Arm) occurred with an onset of > 30 days after the last dose of study drug (ie, not treatment-emergent). Although the exact causes of deaths remain unclear, they were not reported by the Investigator to be due to adverse events and are presumed likely therefore to be disease related or of unknown etiology.

To account for the difference between the treatment arms in duration of exposure, an exposure-adjusted assessment of adverse events leading to death was conducted, which showed a notably lower rate in the Tislelizumab Arm (2.8 deaths per 100 person-months) compared with the ICC Arm (4.7 deaths per 100 person-months).

An assessment of deaths was conducted by geographic region and by baseline PD-L1 expression status. The overall trends and reasons for death in these subgroups were similar to those of the overall population for both the Tislelizumab and ICC Arms.

Table 27. BeiGene: Summary of All Deaths (Safety Analysis Set)

	Tislelizumab (N = 255) n (%)	ICC (N = 240) n (%)
Total Number of Deaths	196 (76.9)	205 (85.4)
Cause of death		
Disease under study	152 (59.6)	163 (67.9)
Indeterminate	18 (7.1)	17 (7.1)
Adverse Event	15 (5.9)	15 (6.3)
Concurrent illness	4 (1.6)	3 (1.3)
Other	7 (2.7)	7 (2.9)
Deaths within 30 days of last dose date	31 (12.2)	20 (8.3)
Cause of death		
Disease under study	18 (7.1)	9 (3.8)
Adverse Event	12 (4.7)	11 (4.6)
Concurrent illness ^a	1 (0.4)	0 (0.0)
Deaths > 30 days of last dose date	165 (64.7)	185 (77.1)
Cause of death		
Disease under study ^b	134 (52.5)	154 (64.2)
Indeterminate	18 (7.1)	17 (7.1)
Adverse Event ^c	3 (1.2)	4 (1.7)
Concurrent illness	3 (1.2)	3 (1.3)
Other	7 (2.7)	7 (2.9)

Percentages were based on N.

* Patients with at least one study medication are included.

^a The death (due to concurrent illness) of 1 patient in tislelizumab arm occurred after the initiation of new anticancer therapy and therefore was not reported as an adverse event.

^b Death events of 3 patients in the tislelizumab arm and 5 patients in the ICC arm had its event onset date within 30 days after last dose and therefore were reported to be an adverse event.

^c The adverse event which was reported to be the cause of death in 1 patient in each arm had its event onset date > 30 days after last dose and was not considered related to the study drug by the investigator, therefore, those two adverse events did not meet the definition of TEAE.

Table 28. BeiGene: Treatment-Emergent Adverse Events Leading to Death by System Organ Class and Preferred Term Excluding Death due to Disease Under Study (Safety Analysis Set)

System Organ Class Preferred Term	Tislelizumab (N = 255) n (%)	ICC (N = 240) n (%)
Patients With at Least One TEAE Leading to Death Excluding Death due to Disease Under Study	14 (5.5)	14 (5.8)
Respiratory, thoracic and mediastinal disorders	5 (2.0)	1 (0.4)
Bronchiectasis	1 (0.4)	0 (0.0)
Haemoptysis	1 (0.4)	0 (0.0)
Pulmonary arterial hypertension	1 (0.4)	0 (0.0)
Pulmonary embolism	1 (0.4)	0 (0.0)
Pulmonary haemorrhage	1 (0.4)	0 (0.0)
Respiratory failure	0 (0.0)	1 (0.4)
General disorders and administration site conditions	3 (1.2)	5 (2.1)
Death	2 (0.8)	3 (1.3)
Sudden death	1 (0.4)	1 (0.4)
Multiple organ dysfunction syndrome	0 (0.0)	1 (0.4)
Infections and infestations	3 (1.2)	5 (2.1)
Pneumonia	3 (1.2)	1 (0.4)
COVID-19	0 (0.0)	1 (0.4)
Septic shock	0 (0.0)	3 (1.3)
Cardiac disorders	1 (0.4)	0 (0.0)
Cardio-respiratory arrest	1 (0.4)	0 (0.0)
Gastrointestinal disorders	1 (0.4)	2 (0.8)
Upper gastrointestinal haemorrhage	1 (0.4)	1 (0.4)
Intestinal ischaemia	0 (0.0)	1 (0.4)
Investigations	1 (0.4)	0 (0.0)
Platelet count decreased	1 (0.4)	0 (0.0)
Blood and lymphatic system disorders	0 (0.0)	1 (0.4)
Febrile neutropenia	0 (0.0)	1 (0.4)

Notes: Percentages are based on N, unless otherwise noted.

Patients with multiple events for a given preferred term and system organ class are counted only once for the preferred term and system organ class, respectively.

Events are sorted by decreasing frequency of system organ class then descending frequency of preferred term within system organ class in the 'Tislelizumab' column.

Adverse events were coded using the MedDRA version 23.0.

Noting the differences in tumor types, disease status, event reporting rules, and durations of follow-up between safety populations, deaths in the All Doses All Indications population, as in Study 302, predominantly occurred > 30 days after the last dose of study drug and were likely due to the underlying malignancies. Treatment-emergent adverse events leading to death occurred in 2.3% of patients in the All Doses All Indications population. Most deaths in the All Doses All Indications population were considered to be unrelated to study drug.

The Applicant's Position:

The majority of deaths were due to disease under study. Deaths due to adverse events (not due to ESCC) were reported in low and similar proportions for both arms (tislelizumab [5.5%] and chemotherapy [5.8%]). The overall trend for death and reason for death were consistent across geographic region and baseline PD-L1 expression status.

The FDA's Assessment:

FDA's analysis identified the same number of total deaths and deaths beyond 30 days after the last dose as the Applicant's Table 27. For deaths within 30 days after the last dose, FDA's analysis counted fewer deaths than the Applicant for both the tislelizumab arm (n = 13) and the ICC arm (n = 11). The reason for this discrepancy is the Applicant counting deaths due to disease progression as fatal AEs in its ADAE dataset (but not the ADSL dataset). See also the discussion of Table 29, below. Regardless, FDA agrees that there were more deaths in the ICC arm compared to the tislelizumab arm and that, in both arms, deaths were most often due to progression of disease.

FDA further examined the total number of deaths in the tislelizumab arm that were classified in the datasets as being due to "indeterminate" (n = 18), "other" (n = 7), and "concurrent illness" (n = 4). After reviewing these CRFs and/or narratives, FDA categorizes deaths in the tislelizumab arm as below (Table 29) with deaths in "other" and "concurrent illness" being re-categorized to either disease under study/progression of disease, adverse event, or indeterminate.

Table 29. RATIONALE-302: Total Deaths in Tislelizumab Arm

Total Deaths	196 (77%)
Disease Under Study	157 (62%)
Indeterminate	21 (8%)
Adverse Event	18 (7%)
Other	0
Concurrent Illness	0

For deaths other than those related to disease progression, the cause of death is difficult to

allocate into a single category, as these deaths are often being due to a combination of events involving the disease itself, comorbidities, and AEs due to treatment. As summarized by the Applicant above, all events of multiorgan failure were attributed to therapy in the ICC arm while the single event reported in the tislelizumab arm was attributed to disease progression, highlighting the challenges to interpret some causes of death common to treatment toxicity and disease progression in patients with advanced disease.

FDA does not agree with the Applicant's analysis summarized in Table 27. After further review of the CRFs and/or narratives, in FDA's analysis 18 deaths in the tislelizumab are due to AEs (where tislelizumab may have contributed to the event; however, causality is difficult to determine in all cases). Examination of the specific AEs resulting in death does not indicate a notable imbalance between the study arms and the events leading to death do not appear differ from what is expected in this patient population undergoing treatment. Of note, 4 patients died of hemorrhages in the tislelizumab arm (Table 28).

FDA does not agree with the Applicant's statement that none of the deaths was associated with an immune-associated adverse event. One patient (ID# (b) (6)) on the tislelizumab arm died from hepatic failure on Day 45 of the study; based on the narrative, immune-mediated hepatitis could not be ruled out.

Serious Adverse Events

Data:

In Study 302, serious adverse events (SAEs) were reported with similar overall incidence in the two treatment arms (41.2% Tislelizumab Arm versus 43.8% ICC Arm). The exposure adjusted event rates for SAEs were lower in the Tislelizumab Arm compared with the ICC Arm at 12.5 per 100 person-months versus 28.9 per 100 person-months, respectively.

By preferred term, pneumonia was the most common SAE reported for both treatment arms (7.1% in both arms) (Table 30). Dysphagia was the only SAE that occurred with $\geq 2\%$ higher incidence in the Tislelizumab Arm compared with the ICC Arm (4.7% versus 1.7%, respectively); the events were generally associated with the underlying ESCC and were not considered treatment related.

SAEs reported with $\geq 2\%$ lower incidence in the Tislelizumab Arm compared with the ICC Arm included diarrhea (0% versus 3.3%), decreased appetite (0.4% versus 2.5%), febrile neutropenia (0% versus 3.3%), neutrophil count decreased (0% versus 4.2%), and white blood cell decreased (0% versus 3.3%).

In both arms, most SAEs were considered unrelated to study drug. The incidence of treatment-related SAEs was lower in the Tislelizumab Arm than in the ICC Arm (14.1% versus 19.6%, respectively) even without taking exposure-adjusted event rates into consideration.

Table 30. BeiGene: Serious Treatment-Emergent Adverse Events With an Incidence $\geq$ 1% by Preferred Term (302 Safety Analysis Set)

Preferred Term	Tislelizumab (N = 255) n (%)	ICC (N = 240) n (%)
Patients with at least one Serious TEAE	105 (41.2)	105 (43.8)
Pneumonia	18 (7.1)	17 (7.1)
Dysphagia	12 (4.7)	4 (1.7)
Oesophageal obstruction	5 (2.0)	1 (0.4)
Pneumonitis	5 (2.0)	2 (0.8)
Hyponatraemia	4 (1.6)	0 (0.0)
Upper gastrointestinal haemorrhage	4 (1.6)	4 (1.7)
Dyspnoea	3 (1.2)	1 (0.4)
General physical health deterioration	3 (1.2)	4 (1.7)
Immune-mediated pneumonitis	3 (1.2)	0 (0.0)
Multiple organ dysfunction syndrome	3 (1.2)	1 (0.4)
Oesophageal stenosis	3 (1.2)	0 (0.0)
Pleural effusion	3 (1.2)	4 (1.7)
Pneumonia aspiration	3 (1.2)	1 (0.4)
Death	2 (0.8)	4 (1.7)
Vomiting	2 (0.8)	3 (1.3)
Acquired tracheo-oesophageal fistula	1 (0.4)	4 (1.7)
Anaemia	1 (0.4)	3 (1.3)
Decreased appetite	1 (0.4)	6 (2.5)
Septic shock	1 (0.4)	4 (1.7)
Diarrhoea	0 (0.0)	8 (3.3)
Febrile neutropenia	0 (0.0)	8 (3.3)
Leukopenia	0 (0.0)	4 (1.7)
Nausea	0 (0.0)	4 (1.7)
Neutrophil count decreased	0 (0.0)	10 (4.2)
White blood cell count decreased	0 (0.0)	8 (3.3)

Notes: Percentages are based on N, unless otherwise noted.

Only preferred terms with an incidence $\geq$ 1% in either 'Tislelizumab' or 'ICC' column are reported.

Patients with multiple events for a given preferred term are counted only once for the preferred term.

Events are sorted by decreasing frequency of preferred term in the 'Tislelizumab' column.

Adverse events were coded using the MedDRA version 23.0.

The Applicant's Position:

As in Study 302, most SAEs in the ESCC and All Doses All Indications populations were considered unrelated to study drug. The incidence and pattern of SAEs in Study 302

Tislelizumab Arm were consistent with those in the All dose All Indications population (34.5%).

The FDA's Assessment:

FDA analyses agree with incidence of SAEs per treatment arm. FDA's analysis of SAEs is summarized in Table 31 below.

Table 31. RATIONALE-302: SAEs >= 1% in Either Treatment Arm

	TISLELIZUMAB N = 255 N (%)	ICC N = 240 N (%)
Patients with serious AEs	105 (41)	105 (44)
Gastrointestinal Disorders		
Dysphagia	12 (4.7)	4 (1.7)
Esophageal Obstruction/Stenosis	8 (3.1)	1 (0.4)
Esophageal Fistula	6 (2.3)	6 (2.5)
Vomiting (GT)	2 (0.8)	3 (1.3)
Diarrhea (GT)	1 (0.4)	9 (3.8)
Nausea	0 (0)	4 (1.7)
Infections and Infestations		
Pneumonia (GT)	22 (9)	18 (8)
Septic Shock	1 (0.4)	4 (1.7)
Respiratory, Thoracic and Mediastinal Disorders		
Pneumonitis (GT)	8 (3.1)	2 (0.8)
Dyspnea (GT)	3 (1.2)	1 (0.4)
Pleural Effusion	3 (1.2)	4 (1.7)
General Disorders and Administration Site Conditions		
General Physical Health Deterioration	3 (1.2)	4 (1.7)
Multiple Organ Dysfunction Syndrome	3 (1.2)	1 (0.4)
Death	2 (0.8)	4 (1.7)
Vascular Disorders		
Hemorrhage (GT)	11 (4.3)	10 (4.2)
Metabolism and Nutrition Disorders		
Hyponatremia	4 (1.6)	0 (0)
Decreased Appetite	1 (0.4)	6 (2.5)
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal Pain (GT)	3 (1.2)	1 (0.4)

	TISLELIZUMAB N = 255 N (%)	ICC N = 240 N (%)
Blood and Lymphatic System Disorders		
Anemia	1 (0.4)	3 (1.3)
Febrile Neutropenia	0 (0)	8 (3.3)
Leukopenia	0 (0)	4 (1.7)
Investigations		
Neutrophil Count Decreased	0 (0)	10 (4.2)
White Blood Cell Count Decreased	0 (0)	8 (3.3)

Group Pneumonia (GT) includes PT terms PNEUMONIA, PNEUMONIA ASPIRATION, PNEUMONIA BACTERIAL, Group Hemorrhage (GT) includes PT terms UPPER GASTROINTESTINAL HEMORRHAGE, HEMOPTYSIS, TUMOR HEMORRHAGE, GASTROINTESTINAL HEMORRHAGE, PULMONARY HEMORRHAGE, ESOPHAGEAL HEMORRHAGE, GASTRIC HEMORRHAGE, TRACHEAL HEMORRHAGE, Group Diarrhea (GT) includes PT terms DIARRHEA, COLITIS, Group Pneumonitis (GT) includes PT terms PNEUMONITIS, IMMUNE-MEDIATED PNEUMONITIS, Group Vomiting (GT) includes PT terms VOMITING, Group Pyrexia (GT) includes PT terms PYREXIA, Group Dyspnea (GT) includes PT terms DYSPNEA, Group Musculoskeletal Pain (GT) includes PT terms BACK PAIN, BONE PAIN, MUSCULOSKELETAL CHEST PAIN, Group Fatigue (GT) includes PT terms FATIGUE, ASTHENIA, , Source: ADSL (Subject-Level Analysis Dataset) - 2021-07-12, ADAE (Adverse Event Analysis Dataset) - 2021-07-12. Variables used: USUBJID, TRT01A, SAFFL, TRTEMFL, AEDECOD, AETOXGRN, AEACN, AACN, AEBODSYS, AESER

FDA's analysis concurs with that of the Applicant regarding the SAEs that occurred at $\geq 1\%$ in either arm with the following notes and/or exceptions below:

- Grouping terms for esophageal fistulas (including esophagomediastinal, tracheoesophageal, and esophagobronchial), incidence for this event is 2.3% and 2.5% in the tislelizumab and ICC arms, respectively. Given the nature of ESCC, esophageal fistulas are an important AE to monitor for, regardless of treatment modality.
- FDA combined diarrhea and colitis into one grouped-term (GT) and calculated the incidence of this event as 0.4% and 3.8% in the tislelizumab and ICC arms respectively.
- FDA combined aspiration pneumonia with pneumonia to calculate the incidence as 9% and 8% in the tislelizumab and ICC arms, respectively.
- FDA combined hemorrhage terms to calculate the incidence as 4.3% and 4.2% in the tislelizumab and ICC arms, respectively.
- FDA combined musculoskeletal pain terms to calculate the incidence as 1.2% and 0.4% in the tislelizumab and ICC arms, respectively.

The SAEs noted above are generally consistent with ESCC or are often associated with cytotoxic chemotherapy (e.g. diarrhea, nausea, febrile neutropenia, decreased neutrophil count, and decreased white blood cell count). For both the tislelizumab arm and the ICC arm, pneumonia was the most frequently reported SAE, as noted by the Applicant, above.

SAEs of dysphagia and pneumonitis appeared to occur more frequently in the tislelizumab arm compared to the ICC arm. The reason for dysphagia is unclear but pneumonitis is a known risk from anti-PD1(L1) antibodies.

Dropouts and/or Discontinuations Due to Adverse Effects

Data:

Tislelizumab was associated with a lower incidence of adverse events (19.2%) that resulted in permanent discontinuation of study treatment compared with the ICC Arm (26.7%) in Study 302. A general trend of higher event rate of adverse events leading to treatment discontinuation was observed across multiple preferred terms in the ICC Arm, without clustering in any specific group. Adverse events leading to dropout/treatment discontinuation by region and by baseline PD-L1 expression status showed similar trends across all subgroups and between arms for each subgroup as those seen in the overall population.

The Applicant's Position:

Fewer adverse events leading to treatment discontinuation were observed in patients in the tislelizumab arm compared with patients in the ICC arm.

The FDA's Assessment:

FDA agrees that 19% and 27% of patients permanently discontinued tislelizumab and ICC, respectively, due to AEs. As with SAEs, the events leading to treatment discontinuation are consistent with morbidity associated with ESCC itself as well as treatment toxicity (e.g. pneumonitis for the tislelizumab arm and diarrhea and fatigue for the ICC arm).

The AEs with incidence $\geq 2\%$ that led to permanent discontinuation of tislelizumab were:

- hemorrhage (2.4%)
- pneumonitis (2.4%)
- pneumonia (2%)

The AEs with incidence $\geq 2\%$ that led to permanent discontinuation of ICC were:

- hemorrhage (2.9%)
- pneumonia (2.1%)
- diarrhea (2.1%)
- fatigue (2.1%)

Dose Interruption/Reduction Due to Adverse Effects

Data:

For tislelizumab, dose modification included delays or interruptions in dosing. For ICC, dose reductions were allowed in addition to delays or interruptions. In Study 302, fewer patients in the Tislelizumab Arm (22.7%) required dose modification of study treatment compared with the ICC Arm (47.9%), suggesting that tislelizumab may be better tolerated than ICC.

The Applicant's Position:

Fewer adverse events leading to dose modification were observed in patients in the tislelizumab group compared with patients in the ICC group.

The FDA's Assessment:

FDA agrees with the assessment above in that fewer dose interruptions were observed in the tislelizumab arm (23% by FDA calculation) compared to the ICC arm (~57% by FDA calculation). Management of dose modifications was different between study arms; while the standard of care with immune checkpoints is dose interruptions until recovery, with chemotherapy, often dose delays are followed by dose reductions.

Significant Adverse Events

Data:

Immune-Mediated Adverse Events

Overall, immune-mediated adverse events of any grade were reported in 54 patients (21.2%) treated with tislelizumab (Table 32). The prespecified adverse event searches for Study 302 included events of immune-mediated hypothyroidism, immune-mediated pneumonitis, immune-mediated skin reactions, immune-mediated colitis, immune-mediated hepatitis, immune-mediated myositis/rhabdomyolysis, immune-mediated adrenal insufficiency, immune-mediated myocarditis, and immune-mediated pituitary dysfunction. Note that the terms “immune-related adverse event” and “immune-mediated adverse event” are used interchangeably across various documents in the submission. Also note that the protocol did not specify collection of immune-mediated adverse events for ICC.

Consistent with other anti-PD-L1 inhibitors, tislelizumab was associated with immune-mediated adverse events. In tislelizumab-treated patients in Study 302, 21.2% reported immune-mediated adverse events of any grade, and 3.5% reported immune-mediated adverse events of $\geq$ Grade 3 (Table 32). Serious immune-mediated adverse events were reported for 5.9% of tislelizumab treated- patients. None of the events was fatal.

Table 33 presents a summary of analyses relevant to immune-mediated adverse events, including adverse events by grade, event outcomes (discontinuation, death), and treatments administered. The most common immune-mediated adverse events (any grade) were immune-mediated- hypothyroidism (9.0%), immune-mediated pneumonitis (7.1%), and immune-mediated skin adverse reaction (2.0%). These immune-mediated adverse events led to tislelizumab treatment discontinuation or dose modification (ie, delay or interruption) in 3.1% and 6.3% of patients, respectively. All patients who experienced immune-mediated

hypothyroidism received hormone replacement therapy. High-dose systemic corticosteroids (≥ 40 mg/day prednisone equivalent) were given as an intervention in 22 of the 54 patients (40.7%) who experienced immune-mediated adverse events; none of the patients received other immunosuppressive drugs (eg, Tumor Necrosis Factor (TNF) inhibitors or mycophenolate mofetil).

The above results were consistent with those seen in the All Doses All Indications population, in which immune-mediated adverse events of any grade were reported in 15.5% of patients and immune-mediated adverse events of $\geq$ Grade 3 were reported in 4.5% of patients. Four patients (0.2%) died from an immune-mediated adverse event (3 from immune-mediated pneumonitis, 1 from immune-mediated hepatitis).

Table 32. BeiGene: Overall Summary of Immune-Mediated Treatment-Emergent Adverse Events (Study 302, Safety Analysis Set)

	Tislelizumab (N = 255) n (%)
Patients with at least one Immune-mediated TEAE	54 (21.2)
Immune-mediated TEAE with Grade 3 or Higher	9 (3.5)
Serious Immune-mediated TEAE	15 (5.9)
Immune-mediated TEAE Leading to Treatment Modification	16 (6.3)
Immune-mediated TEAE Leading to Treatment Discontinuation	8 (3.1)
Immune-mediated TEAE Leading to Death	0 (0.0)

Notes: Percentages are based on N, unless otherwise noted.

Patients with multiple events for a given category are counted only once for the category.

Adverse events were coded using the MedDRA version 23.0. f

Table 33. BeiGene:- Immune-Mediated Treatment-Emergent Adverse Events by Category (Study 302, Safety Analysis Set)

Category	Tislelizumab (N = 255) n (%)						
	Any Grade	Grade 3 or Higher	Led to Treatment Discontinuation	Resulted in Death	Received Systemic Corticosteroids ^a	Received Immunosuppressive Drug ^a	Received Hormone Therapy ^a
Patients with at least one Immune-mediated TEAE	54 (21.2)	9 (3.5)	8 (3.1)	0 (0.0)	35 (64.8)	0 (0.0)	23 (42.6)
Immune-mediated hypothyroidism	23 (9.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	23 (100.0)
Immune-mediated pneumonitis	18 (7.1)	3 (1.2)	5 (2.0)	0 (0.0)	18 (100.0)	0 (0.0)	0 (0.0)
Immune-mediated skin adverse reaction	5 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (100.0)	0 (0.0)	0 (0.0)
Immune-mediated colitis	3 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	3 (100.0)	0 (0.0)	0 (0.0)
Immune-mediated hepatitis	3 (1.2)	2 (0.8)	0 (0.0)	0 (0.0)	3 (100.0)	0 (0.0)	0 (0.0)
Immune-mediated myositis/rhabdomyolysis	3 (1.2)	2 (0.8)	2 (0.8)	0 (0.0)	3 (100.0)	0 (0.0)	0 (0.0)
Immune-mediated adrenal insufficiency	2 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	2 (100.0)	0 (0.0)	0 (0.0)
Immune-mediated myocarditis	2 (0.8)	1 (0.4)	1 (0.4)	0 (0.0)	2 (100.0)	0 (0.0)	0 (0.0)

Notes: Percentages are based on N, unless otherwise noted.

Patients with multiple events for a given category are counted only once.

Events are sorted by decreasing frequency of category in the 'Tislelizumab/Any Grade' column.

Adverse event grades are evaluated based on NCI-CTCAE (version 4.03).

Adverse events were coded using the MedDRA version 23.0.

^a Percentages are based on the number of patients with at least one immune-mediated TEAE under any category for the first row and under each category for all other rows

Infusion-Related Reactions (IRRs)

Infusion-related reactions were identified at the study level in accordance with methods specified in each study protocol. In Study 302, infusion-related reactions occurred in 8 patients (3.1%) of the 255 patients treated with tislelizumab (Table 34). The most frequent PTs were pyrexia (4 patients, 1.6%) and rash (3 patients, 1.2%). All events of infusion-related reactions were either Grade 1 or 2 in severity and none led to dose modification. Two of the 8 patients who

experienced infusion-related reactions were treated with corticosteroids, and 7 of 8 events were resolved.

In the All Doses All Indications population, infusion-related reactions occurred in 83 patients (4.2%) of the 1972 patients treated with tislelizumab. The most frequent PTs were pyrexia (40 patients, 2.0%), rash (5 patients, 0.3%), and nausea (5 patients, 0.3%). Events of infusion-related reactions were typically Grade 1 or 2 in severity; only 6 patients (0.3%) in the All Doses All Indications population had events of $\geq$ Grade 3. A Grade 2 infusion-related hypersensitivity reaction occurred in 1 patient (0.1%) in the All Doses All Indications population; no other infusion-related hypersensitivity reactions were reported. Five patients (0.3%) and 21 patients (1.1%) experienced an infusion-related reaction leading to tislelizumab discontinuation or dose modification, respectively. Twenty-six of the 83 patients (31.3%) who experienced infusion-related reactions were treated with corticosteroids, and 79 of 83 cases (95.2%) were resolved.

The Applicant's Position:

Immune-mediated adverse events were generally low grade and responsive to corticosteroids or hormone therapy as needed. Infusion-related reactions were infrequent, low grade, and occurred at a similar incidence in both arms.

The FDA's Assessment:

FDA agrees with the summary results described in the Applicant's Table 32. As noted above, however, FDA considers that there was an event of autoimmune hepatitis leading to fatal hepatic failure; although the Applicant did not flag this event as an imAE flag, inclusion of this patient would not change the incidence of imAEs significantly (55 patients or 21.6%).

Similarly, FDA analysis demonstrates 10 patients (3.9%) who experienced a $\geq$ Grade 3 imAE compared to the Applicant's calculation of 9 patients (3.5%) who experienced a $\geq$ Grade 3 imAE. The following were the Grade $\geq$ 3 imAEs:

- hepatitis (3 patients)
- pneumonitis (3 patients)
- myositis/rhabdomyolysis (2 patients)
- myocarditis (1 patient)
- hypothyroidism (1 patient)

All of these were Grade 3 events except for 1 of the events of hepatitis (Grade 5, as discussed above) and an event of Grade 4 hypothyroidism. FDA analysis agrees with the remaining data in Table 32 including the use of systemic steroids, hormone therapy, and drug discontinuations. Additionally, though not noted in the Applicant's Table 33, above, FDA found 1 patient who experienced immune-mediated pituitary dysfunction (Grade 2). That patient was treated with systemic steroids and was not discontinued from study therapy. This information is consistent with the Applicant's Table 19 in the Clinical Overview document submitted to the BLA.

The events and frequencies of imAEs in Study 302 are similar to those observed with other anti-PD1/L1 antibodies used as monotherapy. While most events are Grade 1-2, these events should be monitored closely in all patients.

FDA analysis of the ISS population (n = 1972) demonstrated similar conclusions as the Applicant. These findings are summarized in Section 5 of the USPI.

FDA agrees with the frequency of IRRs in Study 302 noted by the Applicant. Eight patients (3.1%) in the tislelizumab arm and 11 (4.6%) patients in the ICC arm experienced an IRR. In the tislelizumab arm, the individual AEs reported were pyrexia, rash, hypotension, and pruritus. All of these were Grade 1 events except for one Grade 2 event of pyrexia.

Treatment Emergent Adverse Events and Adverse Reactions

Data:

In Study 302, the overall safety profile of tislelizumab compared favorably with that of chemotherapy (Table 34). Almost all patients in both arms experienced an adverse event: 95.7% for the Tislelizumab Arm and 98.3% for the ICC Arm. The most patients in the Tislelizumab Arm had only low grade (Grades 1 or 2) adverse events; $\geq$ Grade 3 adverse events occurred in 46.3% of patients in that arm. In contrast, the most patients in the ICC Arm had adverse events $\geq$ Grade 3 (67.9%). Treatment-related adverse events across categories were consistently lower in the Tislelizumab Arm compared with the ICC Arm.

Fewer patients in the Tislelizumab Arm experienced adverse events leading to treatment discontinuation (19.2%) or adverse events leading to dose modification (22.7%) compared with patients in the ICC Arm (26.7% and 47.9%, respectively). Serious adverse events occurred at a similar incidence in both arms (41.2% versus 43.8%), although the exposure-adjusted serious adverse events were lower in the Tislelizumab Arm (12.5 per 100 person-months) than in the ICC Arm (28.9 per 100 person-months). Deaths due to any cause in Study 302 occurred in fewer patients who received tislelizumab than ICC (77.0% versus 83.2%, respectively) (Table 27). Deaths due to adverse events occurred in 14 patients in each arm (5.5% tislelizumab; 5.8% ICC).

In the All Doses All Indications population, a similar safety profile was observed compared with the Study 302 population suggesting consistency of the tislelizumab safety profile across multiple tumor types (Table 35)

Table 34. BeiGene: Overall Summary of Treatment-Emergent Adverse Events (Study 302, Safety Analysis Set and All Doses All Indications Safety Analysis Set)

	Study 302		All Doses All Indications
	Tislelizumab (N = 255) n (%)	ICC (N = 240) n (%)	Tislelizumab (N = 1972) n (%)
Patients with at least one TEAE	244 (95.7)	236 (98.3)	1891 (95.9)
Treatment-related TEAE	187 (73.3)	225 (93.8)	1374 (69.7)
TEAE with Grade 3 or Higher	118 (46.3)	163 (67.9)	868 (44.0)
Treatment-related TEAE with Grade 3 or Higher	48 (18.8)	134 (55.8)	289 (14.7)
Serious TEAE	105 (41.2)	105 (43.8)	680 (34.5)
Treatment-related Serious TEAE	36 (14.1)	47 (19.6)	207 (10.5)
TEAE Leading to Death	35 (13.7)	28 (11.7)	136 (6.9)
Treatment-related TEAE Leading to Death	7 (2.7)	8 (3.3)	21 (1.1)
TEAE Leading to Treatment Discontinuation	49 (19.2)	64 (26.7)	225 (11.4)
Treatment-related TEAE Leading to Treatment Discontinuation	17 (6.7)	33 (13.8)	108 (5.5)
TEAE Leading to Dose Modification	58 (22.7)	115 (47.9)	522 (26.5)
Treatment-related TEAE Leading to Dose Modification	34 (13.3)	106 (44.2)	285 (14.5)
Immune-mediated TEAE	54 (21.2)	NA	305 (15.5)
Immune-mediated TEAE with Grade 3 or Higher	9 (3.5)	NA	88 (4.5)
Serious Immune-mediated TEAE	15 (5.9)	NA	98 (5.0)
Immune-mediated TEAE Leading to Death	0 (0.0)	NA	4 (0.2)
Infusion-related Reaction	8 (3.1)	11 (4.6)	83 (4.2)
Infusion-related Reaction with Grade 3 or Higher	0 (0.0)	0 (0.0)	6 (0.3)

Notes: Percentages are based on N, unless otherwise noted.

Treatment-related TEAE in Study 302 is defined as an TEAE that is assessed by the investigator as causally related to study drug or with missing causal relationship. Dose Modification includes either dose interruption or dose delay for tislelizumab and dose interruption or dose delay or dose reduction for ICC.

Adverse event grades are evaluated based on NCI-CTCAE (version 4.03).

For each row category, a patient with multiple adverse events in that category is counted only once.

Adverse Events

In Study 302, the most frequently reported adverse events (ie, $\geq 5\%$ patient incidence) in the Tislelizumab Arm consisted of various preferred terms, including anemia, weight decreased, cough, pyrexia, decreased appetite, and constipation (Table 35). These preferred terms (PTs) were not typically associated with immune-mediated adverse events, and the incidences of these events were generally similar between the Tislelizumab Arm and the ICC Arm. Adverse events with a $\geq 5\%$ higher incidence reported for the Tislelizumab Arm compared with the ICC Arm were cough, transaminase elevation, and hypothyroidism, consistent with an immune-mediated association.

The most frequently reported adverse events ($\geq 15\%$ patient incidence) in the ICC Arm were predominantly related to hematologic, constitutional, and gastrointestinal events, and these events were also the types of adverse events reported with a higher incidence for ICC compared with tislelizumab. The events were generally consistent with the safety profile of paclitaxel, docetaxel, and irinotecan in the ICC Arm.

In exposure-adjusted analyses, tislelizumab was associated with a substantially lower rate of adverse events of any grade compared with ICC (171.8 per 100 person-months versus 442.3 per 100 person-months).

In the All Doses All Indications population, adverse events of any grade were consistent overall with those in Study 302 Tislelizumab Arm (Table 35).

Table 35. BeiGene: Treatment-Emergent Adverse Events With an Incidence $\geq 5\%$ by Preferred Term (Study 302, Safety Analysis Set)

Preferred Term	Tislelizumab (N = 255) n (%)	ICC (N = 240) n (%)
Patients with at least one TEAE	244 (95.7)	236 (98.3)
Anaemia	78 (30.6)	107 (44.6)
Weight decreased	59 (23.1)	45 (18.8)
Cough	43 (16.9)	28 (11.7)
Pyrexia	41 (16.1)	34 (14.2)
Decreased appetite	40 (15.7)	84 (35.0)
Constipation	39 (15.3)	45 (18.8)
Aspartate aminotransferase increased	37 (14.5)	11 (4.6)
Nausea	36 (14.1)	72 (30.0)
Pneumonia	36 (14.1)	27 (11.3)
Hypoalbuminaemia	34 (13.3)	30 (12.5)
Alanine aminotransferase increased	33 (12.9)	18 (7.5)
Fatigue	33 (12.9)	42 (17.5)
Diarrhoea	32 (12.5)	77 (32.1)
Hyponatraemia	32 (12.5)	33 (13.8)
Hypothyroidism	29 (11.4)	1 (0.4)

Preferred Term	Tislelizumab (N = 255) n (%)	ICC (N = 240) n (%)
Dysphagia	28 (11.0)	20 (8.3)
Vomiting	27 (10.6)	48 (20.0)
Asthenia	26 (10.2)	35 (14.6)
Back pain	26 (10.2)	18 (7.5)
Dyspnoea	24 (9.4)	18 (7.5)
Pruritus	23 (9.0)	11 (4.6)
Rash	21 (8.2)	10 (4.2)
Hypokalaemia	20 (7.8)	22 (9.2)
Insomnia	20 (7.8)	17 (7.1)
Productive cough	18 (7.1)	18 (7.5)
Abdominal pain	17 (6.7)	22 (9.2)
Blood alkaline phosphatase increased	17 (6.7)	5 (2.1)
Hyperglycaemia	16 (6.3)	7 (2.9)
Malaise	16 (6.3)	36 (15.0)
Gamma-glutamyltransferase increased	14 (5.5)	8 (3.3)
Gastroesophageal reflux disease	14 (5.5)	12 (5.0)
Platelet count decreased	14 (5.5)	15 (6.3)
Hypoproteinaemia	13 (5.1)	8 (3.3)
Musculoskeletal pain	13 (5.1)	7 (2.9)
Lymphocyte count decreased	12 (4.7)	22 (9.2)
Dizziness	11 (4.3)	19 (7.9)
Arthralgia	10 (3.9)	13 (5.4)
Abdominal pain upper	9 (3.5)	16 (6.7)
Stomatitis	9 (3.5)	14 (5.8)
White blood cell count decreased	9 (3.5)	98 (40.8)
Leukopenia	8 (3.1)	30 (12.5)
Myalgia	6 (2.4)	14 (5.8)
Neutrophil count decreased	6 (2.4)	94 (39.2)
Neutropenia	2 (0.8)	31 (12.9)
Peripheral sensory neuropathy	2 (0.8)	23 (9.6)
Alopecia	0 (0.0)	42 (17.5)
Febrile neutropenia	0 (0.0)	12 (5.0)

Notes: Percentages are based on N, unless otherwise noted.

Only preferred terms with an incidence $\geq 5\%$ in either 'Tislelizumab' or 'ICC' column are reported.

Patients with multiple events for a given preferred term are counted only once for the preferred term.

Events are sorted by decreasing frequency of preferred term in the 'Tislelizumab' column.

Adverse events were coded using the MedDRA version 23.0.

Table 36. BeiGene: Treatment-Emergent Adverse Events With an Incidence $\geq 5\%$ by Preferred Term (All Doses All Indications Safety Analysis Set)

Preferred Term	Study 302 Tislelizumab (N = 255) n (%)	All Doses All Indications (N = 1972) n (%)
Patients with at least one TEAE	244 (95.7)	1891 (95.9)
Anaemia	78 (30.6)	463 (23.5)
Weight decreased	59 (23.1)	256 (13.0)
Cough	43 (16.9)	298 (15.1)
Pyrexia	41 (16.1)	277 (14.0)
Decreased appetite	40 (15.7)	312 (15.8)
Constipation	39 (15.3)	263 (13.3)
Aspartate aminotransferase increased	37 (14.5)	341 (17.3)
Nausea	36 (14.1)	258 (13.1)
Pneumonia	36 (14.1)	172 (8.7)
Hypoalbuminaemia	34 (13.3)	183 (9.3)
Alanine aminotransferase increased	33 (12.9)	318 (16.1)
Fatigue	33 (12.9)	248 (12.6)
Diarrhoea	32 (12.5)	219 (11.1)
Hyponatraemia	32 (12.5)	138 (7.0)
Hypothyroidism	29 (11.4)	213 (10.8)
Dysphagia	28 (11.0)	64 (3.2)
Vomiting	27 (10.6)	179 (9.1)
Asthenia	26 (10.2)	157 (8.0)
Back pain	26 (10.2)	182 (9.2)
Dyspnoea	24 (9.4)	157 (8.0)
Pruritus	23 (9.0)	209 (10.6)
Rash	21 (8.2)	197 (10.0)
Hypokalaemia	20 (7.8)	130 (6.6)
Insomnia	20 (7.8)	122 (6.2)
Productive cough	18 (7.1)	86 (4.4)
Abdominal pain	17 (6.7)	144 (7.3)
Blood alkaline phosphatase increased	17 (6.7)	121 (6.1)
Hyperglycaemia	16 (6.3)	116 (5.9)
Malaise	16 (6.3)	90 (4.6)
Gamma-glutamyltransferase increased	14 (5.5)	124 (6.3)
Gastrooesophageal reflux disease	14 (5.5)	47 (2.4)
Platelet count decreased	14 (5.5)	92 (4.7)
Hypoproteinaemia	13 (5.1)	49 (2.5)
Musculoskeletal pain	13 (5.1)	103 (5.2)
Arthralgia	10 (3.9)	101 (5.1)
Oedema peripheral	10 (3.9)	99 (5.0)
Blood bilirubin increased	9 (3.5)	161 (8.2)
White blood cell count decreased	9 (3.5)	101 (5.1)

Preferred Term	Study 302 Tislelizumab (N = 255) n (%)	All Doses All Indications (N = 1972) n (%)
Upper respiratory tract infection	8 (3.1)	174 (8.8)
Proteinuria	0 (0.0)	104 (5.3)

Notes: N = Number of patients received at least one dose of Tislelizumab. Percentages are based on N, unless otherwise noted.

Only preferred terms with an incidence $\geq 5\%$ in either the '302 Tislelizumab' column or the 'All Doses All Indications' column are reported.

Patients with multiple events for a given preferred term are counted only once for the preferred term.

Events are sorted by decreasing frequency of preferred term in the '302 Tislelizumab' column.

Adverse events were coded using the MedDRA version 23.0.

$\geq$ Grade 3 Adverse Events

In Study 302, the incidence of $\geq$ Grade 3 adverse events was lower in the Tislelizumab Arm (46.3%) compared with the ICC Arm (67.9%) (Table 37). The most frequently reported $\geq$ Grade 3 adverse events in the Tislelizumab Arm were dysphagia, anemia, and hyponatremia. These PTs were not typically associated with immune-mediated adverse events, and the incidence of these events in the Tislelizumab Arm were either similar or lower than the ICC Arm, except for dysphagia. All $\geq$ Grade 3 dysphagia events in the Tislelizumab Arm were assessed by investigators as related to the tumor.

The most frequently reported $\geq$ Grade 3 adverse events in the ICC Arm were predominantly hematologic events, and these $\geq$ Grade 3 adverse events also occurred at higher incidence in the ICC Arm compared with the Tislelizumab Arm. A number of $\geq$ Grade 3 hematologic adverse events were associated with dose modification and, to a lesser extent, study drug discontinuation. These findings were consistent with known adverse events of $\geq$ Grade 3 of paclitaxel, docetaxel, and irinotecan in the ICC Arm.

In the All Doses All Indications population, $\geq$ Grade 3 adverse events were consistent with those in the Study 302 Tislelizumab Arm, except for a higher dysphagia in Study 302 compared with the All Doses All Indications population (6.3% versus 1.4%). The higher rate of dysphagia in Study 302 is likely due to dysphagia related to the underlying ESCC and disease progression.

Table 37: BeiGene - Grade 3 or Higher Treatment-Emergent Adverse Events With an Incidence $\geq 1\%$ by Preferred Term (Study 302 Safety Analysis Set)

Preferred Term	Tislelizumab (N = 255) n (%)	ICC (N = 240) n (%)
Patients with at least one Grade 3 or Higher TEAE	118 (46.3)	163 (67.9)
Dysphagia	16 (6.3)	7 (2.9)

Preferred Term	Tislelizumab (N = 255) n (%)	ICC (N = 240) n (%)
Anaemia	15 (5.9)	26 (10.8)
Hyponatraemia	14 (5.5)	10 (4.2)
Pneumonia	12 (4.7)	17 (7.1)
Dyspnoea	6 (2.4)	3 (1.3)
Lymphocyte count decreased	6 (2.4)	18 (7.5)
Hypertension	5 (2.0)	0 (0.0)
Oesophageal obstruction	4 (1.6)	1 (0.4)
Oesophageal stenosis	4 (1.6)	1 (0.4)
Pneumonitis	4 (1.6)	2 (0.8)
Pulmonary embolism	4 (1.6)	1 (0.4)
Upper gastrointestinal haemorrhage	4 (1.6)	4 (1.7)
Aspartate aminotransferase increased	3 (1.2)	1 (0.4)
Diarrhoea	3 (1.2)	15 (6.3)
Gamma-glutamyltransferase increased	3 (1.2)	3 (1.3)
General physical health deterioration	3 (1.2)	5 (2.1)
Hypoglycaemia	3 (1.2)	0 (0.0)
Hypophosphataemia	3 (1.2)	0 (0.0)
Multiple organ dysfunction syndrome	3 (1.2)	1 (0.4)
Oesophageal fistula	3 (1.2)	1 (0.4)
Pleural effusion	3 (1.2)	2 (0.8)
Pneumonia aspiration	3 (1.2)	2 (0.8)
Syncope	3 (1.2)	2 (0.8)
Tumour pain	3 (1.2)	1 (0.4)
Weight decreased	3 (1.2)	0 (0.0)
Acquired tracheo-oesophageal fistula	2 (0.8)	4 (1.7)
Alanine aminotransferase increased	2 (0.8)	4 (1.7)
Asthenia	2 (0.8)	5 (2.1)
Death	2 (0.8)	4 (1.7)
Decreased appetite	2 (0.8)	10 (4.2)
Fatigue	2 (0.8)	6 (2.5)
Hypokalaemia	2 (0.8)	6 (2.5)
Malaise	2 (0.8)	4 (1.7)
Vomiting	2 (0.8)	9 (3.8)
Nausea	1 (0.4)	8 (3.3)
Neutropenia	1 (0.4)	16 (6.7)
Septic shock	1 (0.4)	4 (1.7)
White blood cell count decreased	1 (0.4)	48 (20.0)
Febrile neutropenia	0 (0.0)	11 (4.6)
Leukopenia	0 (0.0)	17 (7.1)
Neutrophil count decreased	0 (0.0)	63 (26.3)

Notes: Percentages are based on N, unless otherwise noted.

Adverse event grades are evaluated based on NCI-CTCAE (version 4.03).

Only preferred terms with an incidence $\geq 1\%$ in either 'Tislelizumab' or 'ICC' column are reported.

Patients with multiple events for a given preferred term are counted only once for the preferred term.

Events are sorted by decreasing frequency of preferred term in the 'Tislelizumab' column.

Adverse events were coded using the MedDRA version 23.0.

Treatment-Related Adverse Events

In Study 302, the incidence of treatment-related adverse events, by PT, for all categories including all grades, $\geq$ Grade 3, serious, leading to treatment discontinuation or leading to dose modification, were consistent with the overall adverse event incidences (ie, those assessed regardless of relatedness). For all categories, a lower incidence of treatment-related adverse events was reported in the Tislelizumab Arm than in the ICC Arm.

The Applicant's Position:

The TEAEs with a higher incidence in the Tislelizumab Arm were consistent with the profile of immune-mediated adverse events for tislelizumab, such as hypothyroidism and transaminase elevation. The TEAEs with a higher incidence in the ICC Arm were consistent with the safety profiles of paclitaxel, docetaxel, and irinotecan. The adverse events $\geq$ Grade 3 findings were consistent with the safety profile of paclitaxel, docetaxel, and irinotecan in the ICC Arm.

The FDA's Assessment:

FDA agrees with the overall stated incidence of TEAEs and that patients in the tislelizumab arm had a lower incidence of Grade ≥ 3 events compared to the patients in the ICC arm (46% vs. 68%). FDA also concurs with the description of Grade 5 TEAEs, events leading to permanent discontinuation and dose interruptions, SAEs, imAEs, and IRRs with the exceptions already described throughout this section. As noted above, FDA did not consider Applicant's attribution ("treatment-related") when reviewing AEs. Also, based on FDA assessment, deaths due to adverse events occurred in 18 patients in the tislelizumab arm (see Table 29, above).

See FDA Table 38, below, for FDA-calculated TEAEs occurring in Study 302. The TEAEs, including laboratory findings, with the highest frequency ($\geq 20\%$) in the tislelizumab arm were: 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.

Additional TEAEs that were significantly elevated in the ICC arm compared to the tislelizumab arm include alopecia (18% compared to 0%), peripheral neuropathy (13% compared to 3%), decreased neutrophil count (39% compared to 2.4%), and decreased white blood cell count (41% compared to 3.5%). These TEAEs are consistent with AEs from cytotoxic chemotherapy.

When comparing the tislelizumab arm with the 1,972 ISS population, the frequencies of AEs

generally appear similar with the exception of dysphagia (11 % compared to 3%) which is possibly a function of the specific disease studied in Study 302 (ESCC).

FDA analysis is summarized in Table 38, below.

Table 38. RATIONALE-302: TEAEs (≥ 10%) in Patients with ESCC Receiving Tislelizumab

	TISLELIZUMAB N = 255		ICC N = 240	
	All grades n (%)	Grades 3-4 n (%)	All grades n (%)	Grades 3-4 n (%)
Patients with TEAEs	244 (96)	83 (33)	236 (98)	135 (56)
Gastrointestinal Disorders				
Constipation	39 (15)	0 (0.0)	45 (19)	1 (0.4)
Nausea	36 (14)	1 (0.4)	72 (30)	8 (3.3)
Diarrhea (GT)	33 (13)	3 (1.2)	77 (32)	16 (7)
Dysphagia	28 (11)	16 (6)	20 (8)	7 (2.9)
Abdominal Pain (GT)	27 (11)	2 (0.8)	38 (16)	4 (1.7)
Vomiting (GT)	27 (11)	2 (0.8)	48 (20)	9 (3.8)
Vascular Disorders				
Hemorrhage (GT)	31 (12)	5 (2.0)	25 (10)	7 (2.9)
Endocrine Disorders				
Hypothyroidism (GT)	33 (13)	1 (0.4)	2 (0.8)	0 (0.0)
General Disorders and Administration Site Conditions				
Fatigue (GT)	57 (22)	3 (1.2)	75 (31)	11 (4.6)
Pyrexia (GT)	41 (16)	1 (0.4)	34 (14)	0 (0.0)
Malaise	16 (6)	2 (0.8)	36 (15)	4 (1.7)
Investigations				
Weight Decreased	59 (23)	3 (1.2)	45 (19)	0 (0.0)
Metabolism and Nutrition Disorders				
Decreased Appetite	40 (16)	1 (0.4)	84 (35)	10 (4.2)
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal Pain (GT)	62 (24)	3 (1.2)	59 (25)	3 (1.3)
Infections and Infestations				
Pneumonia (GT)	42 (16)	12 (4.7)	29 (12)	16 (7)
Respiratory, Thoracic and Mediastinal Disorders				
Cough (GT)	55 (22)	1 (0.4)	39 (16)	1 (0.4)

	TISLELIZUMAB N = 255		ICC N = 240	
	All grades n (%)	Grades 3-4 n (%)	All grades n (%)	Grades 3-4 n (%)
Blood and Lymphatic System Disorders				
Anemia	78 (31)	15 (6)	107 (45)	26 (11)
Skin and Subcutaneous Tissue Disorders				
Rash (GT)	28 (11)	0 (0.0)	18 (8)	0 (0.0)

Group Fatigue (GT) includes PT terms FATIGUE, ASTHENIA,

Group Diarrhea (GT) includes PT terms DIARRHOEA, COLITIS,

Group Abdominal Pain (GT) includes PT terms ABDOMINAL PAIN, ABDOMINAL PAIN UPPER ABDOMINAL DISCOMFORT, ABDOMINAL PAIN LOWER, GASTROINTESTINAL PAIN,

Group Hemorrhage (GT) includes PT terms TUMOR HEMORRHAGE, UPPER GASTROINTESTINAL HEMORRHAGE, GASTROINTESTINAL HEMORRHAGE, ESOPHAGEAL HEMORRHAGE, HEMOPTYSIS, HEMATURIA, GASTRIC HEMORRHAGE, EPISTAXIS, TRACHEAL HEMORRHAGE, GINGIVAL BLEEDING, RECTAL HEMORRHAGE, PULMONARY HEMORRHAGE, STOMA SITE HEMORRHAGE, PROCEDURAL HEMORRHAGE,

Group Pneumonia (GT) includes PT terms PNEUMONIA, PNEUMONIA ASPIRATION, PNEUMONIA BACTERIAL, LOWER RESPIRATORY TRACT INFECTION,

Group Vomiting (GT) includes PT terms VOMITING,

Group Musculoskeletal Pain (GT) includes PT terms MUSCULOSKELETAL PAIN, ARTHRALGIA, BACK PAIN, SPINAL PAIN, PAIN IN EXTREMITY, MYALGIA, NECK PAIN, BONE PAIN, NON-CARDIAC CHEST PAIN, MUSCULOSKELETAL CHEST PAIN, ARTHRITIS,

Group Cough (GT) includes PT terms PRODUCTIVE COUGH, COUGH,

Group Pyrexia (GT) includes PT terms PYREXIA, BODY TEMPERATURE INCREASED,

Group Neuropathy Peripheral (GT) includes PT terms PERIPHERAL SENSORY NEUROPATHY, PARAESTHESIA, NEURALGIA, HYPOAESTHESIA, PERIPHERAL SENSORIMOTOR NEUROPATHY,

Group Hypothyroidism (GT) includes PT terms HYPOTHYROIDISM, BLOOD THYROID STIMULATING HORMONE INCREASED,

Group Rash (GT) includes PT terms RASH, ERYTHEMA MULTIFORME, RASH MACULO-PAPULAR, ECZEMA, RASH PRURITIC, RASH FOLLICULAR, SKIN EXFOLIATION, PALMAR-PLANTAR ERYTHRODYSESTHESIA SYNDROME, DERMATITIS, VASCULITIC RASH, DERMATITIS ACNEIFORM, DRUG ERUPTION,

Source: ADSL (Subject-Level Analysis Dataset) - 2021-07-12, ADAE (Adverse Event Analysis Dataset) - 2021-07-12. Variables used: USUBJID, TRT01A, SAFFL, TRTEMFL, AEDECOD, AETOXGRN, AEACN, AACN, AEBODSYS, AESER

To further explore other AEs of interest due to either the disease under study or the mechanism of action of the drug, FDA examined the frequency of fistula formation and ocular toxicities, below.

- Esophageal/upper GI Fistulas

Given the nature of esophageal cancers and the risk of fistulas seen in this patient population, including in the setting of therapy with anti-PD1(L1) antibodies, FDA examined the frequencies of esophageal/upper GI fistula formation in Study 302. In the tislelizumab arm, 12 events of esophageal fistula formation occurred in 11 (4.3%) patients (7 patients or 2.7% had SAEs), including a fatal event of esophagobronchial fistula. In the ICC arm, 16 events of

esophageal/gastric/tracheal fistulas occurred in 10 (4.2%) patients (8 patients or 3.3% had SAEs) and two of these events were fatal (one event of “acquired trachea-esophageal fistula” and one event of “esophageal fistula”). Based on these data, there does not appear to be a significant difference between the treatment arms. Similar incidence of fistulas have been reported in other ESCC studies (Opdivo USPI). See also “Serious Adverse Events” section, above.

- **Ocular Toxicity**

Rare but serious ocular toxicities have been reported with anti-PD1(L1) drugs. A total of 18 (7%) and 8 (3%) of patients experienced eye disorders in the tislelizumab and ICC arms, respectively. None of these events were Grade ≥ 3 . In the tislelizumab arm, In one patient, Grade 2 uveitis was considered to be an imAE on preliminary assessment and treated with topical steroids but this was not adjudicated ultimately by the Applicant as an imAE. The PTs in the tislelizumab arm were visual impairment, vision blurred, uveitis, retinopathy, retinal tear, retinal edema, retinal exudates, ocular hypertension, macular degeneration, lacrimation increased, dry eye, conjunctival hyperemia, chalazion, and cataract. All retinal toxicities occurred in 5 individual patients and were all Grade 1 events. Only 1 of these events was considered recovered/resolved. In the ICC arm, all 9 events (8 patients) were Grades 1-2 and the PTs were: visual acuity reduced, lacrimation increased, eyelid ptosis, blepharitis, vision blurred, visual impairment, and conjunctival pallor.

Although relatively rare, ocular toxicities are a known risk of anti-PD1(L1) drugs and patients must be monitored for any eye or vision complaints.

Laboratory Findings

Data:

Study 302:

Hematology: Overall, ICC was associated with a worsened hematology profile relative to tislelizumab. A greater number of shifts of ≥ 2 NCI-CTCAE toxicity grades for decreased values of hemoglobin and white blood cell counts occurred in the ICC Arm compared with the Tislelizumab Arm. Patients in the ICC Arm experienced a reduction from baseline in mean hemoglobin over time; in contrast, there was an overall increase from baseline in the mean hemoglobin in the Tislelizumab Arm. Patients in the ICC Arm also experienced greater reduction from baseline in mean neutrophil counts over time. There was no clinically meaningful difference between the 2 arms in the means of the lowest postbaseline values for lymphocytes or platelets.

Serum Chemistry: The proportion of patients who reported serum chemistry values with deterioration by ≥ 2 NCI-CTCAE toxicity grades was comparable between the arms. Few patients ($< 10\%$ in each arm) reported serum chemistry values with shifts of ≥ 2 NCI-CTCAE toxicity grades for most parameters, and differences observed between the 2 treatment arms were

not considered meaningful. No clinically meaningful changes from baseline were observed in the median values for serum chemistry analytes of interest (ALT, AST, bilirubin, CK, CK-MB, creatinine, potassium, and sodium) in either treatment arm (Table 39).

Table 39: BeiGene - Summary of Laboratory Tests With Increase in 2 or More NCI-CTCAE Toxicity Grades as Compared With Baseline (Study 302, Safety Analysis Set)

Laboratory Category Laboratory Test	Direction	Tislelizumab (N = 255) n/m (%)	ICC (N = 240) n/m (%)
Hematology			
Hemoglobin	Low	10/240 (4.2)	31/212 (14.6)
Leukocytes	Low	6/240 (2.5)	99/212 (46.7)
Lymphocytes	Low	44/235 (18.7)	61/211 (28.9)
Lymphocytes	High	4/235 (1.7)	1/211 (0.5)
Neutrophils	Low	5/235 (2.1)	95/211 (45.0)
Platelets	Low	6/240 (2.5)	5/212 (2.4)
Biochemistry			
Alanine Aminotransferase	High	7/240 (2.9)	5/210 (2.4)
Albumin	Low	19/240 (7.9)	15/209 (7.2)
Alkaline Phosphatase	High	9/240 (3.8)	2/209 (1.0)
Aspartate Aminotransferase	High	6/240 (2.5)	3/210 (1.4)
Bilirubin	High	8/235 (3.4)	4/205 (2.0)
Creatine Kinase	High	9/209 (4.3)	0/136 (0.0)
Creatinine	High	3/240 (1.3)	0/209 (0.0)
Glucose	Low	3/240 (1.3)	1/209 (0.5)
Glucose	High	23/240 (9.6)	17/209 (8.1)
Potassium	Low	3/240 (1.3)	7/209 (3.3)
Potassium	High	7/240 (2.9)	3/209 (1.4)
Sodium	Low	22/240 (9.2)	17/209 (8.1)

Notes: n is the number of patients with worsen toxicity grade compared with baseline. m is the number of patients with baseline assessment and at least one post-baseline assessment.

Results for hematology and serum chemistry laboratory parameters in the All Doses All Indications populations were consistent with those observed in Study 302, with no clinically relevant mean changes from baseline over time and infrequent clinically significant abnormalities (shifts of ≥ 2 NCI-CTCAE toxicity grades).

No patient in any of the safety populations met criteria for Hy's Law.

The Applicant's Position:

Tislelizumab showed an acceptable safety profile.

The FDA's Assessment:

FDA's analysis of laboratory findings is summarized in Table 40, below. Patients treated with tislelizumab had a greater incidence of increased AST, ALT, alkaline phosphatase, and creatine kinase levels compared to patients in the ICC while patients receiving chemotherapy had a greater incidence of myelotoxicity. These differences are consistent with mechanism of action of each drug class.

Table 40. RATIONALE-302 : All Grade Laboratory Abnormalities Occurring in $\geq 10\%$ of Patients in Any Arm

	TISLELIZUMAB N = 255		ICC N = 240	
	Grades 1-4 n/N evaluable (%)	Grades 3-4 n/N evaluable (%)	Grades 1-4 n/N evaluable (%)	Grades 3-4 n/N evaluable (%)
GLUCOSE Increased	110/240 (46)	9/240 (3.8)	83/209 (40)	4/209 (1.9)
GLUCOSE Decreased	24/240 (10)	1/240 (0.4)	20/209 (10)	1/209 (0.5)
SODIUM Decreased	82/240 (34)	22/240 (9)	76/209 (36)	17/209 (8)
ALBUMIN Decreased	79/240 (33)	2/240 (0.8)	77/209 (37)	2/209 (1.0)
ALKALINE PHOSPHATASE Increased	76/240 (32)	7/240 (2.9)	32/209 (15)	1/209 (0.5)
AST Increased	64/240 (27)	2/240 (0.8)	25/210 (12)	1/210 (0.5)
ALT Increased	54/240 (23)	2/240 (0.8)	32/210 (15)	3/210 (1.4)
PHOSPHATE Decreased	35/236 (15)	9/236 (3.8)	41/207 (20)	7/207 (3.4)
POTASSIUM Decreased	30/240 (13)	3/240 (1.3)	31/209 (15)	7/209 (3.3)
CREATINE KINASE Increased	28/209 (13)	3/209 (1.4)	3/136 (2.2)	0/136 (0.0)
BILIRUBIN Increased	26/235 (11)	4/235 (1.7)	16/205 (8)	1/205 (0.5)
HEMOGLOBIN Decreased	108/240 (45)	14/240 (6)	130/212 (61)	21/212 (10)
PLATELETS Decreased	27/240 (11)	3/240 (1.3)	24/212 (11)	2/212 (0.9)
LEUKOCYTES Decreased	23/240 (10)	2/240 (0.8)	139/212 (66)	66/212 (31)
NEUTROPHILS Decreased	11/235 (4.7)	2/235 (0.9)	117/211 (55)	64/211 (30)

Source: ADSL (Subject-Level Analysis Dataset) - 2021-07-12, ADLB (Labs Analysis Dataset) - 2021-07-12.
Variables used: USUBJID, TRT01A, SAFFL, PARAM, ABLFL, AVAL, ANRLO, ANRHI, EVLLBFL, TRTEDT, ADT, TRTSDT, ADY, ATOXGRHN, ATOXGRLN

Vital Signs

Data:

There were no clinically meaningful changes from baseline in systolic or diastolic blood pressure, pulse rate, temperature, or body weight over time in each arm in Study 302. Analyses of vital signs, physical examination findings, and other observations related to safety were not integrated for Studies 302, 102, 001, 303, 208, 204, and 203. No additional analyses were conducted for this assessment. Any clinically relevant changes in vital signs, physical examination, or other safety-related observations associated with tislelizumab use and those that led to substantial interventions were reported as adverse events.

The Applicant's Position:

Tislelizumab did not appear to have clinically meaningful adverse effects on patient vital signs during any clinical study.

The FDA's Assessment:

The FDA concurs with the Applicant's analysis.

Electrocardiograms (ECGs)/ QT

Data:

The ECG values were calculated and summarized by different methods, including corrected QT interval by Fridericia's formula (QTcF), corrected QT interval by Bazett's formula (QTcB), and the unspecified method. For the patients who had ≥ 1 postbaseline measurement, few patients had a postbaseline value of > 480 msec in the analysis by QTcF method (1 patient in the Tislelizumab Arm) and by QTcB method (1 patient in the ICC Arm). In the analysis by the unspecified method, 3 patients in the Tislelizumab Arm and 3 patients in the ICC Arm had a postbaseline value of > 480 msec. For the patients who had a baseline QTc measurement and ≥ 1 postbaseline QTc measurement, few patients had QTc prolongation of > 60 msec in the analysis by QTcF method (1 patient in the ICC Arm) and by QTcB method (1 patient in the ICC Arm). In the analysis by the unspecified method, 6 patients in the Tislelizumab Arm and 3 patients in the ICC Arm had QTc prolongation of > 60 msec.

The Applicant's Position:

The total number of patients in each arm who had a postbaseline value of > 480 msec (4 patients in the Tislelizumab Arm and 4 patients in the ICC Arm) or QTc prolongation of > 60 msec (6 patients in the Tislelizumab Arm and 5 patients in the ICC Arm) irrespective of QTc measurement method was small, and the differences between the 2 arms were not considered clinically meaningful.

The FDA's Assessment:

The FDA concurs with the Applicant's analysis.

QT

Data:

Refer to section above.

The Applicant's Position:

Refer to section above.

The FDA's Assessment:

Not applicable.

Immunogenicity

Data:

Monitoring of ADA to tislelizumab and titer determination for confirmed positive ADA samples have been performed in all clinical studies included in this submission. NABs were evaluated in the confirmed positive ADA samples.

In Study 302, 14.5% (32/221) of evaluable patients tested positive for treatment-emergent ADA. NABs were detected in 0.5% (1/221) of patients. Exploratory analyses of clinical endpoints in Study 302 showed that the patients who were treatment-emergent ADA-positive had comparable OS to patients who were treatment-emergent ADA-negative, with an HR of 1.16 (95% CI: 0.77, 1.75). In addition, numerically higher ORR (18.8% versus 16.4%) and disease control rate (56.3% versus 51.3%) were noted in the treatment-emergent ADA-positive group than those of the ADA negative group, respectively. However, these minor numerical differences are not considered to be clinically relevant. Overall, comparable safety profiles (incidence rate of imAEs, AESIs, and AEs leading to dose modification or discontinuation) were observed, except patients who were treatment-emergent ADA-positive had a slightly lower rate of safety events of $\geq$ Grade 3 AEs than ADA negative patients (62.5% versus 39.2%, respectively). These trends were not seen when larger sample size from additional studies were compared.

Summary of immunogenicity from seven clinical studies (001, 102, 203, 204, 208, 302, and 303) with total 1785 ADA evaluable patients indicated that 16.5% (295/1785) and 0.6% (11/1785) incidence of treatment-emergent ADA and NABs was observed, respectively, across all dose regimens (0.5 to 10 mg/kg once every 2 weeks, 2.0 or 5.0 mg/kg once every 3 weeks, or 200 mg once every 3 weeks). Of the recommended dose of 200 mg once every 3 weeks across all the aforementioned studies, 16.3% (232/1424) patients had treatment-emergent ADA and NABs were detected in 0.8% (11/1424) patients. Population PK analysis as described in Section 6.3.1 showed that, although treatment-emergent ADA status was a significant covariate, the presence of treatment-emergent ADA did not impact PK, efficacy, or safety to a clinically meaningful extent.

The Applicant's Position:

Based on the totality of available clinical data, ADA status did not have a clinically relevant impact on safety in patients with ESCC.

The FDA's Assessment:

FDA (clinical) agrees and defers to the FDA assessment in Section 6.

8.2.7. Analysis of Submission-Specific Safety Issues

Data:

Not applicable

The Applicant's Position:

Not applicable

The FDA's Assessment:

Not applicable.

8.2.8. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Data:

Validated and most frequently used PROs instruments in oncology studies, esp. in PD-L1 studies, were used measure and to assess HRQoL. These included the EORTC QLQ-C30 to measure general cancer signs and symptoms, its esophageal cancer-specific module, the EORTC QLQ-OES18, and the EQ-5D-5L to measure general health, were used to further characterize treatment benefits of tislelizumab beyond radiographic measures.

The assessment of the HRQoL were based on of the comparison of the key PRO endpoints in esophageal cancer. The PRO key endpoints in this study included the global health status/QoL (GHS) and physical function as measured by the EORTC QLQ-C-30 and esophageal cancer main symptoms of pain, eating, dysphagia and reflux as measured by EORTC QLQ-OES18.

Compliance

The adjusted completion rates (the number of patients who completed the PRO questionnaires divided by the number of patients who were still in treatment at that visit) from baseline through Cycle 6 were > 95% for each questionnaire and were similar in both treatment arms.

Score Changes From Baseline

Changes from baseline to Cycle 6 (mean change [standard deviation]) in HRQoL outcome scores favored the Tislelizumab Arm versus the ICC Arm. Specifically:

Eating and pain symptom scores decreased (indicating improvements from baseline) in the Tislelizumab Arm compared with increases (indicating worsening) in the ICC Arm (Tislelizumab: -2.5 [15.92] and -1.1 [14.29] for eating and pain, respectively; ICC: 6.7 [22.94] and 1.9 [15.36], respectively)

Although both dysphagia and reflux symptom scores slightly worsened in both arms from baseline to Cycle 6, patients in the Tislelizumab Arm experienced less worsening compared with the ICC Arm (Tislelizumab: 1.6 [28.50] and 0.2 [14.22] for dysphagia and reflux, respectively; ICC: 2.7 [37.15] and 1.4 [22.28], respectively)

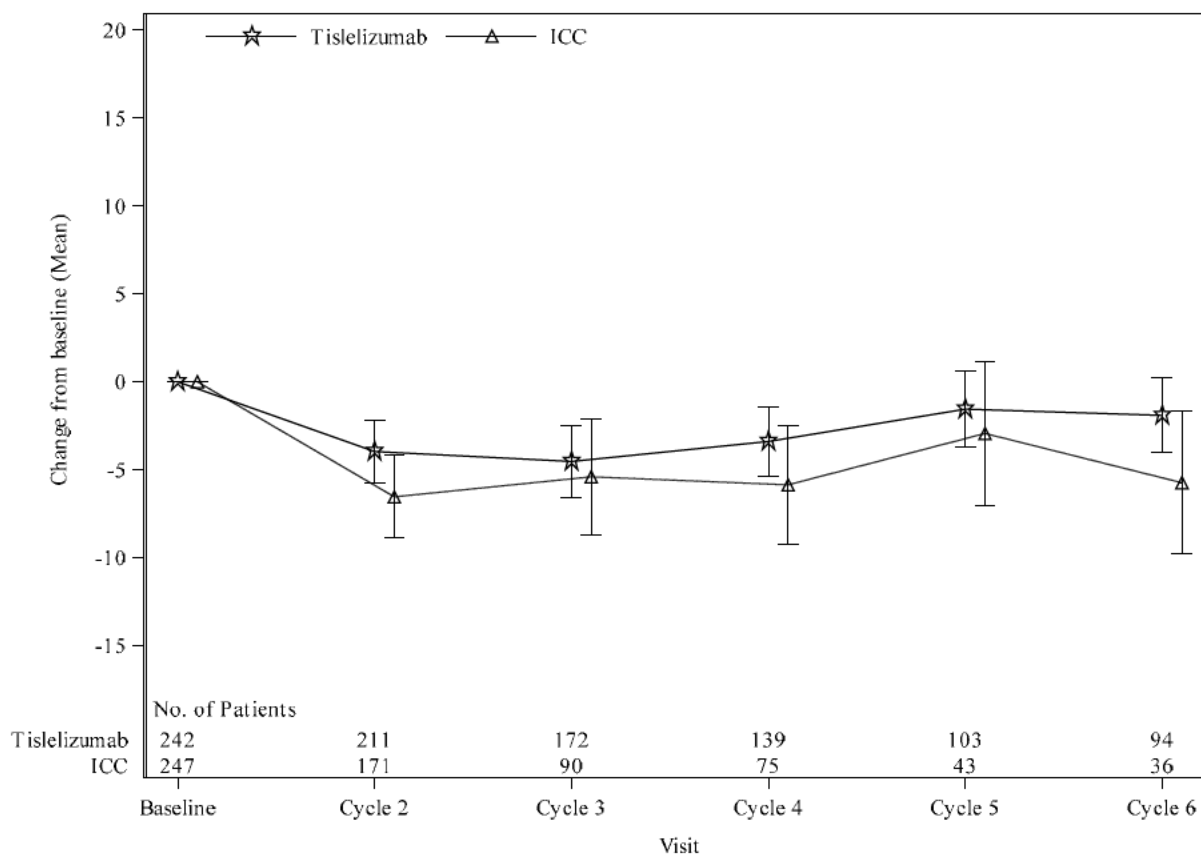
A smaller reduction in physical functioning was observed in the Tislelizumab Arm compared with the ICC Arm (Tislelizumab: -1.9 [10.33]; ICC: -5.7 [12.05]) (Figure 19).

Global health status (GHS) improved from baseline in the Tislelizumab Arm but worsened in the ICC Arm (Tislelizumab: 1.9 [16.45]; ICC: -6.3 [14.82]).

Lastly, overall symptoms indicated by the index score of the QLQ-EOS18, worsened in the ICC Arm whereas is somewhat stabilized in the Tislelizumab Arm (Tislelizumab: -0.6 [8.63]; ICC: 3.0 [12.05]) (Figure 20).

The health state, measured via EQ-5D-5L VAS scores also showed better outcomes for the tislelizumab treat arm (Tislelizumab: 0.6 [14.81]; ICC: 5.9 [16.34]).

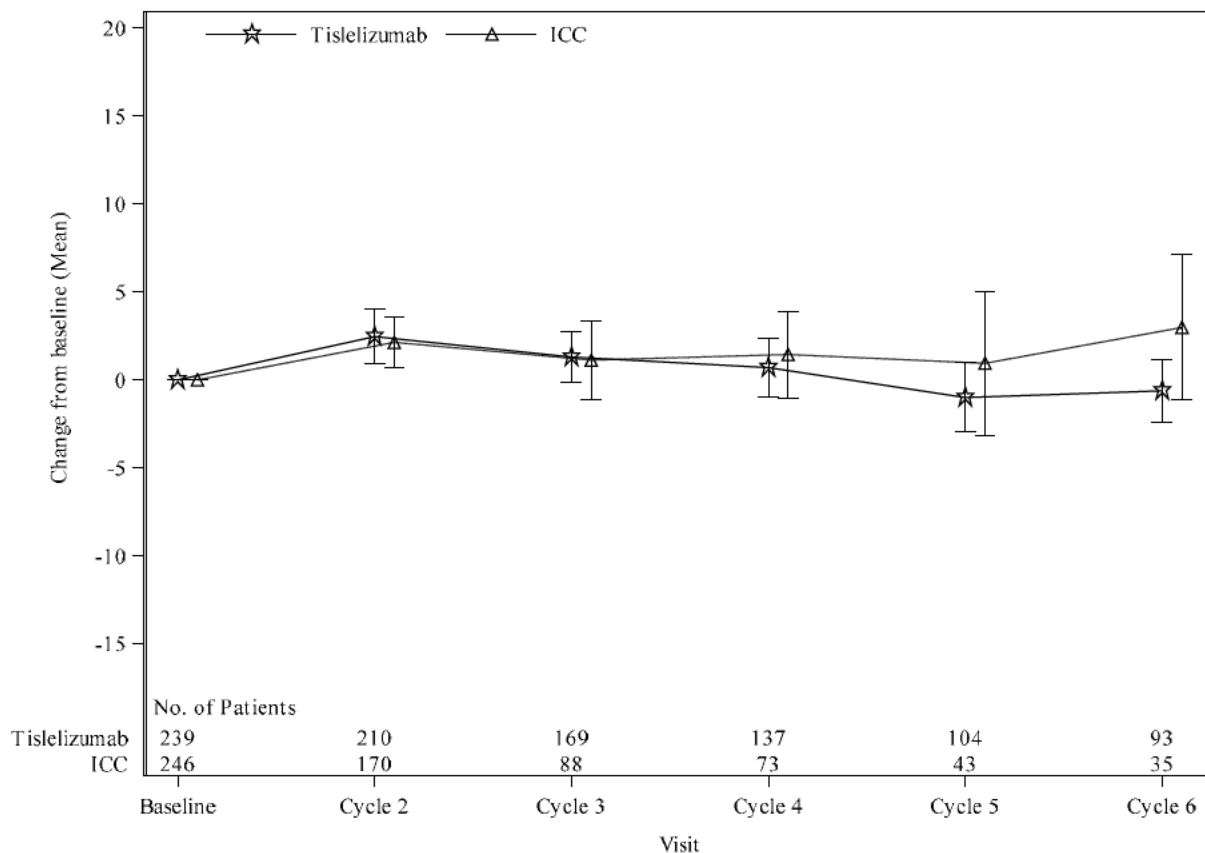
Figure 19: BeiGene - Summary of EORTC QLQ-C30 Scores by Visit - Physical Functioning (Study 302) (ITT Analysis Set)



Source: ADQS. Data cutoff: 01DEC2020. Data extraction: 15JAN2021.

Datapoints represent means and 95% CI.
Increases in scores for physical functioning are improvements for C30.

Figure 20: BeiGene - Summary of EORTC QLQ-OES18 Scores by Visit - Index Sore (Study 302) (ITT Analysis Set)



Source: ADQS. Data cutoff: 01DEC2020. Data extraction: 15JAN2021.

Datapoints represent means and 95% CI.
Increases in scores for index score are deteriorations for OES18.

Median time to clinically meaningful worsening in GHS and physical functioning per EORTC QLQC30 and dysphagia, eating, reflux, and pain per EORTC QLQOES18 was not reached in either arm using the ≥ 10 point threshold. However, in the ITT population, the TTD analysis showed patients treated with tislelizumab were at a lower risk for clinically meaningful worsening of key symptoms of dysphagia (stratified HR of 0.76 [95% CI: 0.53, 1.07], $P = 0.0562$), reflux (0.50 [95% CI: 0.32, 0.80], $P = 0.0014$) as well as worsening of physical function (0.67 [95% CI: 0.45, 1.00], $P = 0.0239$) through the course of treatment. Meanwhile, the PD-L1 vCPS $\geq 10\%$ patients treated with tislelizumab showed to be at lower risk for pain (0.52 [95% CI: 0.24, 1.13], $P = 0.0460$).

Tislelizumab Arm experienced lower risk of clinically meaningful worsening compared to the ICC Arm in physical functioning (stratified HR: 0.67 [95% CI: 0.45 to 1.00]), measured via EORTC QLQ-C30, and symptoms of reflux (stratified HR: 0.50 [95% CI: 0.32 to 0.80]), dysphagia (stratified HR: 0.76 [95% CI: 0.53 to 1.07]) and pain (stratified HR: 0.89 [95% CI: 0.59 to 1.35]), pre-measured via EORTC QLQOES18. No clinically meaningful differences in GHS between the Tislelizumab Arm compared to the ICC Arm were observed (stratified HR: 0.96 [95% CI: 0.65 to 1.41]).

The Applicant's Position:

These findings show that tislelizumab treatment improved symptoms of pain and eating, decreased the risk of worsening of EC symptoms, particularly reflux, dysphagia, physical functioning, and pain in PDL1 sub population, compared with ICC.

The FDA's Assessment:

FDA does not agree with the applicant's position that tislelizumab treatment improved symptoms of pain and eating or decreased the risk of worsening ESCC symptoms. No conclusions can or should be drawn regarding HRQoL given that no alpha was allocated to these endpoints and results are to be considered exploratory only. All p-values presented by the applicant with respect to HRQoL analyses are considered nominal only. Furthermore, FDA does not agree with the proposed 10-point threshold for clinically meaningful worsening. See FDA's comments in Section 8.1.2 regarding the HRQoL secondary endpoints for more details.

8.2.9. Safety Analyses by Demographic Subgroups

Data:

Age

The overall incidence of adverse events was similar among the 3 age subgroups (< 65 years, ≥ 65 to < 75 years, and ≥ 75 years). No clear pattern of higher incidence of adverse events with increasing age was observed.

Numerically higher incidence of constipation, nausea, diarrhea, pyrexia, fatigue, and pruritus was observed for the ≥ 75 years of age subgroup compared with the other two subgroups; these results should be interpreted with caution due to the small sample size of the ≥ 75 years of age subgroup.

Numerically higher incidence of diarrhea, dysphagia, and pyrexia was observed in the ≥ 65 to < 75 years of age subgroup compared with the < 65 years of age subgroup.

Numerically higher incidence of aspartate aminotransferase increased, alanine aminotransferase increased, decreased appetite was observed in the < 65 years of age subgroup compared with the other two subgroups.

The overall incidence of immune-mediated adverse events and the incidence of immune-mediated adverse events under each event category were similar between the subgroups of < 65 years and ≥ 65 to < 75 years, with the exception of immune-mediated pneumonitis (5.7% versus 10.6%, respectively). No immune-mediated adverse events were reported in patients ≥ 75 years of age in the Study 302 Tislelizumab Arm.

Gender

More male patients were enrolled than female patients (84.7% versus 15.3%; [Table 17](#)); this is likely related to the higher incidence of ESCC in male than in female population; the results of adverse events by gender should be interpreted with caution due to the small sample size of the female subgroup.

The overall incidence of adverse events was similar between the male and female subgroups. The incidence of adverse events across most of the PTs was similar between the 2 gender subgroups.

Numerically higher incidence of diarrhea, nausea, back pain, and fatigue was observed in the female subgroup compared with the male subgroup.

Numerically higher incidence of pneumonia, weight decreased, asthenia, and anemia was observed in the male subgroup compared with the female subgroup.

The overall incidence of immune-mediated adverse events was higher in the female subgroup than in the male subgroup (28.2% versus 19.9%). The immune-mediated adverse event of pneumonitis was higher in the female subgroup compared with the male subgroup (12.8% versus 6.0%). The incidence of the other immune-mediated adverse events was similar between the 2 subgroups.

Race

More patients in Study 302 were Asian compared with white (78.8% versus 20.4%). The results of adverse events by race should be interpreted with caution due to the small sample size of the White subgroup. The overall incidence of adverse events was similar between the Asian and White subgroups.

Numerically higher incidence of laboratory-related adverse events was reported in the Asian subgroup than in the White subgroup; these include hyponatremia, hypoalbuminemia, alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased, hypoproteinemia, and blood alkaline phosphatase increased. A similar trend was observed in patients treated with chemotherapy (ICC Arm) in the Asian subgroup.

The two subgroups by race, Asian and white, are almost identical to the two subgroups by region, Asia and Europe/North America. A laboratory evaluation of shifts in NCI-CTCAE grade from baseline to the worst postbaseline grade for hematology parameters and serum chemistry parameters showed similar shifts between the Asia subgroup and the Europe/North America subgroup, which indicated no clinically meaningful regional differences. Hence, there was likely no differences between the Asian and White subgroups based on the shifts in laboratory values.

The higher incidence in laboratory-related adverse events may reflect the differences in reporting of adverse events between regions.

For non-laboratory-related adverse events, numerically higher incidence of weight decrease, pneumonia, and pruritus was observed in the Asian subgroup compared with the White subgroup. Numerically higher incidence of asthenia, diarrhea, fatigue, dysphagia, decreased appetite, nausea, pyrexia, and back pain was observed in the White subgroup compared with the Asian subgroup. Taking considerations noted above, the incidences of the most adverse events were similar between the Asian subgroup and the White subgroup.

The overall incidence of immune-mediated adverse events was higher in the Asian subgroup than in the White subgroup (21.9% versus 15.4%). The immune-mediated adverse event of pneumonitis was higher in the Asian subgroup compared with the White subgroup (8.0% versus 1.9%). The incidences of the other immune-mediated adverse events were similar between the 2 subgroups.

Weight

The overall incidence of adverse events was similar between the 2 baseline weight subgroups (“< Median” and “≥ Median”, where the calculation of median baseline weight of 59.00 kg is based on the Study 302 Safety Analysis Set). The incidence of adverse events across most of the PTs were generally similar between the 2 weight subgroups.

Numerically higher incidence of pruritis, pyrexia, and pneumonia was observed in the “< Median” subgroup compared with the “≥ Median” subgroup.

Numerically higher incidence of asthenia, aspartate aminotransferase increased, alanine aminotransferase increased, and gamma-glutamyl transferase increased was observed in the “≥ Median” subgroup compared with the “< Median” subgroup.

The overall incidence of immune-mediated adverse events was similar between the “< Median” subgroup and the “≥ Median” subgroup (19.4% versus 23.0%). The incidence of immune-mediated adverse events was similar between the 2 subgroups.

Region:

More patient in Study 302 were enrolled in Asia compared with Europe/North America (78.8% versus 21.2%). The results of adverse events by region should be interpreted with caution due to the small sample size of the Europe/North America subgroup.

The overall incidence of adverse events was similar between the Asia and Europe/North America subgroups. The two subgroups by region, Asia and Europe/North America, were almost identical to the two subgroups by race, Asian and white. The findings for adverse events by region were similar with that by race (Section 8.2.9).

The overall incidence of immune-mediated adverse events was higher in the Asia subgroup than in the Europe/North America subgroup (21.9% versus 18.5%). The immune-mediated adverse event of pneumonitis was higher in the Asia subgroup compared with the Europe/North America

subgroup (8.0% versus 3.7%). The incidence of the other immune-mediated adverse events was similar between the 2 subgroups.

The Applicant's Position:

The safety profile of tislelizumab is similar across demographic subgroups (age, gender, race, weight and region).

The FDA's Assessment:

FDA agrees with the Applicant's analysis. However, data based on demographic subgroups should be interpreted with caution as these analyses are exploratory in nature. Additionally, 21% of patients in the study were enrolled outside of Asia, which further reduces strength of conclusions based on demographic groups.

8.2.10. Specific Safety Studies/Clinical Trials

Data:

No new information is provided in the current submission.

The Applicant's Position:

Not applicable

The FDA's Assessment:

There were no special safety studies/clinical trials conducted for this BLA.

8.2.11. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Data:

No information is provided in the current submission.

The Applicant's Position:

Not applicable

The FDA's Assessment:

Not applicable.

Human Reproduction and Pregnancy

Data:

A literature-based assessment of the potential effects of tislelizumab on embryofetal development via weight-of-evidence approach demonstrated that blocking the PD-1/PD-L1 pathway can result in fetal loss in animal models. The potential risks of administering tislelizumab during pregnancy include increased rates of abortion or stillbirth. Based on

tislelizumab's mechanism of action, fetal exposure may increase the risk of developing immune-mediated disorders or altering the normal immune response. Therefore, tislelizumab is not recommended during pregnancy unless the clinical benefit outweighs the potential risk.

There are no data on the presence of tislelizumab in either animal or human milk or on the effect of tislelizumab 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 final dose.

The Applicant's Position:

Tislelizumab is not recommended during pregnancy unless the clinical benefit outweighs the potential risk.

The FDA's Assessment:

FDA acknowledges that tislelizumab has not been studied in pregnant women and is therefore no information to report for use of tislelizumab in pregnancy or lactation.

Pediatrics and Assessment of Effects on Growth

Data:

No information is provided in the current submission.

The Applicant's Position:

On November 10, 2020, tislelizumab received agreement for an amended initial Pediatric Study Plan (b) (4) Refer to section 10.

The FDA's Assessment:

Not applicable.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound and Ability to Drive

Data:

There is no specific antidote for tislelizumab. Patients who experience an overdose should be closely monitored and provided with appropriate supportive treatment.

There is no nonclinical or clinical evidence that tislelizumab has potential for drug abuse, and specific clinical studies evaluating abuse potential have not been conducted.

There is no evidence of withdrawal or rebound phenomena associated with discontinuation of tislelizumab in any clinical study.

No specific studies have been conducted to evaluate the influence of tislelizumab treatment on the ability to drive or operate heavy machinery or impairment of mental ability.

The Applicant's Position:

Neither the effects of overdose of tislelizumab nor an antidote to overdose are known. The potential for tislelizumab drug abuse and dependence is unknown.

The FDA's Assessment:

Based on its pharmacological properties, there are no concerns regarding the potential for abuse, withdrawal, or rebound with tislelizumab.

8.2.12. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Data:

The first marketing authorization (MA) for tislelizumab was granted in China on 27 December 2019, followed by subsequent MAs in April 2020, January 2021, and two indications authorized in June 2021. As of 25 December 2020, a cumulative total of (b) (4) vials of tislelizumab have been supplied to the market in China (equivalent to (b) (4) infusions based on the recommended dose of 200 mg per infusion). This represents an exposure of approximately (b) (4) patient-years (b) (4) patient-months) based on the treatment cycle of every 3 weeks.

The Applicant's Position:

The data available to BeiGene have been analyzed to provide a critical analysis of the benefit-risk profile of tislelizumab in the context of new information on both benefits and risks that emerged during the relevant reporting period (26 December 2019 to 25 December 2020). The benefits and risks (safety experience) of treatment with tislelizumab have been assessed based on both clinical studies and post-marketing experience and overall indicate a positive benefit-risk profile for tislelizumab. BeiGene considers that the benefit-risk profile for tislelizumab in the currently approved indications continues to remain favorable.

The FDA's Assessment:

FDA reviewed the Periodic Benefit-Risk Evaluation Report discussed above and acknowledges the Applicant's position.

Expectations on Safety in the Postmarket Setting

Data:

In addition to the studies presented in this BLA and approved marketing authorizations in China, the following are ongoing or planned clinical studies of tislelizumab that will contribute to safety in the postmarket setting.

The Applicant's Position:

Additional ongoing and planned clinical studies will contribute additional safety information to further elucidate the safety profile of tislelizumab.

The FDA's Assessment:

Not applicable.

8.2.13. Integrated Assessment of Safety

Data:

This comprehensive review, based primarily on the large, well-controlled, pivotal Phase 3 Study 302 and supported by collective data from 1972 tislelizumab-treated patients, establishes that tislelizumab provides a favorable safety profile compared to chemotherapy in patients with advanced or metastatic ESCC after prior systemic therapy. Study 302 allows for a clear comparison of tislelizumab safety against the safety of single-agent chemotherapy, the standard of care at the time of study initiation. Patients in Study 302 are representative of the general ESCC population in terms of age, sex, race, geographic region, disease status, and overall health,

and the study's sample size is adequate to allow for evaluation of safety in important ESCC subgroups. Taken together, the data package is sufficient to characterize the safety of tislelizumab and to guide the management of risks associated with tislelizumab as a treatment for ESCC.

The safety profiles of the treatment arms in Study 302 were differentiated by their distinct mechanisms of action. As with other PD-1 CPIs (Kojima et al 2020; Kato et al 2019), tislelizumab safety was characterized by immune-mediated adverse events, such as hypothyroidism, pneumonitis, and skin adverse reactions. The events were generally low grade and responsive to corticosteroids or hormone therapy as needed. Tislelizumab had notably lower rates of adverse events than ICC (mainly hematologic, gastrointestinal, and neurologic toxicities, constitutional symptoms, and alopecia). As evidenced by the higher rates of treatment discontinuation or delay/interruption due to adverse events with ICC compared with tislelizumab, these toxicities can be dose-limiting for ICC. The overall tislelizumab safety profile appeared consistent across key ESCC patient demographics. No new signals for tislelizumab were identified when safety findings were evaluated in the larger pooled All Doses All Indications population.

The favorable safety results in this submission provide an ample dataset to adequately support the use of tislelizumab monotherapy in the treatment of patients with unresectable recurrent locally advanced or metastatic ESCC after prior systemic therapy.

The Applicant's Position:

The totality of the safety package sufficiently support the use of tislelizumab 200 mg intravenously once every 3 weeks as a single agent to treat patients with unresectable recurrent locally advanced or metastatic ESCC after prior systemic therapy.

The FDA's Assessment:

FDA agrees that Study 302 adequately characterized the safety of tislelizumab for the second line treatment of patients with ESCC. In general, the adverse reactions observed with tislelizumab were consistent with the mechanism of action and toxicity observed in prior clinical studies with tislelizumab and the pharmacological class. The primary risks related to tislelizumab are immune related reactions. These serious risks are adequately addressed in the Warnings and Precautions and Dosage Modifications sections of tislelizumab product labeling. The major safety risks of tislelizumab are toxicities that oncologists frequently manage and the toxicity profile of tislelizumab is considered acceptable when considering the improved survival observed in a patient population with a serious and life-threatening condition.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:

No major statistical issues were identified during review of the data and results submitted in this application. However, FDA notes that there are some uncertainties in evaluating the efficacy results for PDL1 subgroups, including the key secondary endpoint of OS in patients with PD-L1 vCPS $\geq 10\%$, due to missing PDL1 status of 19% of the patients in the ITT population. FDA further notes that only $\sim 10\%$ of the patients in the ITT population had vCPS $< 1\%$ compared to $\sim 71\%$ of the patients with vCPS $\geq 1\%$.

8.4. Conclusions and Recommendations

The FDA's Assessment:

Substantial Evidence of Effectiveness (SEE) was established with one adequate and well-controlled clinical investigation with highly persuasive results that is considered to be the scientific equivalent of two clinical investigations.

Based on the totality of evidence, the product quality, clinical pharmacology, clinical, and statistical review teams determined that the evidence submitted provides substantial evidence of the effectiveness of tislelizumab for the treatment of patients with unresectable or metastatic ESCC after prior systemic therapy that does not include an anti PD-(L)1 inhibitor and recommends approval. The recommended dosage regimen for this indication is 200 mg IV once every 3 weeks.

The data presented in this BLA demonstrating a modest but statistically significant improvement in OS in patients with ESCC was derived from RATIONALE-302, a multicenter, randomized, open-label, active-controlled trial. Patients were randomized to receive tislelizumab or investigator's choice of cytotoxic chemotherapy (paclitaxel, docetaxel, or irinotecan). The median OS was 8.6 months [95% CI: 7.5, 10.4] in the tislelizumab arm compared to 6.3 months [95% CI: 5.3, 7.0] in the ICC arm with a stratified hazard ratio of 0.70 [95% CI: 0.57, 0.85, $p = 0.0001$]. Tislelizumab was generally well tolerated and fewer adverse events were reported than in patients receiving chemotherapy. Immune-related adverse events, characteristic of anti-PD1(L1) drugs, including hypothyroidism, pneumonitis, and rash, occurred in approximately 20% of patients receiving tislelizumab. The adverse reaction profile observed in patients receiving tislelizumab in RATIONALE-302 was consistent with the known tislelizumab profile in different studies across indications and the pharmacologic class. These adverse reactions were generally manageable with dose delays and supportive care in most patients, although at least one fatal event was reported.

A review issue considered during the review of this application is the applicability to the U.S. population. Of note, randomization was stratified by location: Asia [excluding Japan] versus Japan versus United States [US]/European Union [EU]). Only 21% of patients in Study 302 were

from non-Asian countries and only 2 patients were from the U.S. (both randomized to the tislelizumab arm). Although worldwide ESCC is the dominant histological subtype (~ 90%) of esophageal cancer (EC), in the US, only approximately 1/3 of patients have ESCC and the majority of patients have esophageal adenocarcinomas. Although only exploratory in nature, forest plot of demographic subgroups of the ITT efficacy population do not indicate differential activity based on race/ethnicity (of those explored) or for patients in Europe/North America. Importantly, based on the SEER database analysis, there are no differences in outcomes for patients with ESCC based on race or ethnicity (Then EO, 2020). Although minorities have not been adequately represented in the study, based on the epidemiological data, tislelizumab's mechanism of action, known safety profile of the drug class, and the clinical pharmacology conclusions, the review team agrees that the study results are applicable to the US population. Based on FDA Clinical Pharmacology analyses, no clinically meaningful difference in PK of tislelizumab were found for in patients based on race (Asian, White, and Black); a flat relationship between exposure and efficacy and safety was observed.

Another review issue considered was whether labeling would inform of the results of the key secondary endpoint of OS in patients with PD-L1 expression $\geq 10\%$ and whether the indication should be restricted based on tumor PD-L1 expression subgroups. The primary endpoint was OS in the ITT population but the key secondary endpoint was OS in the vCPS $\geq 10\%$ population. A survival benefit from tislelizumab was observed in both populations with a HR for OS 0.70 in the ITT population and 0.53 in the vCPS $\geq 10\%$ population. However, approximately 19% of patients in Study 302 had missing vCPS information and the Applicant did not submit data supporting a 10% vCPS cutoff versus other cutoffs in patients with ESCC with disease progression after first-line treatment. In addition, the subset of patients with PD-L1 expression $< 1\%$ was too small to derive conclusions. Thus, the indication recommended for approval is based on the ITT population.

X

X

Abhishek Bhattacharjee, PhD
Primary Statistical Reviewer

Joyce Cheng, PhD
Statistical Team Leader

X

X

BLA 761232 - Multi-disciplinary Review and Evaluation
TEVIMBRA – tislelizumab-jsgr

Lorraine Pelosof, MD PhD
Primary Clinical Reviewer

Sandra Casak, MD
Clinical Team Leader

9. Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

No advisory committee meeting was convened for this Application because the application did not raise significant public health questions regarding the role of tislelizumab for this indication, and outside expertise was not necessary as there were no issues that warranted the Committee's input. This is the second-in class product to be approved for the treatment of patients with advanced unresectable or metastatic ESCC with disease progression after first-line treatment.

10. Pediatrics

The Applicant's Position:

The Sponsor received agreement from the Agency on the initial Pediatric Study Plan (iPSP),

(b) (4)

As the submission of the first original BLA for tislelizumab was planned for 18 August 2020, BeiGene submitted an amendment to the agreed iPSP on 10 November 2020 for the proposed indication (IND 135699 [SN0177]) and received agreement on the full waiver request for all pediatric age groups on 10 December 2020 (as per PREA requirements of PREA for iPSP).

A summary of agreed iPSPs granted under IND 135699 is provided in Table 43.

Table 43: BeiGene - Summary of Agreed Initial Pediatric Study Plans for Tislelizumab Under IND 135699

Agreed iPSP Indication	Application No.	Date of Agreement Letter
(b) (4)		

The FDA's Assessment:

FDA agrees with the Applicant's rationale provided in the iPSP that tislelizumab should be exempted from the PREA and FDARA requirements for pediatric studies.

11. Labeling Recommendations

Data:

This is an original application. Please see annotated label in section 1.14.1.2 for the proposed label.

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	Applicant's Proposed Labeling	FDA's proposed Labeling
	indicated for the treatment of patients with unresectable recurrent locally advanced or metastatic esophageal squamous cell carcinoma after prior systemic therapy	Added modifier to prior systemic therapy (not indicated if already received prior anti-PD1(L1) agent).
Severe and Fatal Immune-Mediated Adverse Reactions (5.1)		Added data on re-challenge after particular imAEs.
Complications of Allogeneic HSCT (5.3)		Added this section.
Adverse Reactions (6.1)		Added main exclusion criteria for Study 302. Added dosing of ICC arm chemotherapy drugs. Added adverse reactions including laboratory abnormalities that occurred in $\geq 20\%$ of patients. Revised Tables 2 and 3 (Adverse Reactions and Laboratory Abnormalities).
Clinical Studies (14.1)		Revised this section to be consistent with other USPI for anti-PD1(L1) agents. Removed (b) (4)

The Applicant's Position:

Not applicable

The FDA's Assessment:

See table above summarizing significant labeling changes. Please also refer to FDA's Risk: Benefit assessment in Section 1 of this review. The USPI was revised following current labeling policies.

12. Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:

There are no safety issues identified at this time requiring Risk Evaluation and Mitigations Strategies. Tislelizumab is the 8th approved PD-1/PD-L1 targeting monoclonal antibody and the second in class for the treatment of patients with ESCC with relapsed/refractory disease.

13. Postmarketing Requirements and Commitment

The FDA's Assessment:

The following postmarketing commitments will be included in the approval letter:

- 4576-1: Develop a reliable endotoxin detection method that can overcome the LER phenomenon for the tislelizumab drug product.
 - Final Protocol Submission: 03/2022 (already submitted)
 - Study/Trial Completion: 09/2024
 - Final Report Submission: 03/2024
- 4576-2: Implementation of in-line pressure monitoring of sterile filtration.
 - Final Protocol Submission: 02/2022 (already submitted)
 - Study/Trial Completion: 12/2023
 - Final Report Submission: 05/2024

14. Division Director (DHOT) (NME ONLY)

X

15. Division Director (OCP)

X

16. Division Director (OB)

X

17. Division Director (Clinical)

I agree with the overall approval recommendations for tislelizumab-jsgr (tislelizumab) from the review teams. Study RATIONALE-302 demonstrated an improvement in OS for tislelizumab when compared to investigators' choice of chemotherapy. RATIONALE-302 was a multi-regional trial; however, most patients were enrolled in Asia (consistent with the lower incidence rate of ESCC in the US and Europe). The study enrolled a limited number of patients in Asia outside of China and close to 20% of patients in Europe or North America. The point estimate for the treatment effect in Europe and North America was favorable (0.55) and the PK of tislelizumab across races (Asian, White patients, and Black patients – with data collected beyond RATIONALE-302) appeared comparable.

Because FDA inspectors were not able to travel to China due to COVID-19 restrictions in China, action on this application was delayed (i.e., past the PDUFA deadline). FDA carefully considered the potential impact of the delayed action. Notably, this application does not address an unmet medical need as there are other treatment options in the same therapeutic class available to patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma (ESCC) after prior fluoropyrimidine- and platinum-based chemotherapy and also for patients with unresectable advanced or metastatic esophageal squamous cell carcinoma as first-line treatment in combination with chemotherapy (See Section 2.2).

X

18. Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X

19. Appendices

19.1. References

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19.2. Financial Disclosure

The Applicant's Position:

All financial disclosures and additional processes to minimize bias are described in Section 8.1.2.

The FDA's Assessment:

FDA agrees with the Applicant's position. See also "Financial Disclosure" in Section 8.1.2, above.

Covered Clinical Study (Name and/or Number):* **BGB-A317-302**

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>1138</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>3</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u> Significant payments of other sorts: <u>3</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in study: <u>0</u> Sponsor of covered study: <u>BeiGene</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>12</u>		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

19.3. Nonclinical Pharmacology/Toxicology

Data:

All data presented in section 5, Nonclinical Pharmacology/Toxicology.

The Applicant's Position:

Not Applicable

The FDA's Assessment:

See Section 5.

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

19.4.1. Bioanalytical

FDA Assessment:

Summary of Bioanalytical Method Validation and Performance

In Study GBG-A317-001 and BGB-A317-302, serum tislelizumab concentrations were measured using a validated antigen-binding enzyme-linked immunosorbent assay (ELISA) method. The method performance is summarized in Table 44 and Table 45.

Table 44. Summary Method Performance of a Bioanalytical Method Validated by (b) (4) to Measure Tislelizumab (BGB-A317) in Human Serum

Bioanalytical method validation report name, amendments, and hyperlinks	Validation of an ELISA Method for the Measurement of BGB-A317 in Human Serum (Report VAL136)
Method description	This assay method employs the quantitative indirect enzyme immunoassay technique. The tislelizumab antigen, human PD-1 (PDCD1) protein, is coated on a 96-well immunoplate and then blocked using a nonspecific protein-blocking buffer. Samples for calibration and quality control and clinical study samples are pipetted into the wells. Tislelizumab is bound to the immobilized human PD-1 (PDCD1) in the immunoplate. After washing away any unbound substrate, a horseradish peroxidase (HRP)-conjugated goat anti-human IgG (fragment crystallizable [Fc] region specific) HRP secondary antibody is added to the wells. Then after a second washing, HRP conjugate bound complexes are quantified by catalysis of color development using the chromogenic substrate, tetramethylbenzidine, with a spectrophotometer.
Materials used for calibration curve & concentration	BGB-A317 in human serum: 78.125, 156.250, 312.500, 625, 1250, 2500, 5000, 10,000, 20,000, 40,000, and 80,000 ng/mL
Validated assay range	400 to 40,000 ng/mL
Material used for QCs & concentration	400, 1200, 8000, 32,000, and 40,000 ng/mL

Minimum required dilutions (MRDs)	1:200		
Source & lot of reagents (LBA)	PD-1/His: Supplier: BeiGene (Beijing) Co., Ltd, Lot No.: 20150326; Peroxidase conjugated goat anti-human IgG Fc: Supplier: (b) (4) Lot No.: 062M4189		
Regression model & weighting	5 PL; with no weighting factor		
Validation parameters	Method validation summary		Source location
Calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ	7	Table 3 of Report VAL136
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-5.6% to 6.8%	Table 3 of Report VAL136
	Cumulative precision (%CV) from LLOQ to ULOQ	≤ 11.5%	Table 3 of Report VAL136
QCs performance during accuracy & precision	<u>Cumulative accuracy (%bias) in 5 QCs</u> QCs: 400 ng/mL (LLOQ), 1200 ng/mL (QCL), 8000 ng/mL (QCM), 32,000 ng/mL (QCH), 40,000 ng/mL (ULOQ)	-14.4% to 3.0%	Table 5 of Report VAL136
	<u>Inter-batch %CV</u> QCs: 400 ng/mL (LLOQ), 1200 ng/mL (QCL), 8000 ng/mL (QCM), 32,000 ng/mL (QCH), 40,000 ng/mL (ULOQ)	≤ 16.7%	Table 5 of Report VAL136
	<u>Total error</u> QCs: 400 ng/mL (LLOQ), 1200 ng/mL (QCL), 8000 ng/mL (QCM), 32,000 ng/mL (QCH), 40,000 ng/mL (ULOQ)	≤ 23.6%	Table 5 of Report VAL136
Selectivity & matrix effect	10 lots of individual human serum unspiked (blank) and spiked at QCH and QCL were tested. At QCH, %bias exceeds 20% in 2 out of ten samples, %bias ranges from -16.8% to 10.3% in other 8 samples; At QCL, %Bias exceeds 20% in 1 out of ten samples, %bias ranges from -17.0% to 9.0% in other 9 samples. 9 out of 10 individuals unspiked were BLQ. The data indicates there were no marked matrix effects in normal matrix.		Table 8 of Report VAL136
Interference & specificity	Not applicable		Not applicable
Hemolysis effect	Not applicable		Not applicable

Lipemic effect	Not applicable	Not applicable
Dilution linearity & hook effect	10,000 ng/mL, 4,050-fold dilution. No hook effect was observed. %bias: -16.4% to -1.1%	Table 6 of Report VAL136
Bench-top/process stability	Stable for 19 hours 15 mins in human serum at room temperature.	Table 9 of Report VAL136
Freeze-Thaw stability	Stable for 4 freeze-thaw cycles at -80°C	Table 11 of Report VAL136
Long-term storage	Stable for 179 days at -20°C; Stable for 806 days at -80°C	Table 5 of Report STAB054 (attachment of Report VAL136)
Parallelism	Neat and serially diluted incurred subject samples from three different subjects were analyzed. One subject sample had %bias between -9.0% and 9.6%, the second had %bias between -11.4% and -0.3%, and the third had %bias between -14.6% and 12.1%. These met the acceptance criteria for parallelism.	Table 7 of Report VAL136
Carry over	Not applicable	Not applicable
Method performance in BGB-A317 Study 001 Interim Immunoassay Bioanalytical Phase PK Report for BGB-A317 study 001 (Report DBK)		
Assay passing rate	183/207 (88.4%) plates passed	Table 1 of Report DBK
Standard curve performance	Cumulative bias range: -2.3% to 7.3% Cumulative precision: ≤ 18.4% CV	Table 3 of Report DBK
QC performance	- Cumulative bias range: -5.2% to -0.3% - Cumulative precision: ≤ 15.3% CV - TE: ≤ 18.2%	Table 4 of Report DBK
Method reproducibility	Part 1A: Incurred sample reanalysis was performed in 7.8% of samples and 86.9% of samples met the pre-specified criteria. Part 1B: Incurred sample reanalysis was performed in 7.2% of samples and 93.0% of samples met the pre-specified criteria.	Table 6 and Table 7 of Report DBK
Study sample analysis/stability	39 samples were analyzed outside of the established stability timeframe of 806 days at nominal -80°C, with sample ages at analysis ranging from 811 to 1127 days since collection. These results have been flagged as such in the results comments column.	

Abbreviations: BLQ: below limit of quantitation; % CV, coefficient of variation percentage; DBK, bioanalytical project code of this study; ELISA, enzyme-linked immunosorbent assay; HRP, horseradish peroxidase; IgG, immunoglobulin G; LLOQ, lower limit of quantitation; PL, parameter logistic; QC: quality control; QCL: low quality control sample; QCM: medium quality control sample; QCH: high quality control sample; ULOQ, upper limit of quantification.

Table 45. Summary Method Performance of a Bioanalytical Method Validated by
to Measure Tislelizumab (BGB-A317) in Human Serum

(b) (4)

Bioanalytical method validation report name, amendments, and hyperlinks	Validation of a Method for the determination of BGB-A317 in Human Serum using Enzyme-Linked Immunosorbent Assay (ELISA) (Report 8354-363)		
Method description	This assay method employs the quantitative indirect enzyme immunoassay technique. The tislelizumab antigen, human PD-1 (PDCD1) protein, is coated on a 96-well immunoplate and then blocked using a nonspecific protein-blocking buffer. Samples for calibration and quality control, and clinical study samples are pipetted into the wells. Tislelizumab is bound to the immobilized human PD-1 (PDCD1) in the immunoplate. After washing away any unbound substrate, a horseradish peroxidase (HRP)-conjugated goat antihuman IgG (fragment crystallizable [Fc] region specific) secondary antibody is added to the wells. Then after a second washing, HRP conjugate bound complexes are quantified by catalysis of color development using the chromogenic substrate, tetramethylbenzidine, with a spectrophotometer.		
Materials used for calibration curve & concentration	BGB-A317 in human serum: 100, 200, 400, 625, 1250, 2500, 5000, 10,000, 20,000, 40,000, and 80,000 ng/mL		
Validated assay range	400 to 40,000 ng/mL		
Material used for QCs & concentration	400, 1200, 8000, 32,000, and 40,000 ng/mL		
Minimum required dilutions (MRDs)	1:200		
Source & lot of reagents (LBA)	PD-1/His: Supplier: BeiGene (Beijing) Co., Ltd, Lot No.: 20161108; Goat anti-Human IgG (Fc specific) HRP: Supplier: (b) (4) Lot No.: 023M4782		
Regression model & weighting	5 PL (Marquardt); 1/Y ²		
Validation parameters	Method validation summary		Source location
Calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ	8	Table 1 of Report 8354-363
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-1.3% to 3.0%	Table 1 of Report 8354-363
	Cumulative precision (%CV) from LLOQ to ULOQ	≤ 8.0%	Table 1 of Report 8354-363
QCs performance during accuracy & precision	<u>Cumulative accuracy (%bias) in 5 QCs</u> QCs: 400 ng/mL (LLOQ), 1200 ng/mL (LQC), 8000 ng/mL (MQC), 32000 ng/mL (HQC), 40000 ng/mL (ULOQ)	-2.3% to 18.0%	Table 3-2 of Report 8354-363
	<u>Inter-batch %CV</u> QCs: 400 ng/mL (LLOQ),	≤ 12.8%	Table 3-2 of Report 8354-363

	1200 ng/mL (LQC), 8000 ng/mL (MQC), 32000 ng/mL (HQC), 40000 ng/mL (ULOQ)		
	Total error QCs: 400 ng/mL (LLOQ), 1200 ng/mL (LQC), 8000 ng/mL (MQC), 32000 ng/mL (HQC), 40000 ng/mL (ULOQ)	≤ 22.4%	Table 3-2 of Report 8354- 363
Selectivity & matrix effect	10 lots of individual human serum unspiked (blank) and spiked at LLOQ and ULOQ were tested. At ULOQ, %bias ranges from -17.5% to 19.8%; At LLOQ, %bias exceeds 25% in 1 out of ten samples, and %bias ranges from 4.8% to 22.3% in other 9 samples. The data indicates there were no marked matrix effects in normal matrix.		Table 5-1 of Report 8354- 363
Interference & specificity	No interference was observed for the detection of BGB-A317 with BGB-A425 concentration up to 400 µg/mL; No interference was observed for the detection of BGB-A317 with BGB-A333 concentration up to 1000 µg/mL; No interference was observed for the detection of BGB-A317 with BGB-A1217 concentration up to 1000 µg/mL; No interference was observed for the detection of BGB-A317 with ZW25 concentration up to 1000 µg/mL; No interference was observed for the detection of BGB-A317 with BGB-A445 concentration up to 500 µg/mL.		Table 6-1, 6- 2, 6-3, 6-4, and 6-5 of Report 8354- 363 Addendum 01
Hemolysis effect	5 duplicates of pooled matrix unspiked (blank) and spiked at LLOQ and ULOQ. %bias: -19.8% to 14.5%.		Table 5-2 of Report 8354- 363
Lipemic effect	5 duplicates of pooled matrix unspiked (blank) and spiked at LLOQ and ULOQ. %bias: 3.5% to 17.8%.		Table 5-3 of Report 8354- 363
Dilution linearity & hook effect	400,000 ng/mL, 2000-fold dilution. No hook effect was observed. %bias: -9.0% to -13.8%		Table 6 of Report 8354- 363
Bench-top/process stability	Stable for 72 hours in human serum at room temperature.		Table 4 of Report 8354- 363 Addendum 01
Freeze-Thaw stability	Stable for 6 freeze-thaw cycles at -60°C to -80°C		Table 7 of Report 8354- 363
Long-term storage	Stable for 32 days at -15°C to -30°C; Stable for 404 days at -60°C to -80°C		Table 10-1 of Report 8354- 363; Table 5 of Report 8354- 363

		Addendum 01
Parallelism	Not applicable	Not applicable
Carry over	Not applicable	Not applicable
Method performance in study BGB-A317-302 Determination the Concentration of BGB-A317 in Human Serum Samples using ELISA, anti-BGB-A317 antibodies (ADA) and anti-BGB-A317 neutralizing antibody (NAb) in Human Serum Samples using ECL from Clinical Study Protocol Number BGB-A317-302 (Report 8375-776)		
Assay passing rate	51/57 (89.5%) runs passed	Table 1 of Report 8375-776
Standard curve performance	Cumulative bias range: -1.8% to 6.1% Cumulative precision: $\leq 4.3\%$ CV	Table 2 of Report 8375-776
QC performance	- Cumulative bias range: -1.0% to 2.1% - Cumulative precision: $\leq 16.5\%$ CV - TE: Not applicable.	Table 6 of Report 8375-776
Method reproducibility	Incurred sample reanalysis was performed in 8.9% of study samples, and 98.2% of samples met the prespecified criteria.	Table 10 of Report 8375-776
Study sample analysis/ stability	The longest possible storage duration (from sample collection to sample analysis) of the study samples is 778 days. The matrix stability for 806 days at -80°C was completed at ^{(b) (4)} (Report number: VAL136). All samples were analyzed within the above established storage stability duration, as well as established benchtop and freeze-thaw stability.	

Abbreviations: % CV, coefficient of variation percentage; ECL, electrochemiluminescent; ELISA, enzyme-linked immunosorbent assay; HQC: high quality control sample; HRP, horseradish peroxidase; IgG, immunoglobulin G; LLOQ, lower limit of quantitation; LQC: low quality control sample; MQC: medium quality control sample; PL, parameter logistic; QC, quality control; ULOQ, upper limit of quantification.

19.4.2. Population PK Analysis

Population PK Summary Table

General Information		
Objectives of PPK Analysis		<i>Characterize the PK profile of tislelizumab in patients with cancer.</i> <i>Evaluate the effect of patient demographics, pathophysiologic factors, immunogenicity, and organ function etc. on tislelizumab PK</i> <i>Evaluate impact of body weight distribution on flat dosing and body weight-based dosing regimens using population PK simulation approach.</i> <i>Predict individual tislelizumab exposure for E-R analysis</i>
Study Included		<i>Phase I:</i> <i>BGB-A317-001, BGB-A317-102</i> <i>Phase II:</i> <i>BGB-A317-203, BGB-A317-204, BGB-A317-205, BGB-A317-206, BGB-A317-208, BGB-A317-209</i> <i>Phase III:</i> <i>BGB-A317-302, BGB-A317-303, BGB-A317-304, and BGB-A317-307.</i> <i>Table 46)</i>
Dose(s) Included		<i>0.5 mg/kg, 2 mg/kg, 5 mg/kg, or 10 mg/kg Q2W; 2 mg/kg or 5 mg/kg Q3W; and 200 mg Q3W</i>
Population Included		Classical Hodgkin lymphoma (cHL): 70 Colorectal cancer (CRC): 81 Esophageal carcinoma other than ESCC: 373 Gastric cancer (GC): 102 Hepatocellular carcinoma (HCC): 316 Nasopharyngeal carcinoma (NPC): 21 Non-small cell lung cancer (NSCLC): 1151 Ovarian cancer (OC): 52 Urothelial bladder cancer (UC): 151 Other: 279 <i>264 patients (ITT) were involved in the pivotal study BGB-A317-302.</i>
Population Characteristics (Table XX)	General	<i>Age median (year): 60 (range: 18-90; 846, 33% subj ≥65; 109, 4.2% subj ≥75)</i> <i>Weight median (kg): 65 (range: 31.9 - 170)</i> <i>Gender: 1920 (74%) male</i>

		<i>Race:</i> 528 (20.3%) <i>White</i> , 1991 (76.7%) <i>Asian</i> , 10 (0.4%) <i>Black or African American</i> 44 (1.7%) <i>Others</i> 23 (0.9%) <i>Missing</i>	
	Organ Impairment	<i>Hepatic (NCI):</i> 2182 (84.2%) <i>Normal</i> , 396 (15.3%) <i>Mild Impairment</i> , 12 (0.5%) <i>Moderate Impairment</i> , 2 (0.08%) <i>Severe Impairment</i> , 4 (0.15%) <i>Missing</i> <i>Renal (eGFR):</i> 1223 (47.1%) <i>Normal</i> , 1046 (40.3%) <i>Mild Impairment</i> , 320 (12.3%) <i>Moderate Impairment</i> , 5 (0.2%) <i>Severe Impairment</i> , 2 (0.08%) <i>Missing</i>	
	Pediatrics (if any)	NA	
No. of Patients, PK Samples, and BLQ		14848 measurable serum samples from 2601 subjects 54 (0.36%) BLQ samples	
Covariates Evaluated	Static	Age, sex, race, eGFR, Albumin, bilirubin, AST, ALT, LDH, ECOG, ADA, ADA onset, ADA duration, tumor size, tumor type.	
	Time-varying	ADA	
Final Model		Summary	Acceptability [FDA's comments]
Software and Version		Population PK model parameter estimation and evaluation were implemented with NONMEM 7, Version 7.4.3 (b) (4) Perl-Speaks-NONMEM (PsN) Version 4.2 (b) (4) and R 3.5.3 or above.	Acceptable
Model Structure		3-compartment model with first order elimination from the central	Acceptable

	<i>compartment, and redistribution into the peripheral compartments</i>	
Model Parameter Estimates	Table 49	
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)	<i>The typical values of CL, Vc, V2, and V3 were well-estimated (RSE% < 5%). The estimated covariate coefficients of sex, age, ALB, TUMSZ, ADA, and TUMTP were also well-estimated (RSE% ranging from 5.50% to 51.7%).</i>	Acceptable
BLQ for Parameter Accuracy	<i>BLQ samples were excluded from population PK analysis</i>	Acceptable due to the low proportion of BLQ samples
GOF, VPC and NPC	Figure 21, Figure 22 and Table 50	Acceptable
Significant Covariates and Clinical Relevance	Table 51 and Figure 23	Acceptable

Table 46. Summary of studies included in the Population PK analysis

Region	Study No.	Title	Phase	Dose Regimen	Planned N
Global	BGB-A317-001	A Phase 1A/1B, Open Label, Multiple Dose, Dose Escalation and Expansion Study to Investigate the Safety, Pharmacokinetics and Antitumor Activities of the anti-PD-1 Monoclonal Antibody BGB-A317 in Subjects with Advanced Tumors	1a/1b	0.5 mg/kg, 2 mg/kg, 5 mg/kg, or 10 mg/kg Q2W; 2 mg/kg or 5 mg/kg Q3W; and 200 mg Q3W	451
China	BGB-A317-102	Phase III Study Investigating Safety, Tolerability, Pharmacokinetics and Preliminary Antitumor Activities of Anti-PD-1 Monoclonal Antibody BGB-A317 in Chinese Patients with Advanced Solid Tumors	1/2	200 mg Q3W	300
China	BGB-A317-203	A Single Arm, Multicenter, Phase 2 Study of BGB-A317 as Monotherapy in Relapsed or Refractory Classical Hodgkin Lymphoma	2	200 mg Q3W	70
China/Korea	BGB-A317-204	A Single-Arm, Multicenter Phase 2 Study of BGB-A317 in Patients with Previously Treated PD-L1+ Locally Advanced or Metastatic Urothelial Bladder Cancer	2	200 mg Q3W	113
China	BGB-A317-205	A Phase 2, Multi-Cohort Study to Investigate the Safety, Pharmacokinetics and Preliminary Antitumor Activity of the anti-PD-1 Monoclonal Antibody BGB-A317 in Combination with Chemotherapy as First-Line Treatment in Adults with Inoperable, Locally Advanced or Metastatic Esophageal, Gastric, or Gastroesophageal Junction Carcinoma	2	200 mg Q3W	30
China	BGB-A317-206	A Phase II, Open-Label, Multi-Cohort Study to Investigate the Preliminary Antitumor Activity, Safety, and Pharmacokinetics of the anti-PD-1 Monoclonal Antibody BGB-A317 in Combination with Chemotherapy as First-Line Treatment in Chinese Subjects with Locally Advanced or Metastatic Lung Cancer	2	200 mg Q3W	54
Global	BGB-A317-208	A Phase 2, Open-label, Multicenter Study to Investigate the Efficacy, Safety, and Pharmacokinetics of the Anti-PD-1 Monoclonal Antibody BGB-A317 in Patients with Previously Treated Hepatocellular Unresectable Carcinoma	2	200 mg Q3W	249
China	BGB-A317-209	A Single-Arm, Multi-Center, Open-Label, Phase 2 Study to Evaluate Efficacy and Safety of Tislelizumab (BGB-A317), an anti-PD-1 Monoclonal Antibody, as Monotherapy in Patients with Previously-Treated Locally Advanced Unresectable or Metastatic Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Solid Tumors	2	200 mg Q3W	78
Global	BGB-A317-302	A Randomized, Controlled, Open-label, Global Phase 3 Study Comparing the Efficacy of the anti-PD-1 Antibody Tislelizumab (BGB-A317) versus Chemotherapy as Second Line Treatment in Patients with Advanced Unresectable/Metastatic Esophageal Squamous Cell Carcinoma	3	200 mg Q3W	264
Global	BGB-A317-303	A Phase 3, Open-Label, Multicenter, Randomized Study to Investigate the Efficacy and Safety of BGB-A317 (Anti-PD1 Antibody) Compared with Docetaxel in Patients with Non-Small Cell Lung Cancer Who Have Progressed on a Prior Platinum-Containing Regimen	3	200 mg Q3W	532
China	BGB-A317-304	A Phase 3, Open-Label, Multicenter, Randomized Study to Investigate the Efficacy and Safety of Tislelizumab (BGB-A317) (Anti-PD1 Antibody) Combined With Platinum-Pemetrexed Versus Platinum-Pemetrexed Alone as First-line Treatment for Patients With Stage IIIB or IV Non-Squamous Non-Small Cell Lung Cancer	3	200 mg Q3W	222
China	BGB-A317-307	A Phase 3, Multicenter, Randomized Open-Label Study to Compare the Efficacy and Safety of Tislelizumab (BGB-A317, Anti-PD1 Antibody) Combined With Paclitaxel Plus Carboplatin or Nab-Paclitaxel Plus Carboplatin Versus Paclitaxel Plus Carboplatin Alone as First-Line Treatment for Untreated Advanced Squamous Non-Small Cell Lung Cancer	3	200 mg Q3W	238

Source: PopPK Report BGB-A317-CP-008, Page 22, Table 4.

Table 47. Baseline continuous covariates (median [min, max]) in the Population PK dataset.

Study	AGE (year)	WT (kg)	ALB (g/L)	ALT (U/L)	AST (U/L)	BIL (μmol/L)	eGFR (mL/min/1.73 m ²)	CREAT (μmol/L)	LDH (U/L)	TUMSZ (mm)
BGB-A317-001 (N=450)	61.0 [18.0,81.0]	69.1 [31.9,129]	37.0 [17.0,50.0]	18.0 [4.00,340]	24.0 [5.00,338]	8.00 [2.00,96.0]	89.8 [30.7,146]	71.8 [29.2,186]	236 [87.0,6010]	71.0 [10.0,310]
BGB-A317-102 (N=300)	56.5 [18.0,82.0]	62.0 [40.0,105]	41.8 [26.2,53.0]	18.0 [3.00,103]	25.0 [8.00,134]	10.8 [4.20,29.9]	94.8 [42.9,147]	70.5 [34.0,136]	224 [111,2564]	61.5 [10.0,355]
BGB- A317-203 (N=70)	32.5 [18.0,69.0]	66.0 [40.0,93.0]	43.0 [26.7,53.2]	15.0 [2.50,80.0]	19.1 [9.00,91.4]	9.65 [4.20,75.9]	119 [62.5,162]	56.9 [21.5,116]	213 [126,842]	1775 [136,11266]
BGB- A317-204 (N=112)	62.5 [36.0,81.0]	65.5 [36.0,94.5]	42.7 [23.0,435]	15.0 [6.00,79.0]	19.0 [6.10,86.0]	8.80 [0.513,21.1]	67.2 [30.0,112]	93.4 [44.9,194]	204 [102,1452]	69.4 [15.0,239]
BGB- A317-205 (N=30)	60.5 [42.0,74.0]	55.0 [38.0,88.0]	40.6 [25.4,48.6]	14.0 [4.00,129]	18.0 [10.0,137]	12.0 [5.20,21.8]	98.3 [61.4,119]	69.5 [44.0,113]	184 [114,1123]	44.3 [15.0,151]
BGB- A317-206 (N=54)	61.0 [36.0,75.0]	65.3 [36.0,109]	41.9 [30.5,48.2]	16.8 [4.30,137]	19.0 [11.0,68.9]	10.4 [5.00,20.9]	96.6 [76.0,124]	68.0 [32.8,96.0]	223 [132,892]	82.0 [12.0,194]
BGB- A317-208 (N=248)	62.0 [28.0,90.0]	69.0 [40.0,113]	41.9 [28.0,52.0]	30.0 [6.00,158]	38.0 [13.0,195]	12.0 [2.00,35.2]	96.8 [31.0,143]	69.2 [39.0,165]	203 [123,1713]	75.3 [10.0,408]
BGB- A317-209 (N=76)	53.5 [19.0,81.0]	63.3 [35.0,85.0]	42.4 [33.0,53.3]	13.6 [4.00,80.0]	21.0 [6.00,130]	9.95 [3.30,25.0]	103 [52.8,151]	60.0 [30.0,113]	217 [127,2820]	59.5 [11.0,204]
BGB- A317-302 (N=264)	62.0 [29.0,83.0]	58.2 [35.1,170]	41.6 [26.0,54.4]	15.0 [4.00,225]	19.0 [7.00,98.0]	8.55 [2.90,33.0]	97.0 [36.0,134]	69.0 [32.6,168]	183 [107,2401]	42.0 [10.0,261]
BGB- A317-303 (N=532)	61.0 [28.0,88.0]	66.4 [35.0,130]	42.5 [27.0,380]	17.0 [3.00,157]	20.0 [6.00,104]	8.53 [2.05,30.8]	93.9 [35.7,138]	70.9 [31.4,177]	204 [93.0,1311]	58.0 [10.0,380]
BGB- A317-304 (N=222)	60.0 [27.0,75.0]	64.0 [41.0,100]	42.0 [26.8,61.3]	18.0 [7.00,99.0]	20.0 [9.00,71.6]	10.3 [3.00,29.8]	97.6 [47.4,135]	66.0 [43.6,136]	211 [102,1228]	67.3 [10.0,230]
BGB- A317-307 (N=238)	62.0 [38.0,74.0]	62.0 [45.0,113]	40.8 [28.2,54.1]	18.0 [2.70,88.0]	19.0 [8.70,113]	10.2 [3.50,29.4]	96.9 [57.4,128]	68.4 [39.0,112]	208 [116,1409]	79.3 [15.0,207]
Total (N=2596)	60.0 [18.0,90.0]	65.0 [31.9,170]	41.1 [17.0,435]	18.0 [2.50,340]	22.0 [5.00,338]	9.30 [0.513,96.0]	94.9 [30.0,162]	70.0 [21.5,194]	207 [87.0,6010]	63.3 [10, 408]

Source: PopPK Report BGB-A317-CP-008, Page 32, Table 7.

Table 48. Baseline categorical covariates (N (%)) in the Population PK dataset.

	001 (N=450)	102 (N=300)	203 (N=70)	204 (N=112)	205 (N=30)	206 (N=54)	208 (N=248)	209 (N=76)	302 (N=264)	303 (N=532)	304 (N=222)	307 (N=238)	Total (N=2596)
Sex													
Male	246 (54.7%)	207 (69.0%)	40 (57.1%)	83 (74.1%)	25 (83.3%)	40 (74.1%)	216 (87.1%)	40 (52.6%)	224 (84.8%)	414 (77.8%)	167 (75.2%)	218 (91.6%)	1920 (74.0%)
Female	204 (45.3%)	93 (31.0%)	30 (42.9%)	29 (25.9%)	5 (16.7%)	14 (25.9%)	32 (12.9%)	36 (47.4%)	40 (15.2%)	118 (22.2%)	55 (24.8%)	20 (8.4%)	676 (26.0%)
Race													
White	289 (64.2%)	—	—	—	—	—	96 (38.7%)	—	51 (19.3%)	92 (17.3%)	—	—	528 (20.3%)
Asian	130 (28.9%)	300 (100%)	70 (100%)	112 (100%)	30 (100%)	54 (100%)	125 (50.4%)	76 (100%)	211 (79.9%)	423 (79.5%)	222 (100%)	238 (100%)	1991 (76.7%)
Black or African American	5 (1.1%)	—	—	—	—	—	4 (1.6%)	—	—	1 (0.2%)	—	—	10 (0.4%)
Others	26 (5.8%)	—	—	—	—	—	2 (0.8%)	—	—	16 (3.0%)	—	—	44 (1.7%)
Missing	—	—	—	—	—	—	21 (8.5%)	—	2 (0.8%)	—	—	—	23 (0.9%)
ECOG													
0	169 (37.6%)	80 (26.7%)	48 (68.6%)	53 (47.3%)	5 (16.7%)	9 (16.7%)	129 (52.0%)	34 (44.7%)	69 (26.1%)	117 (22.0%)	51 (23.0%)	55 (23.1%)	819 (31.5%)
1	281 (62.4%)	220 (73.3%)	22 (31.4%)	59 (52.7%)	25 (83.3%)	45 (83.3%)	119 (48.0%)	42 (55.3%)	195 (73.9%)	415 (78.0%)	171 (77.0%)	183 (76.9%)	1777 (68.5%)
ADA													
Negative	383 (85.1%)	257 (85.7%)	64 (91.4%)	94 (83.9%)	23 (76.7%)	47 (87.0%)	181 (73.0%)	64 (84.2%)	222 (84.1%)	452 (85.0%)	174 (78.4%)	175 (73.5%)	2136 (82.3%)
Positive	66 (14.7%)	43 (14.3%)	6 (8.6%)	18 (16.1%)	7 (23.3%)	7 (13.0%)	50 (20.2%)	12 (15.8%)	32 (12.1%)	80 (15.0%)	48 (21.6%)	63 (26.5%)	432 (16.6%)
Missing	1 (0.2%)	—	—	—	—	—	17 (6.9%)	—	10 (3.8%)	—	—	—	28 (1.1%)
THERAPY													
Monotherapy	450 (100%)	300 (100%)	70 (100%)	112 (100%)	—	—	248 (100%)	76 (100%)	254 (96.2%)	532 (100%)	—	—	2042 (78.7%)
Combotherapy	—	—	—	—	30 (100%)	54 (100%)	—	—	—	—	222 (100%)	238 (100%)	544 (21.0%)
Missing	—	—	—	—	—	—	—	—	10 (3.8%)	—	—	—	10 (0.4%)
TUMTP													
	001 (N=450)	102 (N=300)	203 (N=70)	204 (N=112)	205 (N=30)	206 (N=54)	208 (N=248)	209 (N=76)	302 (N=264)	303 (N=532)	304 (N=222)	307 (N=238)	Total (N=2596)
cHL	—	—	70 (100%)	—	—	—	—	—	—	—	—	—	70 (2.7%)
CRC	21 (4.7%)	14 (4.7%)	—	—	—	—	—	46 (60.5%)	—	—	—	—	81 (3.1%)
EC	54 (12.0%)	26 (8.7%)	—	—	15 (50.0%)	—	—	14 (18.4%)	264 (100%)	—	—	—	373 (14.4%)
GC	54 (12.0%)	24 (8.0%)	—	—	15 (50.0%)	—	—	9 (11.8%)	—	—	—	—	102 (3.9%)
HCC	50 (11.1%)	18 (6.0%)	—	—	—	—	248 (100%)	—	—	—	—	—	316 (12.2%)
NPC	—	21 (7.0%)	—	—	—	—	—	—	—	—	—	—	21 (0.8%)
NSCLC	49 (10.9%)	56 (18.7%)	—	—	—	54 (100%)	—	—	—	532 (100%)	222 (100%)	238 (100%)	1151 (44.3%)
OC	51 (11.3%)	—	—	—	—	—	—	1 (1.3%)	—	—	—	—	52 (2.0%)
UC	17 (3.8%)	22 (7.3%)	—	112 (100%)	—	—	—	—	—	—	—	—	151 (5.8%)
Other	154 (34.2%)	119 (39.7%)	—	—	—	—	—	6 (7.9%)	—	—	—	—	279 (10.7%)
Line of Therapy													
0	88 (19.6%)	—	—	—	—	—	—	—	—	—	—	—	88 (3.4%)
1	152 (33.8%)	—	—	—	30 (100%)	54 (100%)	—	39 (51.3%)	—	—	222 (100%)	238 (100%)	735 (28.3%)
2	99 (22.0%)	—	28 (40.0%)	—	—	—	138 (55.6%)	25 (32.9%)	254 (96.2%)	532 (100%)	—	—	1076 (41.4%)
3	61 (13.6%)	—	15 (21.4%)	—	—	—	102 (41.1%)	7 (9.2%)	—	—	—	—	185 (7.1%)
≥4	50 (11.1%)	—	27 (38.6%)	—	—	—	8 (3.2%)	4 (5.3%)	—	—	—	—	49 (1.9%)
Missing	—	300 (100%)	—	112 (100%)	—	—	—	1 (1.3%)	10 (3.8%)	—	—	—	423 (16.3%)

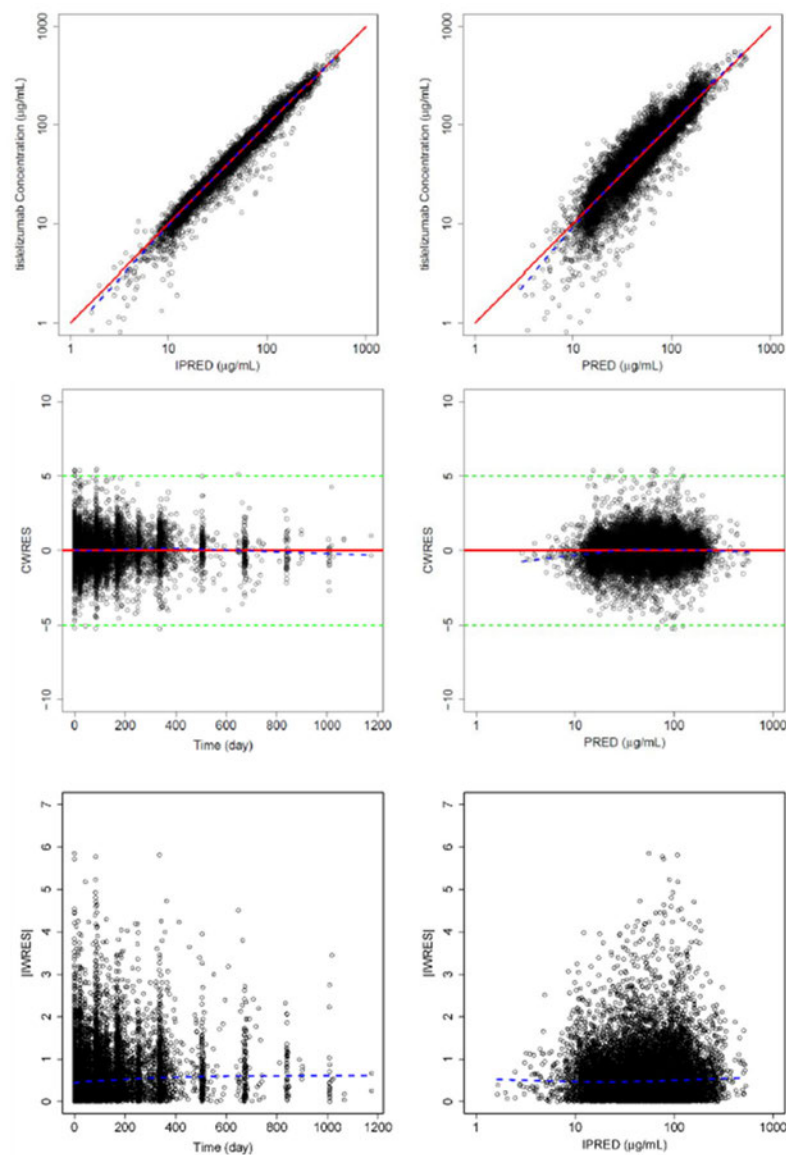
Source: PopPK Report BGB-A317-CP-008, Page 33-34, Table 8.

Table 49. Summary of final population pk parameters.

Parameter	Parameter Description	Final PopPK Model		
		Estimate (% RSE)	Median (95% CI) from bootstrapping	Shrinkage (%)
$\exp(\theta_1)*24$	Clearance, CL (L/day)	0.153 (0.816%)	0.154 (0.151, 0.157)	15.9%
θ_7	Influence of WT on CL	0.565 (5.95%)	0.562 (0.491, 0.631)	-
θ_{10}	Influence of ALB on CL	-0.457 (11.2%)	-0.443 (-0.648, -0.229)	-
θ_{11}	Influence of TUMSZ on CL	0.0735 (10.4%)	0.0757 (0.056, 0.0953)	-
θ_{13}	Influence of ADA on CL	0.111 (13.8%)	0.110 (0.0783, 0.146)	-
θ_{14}	Influence of TUMTP of GC on CL	0.069 (48.2%)	0.0778 (-0.00319, 0.161)	-
θ_{15}	Influence of TUMTP of cHL on CL	-0.216 (17.1%)	-0.215 (-0.294, -0.137)	-
$\exp(\theta_2)$	Central volume, V_c (L)	3.05 (0.498%)	3.05 (3.02, 3.08)	15.7%
θ_8	Influence of WT on V_c	0.397 (5.50%)	0.395 (0.354, 0.437)	-
θ_9	Influence of Sex on V_c	-0.116 (8.30%)	-0.116 (-0.135, -0.0997)	-
θ_{12}	Influence of Age on V_c	0.0966 (51.7%)	0.0957 (0.0602, 0.132)	-
$\exp(\theta_3)*24$	Inter-compartmental clearance, Q_2 (L/day)	0.740 (4.55%)	0.746 (0.616, 0.944)	-
$\exp(\theta_4)$	Peripheral volume, V_2 (L)	1.27 (2.02%)	1.27 (1.14, 1.43)	55.8%
$\exp(\theta_5)*24$	Inter-compartmental clearance, Q_3 (L/day)	0.092 (3.23%)	0.0923 (0.0796, 0.104)	-
$\exp(\theta_6)$	Peripheral volume, V_3 (L)	2.10 (3.89%)	2.06 (1.81, 2.30)	44.4%
ω_{CL,V_c}^2	Covariance (CL, V_c)	0.020 (6.43%)	0.0198 (0.0167, 0.0227)	-
Inter-Individual Variability (%RSE)	CL	26.3 (1.84%)	26.4 (25.2, 27.7)	-
	V_c	16.7 (2.05%)	16.7 (15.8, 17.6)	-
	V_2	74.7 (1.88%)	76.3 (65.0, 86.8)	-
	V_3	99.9 (4.06%)	97.3 (85.7, 110)	-
σ_p	Proportional residual error (%)	12.6 (1.08%)	12.6 (12.0, 13.2)	17.8%
σ_a	Additive residual error (µg/mL)	2.09 (9.31%)	2.06 (1.79, 2.33)	17.8%

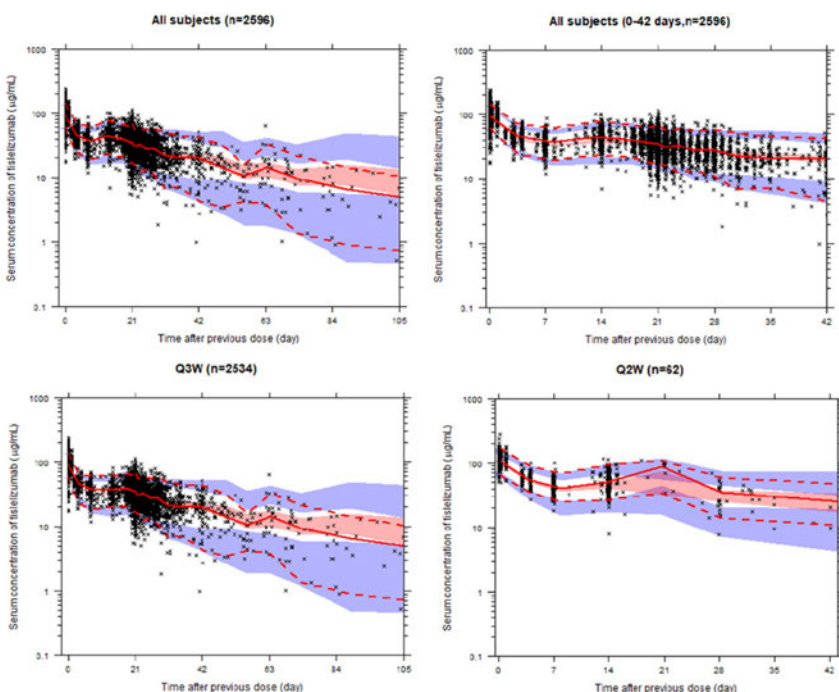
Source: PopPK Report BGB-A317-CP-008, Page 40, Table 11.

Figure 21. Goodness of fit plots for the final population PK model



Source: PopPK Report BGB-A317-CP-008, Page 42-43, Figure 6-7.

Figure 22. Prediction-corrected visual predictive check of tislelizumab serum concentration-time profiles across all studies or stratified by dosing regimen.



Source: PopPK Report BGB-A317-CP-008, Page 47-48, Figure 11-12.

Table 50. Summary of numerical predictive check.

Range above/below simulated prediction intervals	% Observed data points within the range	
	Expected	Actual
Above 95 th percentile	5.00	4.62%
Above 75 th percentile	25.0	33.3%
Above 50 th percentile	50.0	60.6%
Below 50 th percentile	50.0	39.4%
Below 25 th percentile	25.0	17.3%
Below 5 th percentile	5.00	1.89%

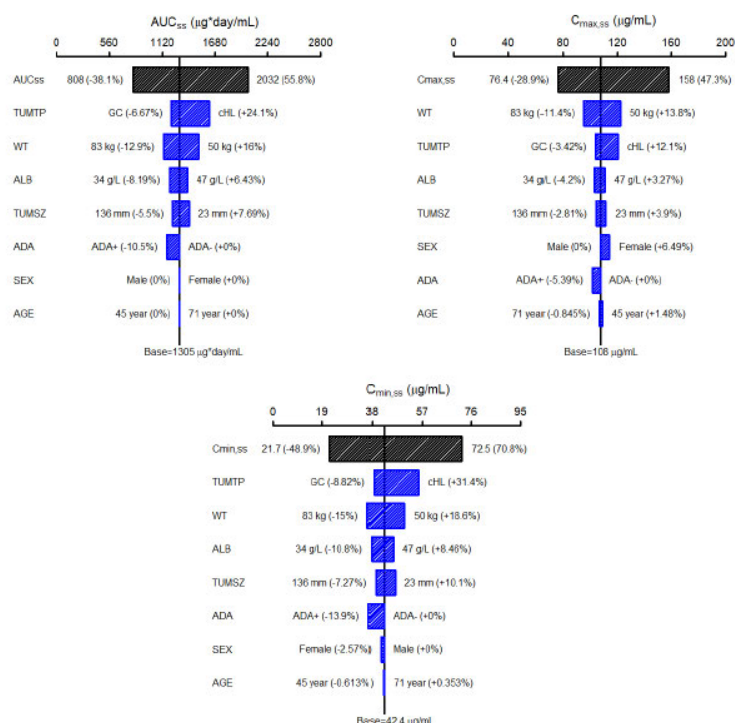
Source: PopPK Report BGB-A317-CP-008, Page 51, Table 13.

Table 51. Key PK parameters and covariate effects for representative subjects.

PK Parameters and Baseline Covariates		Estimate	% Change from Typical
Typical CL (L/day, 65 kg, ALB=41 g/L, TUMSZ=63 mm, tumors except cHL and GC)		0.153	—
Weight (kg)	10 th percentile (50 kg)	0.132	-13.8
	90 th percentile (83 kg)	0.176	+14.8
Albumin (g/L)	10 th percentile (34 g/L)	0.167	+8.92
	90 th percentile (47 g/L)	0.144	-6.04
Tumor size (mm)	10 th percentile (23 mm)	0.142	-7.14
	90 th percentile (136 mm)	0.162	+5.82
ADA	Treatment-emergent ADA positive	0.171	+11.7
Tumor type	Gastric cancer (GC)	0.164	+7.15
	Classical Hodgkin lymphoma (cHL)	0.123	-19.4
Typical V _c (L, male, 65 kg, 60 years)		3.05	—
Weight (kg)	10 th percentile (50 kg)	2.75	-9.88
	90 th percentile (83 kg)	3.36	+10.2
Sex	Female	2.71	-11.0
Age (year)	10 th percentile (45 years)	2.96	-2.74
	90 th percentile (71 years)	3.10	+1.64
Typical Q ₂ (L/day)		0.74	—
Typical V ₂ (L)		1.27	—
Typical Q ₃ (L/day)		0.092	—
Typical V ₃ (L)		2.10	—
Proportional residual error (%)		12.6	—
Additive residual error (µg/mL)		2.09	—

Source: PopPK Report BGB-A317-CP-008, Page 41, Table 12.

Figure 23. Sensitivity analysis plot comparing the effect of covariates on tislelizumab steady state exposure (AUC_{ss}, C_{max,ss} and C_{min,ss})

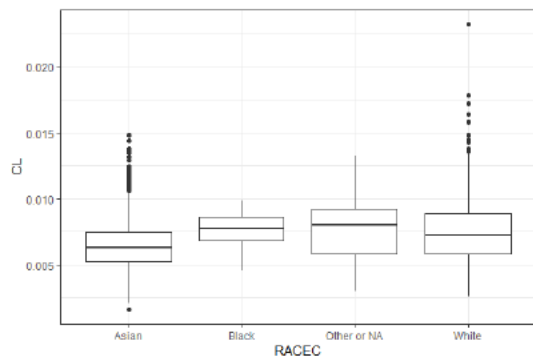


Source: PopPK Report BGB-A317-CP-008, Page 53, Figure 15.

FDA's Assessment:

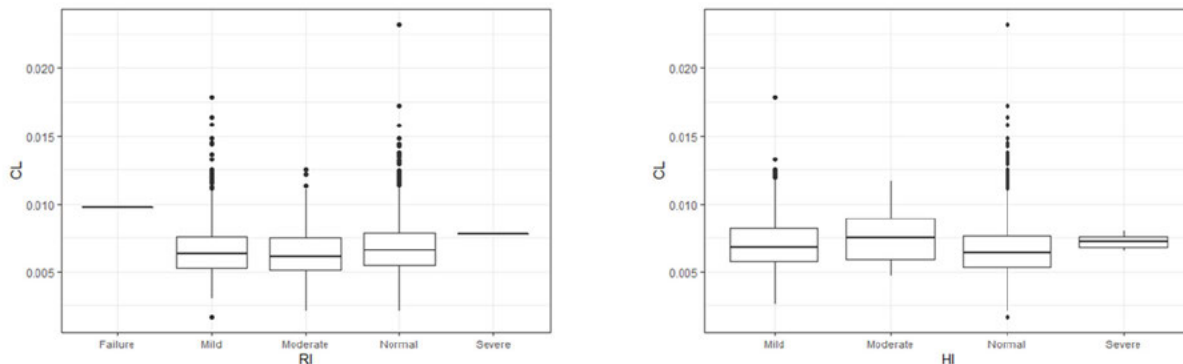
Applicant's population PK analysis was assessed during the review. The population PK model was generally acceptable due to good agreement between model predictions and observations. In the population PK model, race was not identified as significant covariate. Empirical Bayes estimates of tislelizumab clearance among Asian, White, and Black or African American races were shown in Figure 24. White and Black or African American subjects showed slightly higher clearance than Asian subjects, which were mainly due to the relatively high bodyweight in these subjects comparing with Asian subjects. Tislelizumab exposure was expected to be similar between different races. Renal and hepatic functions were not identified as significant covariates either. Patients with renal impairment (mild & moderate) and hepatic impairment (mild & moderate) are expected to have similar tislelizumab exposure as patients with normal renal and hepatic function. (Figure 25)

Figure 24. Empirical Bayes estimates of clearance in different races.



Source: Reviewer’s analysis.

Figure 25. Empirical Bayes estimates of clearance in subjects with different renal and hepatic functions.



Source: Reviewer’s analysis.

19.4.3. Exposure-Response Analysis for Efficacy

ER Efficacy Summary Table

General Information	
Goal of ER analysis	Explore the exposure-response (E-R) relationship between tislelizumab exposure metrics and efficacy endpoints using data from Study BGB-A317-302.
Study Included	Study BGB-A317-302.
Endpoint	Primary: Overall survival Secondary: objective response rate (ORR)

No. of Patients (total, and with individual PK)		254 patients for OS 236 patients for ORR	
Population Characteristics (Table 52)	General	Age median (range): 62 (40 -83) yr Weight median (range): 58.7 (37.4 – 170) kg Gender: 216 (85%) males Race: White: 51 (20.1%) Asian: 201 (79.1%) Other: 2 (0.8%)	
	Pediatrics (if any)	Not applicable	
Dose(s) Included		200 mg IV Q3W	
Exposure Metrics Explored (range)		$C_{avg, ss}$: 26.9 - 188 µg/mL $C_{max, ss}$: 64.2 – 260.8 µg/mL $C_{min, ss}$: 12.4 – 149.4 µg/mL $C_{avg, dose1}$: 16.4 – 67.3 µg/mL	
Covariates Evaluated		age, age group (<65 years vs. ≥65 years), body weight [WT], sex, race [White, Asian, and Other], tumor size [TUMSZ], albumin [ALB], estimated glomerular filtration rate [eGFR], alanine aminotransferase [ALT], aspartate aminotransferase [AST], bilirubin [BIL], lactate dehydrogenase [LDH], ECOG status [0 vs. ≥1], anti-drug antibodies status [ADA, treatment-emergent ADA status], and tumor growth rate (TGR)	
Final Model Parameters		Summary	Acceptability [FDA’s comments]
Model Structure		OS: Kaplan-Meier survival curves and Cox proportional hazards model ORR: Linear logistic regression model	Acceptable
Model Parameter Estimates		Table 53, Table 54	Acceptable
Covariates and Clinical Relevance		Figure 26	Acceptable
Visualization of E-R relationships		Figure 27 and Figure 29	Acceptable
		The ER relationship of OS in the ITT population was explored by Kaplan-Meier curves stratified by	Acceptable

	<i>exposure ($C_{avg,dose1}$) quartiles. A longer OS was observed in the highest tislelizumab exposure quartile compared to those patients in the lower three quartiles. In Cox proportional hazard model, ALB, tumor growth rate (TGR) and the highest exposure quartile (Q4) were identified as significant predictor relative to the lowest exposure quartile (Q1). However, the ER relationship is likely inconclusive due to the imbalance in the baseline factors. (Figure 28) The exposure-response relationship of the ORR was explored by the probability of response plots. Although the plots showed that a slightly positive trend between tislelizumab exposure and the ORR, logistic regression analysis indicated that neither tislelizumab Exposure nor race is significant predictor in ER analysis.</i>	
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Table 52. Summary of baseline Characteristics in E-R efficacy analysis.

Characteristics	BGB-A317-302 (N=254)
Continuous Covariates (abbreviation, unit)	Median [min, max]
Age (years)	62.0 [40.0, 83.0]
Weight (WT, kg)	58.7 [37.4, 170]
Total bilirubin (BIL, mmol/L)	8.55 [2.90, 33.0]
Alanine aminotransferase (ALT, IU/L)	15.0 [4.00, 225]
Aspartate aminotransferase (AST, IU/L)	19.0 [7.00, 98.0]
Albumin (ALB, g/L)	41.7 [26.0, 54.4]
Creatinine (CREAT, mmol/L)	69.0 [32.6, 168]
Estimated glomerular filtration rate (eGFR, mL/min/m ²)	96.7 [36.0, 134]
Lactate dehydrogenase (LDH, U/L)	182 [107, 2401]
Tumor size (TUMSZ, mm)	42.0 [10.0, 261]
Categorical Covariates (abbreviation, group)	N (%)
Sex (M/F)	216/38 (85.0%/15.0%)
Race (White/Asian/Other)	51/201/2 (20.1%/79.1%/0.787%)
ECOG (0/1)	63/191 (24.8%/75.2%)
PD-L1 (negative/positive/missing)	115/89/50 (45.3%/35.0%/19.7%)
Anti-drug antibodies (ADA, negative/positive)	222/32 (87.4%/12.6%)

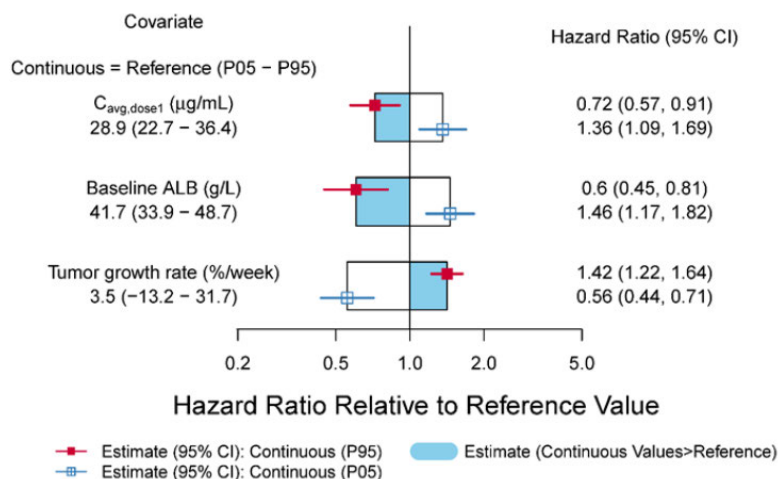
Source: BGB-A317-CP-011, Page 18, Table 1.

Table 53. Cox proportional hazard model parameters for OS in tislelizumab treated patients.

Run#	Predictor Variables	Parameter Estimates		Wald p-value	95% CI for β	
		β	exp(β)		Lower	Upper
33	Log(ALB)	-2.4333	0.0877	0.0009	-3.8651	-1.0014
	Log(C _{avg,dose1})	-1.3475	0.2599	0.0056	-2.3017	-0.3934
	TGR	0.0207	1.0209	<0.0001	0.012	0.0294

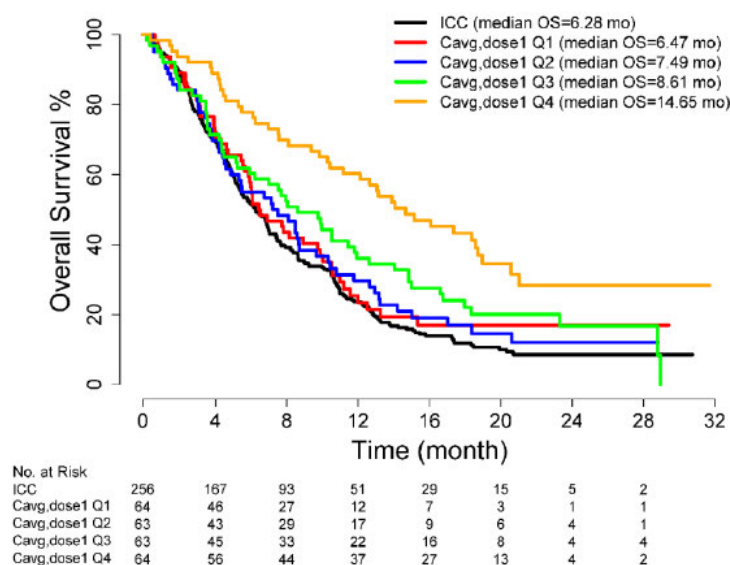
Source: BGB-A317-CP-011, Page 26, Table 4.

Figure 26. Estimated effects of significant prognostic factors and $C_{avg,dose1}$ on the hazard ratio of OS in tislelizumab treated patients



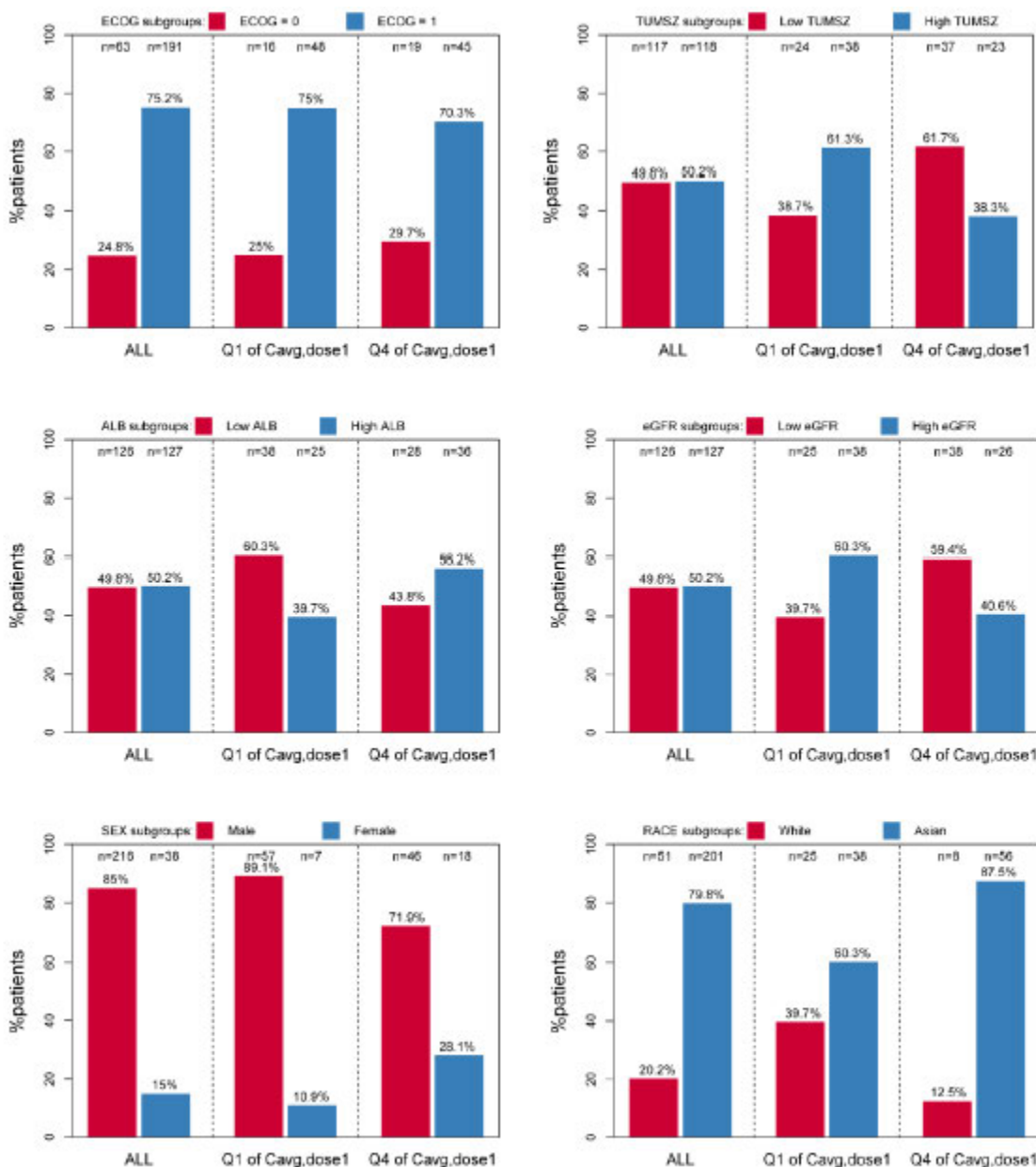
Source: BGB-A317-CP-011, Page 26, Figure 6.

Figure 27. Kaplan–Meier OS curves stratified by $C_{avg,dose1}$ quartiles in ITT population.



Source: BGB-A317-CP-011, Page 21, Figure 3.

Figure 28. Proportion of tislelizumab treated patients with each potential baseline risk factor indicating differentiation in OS in extreme Cavg,dose1 quartile (Q1 and Q4)



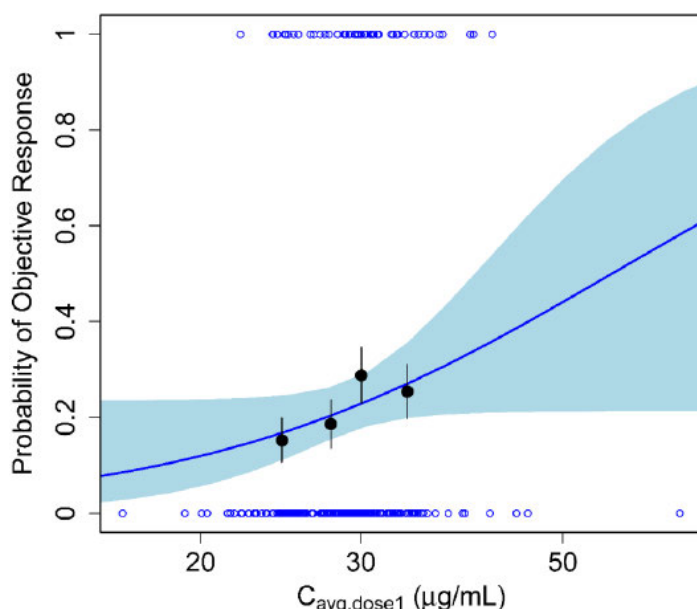
Source: BGB-A317-CP-011, Page 24, Figure 5.

Table 54. Logistic regression analysis model parameters for ORR

Final Logistic Model	Parameter	Estimates (SE)	p-value
$\text{logit}(P(Y_i = 1)) = \beta_0 + \beta_1 \cdot \log(C_{\text{avg,dose1}})$	β_0	-7.74 (3.39)	0.0224
	β_1	1.92 (0.999)	0.0548

Source: BGB-A317-CP-011, Page 35, Table 10.

Figure 29. Logistic regression of probability of objective response versus exposure

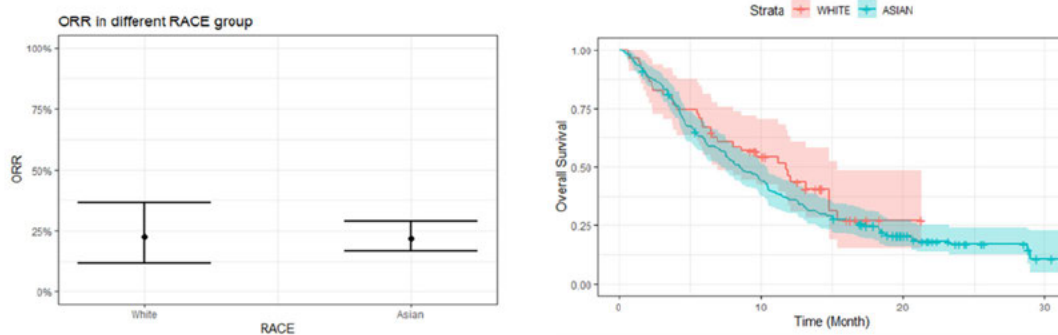


Source: BGB-A317-CP-011, Page 35, Figure 13.

The FDA's Assessment:

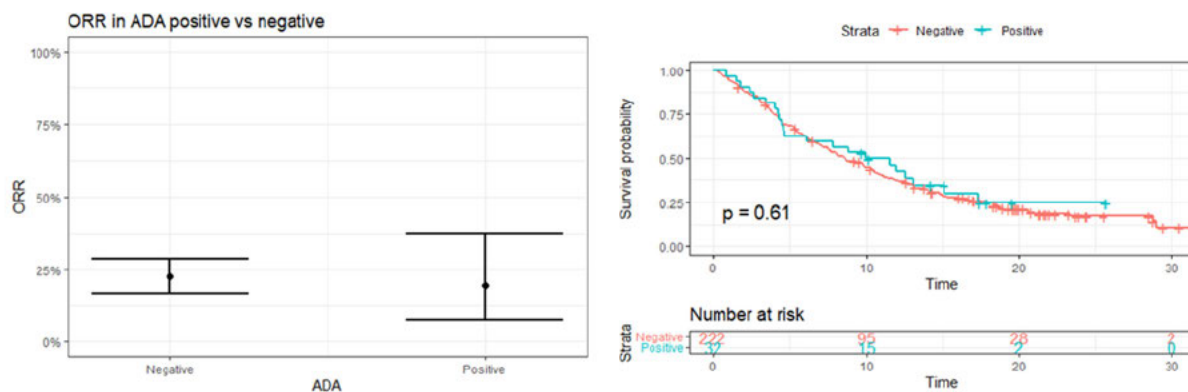
Applicant's ER efficacy analysis was verified by the reviewer. Relatively longer overall survival time and higher ORR was observed in patients with highest quartile tislelizumab exposure. However, the effect of tislelizumab exposure on survival and ORR may be confounded by an imbalance in baseline factors of patients in different quartiles of tislelizumab exposure. Higher baseline tumor sizes were observed in patients with lower exposure ($C_{\text{avg,dose1}}$) of tislelizumab, which may affect the ER relationship (Figure 23). The race effect on OS and ORR was shown in Figure 30. No clear difference was observed between White and Asian patients. The efficacy in Black patients was not evaluated due to limited number patients in the analysis. The ADA effect on OS and ORR was shown in Figure 31 and no clear difference was observed between patients with positive and negative ADA status.

Figure 30. Comparison of ORR and OS in White and Asian patients in Study BGB-A317-302.



Source: Reviewer's analysis.

Figure 31. Comparison of ORR and OS in patients with negative and positive ADA status in Study BGB-A317-302.



Source: Reviewer's analysis

19.4.4. Exposure-Response Analysis for Safety

ER Safety Summary Table

General Information	
Goal of ER analysis	Explore the E-R relationship between tislelizumab exposure metrics and safety endpoints using data in tislelizumab treated patients.
Study Included	BGB-A317-001, BGB-A317-102, BGB-A317-203, BGB-A317-204, BGB-A317-302
Population Included	Patients with solid tumor and cHL

Endpoint		any adverse event (AE) $\geq$ grade 3 (G3AE), AEs leading to treatment discontinuation (AEDISC), AEs leading to dose modification (AEDOSEC), immune mediated AEs (IMAE), infusion related reactions (IRR) and AEs of special interest (AESI= IMAE +IRR).
No. of Patients (total, and with individual PK)		932 Patients with solid tumor and cHL. 254 patients treated with tislelizumab (200 mg IV Q3W) in Study BGB-A317-302.
Population Characteristics (Table 56 & Table 52)	General	BGB-A317-001, BGB-A317-102, BGB-A317-203, BGB-A317-204: -Age median (range): 59 (18 -82) yr -Weight median (range): 65.9 (31.9 -128.8) kg -Gender: 576 (61.8%) males -Race: White: 289 (31%) Asian: 621 (67%) Other: 31 (2%) BGB-A317-302: <i>Age median (range): 62 (40 -83) yr</i> <i>Weight median (range): 58.7 (37.4 – 170) kg</i> <i>Gender: 216 (85%) males</i> <i>Race:</i> <i>White: 51 (20.1%)</i> <i>Asian: 201 (79.1%)</i> <i>Other: 2 (0.8%)</i>
Dose(s) Included		Table 55 and 200 mg IV Q3W in Study BGB-A317-302
Exposure Metrics Explored (range)		BGB-A317-001, BGB-A317-102, BGB-A317-203, BGB-A317-204: $C_{avg, ss}$: 6.8 - 401.8 $\mu\text{g/mL}$ $C_{max, ss}$: 13.9 - 584.9 $\mu\text{g/mL}$ $C_{min, ss}$: 3.7 - 316.2 $\mu\text{g/mL}$ $C_{avg, dose1}$: 4.4 - 166.5 $\mu\text{g/mL}$ BGB-A317-302: $C_{avg, ss}$: 26.9 - 188 $\mu\text{g/mL}$ $C_{max, ss}$: 64.2 – 260.8 $\mu\text{g/mL}$ $C_{min, ss}$: 12.4 – 149.4 $\mu\text{g/mL}$ $C_{avg, dose1}$: 16.4 – 67.3 $\mu\text{g/mL}$
Final Model Parameters		Summary Acceptability [FDA's comments]

Model Structure	Logistic regression analysis	Acceptable
Model Parameter Estimates	IMAE: Table 57 AEs of special interest: Table 58	Acceptable
Visualization of E-R relationships	Figure 32	Acceptable
Overall Clinical Relevance for ER	No clinically relevant E-R relationship was observed between tislelizumab exposure and the safety endpoints of probability of any AE $\geq$ grade 3, AEs leading to treatment discontinuation, infusion-related reaction, and AEs leading to dose modification. Slightly positive E-R trend was observed for immune-mediated AE and AEs of special interest. While logistic regression analysis showed no significant E-R relationship after including effect of tumor type. In Study BGB-A317-302, similar results were observed that there was no evidence of higher tislelizumab exposure leading to increased rates of the safety endpoints. (Figure 33)	The result was checked by the reviewer. Although no significant ER relationship were identified for selected safety endpoints, the positive relationships were observed for IMAE and AESI in the pooled dataset (Figure 34).

Table 55. Summary of dose regimens in ER safety analysis in Study BGB-A317-001, BGB-A317-102, BGB-A317-203, BGB-A317-204

Dose Regimen	BGB-A317-001 ^a (N=450)	BGB-A317-102 ^b (N=300)	BGB-A317-203 (N=70)	BGB-A317-204 ^c (N=112)	Overall (N=932)
0.5 mg/kg Q2W	3 (0.7%)	-	-	-	3 (0.3%)
10 mg/kg Q2W	7 (1.6%)	-	-	-	7 (0.8%)
2 mg/kg Q2W	26 (5.8%)	-	-	-	26 (2.8%)
2 mg/kg Q3W	21 (4.7%)	-	-	-	21 (2.3%)
200 mg Q3W	13 (2.9%)	300 (100%)	70 (100%)	112 (100%)	495 (53.1%)
5 mg/kg Q2W	26 (5.8%)	-	-	-	26 (2.8%)
5 mg/kg Q3W	354 (78.7%)	-	-	-	354 (38.0%)

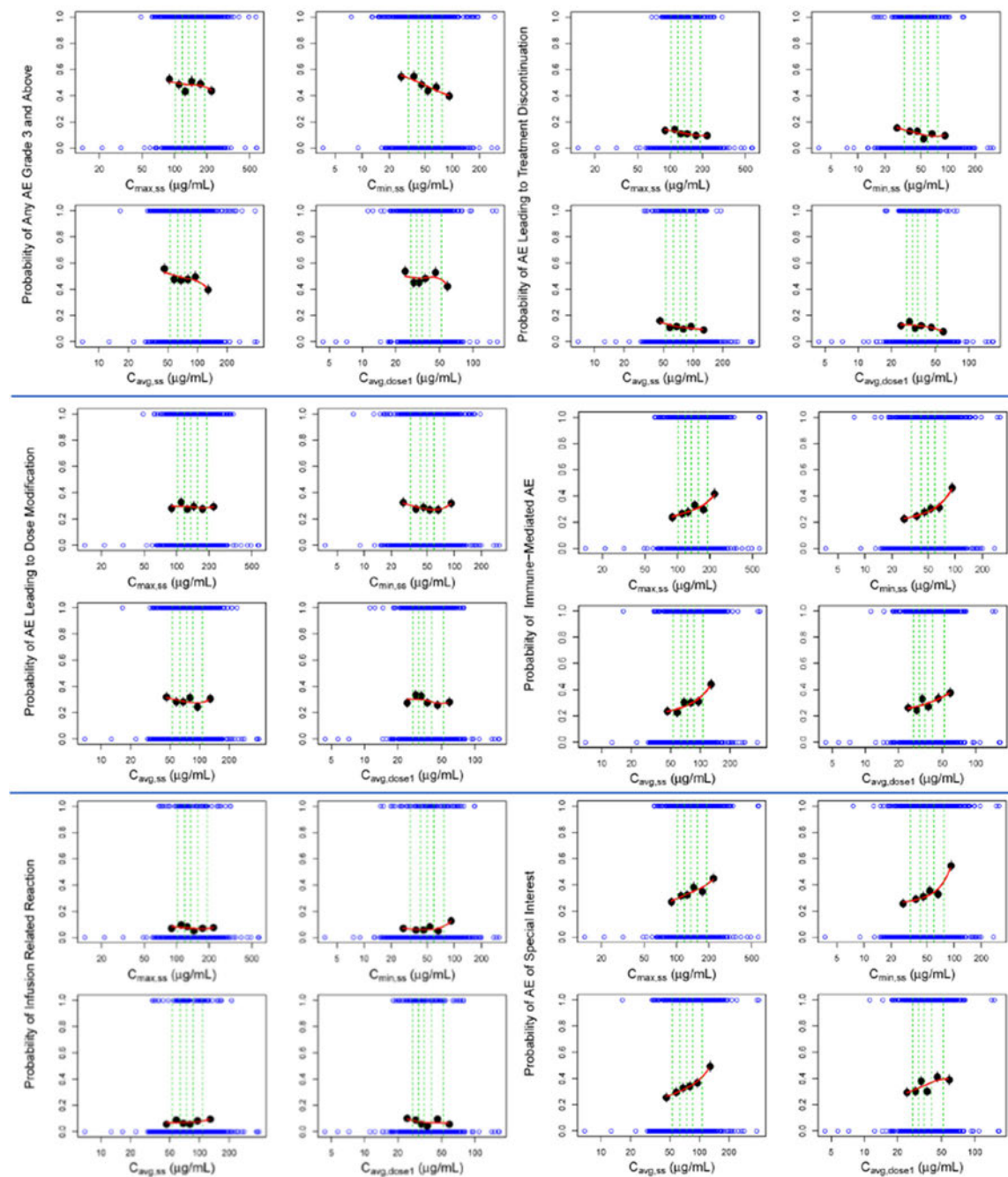
Source: BGB-A317-CP-0091, Page 17, Table 1.

Table 56. Summary of baseline Characteristics in E-R safety analysis in Study BGB-A317-001, BGB-A317-102, BGB-A317-203, BGB-A317-204

Characteristics	All	BGB-A317-001	BGB-A317-102	BGB-A317-203	BGB-A317-204
No. of subjects	932	450	300	70	112
Clinical Features					
Age (years, mean $\pm$ SD)	56.8 $\pm$ 13.0	59.5 $\pm$ 12.0	55.5 $\pm$ 11.5	36.2 $\pm$ 12.7	62.0 $\pm$ 7.86
Sex (M/F)	576/356	246/204	207/93	40/30	83/92
Weight (kg, mean $\pm$ SD)	67.3 $\pm$ 14.4	70.6 $\pm$ 16.2	62.9 $\pm$ 11.6	66.9 $\pm$ 13.2	65.8 $\pm$ 11.2
BIL (μ mol/L, mean $\pm$ SD)	10.1 $\pm$ 6.26	8.79 $\pm$ 6.34	12.1 $\pm$ 5.11	11.6 $\pm$ 9.62	9.15 $\pm$ 4.24
ALT (IU/L, mean $\pm$ SD)	23.0 $\pm$ 22.1	24.3 $\pm$ 27.7	23.3 $\pm$ 15.9	20.1 $\pm$ 16.4	18.8 $\pm$ 11.5
AST (IU/L, mean $\pm$ SD)	29.0 $\pm$ 20.8	31.7 $\pm$ 25.1	29.2 $\pm$ 16.9	22.0 $\pm$ 11.9	22.2 $\pm$ 11.2
Albumin (g/L, mean $\pm$ SD)	40.3 $\pm$ 19.8	36.7 $\pm$ 5.62	41.6 $\pm$ 4.59	41.9 $\pm$ 5.85	50.6 $\pm$ 53.9
Creatine (μ mol/L, mean $\pm$ SD)	76.4 $\pm$ 23.6	75.3 $\pm$ 21.9	73.0 $\pm$ 20.1	62.7 $\pm$ 20.0	98.8 $\pm$ 27.4
EGFR (mL/min/m ² , mean $\pm$ SD)	89.5 $\pm$ 22.2	87.7 $\pm$ 20.0	93.5 $\pm$ 19.1	116 $\pm$ 20.8	69.5 $\pm$ 18.4
LDH (U/L, mean $\pm$ SD)	297 $\pm$ 301	312 $\pm$ 367	304 $\pm$ 256	253 $\pm$ 135	244 $\pm$ 160
Tumor size (mm, mean $\pm$ SD)	255 $\pm$ 908	84.4 $\pm$ 57.5	71.6 $\pm$ 49.0	2420 $\pm$ 2440	76.7 $\pm$ 45.6
Race (White/Asian/Other)	289/612/31	289/130/31	0/300/0	0/70/0	0/112/0
ECOG (0/1)	350/582	169/281	80/220	48/22	53/59
ADA [% (Positive/All)]	14.3% (133/932)	14.7% (66/450)	14.3% (43/300)	8.6% (6/70)	16.1% (18/112)
Clinical Responses					
Any AE grade 3 and above [% (Yes/All)]	48.0% (447/932)	48.9% (220/450)	46.7% (140/300)	31.4% (22/70)	58.0% (65/112)
Immune-mediated AE [% (Yes/All)]	30.4% (283/932)	36.2% (163/450)	19.7% (59/300)	38.6% (27/70)	30.4% (34/112)
AEs leading to treatment discontinuation [% (Yes/All)]	11.5% (107/932)	8.9% (40/450)	12.7% (38/300)	5.7% (4/70)	22.3% (25/112)
Infusion-related reaction [% (Yes/All)]	7.5% (70/932)	6.4% (29/450)	2.0% (6/300)	44.3% (31/70)	3.6% (4/112)
AEs leading to dose modification [% (Yes/All)]	29.3% (273/932)	28.7% (129/450)	31.3% (94/300)	17.1% (12/70)	33.9% (38/112)
AEs of special interest [% (Yes/All)]	34.8% (324/932)	39.3% (177/450)	20.7% (62/300)	70.0% (49/70)	32.1% (36/112)
C _{avg,dose1} (μ g/mL, mean $\pm$ SD)	38.8 $\pm$ 15.4	47.1 $\pm$ 18.0	31.0 $\pm$ 5.50	32.1 $\pm$ 5.79	30.2 $\pm$ 4.44

Source: BGB-A317-CP-0091, Page 31, Table 18.

Figure 32. Probability of safety endpoints versus tislelizumab exposure in Study BGB-A317-001, BGB-A317-102, BGB-A317-203, BGB-A317-204



Source: BGB-A317-CP-0091, Page 35-46, Figure 14, 16, 18, 20, 22 and 24.

Table 57. Logistic regression model parameters for immune-mediated AEs in Study BGB-A317-001, BGB-A317-102, BGB-A317-203, BGB-A317-204

Predictor	Parameter Estimates	p-value
Intercept		
cHL	4.84 (4.94)	0.327
EC	-4.1 (5.1)	0.421
GC	-12.9 (6.32)	0.0412
HCC	-1.51 (4.87)	0.756
NSCLC	-9.39 (3.93)	0.0168
OC	-3.31 (3.01)	0.272
UC	-8.31 (3.26)	0.0109
Other	-3.75 (1.55)	0.0155
Slope of $\log(C_{\max,12})$		
cHL	-1.09 (1.02)	0.283
EC	0.56 (1.02)	0.583
GC	2.28 (1.27)	0.0729
HCC	0.205 (0.963)	0.832
NSCLC	1.76 (0.786)	0.0254
OC	0.504 (0.574)	0.38
UC	1.54 (0.674)	0.0219
Other	0.597 (0.31)	0.0543

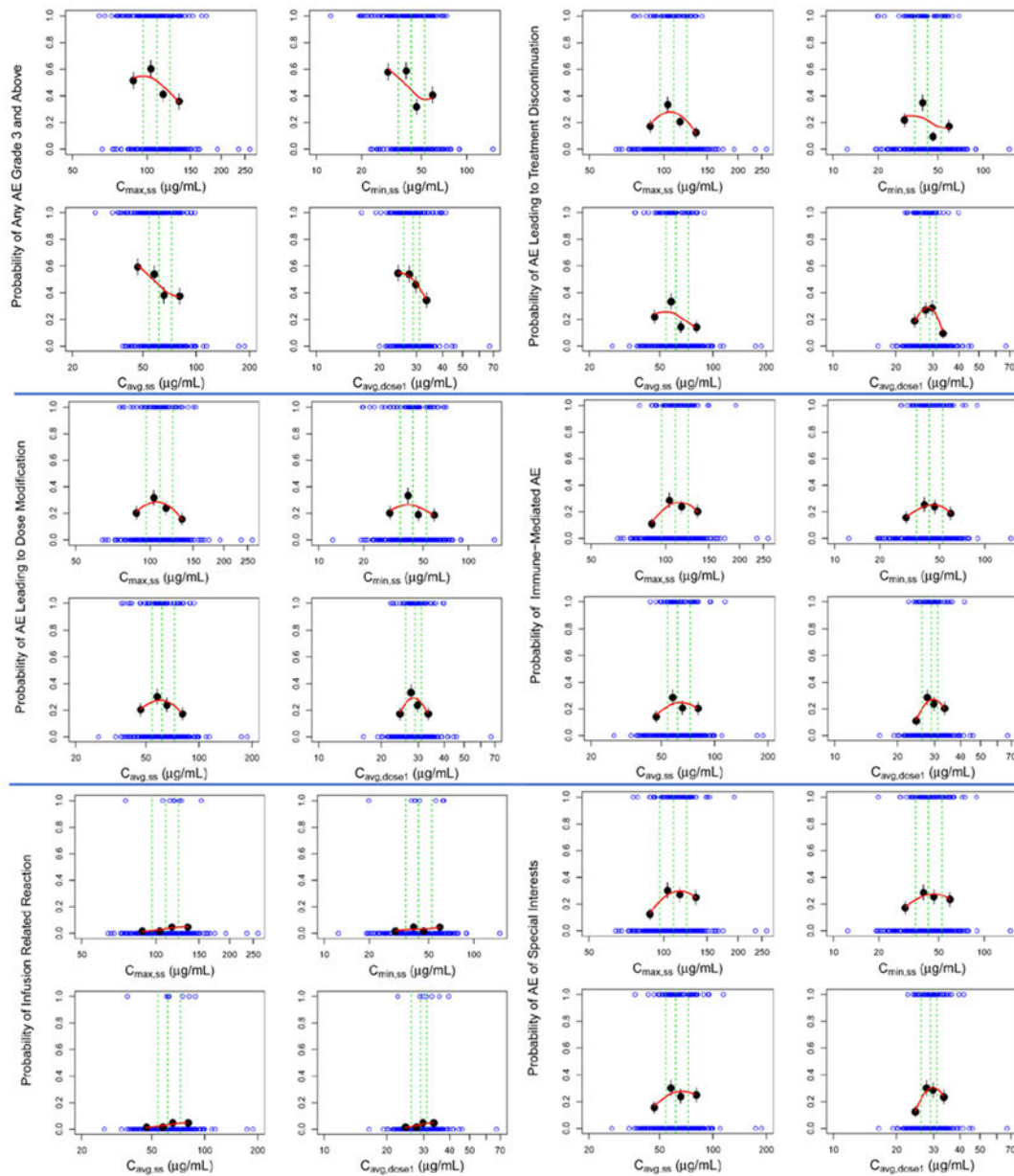
Source: BGB-A317-CP-0091, Page 40, Table 24.

Table 58. Logistic regression model parameters for AEs of special interest in Study BGB-A317-001, BGB-A317-102, BGB-A317-203, BGB-A317-204

Predictor	Parameter Estimates	p-value
Intercept		
cHL	5.88 (5.4)	0.276
EC	-2.94 (4.69)	0.531
GC	-12.1 (6.05)	0.0455
HCC	-4.64 (4.91)	0.344
NSCLC	-10.5 (3.98)	0.00836
OC	-2.79 (2.85)	0.328
UC	-9.09 (3.3)	0.00592
Other	-3.48 (1.52)	0.0225
Slope of $\log(C_{\max, w})$		
cHL	-1.03 (1.11)	0.35
EC	0.383 (0.941)	0.684
GC	2.14 (1.22)	0.0795
HCC	0.849 (0.97)	0.381
NSCLC	1.99 (0.795)	0.0125
OC	0.438 (0.545)	0.422
UC	1.73 (0.683)	0.0111
Other	0.557 (0.306)	0.0683

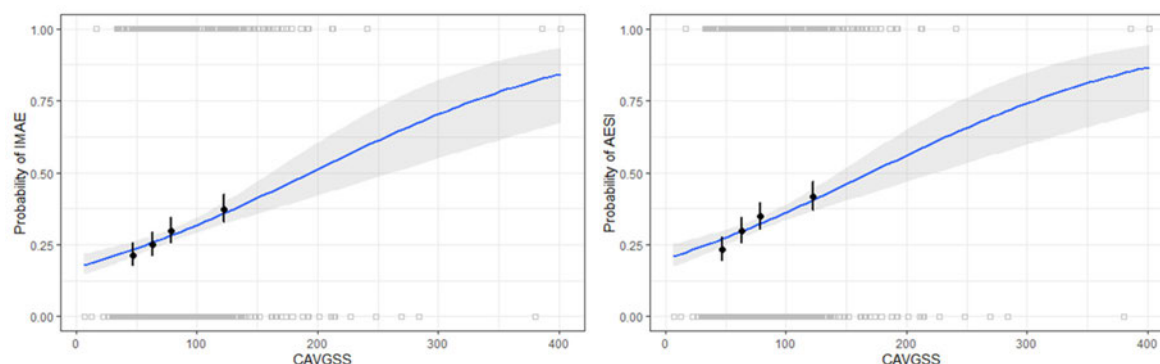
Source: BGB-A317-CP-0091, Page 47, Table 28.

Figure 33. Probability of safety endpoints versus tislelizumab exposure in Study BGB-A317-302



Source: BGB-A317-CP-011, Page 38-48, Figure 15, 17, 19, 21, 23 and 25.

Figure 34. Rate of IMAE and AESI versus $C_{avg,ss}$ in pooled dataset.

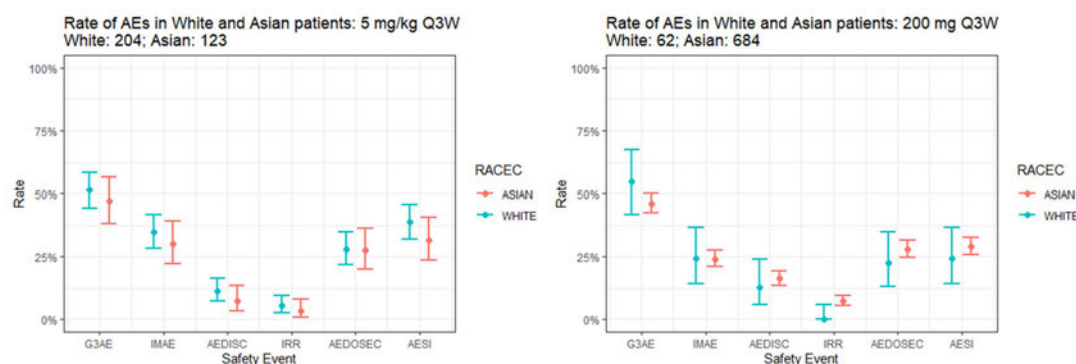


Source: Reviewer's analysis.

The FDA's Assessment:

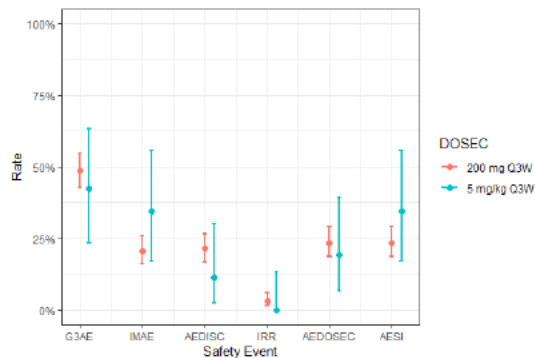
Applicant's analysis was checked by the reviewer. Safety data from Study BGB-A317-001, BGB-A317-102, BGB-A317-203, BGB-A317-204, BGB-A317-302 were pooled for further ER analysis. Among patients receiving 5 mg/kg or 200 mg Q3W tislelizumab treatment, no significant differences were observed between Asian and White patients. (Figure 35) Among patients receiving 5 mg/kg or 200 mg Q3W, no clear difference on AE rates were observed between ADA positive and ADA negative patients (Figure 38). The selected AEs in Black or African American patients was not evaluated due to limited number patients in the analysis. The probability of safety endpoints in different dose group in subjects with ESCC were shown in Figure 36. Higher rates of IMAE and AESI were observed in patients receiving 5 mg/kg tislelizumab than 200 mg which appears consistent to the slightly positive ER trends observed in Figure 37, while none of them were significant in ESCC patients.

Figure 35. Rate of safety endpoints versus races (White and Asian) in subjects received 5 mg/kg or 200 mg Q3W tislelizumab.



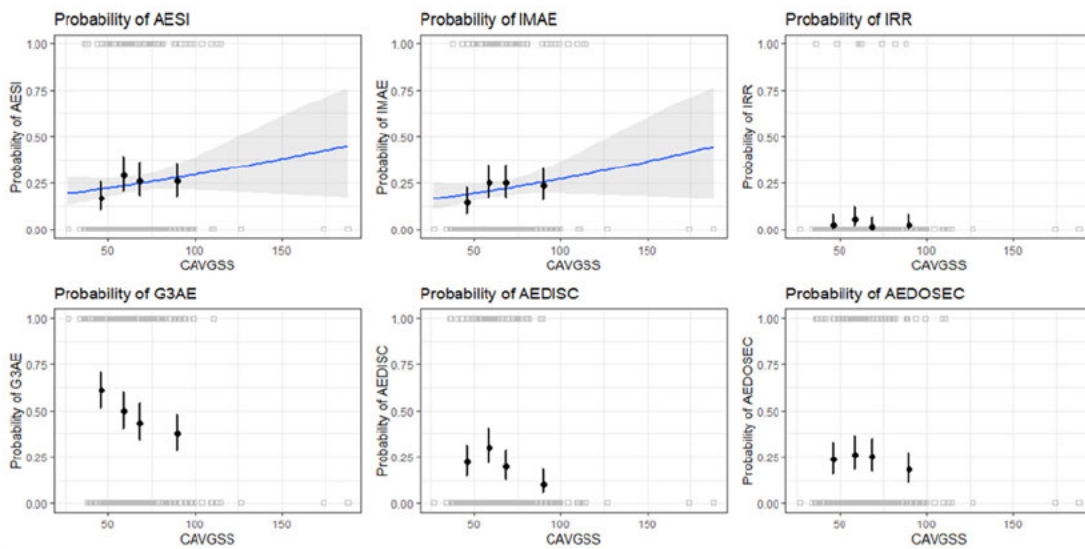
Source: Reviewer's analysis.

Figure 36. Rate of safety endpoints in patients with ESCC received different dose of tislelizumab.



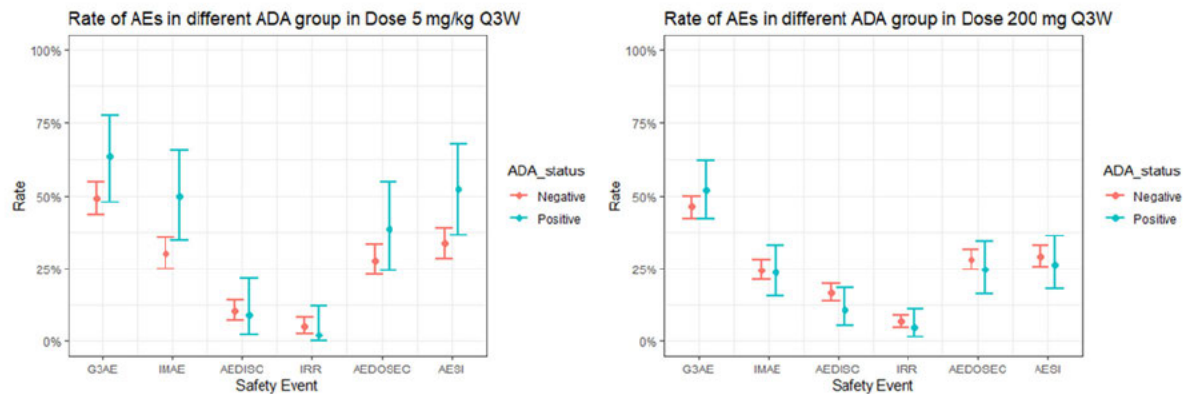
Source: Reviewer's analysis

Figure 37. Probability of safety endpoints versus $C_{avg,ss}$ of tislelizumab in patients with ESCC.



Source: Reviewer's analysis

Figure 38. Rate of safety endpoints versus ADA status in subjects received 5 mg/kg or 200 mg Q3W tislelizumab.



Source: Reviewer's analysis

19.5. Additional Safety Analyses Conducted by FDA

The FDA's Assessment:

Not applicable.

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Team Leader	Matthew Thompson	OOD/DHOT	Sections: 5	Select one: ☒ Authored ☒ Approved
	Signature: Matthew D. Thompson -S  Digitally signed by Matthew D. Thompson -S Date: 2022.10.25 07:22:10 -04'00'			
Nonclinical Division Director	John Leighton	OOD/DHOT	Sections: 5	Select one: ☒ Approved
	Signature: John K. Leighton -S  Digitally signed by John K. Leighton -S Date: 2022.10.25 07:26:39 -04'00'			
Clinical Pharmacology Reviewer	Edwin Chow	CDER/OTS/OCP/DCPII	Sections: 6, OCP Appendices	Select one: ☒ Authored
	Signature: Edwin C. Chow -S  Digitally signed by Edwin C. Chow -S Date: 2022.10.25 08:43:47 -04'00'			
Clinical Pharmacology Team Lead	Jason Moore	CDER/OTS/OCP/DCPII	Sections: 6, OCP Appendices	Select one: ☒ Authored ☒ Approved
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DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Pharmacometrics Reviewer	Yangbing Li	CDER/OTS/O CP/DPM	Sections: 6, OCP Appendices	Select one: ☒ Authored
	Signature: Yangbing Li -S (Affiliate) Digitally signed by Yangbing Li -S (Affiliate) Date: 2022.10.25 09:38:39 -04'00'			
Pharmacometrics Team Leader	Jiang Liu	CDER/OTS/O CP/DPM	Sections: 6, OCP Appendices	Select one: ☒ Authored ☒ Approved
	Signature: Jiang Liu -S Digitally signed by Jiang Liu -S Date: 2022.10.25 09:45:03 -04'00'			
Clinical Pharmacology Division Director	Nam Atiqur Rahman	CDER/OTS/O CP/DCPII	Sections: 6, OCP Appendices	Select one: ☒ Approved
	Signature: Nam A. Rahman -S Digitally signed by Nam A. Rahman -S Date: 2022.10.25 09:50:15 -04'00'			
Clinical Reviewer	Lorraine Pelosof	CDER/OND/O OD/DO3	Sections: 1,2,3,4, 7, 8, 9, 11, 19	Select one: ☒ Authored
	Signature: Lorraine Pelosof -S Digitally signed by Lorraine Pelosof -S Date: 2022.10.25 12:34:28 -04'00'			
Clinical Team Leader	Sandra Casak	CDER/OND/O OD/DO3		Select one: ☐ Authored ☐ Approved
	Signature: See final signature in AA			
Statistical Team Leader	Joyce Cheng	OB/DBV	Sections: 1, 8	Select one: ☒ Authored ☒ Approved
	Signature: Joyce Cheng -S Digitally signed by Joyce Cheng -S Date: 2022.10.25 15:21:28 -04'00'			
Division Director (OB)	Shenghui Tang	OB/DBV	Sections: 1, 8	Select one: ☒ Approved
	Signature: Shenghui Tang -S Digitally signed by Shenghui Tang -S Date: 2022.10.25 15:41:55 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Associate Director for Labeling (ADL)	Doris Auth	OCE	Sections: Label	Select one: ☒ Approved
	Signature: Doris Auth -S  Digitally signed by Doris Auth -S Date: 2024.01.10 15:29:48 -05'00'			
Cross-Disciplinary Team Leader (CDTL)	Sandra Casak	CDER/OND/OOD/D O3		Select one: ☐ Authored ☐ Approved
	Signature: See final signature in AA			
Division Director	Steven Lemery	CDER/OND/OOD/D O3		Select one: Authored Approved
	Signature: See final signature in AA			

BLA 761232

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Acting Division Director	Haleh Saber	OOD/DHOT	Sections: 5	Select one: ☐ Authored ☒ Approved
	Signature: Haleh Saber -S Digitally signed by Haleh Saber -S Date: 2024.02.26 10:27:40 -05'00'			

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

/s/

SANDRA J CASAK
03/13/2024 09:26:58 AM

STEVEN J LEMERY
03/13/2024 10:20:57 AM

PAUL G KLUETZ
03/13/2024 10:36:14 AM