17 October 2024
EMA/510873/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tevimbra

International non-proprietary name: Tislelizumab

Procedure No. EMEA/H/C/005919/II/0006

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

1L	first line
2L	second line
5-FU	fluorouracil
ACS	American Cancer Society
ADA	antidrug antibody
ADR	adverse drug reaction
AE	adverse event
ALB	albumin
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
Arm P+PtF	placebo in combination with fluoropyrimidine- (capecitabine or 5-FU) and platinum-(oxaliplatin or cisplatin) based chemotherapy
Arm T+PtF	tislelizumab in combination with fluoropyrimidine- (capecitabine or 5-FU) and platinum-(oxaliplatin or cisplatin) based chemotherapy
AST	aspartate aminotransferase
BOR	best overall response
BMI	body mass index
BIRC	Blinded Independent Central Review
CBR	clinical benefit rate
cHL	classical Hodgkin lymphoma
CI	confidence interval
Cmax	the observed maximum plasma (or serum or blood) concentration following drug administration
CMH	Cochran-Mantel-Haenszel
CO	clinical overview
CPI	checkpoint inhibitor
CPS	combined positive score
CR	complete response
CRC	colorectal cancer
CSCO	Chinese Society of Clinical Oncology
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DKMA	The Danish Medicines Agency
dMMR	mismatch repair deficient
DOR	duration of response
DCO	data cutoff
EAIR	exposure-adjusted incidence rate
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EORTC	European Organization for Research and Treatment of Cancer
EQ-5D-5L	European Quality of Life 5-Dimension 5-Level Questionnaire
eGFR	estimated glomerular filtration rate
EGFR	epidermal growth factor receptor
EOP2	End of Phase II
ER	exposure-response
ESCC	esophageal squamous cell carcinoma
FIH	first in human
GC	gastric cancer
GCP	good clinical practice
G/GEJ	gastric or gastroesophageal junction
GEA	gastroesophageal adenocarcinoma
GHS	global health status
HA	health authority
HCC	hepatocellular carcinoma
HER2	human epidermal growth factor receptor 2
HR	hazard ratio
HRQoL	health-related quality of life
IA	interim analysis
ICC	investigator-chosen chemotherapy
IDMC	Independent Data Monitoring Committee
IgG	immunoglobulin G

imAEs	immune-mediated AEs
imTEAE	immune-mediated treatment emergent adverse event
IR	incidence rate
IRC	Independent Review Committee
IRR	infusion-related reaction
ITT	Intent-to-Treat (analysis set)
JGCA	Japan Gastric Cancer Association
KD	equilibrium dissociation constant
KM	Kaplan-Meier
LDH	lactate dehydrogenase
MAA	Marketing Authorization Application
MEB, NL	Medicines Evaluation Board, Netherlands
MedDRA	Medical Dictionary for Regulatory Activities
mOS	median overall survival
mPFS	median progression-free survival
MRCT	multi-regional clinical trial
MSI-H	microsatellite instability-high
MTD	maximum tolerated dose
NAb	neutralizing antibody
NCCN	National Comprehensive Cancer Network
NCICTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NE	not estimable
NMPA	Center for Drug Evaluation of National Medical Products Administration (China)
NR	not reached
NSCLC	non-small-cell lung cancer
NT	not tested
ORR	objective response rate
OS	overall survival
QoL	quality of life
PBRER	Periodic Benefit Risk Evaluation Report
PD-1	programmed cell death-1
PD-L1	programmed cell death ligand-1
PD-L2	programmed cell death ligand-2
PEI	Paul Ehrlich Institute
PFS	progression-free survival
PFS2	progression-free survival after next line of anticancer therapy
PK	pharmacokinetic
PMDA	Pharmaceuticals and Medical Devices Agency
PopPK	population PK
PR	partial response
RDI	relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumors
RMST	restricted mean survival time
ROW	rest of the world
RP2D	recommended Phase II dose
SAE	serious adverse event
SAP	statistical analysis plan
sBLA	Supplementary Biologics License Application
TAP	tumor area positivity
TEAE	treatment-emergent adverse event
TIC	tumor immune cell
TTD	time to deterioration
TTR	time to response
ULN	upper limit of normal
VAS	visual analog scale
VEGFR	vascular endothelial growth factor receptor

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Beigene Ireland Limited submitted to the European Medicines Agency on 8 February 2024 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include in combination with platinum and fluoropyrimidine-based chemotherapy the first-line treatment of adult patients with human epidermal growth factor receptor-2 (HER-2)-negative locally advanced unresectable or metastatic gastric or gastroesophageal junction (G/GEJ) adenocarcinoma for TEVIMBRA, based on results from the phase 3 study BGB-A317-305 (study 305); this is a global, randomized, double-blind, placebo-controlled study at the approved registrational dosing regimen for Tevimbra (200 mg administered IV Q3W), in combination with platinum and fluoropyrimidine-based chemotherapy, in adult patients with HER-2 negative locally advanced unresectable or metastatic gastric or gastroesophageal junction (G/GEJ) adenocarcinoma. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 1.2 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the Product Information.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0142/2019 on the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH received Scientific Advice from the CHMP on 28 June 2018 (EMEA/H/SA/3646/4/2018/II)23 February 2023 (EMA/SA/0000121172). The Scientific Advice pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jan Mueller-Berghaus

Timetable	Actual dates
Submission date	8 February 2024
Start of procedure:	2 March 2024
CHMP Rapporteur Assessment Report	26 April 2024
PRAC Rapporteur Assessment Report	2 May 2024
Updated PRAC Rapporteur Assessment Report	23 May 2024
PRAC Outcome	16 May 2024
CHMP members comments	21 May 2024
Updated CHMP Rapporteur(s) (Joint) Assessment Report	23 May 2024
Request for supplementary information (RSI)	30 May 2024
CHMP Rapporteur Assessment Report	12 September 2024
CHMP members comments	07 October 2024
Updated CHMP Rapporteur Assessment Report	10 October 2024
Opinion	17 October 2024

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

This application concerns an extension of indication for tislelizumab (Tevimbra) to include the 1L treatment of locally advanced unresectable or metastatic HER2-negative gastric or gastroesophageal junction (GEJ) adenocarcinoma.

State the claimed therapeutic indication

The initially proposed new indication for Tevimbra in this procedure was:

"Tevimbra, in combination with platinum and fluoropyrimidine-based chemotherapy, is indicated for the first-line treatment of adult patients with human epidermal growth factor receptor-2 (HER-2)-negative locally advanced unresectable or metastatic gastric or gastroesophageal junction (G/GEJ) adenocarcinoma".

Disease - epidemiology and biologic features

Gastric cancer (GC) is the fifth most common cancer worldwide and the fourth leading cause of cancer-related death. The prevalence is notably higher in Eastern Asia than in the rest of the world. In Europe,

estimates for GC in 2020 are approximately 136,000 new cases. Estimated GC deaths for Europe in 2020 are approximately 97,000 *(WHO 2020).*

Adenocarcinoma is the dominant histologic subtype of GC worldwide (approximately 90%). Approximately 80% are true GCs (non-cardia), and the remainder are GEJ cancers (cardia). Approximately 75% of the patients with G/GEJ are HER2 negative *(Lordick et al 2022)*.

Clinical presentation, diagnosis and stage/prognosis

GC is an aggressive solid tumor with poor prognosis. G/GEJ cancer is asymptomatic in its early stages, so the initial diagnosis generally occurs when the tumor is advanced and the treatment choices are limited.

In most countries, patients with G/GEJ cancer are diagnosed in late stage disease or Stage IV disease, except in the few countries like Japan and South Korea, where early detection screening is widely performed, which contributes to the low rate of mortality in these regions *(Eusebi et al 2020)*.

Although the 5-year survival rate is 70% when tumors are localized, this falls to 32% if the cancer has extended into the gastric wall or metastasized to locoregional lymph nodes, and further reduced to 6% if the tumor has metastasized to distant sites *(ACS 2022)*. The overall 5-year relative survival of GC is about 20%-30% in most areas worldwide, including North America and Europe. GC survival is higher in East Asia with the 5-year survival rate being 67% in Korea, 69% in Japan and 36% in China in recent years *(Ilic 2022)*.

Management

Treatment of advanced stage G/GEJ cancer is based on systemic therapy. The preferred chemotherapy regimen for HER2 negative disease in the first-line setting is fluoropyrimidine (fluorouracil or capecitabine) combined with either oxaliplatin or cisplatin *(NCCN Guidelines v2. 2023)*.

During the conduct of Study 305, Phase III studies of immune checkpoint inhibitors in the first-line setting of advanced G/GEJ cancer have reported study outcomes. In September 2021, nivolumab in combination with fluoropyrimidine- and platinum-containing chemotherapy was approved by EMA for the 1L treatment of patients with HER2 negative advanced or metastatic G/GEJ or esophageal adenocarcinoma with tumors expressing PD-L1 CPS $\geq$ 5 for use. In December 2023, pembrolizumab received an EU approval in combination with fluoropyrimidine- and platinum-containing chemotherapy for the 1L treatment of locally advanced unresectable or metastatic HER2-negative G/GEJ adenocarcinoma in patients with PD-L1 CPS $\geq$ 1.

Most recently, zolbetuximab (an anti-Claudin-18.2 antibody) plus chemotherapy as 1L treatment demonstrated a survival benefit in patients with Claudin-18.2 positive (nearly 40% of screened patients met the definition of Claudine 18.2 positivity used in that study) and HER2 negative advanced G/GEJ cancer *(Shitara et al 2023, Xu et al 2023)*.

Study 305 was launched as part of the wave of clinical development of immune CPIs for the treatment of this disease. The option of first-line treatment with tislelizumab in combination with chemotherapy strengthens the treatment armamentarium for gastric cancer.

2.1.2. About the product

Tislelizumab (BGB-A317) is a humanized immunoglobulin (Ig) G4 variant monoclonal antibody against programmed cell death protein-1 (PD-1), that competitively blocks the binding of both programmed

cell death protein ligand-1 (PD-L1) and PD-L2, thereby inhibiting PD-1-mediated negative signalling and enhancing the functional activity of T cells in in-vitro cell-based assays[1].

Tislelizumab was approved for the treatment of 2L ESCC on 15-September-2023 under the tradename Tevimbra, and a Type II variation to extend the indication to 1L ESCC was submitted in January 2024. In February 2024, CHMP recommended an approval for tislelizumab (tradename Tizveni) for the 1L and 2L treatment of NSCLC. Both approvals have been reconciled under the tradename Tevimbra.

The final approved indication is:
Tevimbra, in combination with platinum and fluoropyrimidine-based chemotherapy, is indicated for the first-line treatment of adult patients with HER-2-negative locally advanced unresectable or metastatic gastric or gastroesophageal junction (G/GEJ) adenocarcinoma whose tumours express PD-L1 with a tumour area positivity (TAP) score ≥ 5%.

The approved dosing regimen of tislelizumab as monotherapy or in combination treatment with chemotherapy is 200 mg IV Q3W.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

This application is based on the pivotal Study 305 that randomised 997 patients with locally advanced unresectable or metastatic G/GEJ adenocarcinoma to receive tislelizumab vs. placebo in combination with fluoropyrimidine- and platinum-based chemotherapy as 1L treatment. Preliminary tislelizumab monotherapy data in gastric cancer came from two studies in solid tumors: the FIH dose escalation and expansion Study 001 including 54 patients with GC, and the Phase I/II dose verification and expansion Study 102 study including 24 patients in the GC cohort (please see Table 4.3 1). First-line combination therapy was evaluated in the phase 2 Study 205 that treated 15 patients with G/GEJ adenocarcinoma with tislelizumab and CapOx (and 15 ESCC patients with tislelizumab and cisplatin/5-FU).

European scientific advice procedures

In June 2018, the MAH received scientific advice from CHMP and the MEB, NL on the proposed clinical development of tislelizumab in gastric/GEJ adenocarcinoma (EMEA/H/SA/3646/4/2018/II). Study 305 was originally planned with dual primary endpoints of PFS and OS. Following consistent feedback on the important role of OS, the study was amended to remove PFS by IRC as a primary endpoint, and to include PFS by investigator assessment as a secondary endpoint. Other key design parameters of Study 305, such as patient population, stratification factors, selection of the chemotherapies, and statistical analysis method were generally agreed on. However, CHMP recommended to include patients with ECOG 2 and discouraged the interim analysis of OS. In addition, CHMP highlighted that a claim based on the

[1] *References:*

World Health Organization (2020) Europe; Source: Globocan 2020. https://gco.iarc.fr/today/data/factsheets/populations/908-europe-fact-sheets.pdf. Accessed 30-Sep-2021.

Lordick F et al (2022). Gastric cancer: ESMO Clinical Practice Guideline. Ann Oncol; 33(10):1005-20.

Eusebi LH et al (2020). Gastric cancer prevention strategies: A global perspective. J Gastroenterol Hepatol; 35(9):1495–502.

American Cancer Society (2022) Stomach cancer survival rates. https://www.cancer.org/cancer/stomach-cancer/detection-diagnosis-staging/survival-rates.html.

Ilic M et al (2022). Epidemiology of stomach cancer. World J Gastroenterol; 28(12):1187-203.

Shitara et al. (2023). Lancet; 401(10389):1655-68.

Xu RH et al. (2023). J Clin Oncol; 41(Suppl 36):405736.

ITT population would depend on the results in the PD-L1 negative subgroup. CHMP emphasized the need for retrospective analyses of thresholds to confirm that there is not a subgroup in whom the effect is obviously irrelevant (of note, in the SA of 2018 the PD-L1 positive population was defined as ≥1% expression in Tumor Cells (TC) or ≥25% in Immune Cells (IC)). The MEB, NL, also strongly advised to provide a proper justification for any PD-L1 definition/cut-off at the time of submission.

Pre-submission meetings were conducted with the Rapporteur PEI Germany and Co-Rapporteur DKMA Denmark (25-Jul-2023 and 25-Aug-2023) to obtain agreement that the data from Study 305 are adequate to support an indication extension for 1L G/GEJ adenocarcinoma. Further analysis of efficacy data by PD-L1 subgroups based on various PD-L1 cutoffs were requested to justify a broad indication in patients regardless of PD-L1.

In addition, the MAH received Scientific Advice from the CHMP on 23 February 2023 (EMA/SA/0000121172) on the proposed algorithm and methodology for identification of immune-mediated AEs for tislelizumab for use in future submissions.

2.1.4. General comments on compliance with GCP

The assessment of the clinical study data did not raise any specific concerns questioning GCP compliance.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

According to the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00) proteins are exempted from the submission of ERA studies because they are unlikely to result in significant risk to the environment. Tislelizumab is a protein, therefore an ERA has not been submitted by the MAH which is acceptable.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 1: Overview of Tislelizumab Studies Including Patients with Gastric Cancer Clinical Studies (excerpt from SCE Table 1)

Study number	Phase, Design	N	Patient population	Treatment regimen	Efficacy Measures
BGB-A317-001	IA/IB 2 stage, open label, dose escalation and expansion	Total: 451; 54 with GC	Advanced or metastatic (unresectable) **solid tumors**	Tislelizumab 0.5, 2, 5, or 10 mg/kg Q2W or 2 or 5mg/kg Q3W	ORR, DCR, DOR, PFS, CBR, OS
BGB-A317-102	I/II 2 phase, open label, dose verification	Total: 300; 24 with GC	Advanced or metastatic (unresectable) **solid tumors**	Tislelizumab 200 mg IV Q3W[a]	ORR, DCR, CBR, DOR, PFS, OS
BGB-A317-205	II Open label (single arm) multi-cohort	Total: 30; 15 with GC	Advanced inoperable G/GEJ cancer, with no previous systemic therapy	Tislelizumab 200 mg IV Q3W in combination with chemotherapy (oxaliplatin[c] + capecitabine[e])	ORR, DOR, PFS, CBR, DCR, OS
BGB-A317-305 (pivotal study)	III Randomized, double-blind, placebo-controlled	PD-L1-positive analysis set: 546 ITT analysis set: 997	Advanced unresectable or metastatic G/GEJ cancer, with no previous systemic therapy	Tislelizumab 200 mg IV Q3W or matched placebo in combination with fluoropyrimidine-(capecitabine[e] or 5-FU[d]) and platinum-(oxaliplatin[c] or cisplatin[f]) based chemotherapy	Dual primary endpoint: OS in PD-L1-pos. and ITT pop. Secondary endpoints: PFS, ORR and DOR and HRQoL

[a] except patients in the PhI PK substudy who received 200 mg tislelizumab on Day 1 with an interval of 4 weeks for Cycle 1, and Q3W thereafter
[c] 130 mg/m^2 IV on Day 1 of each 21-day cycle, for a total of 6 cycles
[d] 800 mg/m^2 IV daily on Days 1-5 of each 21-day cycle, for a total of 6 cycles
[e] 1000 mg/m^2 orally twice daily, Days 1-14 of each 21-day cycle, for a total of 6 cycles with continuation post Cycle 6 optional (Study 305) or until disease progression (Study 205).
[f] 80 mg/m² IV on Day 1 of each 21-day cycle, for a total of 6 cycles

2.3.2. Pharmacokinetics

The recommended dose of tislelizumab is equal to the previously approved posology in adult patients with unresectable, locally advanced or metastatic oesophageal squamous cell carcinoma after prior platinum-based chemotherapy (200 mg IV Q3W, until disease progression or unacceptable toxicity).

Pharmacokinetics of tislelizumab have been adequately characterized throughout the initial marketing authorization procedure. Therefore, in this variation assessment report, only summarized data on tislelizumab ADME, dose proportionality, special populations and interaction studies are presented. More detailed information can be found in the EPAR for Procedure No. EMEA/H/C/005919/0000.

Previously, an original PopPK analysis was performed based on pooled data (PK, dosing information, demographics, and patient or disease characteristics) across several clinical studies (Studies 001, 102, 203, 204, 205, 206, 208, 209, 302, 303, 304, and 307).

PK data from Study 305 were not included in the development of the original PopPK model but were used for external validation to assess the predictive performance and robustness of the population PK model for Study 305. Only sparse samples were collected in the pivotal Study 305.

Table 2: Analyses supporting the assessment of tislelizumab clinical pharmacology.

Analysis	Studies included in the analysis
Non-compartmental PK analysis	Study 001, Study 102
PopPK analysis	Full PK analysis set, including Studies 303, 304, 307, 001, 102, 203, 204, 205, 206, 208, 209, and 302 (as previously included in the second-line (2L) esophageal squamous cell carcinoma [ESCC] submission) External validation for Study 305 data
ER analysis on efficacy	Pivotal Study 305 dataset for ER efficacy (1L G/GEJ cancer)
ER analysis on safety	Pivotal Study 305 dataset for ER safety Studies providing supportive data for ER safety: The pool of patients from all tislelizumab monotherapy studies of various tumor types and various dose levels, including Studies 001, 102, 203, 204, 208, 302, and 303
Antidrug antibody (ADA) summary in the study CSRs	ADA analysis set of Study 305

Bioanalytical methods

Biopharmaceutics information was submitted with the dossier in the 2L treatment of ESCC in the summary of biopharmaceutics [SBP]. Bioanalytical methods and assays for quantification of tislelizumab concentration and for determination of ADA response to tislelizumab were found to be adequately validated and overall acceptable for their intended purpose. No new information is provided with the current dossier, as there is no change in bioanalytical methods and assays.

Population PK model

The PopPK model was developed from the pooled PK analysis dataset from 2596 patients across 12 clinical studies (Studies 001, 102, 203, 204, 205, 206, 208, 209, 302, 303, 304, and 307) to quantitatively describe the PK properties of tislelizumab and identify sources of interindividual variability. A nonlinear mixed effects modeling approach was used for the PopPK analysis. The impact of potential covariates, such as baseline age, body weight, sex, race (Asian/White/Other), estimated glomerular filtration rate (eGFR), bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, tumor type, tumor size, lactate dehydrogenase (LDH), Eastern Cooperative Oncology Group (ECOG) status, and treatment-emergent ADA status on the PK of tislelizumab was investigated.

Tislelizumab PK was confirmed linear in the dose range tested and can be adequately described by a three-compartment disposition model with linear CL. No-time varying CL was observed in this analysis.

• For a typical male patient with tumors except cHL and GC, age of 60 years body weight of 65 kg, albumin of 41 g/L, tumor size of 63 mm, and ADA negative, the estimated CL was 0.153 L/day, Vc was 3.05 L, Q2 was 0.740 L/day, V2 was 1.27 L, Q3 was 0.092 L/day, and V3 was 2.10 L. Interindividual variability on CL, Vc, V2, and V3 were 26.3%, 16.7%, 74..7%, and 99.9%, respectively. The steady-state volume of distribution was 6.42 L.

• The geometric mean elimination half-life was 23.8 days with a CV of 31.0%. The time to reach 90% steady-state level was approximately 84 days (12 weeks). Baseline body weight, age, sex, albumin, tumor size, tumor type, and ADA were identified as statistically significant covariates on the PK of tislelizumab.

• Body weight was the most influential covariate on tislelizumab exposure. Tumor type had a modest effect on tislelizumab exposure, and baseline albumin, tumor size, ADA, age, and sex had small effects on tislelizumab exposure.

• Simulations with 200 mg Q3W flat dose regimen and 3 mg/kg body weight-based dosing regimen showed comparable means and variability in exposure, thereby confirming that weight-based dosing does not confer additional advantages over 200 mg flat dose.

Other covariates evaluated, including race, eGFR, ALT, AST, BIL, LDH, and ECOG did not show statistically significant impact on the PK of tislelizumab. In Japanese patients, tislelizumab CL and exposure metrics (AUCss, Cmax,ss and Cmin,ss) were lower and higher respectively, as compared to other race groups.

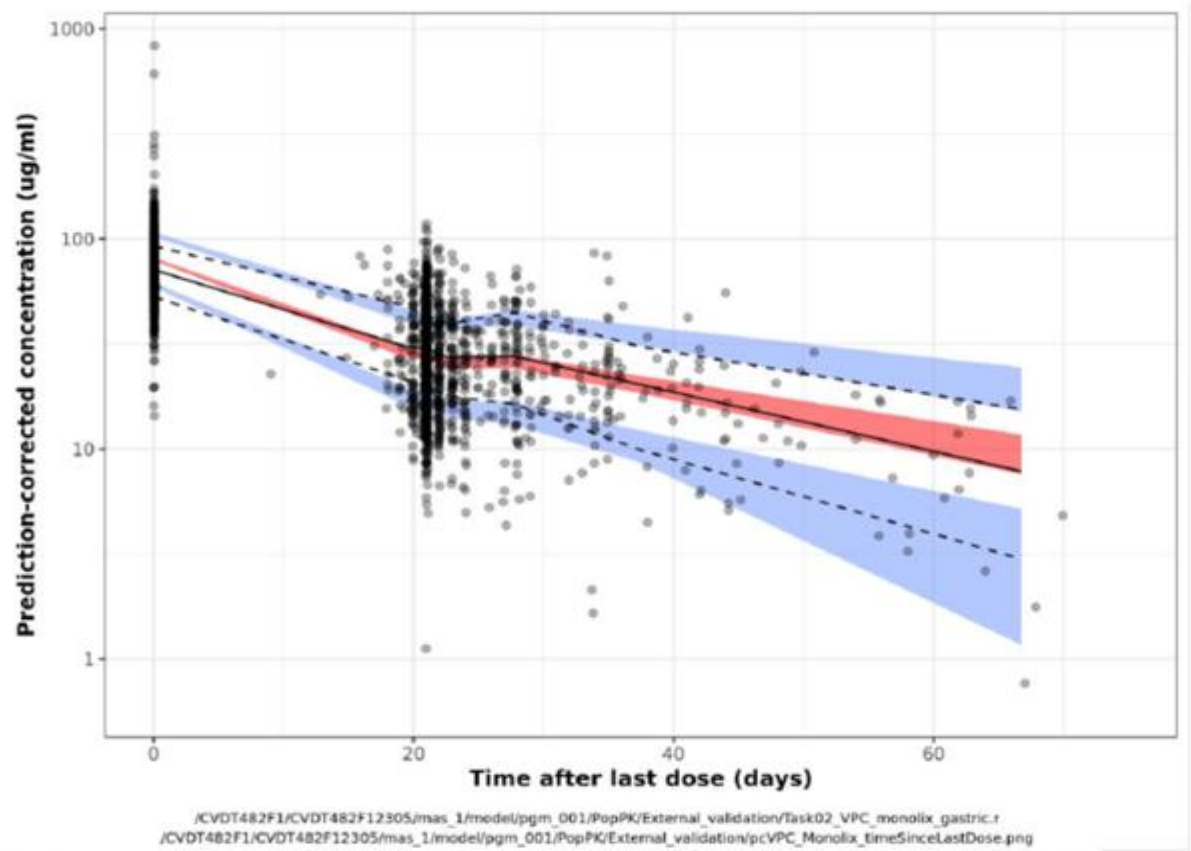
External validation of the PopPK model with Study 305

Since Study 305 was not incorporated in the original PopPK dataset, and only sparse samples were collected in this study, an external validation was performed to verify the predictive performance of the final PopPK model for Study 305. External validation was performed on Study 305 dataset (Cut-off date: 08-Oct-2021) and was not updated using latest cut-off date.

The ability of the existing PopPK model to reproduce the distribution of tislelizumab concentration data over time was evaluated using prediction-corrected visual predictive check (pcVPC) based on 500 simulated replicates of the Study 305 dataset.

The pcVPC plot showed that the observed 5th, 50th, and 95th percentiles of the concentration-time profiles were generally contained within the simulation-based 90% confidence intervals for the corresponding model predicted 5th, 50th, and 95th percentiles. These results suggest that the existing PopPK model adequately predicted the central tendency and variability of the serum tislelizumab concentrations following IV administration of 200 mg Q3W in the Study 305 patient population.

Figure 1: Prediction-corrected concentration (µg/ml) vs. time after last dose (PopPK analysis set)



Black dots represent observed concentrations, the two dashed lines represent the 5th and 95th percentiles of the observed concentrations, while the solid black line represents the 50th percentile of the observations. The blue shaded areas represent 90% confidence interval for 5th and 95th percentile, while the red shaded area represents 90% confidence interval for 50th percentile.

The PopPK model report states that the final PopPK model was initially developed in NONMEM and has been translated into and qualified in Monolix to support further analyses. A model qualification report which included an evaluation of the translated Monolix model with regard to convergence of estimated population/individual PK parameters and predicted PK metrics between the Monolix model and the previous NONMEM model was newly provided within the dossier of variation II-03. Question raised within this procedure are also applicable for this variation.

Absorption

In Study 001, noncompartmental PK analysis revealed a Cmax after the first dose of tislelizumab (200 mg Q3W) of 76.1 µg/mL. In Cycle 4 or Cycle 5, Cmax was determined to be 89.5 µg/mL. In Study 102, Cmax in Cycle 1 and Cycle 5 was determined to be 66.5 µg/mL and 126 µg/mL, respectively.

The estimate for steady-state Cmax derived by population PK analysis was 110 µg/mL.

100% bioavailability is expected as tislelizumab is administered by IV infusion.

Distribution

Based on population PK analysis: Vc, V2, and V3 = 3.05 L, 1.27 L, and 2.10 L, respectively.

Vd,ss = 6.42 L

Elimination

Tislelizumab as monoclonal antibody is metabolized by protein catabolism via the reticuloendothelial system or target-mediated disposition. Due to its large molecular size, renal excretion of intact tislelizumab is unlikely.

The geometric mean elimination half-life was estimated to be 23.8 days. Clearance was estimated to be 0.153 L/day based on the original NONMEM PopPK model.

Dose proportionality and time dependencies

PK of tislelizumab was shown to be linear and dose-proportional at dosing regimens of 0.5 mg/kg to 10 mg/kg once every 2 or 3 weeks and 200 mg Q3W. Steady-state accumulation ratio of tislelizumab PK exposure is approximately 2-fold.

Pharmacokinetics in target population

Study BGB-A317-305 (Study 305)

A total of 997 patients were randomized in a 1:1 ratio to receive tislelizumab plus chemotherapy (Arm A: 501 patients) or placebo plus chemotherapy (Arm B: 496 patients). PK data were available for a total of 496 patients (PD-L1 Positive population: 270 patients).

Pharmacokinetic results and conclusions:

As of the PK data cut-off date of 31-Aug-2022, the mean (±SD) Ctrough (pre-dose) and Cmax (post-dose) following the intravenous doses of tislelizumab 200 mg every 3 weeks, stratified by treatment cohorts up to Cycle 17, are presented by PD-L1 expression in Table 3.

The results from patients with PD-L1 score ≥ 5% were consistent with those of the ITT population. The pharmacokinetic results of Study 305 were consistent with the existing studies.

Table 3: Summary of tislelizumab serum concentrations in Study 305 (PK Analysis Set)

	Tislelizumab serum concentrations (µg/mL) (Mean ± standard deviation)			
	PD-L1 Positive (N = 270)		Total (ITT) (N = 496)	
Cycle	Pre-dose	Post-dose	Pre-dose	Post-dose
CYCLE 1 DAY 1	NC (n=263)	62.6 ± 15.99 (n=261)	NC (n=479)	63.5 ± 19.92 (n=479)
CYCLE 2 DAY 1	16.0 ± 5.54 (n=246)	NA	16.5 ± 5.78 (n=453)	NA
CYCLE 5 DAY 1	33.8 ± 13.08 (n=193)	93.5 ± 35.87 (n=191)	34.8 ± 12.76 (n=349)	94.1 ± 31.15 (n=348)
CYCLE 9 DAY 1	42.6 ± 17.27 (n=130)	NA	43.9 ± 18.07 (n=216)	NA
CYCLE 17 DAY 1	48.0 ± 17.42 (n=73)	NA	49.5 ± 17.75 (n=116)	NA

All population: 496 patients; Sex (Males/Females): 341/155; Age: 58.8 (23-86) years; Body weight: 60.8 (32.1-112) kg. 3.0% (76/2516) of samples were excluded from the summary due to aberrant sample collection information.

PD-L1 Positive population: 270 patients; Sex (M/F): 189/81; Age: 59.8 (23-83) years; Body weight: 61.4 (32.1-112) kg. 2.9% (41/1398) of sample were excluded from the summary due to aberrant sample collection information.

Post-dose: within 30 minutes after the end of infusion.

Source: [Study 305 FA CSR-Table 29]

Special populations

In the population PK model, baseline body weight, albumin level, tumour size of solid tumours, ADA status (treatment-emergent ADA), and tumour type were identified as significant covariates on CL. Baseline body weight, sex, and age were identified as significant covariates on Vc. However, simulated mean exposure differences observed in patients with impaired renal or hepatic function, different gender, different race (Asian vs. White), different body weight, and in the elderly were rather small compared to the overall variability of tislelizumab exposure.

Renal impairment

Renal function was not identified as a significant covariate. The mean simulated exposures (AUCss, Cmax,ss and Cmin,ss) in mild, moderate, or severe renal impairment were up to 10.7% higher, 18.5% higher, and 50.5% higher, respectively, compared with those of subjects with normal renal function. The number of patients with severe renal impairment (n=5) was low and not sufficient to draw definite conclusions on severely renally impaired patients.

Hepatic impairment

The liver function laboratory tests (AST, ALT, or total bilirubin) were not found to be significant covariates on tislelizumab PK in the popPK analysis. The mean simulated exposures (AUCss, Cmax,ss and Cmin,ss) in mild, moderate, or severe hepatic impairment were up to 8.71% lower, 15.4% lower, and 9.12% lower, respectively, compared with those of in subjects with normal hepatic function. Data are not sufficient to draw definite conclusions in patients with severe hepatic impairment (n = 2).

Gender

Gender was found to be a significant covariate on the Vc (volume of distribution in the central compartment). The typical Vc estimate was 11% lower for female than male. The geometric mean of simulated exposures (AUCss, Cmax,ss and Cmin,ss) in female subjects was 14.7% to 19.0% higher compared with those of in male subjects.

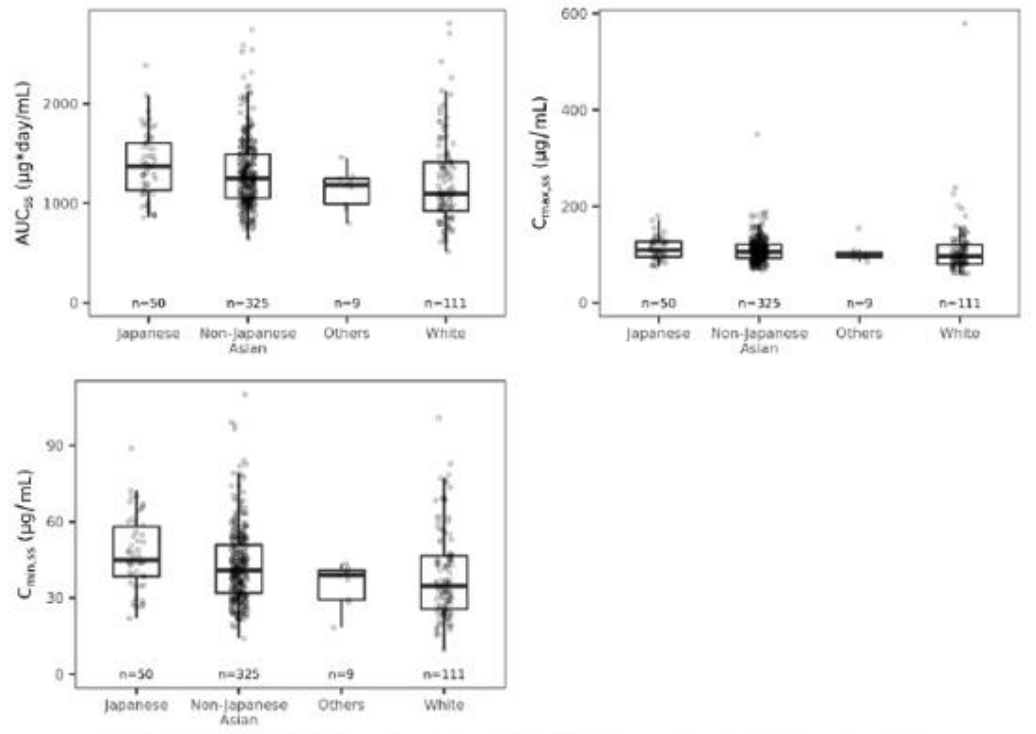
Race

The original popPK analysis showed that race was not a significant covariate on the PK parameters (CL and Vc) of tislelizumab. The simulated geometric mean exposures (AUCss, Cmax,ss, and Cmin,ss) of the Asian patient population (the majority of Asian patients are Chinese) from 12 studies were approximately 12% to 21% higher than those of white patients.

Using the individual PopPK predicted parameters, simulations were conducted between different sub-populations (Asian, Non-Asian, Japanese, Non-Japanese, White, and others) to evaluate race with the patient population from Study 305. Clearance and steady state exposure metrics (Cmin,ss, Cmax,ss, AUCss) in non-Japanese Asian, White, and Other race patients were up to 13.33% higher and 3.13% – 24.54% lower compared to Japanese patients, respectively.

However, these differences are relatively small in comparison to the overall variability of exposures (geometric CV% range: 24.70% – 37.44%); and individual exposure values in Asian patients were mostly within the range of those in non-Asian patients (Figure 2).

Figure 2: Simulated steady state exposure of tislelizumab by Japanese,non−Japanese Asian and White following 200 mg Q3W dosing



/CVDT482F1/CVDT482F12305/mas_1/model/pgm_001/PopPK/Ethnic_sensitivity/Task01_Ethnic_Sensitivity.R
:VDT482F1/CVDT482F12305/mas_1/model/pgm_001/PopPK/Ethnic_sensitivity/AUC_Cmax_Cmin_ss_Jap_NonJap_WHt_Oth_boxplot.pn

Source: [Pop PK Report Addendum 1: 1L G/GEJ-Figure 5-4]

Region

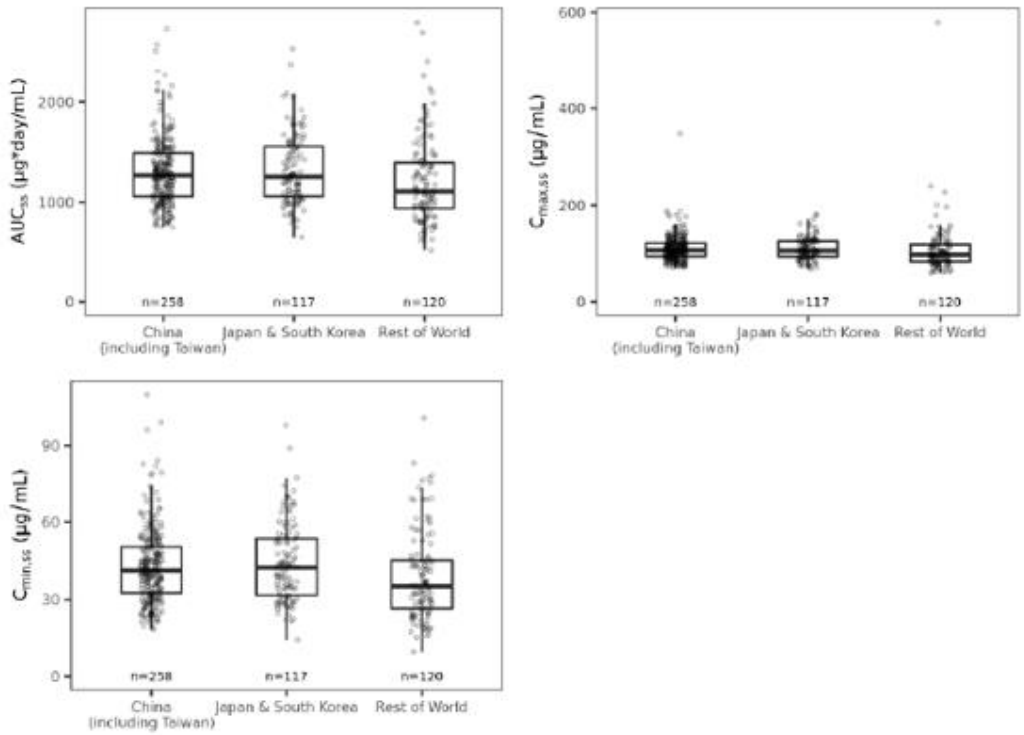
To assess the impact of region on PK of tislelizumab, the model predicted steady-state exposures were assessed by region (as per enrollment stratification: China [including Taiwan] vs. Japan and South Korea vs. rest of the world [ROW]).

Clearance in Japan and South Korea vs. ROW patients was 6.25% lower and 6.25% higher compared to China (including Taiwan) patients, respectively. Steady-state exposure metrics (Cmin,ss, Cmax,ss, and AUCss) in ROW patients were 5.73% – 12.92% lower compared to China (including Taiwan)

patients. Cmin,ss and AUCss in Japan and South Korea patients were higher compared to China, 2.78% and 1.62%, respectively; Cmax was slightly lower (0.52%).

These differences were considered small relative to the overall variability of exposures (geometric CV% range: 24.70% - 37.44%) and individual exposure values of patients across different regions largely overlap with each other (Figure 3).

Figure 3: Simulated steady state exposure of tislelizumab by China(including Taiwan) vs. Japan and South Korea vs. RoW Asia (excluding Japan) vs. Japan vs. RoW following 200 mg Q3W dosing



Source: [Pop PK Report Addendum 1: 1L G/GEJ-Figure 5-5]

Weight

Body weight was identified as a significant covariate on the CL, and Vc of tislelizumab in the final PopPK model. Increased body weight was associated with increased CL and Vc values. Therefore, subjects with higher body weight are predicted to have lower exposure. The geometric mean simulated exposures (AUCss, Cmax,ss and Cmin,ss) in the lowest and highest quartile of body weight were up to 14.5% higher and 17.3% lower, respectively, compared with those of the overall population.

Children

Tislelizumab has no study conducted in pediatric subjects.

Pharmacokinetic interaction studies

No formal drug-drug interaction studies have been conducted with tislelizumab. The drug interaction potential of tislelizumab is expected to be low based on the nature of therapeutic antibody drugs and the knowledge on antibodies of the same class of PD-1 checkpoint inhibitors.

Population PK analysis:

The impact of combination therapy on the covariate-adjusted tislelizumab PK parameters (CL and Vc) was evaluated in post hoc analysis based on the final population PK model. The result suggested a significant correlation ($p < 0.0001$) between the covariate-adjusted CL and therapy. In order to evaluate the impact of therapy on tislelizumab exposure, the predicted steady state exposures following 200 mg Q3W dosing were summarized and plotted by therapy. The mean simulated exposures (AUCss, Cmax,ss and Cmin,ss) in subjects with combotherapy were up to 8.79% higher compared with those of subjects with monotherapy in the overall population. These differences were very small relative to the overall variability of exposures.

2.3.3. Pharmacodynamics

No specific pharmacodynamic endpoint were investigated in Study 305.

An exposure-response analysis was conducted to evaluate the relationship between the exposure of tislelizumab and selected efficacy and safety endpoints, based on data from the pivotal study BGB-A317-305.

Immunogenicity of tislelizumab in combination with chemotherapy was assessed as exploratory objective in Study 305.

Mechanism of action

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

Tislelizumab is a humanized IgG4 variant monoclonal antibody against PD-1, binding to the extracellular domain of human PD-1 with high specificity and affinity (KD = 0.15 nM). It competitively blocks the binding of both PD-L1 and PD-L2, inhibiting PD-1-mediated negative signaling, and enhancing the functional activity in T-cells in in vitro cell-based assays. Tislelizumab does not bind to Fc gamma receptors and C1q and therefore does not induce antibody-dependent cellular cytotoxicity or complement-dependent cytotoxicity.

Primary and secondary pharmacology

Immunogenicity

Integrated immunogenicity analysis

To support the current submission, the immunogenicity profile was evaluated in patients with G/GEJ adenocarcinoma in Study 305 treated with tislelizumab 200 mg Q3W in combination with fluoropyrimidine- and platinum-based chemotherapy in the 1L setting. Results from Study 305 were generally consistent with that observed in other Phase III studies.

For the tislelizumab 200 mg Q3W dose regimen across Study 305 and 10 prior tislelizumab studies, the incidence of treatment-emergent ADA was 16.3% among 1424 evaluable patients in 7 monotherapy studies and 23.4% among 962 evaluable patients in 4 combination therapy studies. Neutralizing antibodies were detected in 0.9% of all 2747 evaluable patients, with no altered efficacy or safety

outcomes. The PK, efficacy, and safety profiles in patients with treatment-emergent ADA were broadly comparable between the monotherapy and combination therapy studies.

Table 4: -ADA incidence by dose regimen – Studies 001, 102, 203, 204, 206, 208, 302, 303, 304, 305, 307 (ADA evaluable patients)

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/kgQ2W	001	3	1 (33.3)	0	1 (33.3)	0	1 (33.3)	0
2 mg/kg Q2W		21	6 (28.6)	0	6 (28.6)	2 (9.5)	4 (19.0)	0
5 mg/kg Q2W		25	5 (20.0)	0	5 (20.0)	4 (16.0)	1 (4.0)	0
10 mg/kg Q2W		6	1 (16.7)	0	1 (16.7)	1 (16.7)	0	0
2 mg/kg Q3W		19	6 (31.6)	0	6 (31.6)	3 (15.8)	3 (15.8)	0
5 mg/kg Q3W		287	44 (15.3)	1 (0.3)	43 (15.0)	21 (7.3)	22 (7.7)	0
Study 001 Weight-based dosing mono[1]		**361**	**63 (17.5)**	**1 (0.3)**	**62 (17.2)**	**31 (8.6)**	**31 (8.6)**	**0**
200 mg Q3W	001	11	3 (27.3)	0	3 (27.3)	1 (9.1)	2 (18.2)	1 (9.1)
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	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
200 mg Q3W	208	231	50 (21.6)	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)
200 mg Q3W mono[1]		**1424**	**232 (16.3)**	**8 (0.6)**	**224 (15.7)**	**137 (9.6)**	**87 (6.1)**	**11 (0.8)**
200 mg Q3W T+chemo	206	51	7 (13.7)	0	7 (13.7)	1 (2.0)	6 (11.8)	0
200 mg Q3W T+PP	304	213	48 (22.5)	2 (0.9)	46 (21.6)	12 (5.6)	34 (16.0)	2 (0.9)
200 mg Q3W T+PC	307	115	43 (37.4)	2 (1.7)	41 (35.7)	18 (15.7)	23 (20.0)	1 (0.9)
200 mg Q3W T+nPC	307	113	20 (17.7)	0	20 (17.7)	10 (8.8)	10 (8.8)	4 (3.5)
200 mg Q3W T+PtF	305	470	107 (22.8)	1 (0.2)	106 (22.6)	64 (13.6)	42 (8.9)	6 (1.3)
200 mg Q3W combo[2]		**962**	**225 (23.4)**	**5 (0.5)**	**220 (22.9)**	**105 (10.9)**	**115 (12.0)**	**13 (1.4)**
200 mg Q3W total		**2386**	**457 (19.2)**	**13 (0.5)**	**444 (18.6)**	**242 (10.1)**	**202 (8.5)**	**24 (1.0)**
Total		**2747**	**520 (18.9)**	**14 (0.5)**	**506 (18.4)**	**273 (9.9)**	**233 (8.5)**	**24 (0.9)**

Source: [Report BGB-A317-CP-012-Table 2], [Study 208 IAR-Table 2], [Study 302 IAR-Table 2], [Study 303 IAR-Table 2], [Study 206 CSR-Table 14.3.8], [Study 304 IAR-Table 2], [Study 307 IAR-Table 2], [Study 305 IAR-Table 5-2]
ADA=anti-drug antibodies; NAb=neutralizing antibody, Q2W=once every 2 weeks; Q3W=once every 3 weeks; T+PC=tislelizumab + paclitaxel + carboplatin; T+nPC=tislelizumab + nab-paclitaxel + carboplatin;

Immunogenicity in Study 305

Of the 470 ADA-evaluable patients in Study 305, 107 (22.8%) patients had treatment-emergent ADA, with 106 (22.6%) having treatment-induced ADA and 1 (0.2%) having treatment-boosted ADA. Persistent ADA were reported in 64 (13.6%) patients and transient ADA in 42 (8.9%) patients. Neutralizing antibodies were detected in 6 (1.3%) patients, with no evidence of altered PK or clinical outcomes.

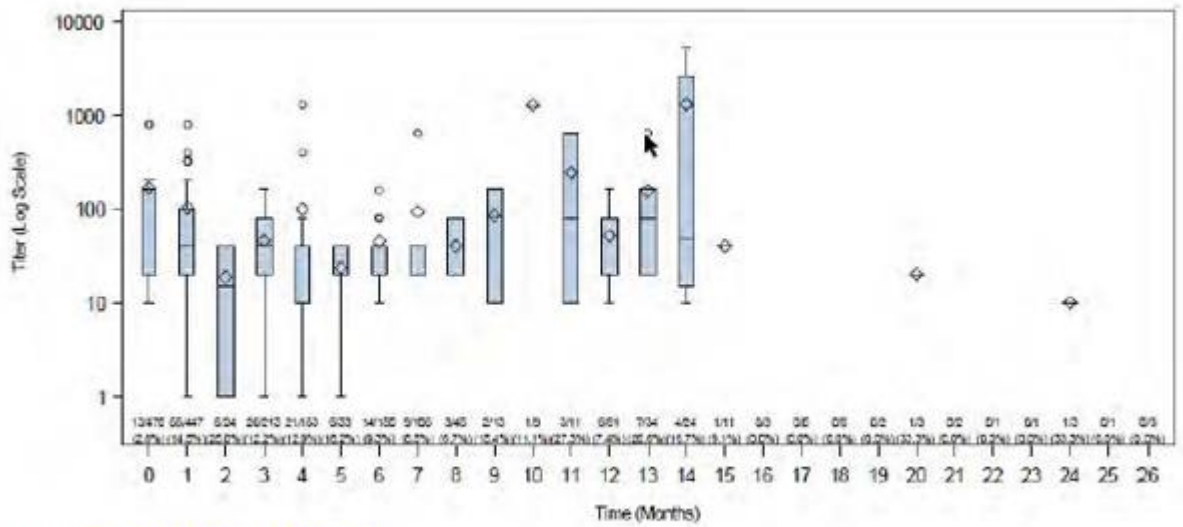
Table 5: Summary of immunogenicity results for Study 305 (ADA analysis set)

	T+PtF, Arm A N = 470 n (%)
Treatment-emergent ADA	107 (22.8)
Treatment-boosted ADA	1 (0.2)
Treatment-induced ADA	106 (22.6)
Persistent ADA response	64 (13.6)
Transient ADA response	42 (8.9)
NAb positive	6 (1.3)

Source: Table 4-1 SCE

The incidence of ADA in Study 305 (22.8%) was higher than that observed in the Phase III monotherapy studies 302 and 303 (14.5% and 15.8%, respectively) and within the range seen in the Phase III combination therapy studies 304 and 307 (17.7% to 37.4%). The pattern of ADA incidence was similar in PD-L1-positive patients.

Figure 4: Median and range of ADA titers over time for tislelizumab in combination with chemotherapy – Study 305 (ADA evaluable patients)

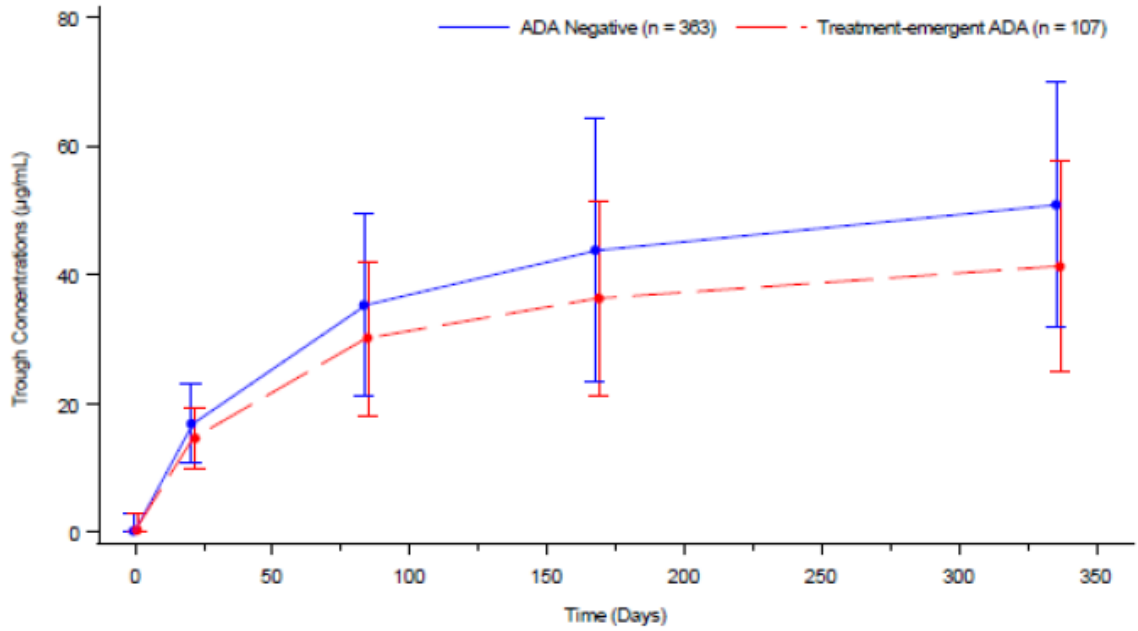


Source: [Study 305 IAR-Figure 5-3]

Impact of ADA on PK (Studies 304, 305 and 307: tislelizumab combination therapy)

Mean values of the observed tislelizumab trough concentrations in treatment-emergent ADA positive patients were lower than those observed for ADA negative patients.

Figure 5: ADA impact on mean (± SD) trough tislelizumab serum concentrations for tislelizumab 200 mg Q3W + chemotherapy – Study 305 (ADA evaluable patients)



Source: [Study 305 IAR-Figure 5-7]

Source: Figure 5-2 ISI v2.1

Impact of ADA on clinical efficacy in Study 305

The potential impact of ADA on clinical efficacy in tislelizumab-treated patients was assessed based on the clinical endpoints of overall survival (OS), progression-free survival (PFS), objective response rate, disease control rate, clinical benefit rate, duration of response, and tumor size. Analyses were performed for all patients and PD-L1 positive patients in the applicable analysis set.

The principal stratum estimand strategy (Bornkamp B et al 2021) was used to assess the potential impact of ADA on the primary efficacy endpoint of OS in the ITT analysis set.

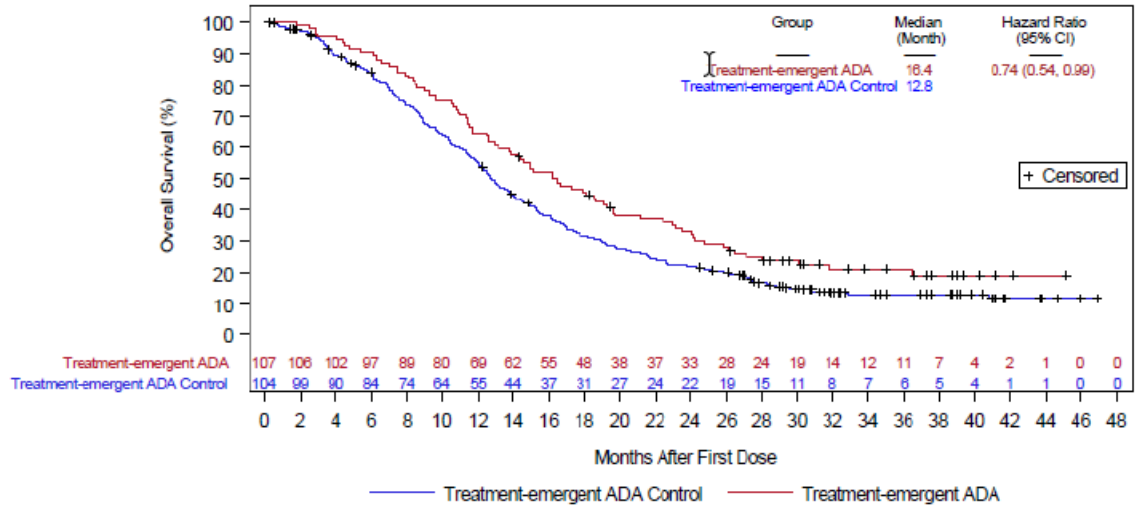
Overall survival

Table 6: Analysis of overall survival using the principal stratum method in patients (ITT analysis set)

Landmark[a,c]	Variable selection[b]	Baseline covariates selected[d]	Treatment-emergent ADA HR (95% CI)	ADA negative HR (95% CI)
No	No	All covariates	0.74 (0.54, 0.99)	0.73 (0.61, 0.86)
No	Yes	Smoking status, Albumin, Neutrophil-to-lymphocyte ratio	0.71 (0.52, 0.96)	0.74 (0.62, 0.87)
Yes	No	All covariates	0.97 (0.65, 1.46)	0.71 (0.61, 0.83)
Yes	Yes	Alcohol consumption, Albumin, Neutrophil-to-lymphocyte ratio	0.92 (0.61, 1.37)	0.72 (0.61, 0.84)

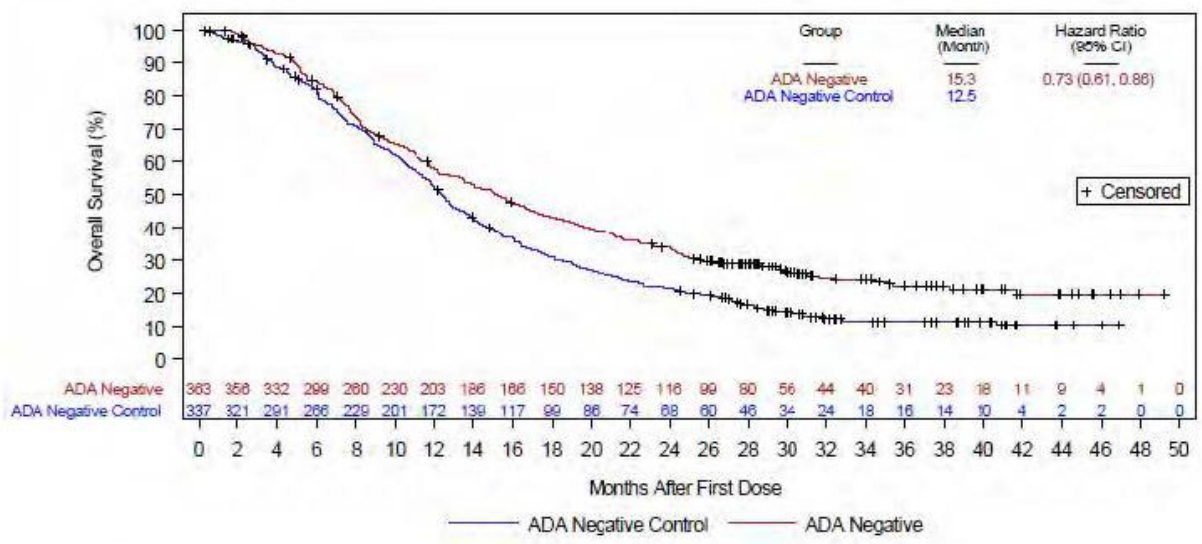
Source: Appendix-Table 12

Figure 6: Overall survival in ADA-positive group compared to corresponding adjusted controls in ITT population – Study 305 (ITT analysis set))



Kaplan-Meier plot shown for analysis with 'No landmark with no variable selection'
Source: [Study 305 IAR-Figure 5-11]

Figure 7: Overall survival in ADA-negative group compared to corresponding adjusted controls in ITT population – Study 305 (ITT analysis set)



Kaplan-Meier plot shown for analysis with 'No landmark with no variable selection'
Source: [Study 305 IAR-Figure 5-12]

Descriptive analysis of overall survival using principal stratum strategy

Based on descriptive subgroup analyses, there was no consistent trend for the impact of ADA on OS across the Phase III studies. Kaplan-Meier (KM) curves for OS in the two ADA groups largely overlapped throughout Studies 302, 303, and 305 with HRs of approximately 1, while there were divergent KM curves in Studies 304 and 307. The difference between the ADA groups observed in Studies 304 and 307 is not considered to be clinically meaningful. For all comparisons, the 95% confidence intervals (CIs) for the hazard ratios were wide and all crossed.

1. These descriptive comparisons should be interpreted with caution due to the potential bias in comparing between outcome-driven groups based on post-baseline ADA and due to the variation arising from the small number of patients in the ADA-positive group.

The OS HR estimates (with 95% CI) and median OS for ADA-positive vs. ADA-negative patients were as follows:

• HR=1.05 (95% CI: 0.67, 1.65); median OS of 10.0 vs. 10.3 months in Study 302 with tislelizumab monotherapy [ISI v2.0-Figure 5-12].

• HR=1.16 (95% CI: 0.84, 1.61); median OS of 17.1 vs. 18.6 months in Study 303 with tislelizumab monotherapy [ISI v2.0-Figure 5-13].

• HR=1.23 (95% CI: 0.76, 1.99); median OS of 17.8 vs. 21.4 months for the T+PP combination therapy in Study 304 [ISI v2.0-Figure 5-14].

• HR=1.11 (95% CI: 0.61, 2.04); median OS of 22.8 vs. 26.1 months for the T+PC combination therapy in Study 307 [ISI v2.0-Figure 5-15]; and HR=1.89 (95% CI: 0.95, 3.75); median OS of 17.0 vs. not estimable for the T+nPC combination therapy in Study 307 [ISI v2.0-Figure 5-15].

- HR=0.98 (95% CI: 0.77, 1.26); median OS of 16.4 vs. 15.3 months in the overall ADA evaluable population of Study 305 for tislelizumab in combination with fluoropyrimidine and platinum-based chemotherapy.

Table 7: Clinical response endpoints for tislelizumab-treated patients by ADA status – Studies 001, 102, 203, 204, 208, 302, 303, 304, 305, 307 (ADA evaluable patients)

Clinical Endpoint	Treatment-emergent ADA positive	Treatment-emergent ADA negative
Tislelizumab monotherapy		
Studies 001, 102, 203 and 204 – All patients		
Objective Response - n/N (%)	25/133 (18.8)	171/693 (24.7)
Disease Control - n/N (%)	61/133 (45.9)	370/693 (53.4)
Clinical Benefit - n/N (%)	34/133 (25.6)	208/693 (30.0)
Studies 001, 102, and 204 – Solid tumors		
Objective Response - n/N (%)	20/127 (15.7)	115/629 (18.3)
Disease Control - n/N (%)	56/127 (44.1)	311/629 (49.4)
Clinical Benefit - n/N (%)	34/127 (26.8)	208/629 (33.1)
Study 208 – HCC		
Objective Response - n/N (%)	12/50 (24.0)	21/181 (11.6)
Disease Control - n/N (%)	32/50 (64.0)	94/181 (51.9)
Clinical Benefit - n/N (%)	15/50 (30.0)	45/181 (24.9)
Study 302 – 2L ESCC		
Objective Response - n/N (%)	6/32 (18.8)	31/189 (16.4)
Disease Control - n/N (%)	18/32 (56.3)	97/189 (51.3)
Study 303 – NSCLC		
Objective Response - n/N (%)	20/80 (25.0)	85/427 (19.9)
Disease Control - n/N (%)	45/80 (56.3)	230/427 (53.9)
Clinical Benefit - n/N (%)	39/80 (48.8)	193/427 (45.2)
Tislelizumab combination therapy		
Study 304 – NSCLC: T+PP		
Objective Response - n/N (%)	26/48 (54.2)	86/165 (52.1)
Disease Control - n/N (%)	46/48 (95.8)	148/165 (89.7)
Clinical Benefit - n/N (%)	38/48 (79.2)	120/165 (72.7)
Study 307 – NSCLC: T+PC		
Objective Response - n/N (%)	24/43 (55.8)	50/72 (69.4)
Disease Control - n/N (%)	35/43 (81.4)	68/72 (94.4)
Clinical Benefit - n/N (%)	32/43 (74.4)	63/72 (87.5)
Study 307 – NSCLC: T+nPC		
Objective Response - n/N (%)	10/20 (50.0)	64/93 (68.8)
Disease Control - n/N (%)	20/20 (100)	88/93 (94.6)
Clinical Benefit - n/N (%)	14/20 (70.0)	81/93 (87.1)
Study 305 – G/GEJ cancer: T+PtF		
Objective Response – n/N (%)	53/107 (49.5)	182/363 (50.1)
Disease Control – n/N (%)	100/107 (93.5)	344/363 (94.8)
Clinical Benefit – n/N (%)	69/107 (64.5)	245/363 (67.5)

Source: [Report BGB-A317-CP-012-Table 9 and Table 10], [Study 208 IAR-Table 7], [Study 302 IAR-Table 7], [Study 303 IAR-Table 7], [Study 304 IAR-Table 7], [Study 307 IAR-Table 7], [Study 305 IAR-Table 5-6]
ESCC=esophageal cancer, G/GEJ=gastric/gastroesophageal junction; HCC=hepatocellular carcinoma;

Impact of ADA on safety

Table 8: Treatment-emergent adverse events by ADA status

	Treatment-emergent ADA positive n (%)	Treatment-emergent ADA negative n (%)
Monotherapy studies (001, 102, 203, 204, 208, 302, and 303), N	232	1192
Immune-mediated AEs, n (%)	41 (17.7)	216 (18.1)
Infusion-related reactions, n (%)	9 (3.9)	43 (3.6)
AEs Grade ≥ 3, n (%)	118 (50.9)	468 (39.3)
SAEs, n (%)	86 (37.1)	354 (29.7)
AEs causing treatment discontinuation, n (%)	25 (10.8)	122 (10.2)
AEs causing dose modification, n (%)	67 (28.9)	296 (24.8)
Combination therapy studies in NSCLC (304: T+PP, 307: T+PC and T+nPC), N	111	330
Immune-mediated AEs, n (%)	29 (26.1)	89 (27.0)
Infusion-related reactions, n (%)	4 (3.6)	8 (2.4)
AEs Grade ≥ 3, n (%)	95 (85.6)	258 (78.2)
SAEs, n (%)	51 (45.9)	126 (38.2)
AEs causing treatment discontinuation, n (%)	15 (13.5)	44 (13.3)
AEs causing dose modification, n (%)	68 (61.3)	223 (67.6)
Combination therapy study in G/GEJ cancer (305: T+PtF), N	107	363
Immune-mediated AEs, n (%)	35 (32.7)	115 (31.7)
Infusion-related reactions, n (%)	5 (4.7)	17 (4.7)
AEs Grade ≥ 3, n (%)	75 (70.1)	247 (68.0)
SAEs, n (%)	41 (38.3)	149 (41.0)
AEs causing treatment discontinuation, n (%)	18 (16.8)	50 (13.8)
AEs causing dose modification, n (%)	55 (51.4)	182 (50.1)

Source: [ISI v2.0 Appendix 2-Table 3], [Study 305 IAR-Table 5-9]
T+PC=tislelizumab + paclitaxel + carboplatin; T+nPC=tislelizumab + nab-paclitaxel + carboplatin; T+PP=tislelizumab + pemetrexed + platinum (cisplatin or carboplatin); T+PtF= tislelizumab + platinum + fluoropyrimidine; ADA = anti-drug antibody; AE = adverse event; AEs Grade ≥3 = treatment-emergent adverse events greater than or equal to grade 3; SAE = serious AE.
Patients in Study 001 with weight-based dosing Q2W/Q3W were excluded from this table.

In all the other studies the rates of imAEs, IRRs, AEs causing treatment discontinuation, and AEs causing dose modification were comparable between the ADA groups, while the rate of SAEs and Grade ≥ 3 AEs, were higher in the ADA-positive group. For study 305 rates were generally comparable between the ADA groups.

2.3.4. PK/PD modelling

The qualified final PopPK (Monolix) model was used to obtain empirical Bayes estimates of individual PK parameters of all tislelizumab-treated subjects in study 305 based on actual dosing records including dose, infusion rate and dosing interval.

The following exposure metrics were calculated:

- Maximum concentration after the 1st dose (Cmax,dose1),
- Average concentration after the 1st dose (Cavg,dose1).

Cavg,dose1 was used for analysis of the exposure-efficacy relationship, and Cmax,dose1 was used for analysis of the exposure-safety relationship. Cavg and Cmax at steady state were not tested in the ER

analysis, since previous analysis based on the PopPK model (PopPK Report) showed that Cavg at steady state was highly correlated with that after the 1st dose, consistent with the conclusion that CL was not time-dependent. Dose reductions were not allowed in the study design, and thus time-averaging of exposure was not required.

Exposure-efficacy analysis:

The exposure-efficacy relationship for tislelizumab was explored using efficacy datasets containing data from 495 patients assigned to tislelizumab arm by randomization, who received at least one dose of tislelizumab in combination with platinum and fluoropyrimidine-based chemotherapy, and had PopPK model predicted Cavg,dose1 for exposure-efficacy. The efficacy endpoints analyzed were OS (primary endpoint), PFS, and responders/non-responders status based on BOR (secondary endpoints).

Exposure versus OS and PFS

There was no statistically significant relationship between Cavg,dose1 and OS or PFS. There was limited separation between the Kaplan-Meier curves when stratified by quartiles of Cavg,dose1 (**Figure 9** and **Figure 10** respectively, for OS and PFS). Cox regression models were also used to evaluate the relationship between the PopPK-predicted Cavg,dose1 and OS or PFS. The slopes (coefficient of log of Cavg,dose1) were small and the 95% CI included zero, suggesting that there could be no statistically significant relationship between Cavg,dose1 and OS or PFS across the exposures evaluated.

Forest plots illustrated that there was no statistically significant relationship between Cavg,dose1 and the risk of disease progression or death, since the 95% CIs of HRs of 25th and 75th percentiles versus median Cavg,dose1 crossed the line of null effect.

Figure 8: Kaplan-Meier curves of OS stratified by Cavg,dose1 quartiles - 1LG/GEJ (1LGCPK-efficacy set)

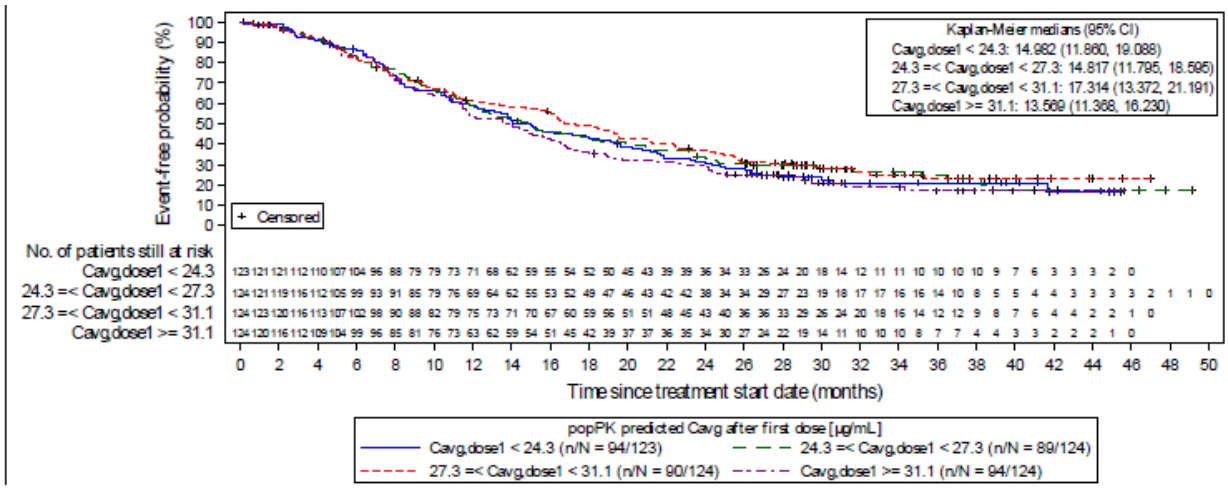
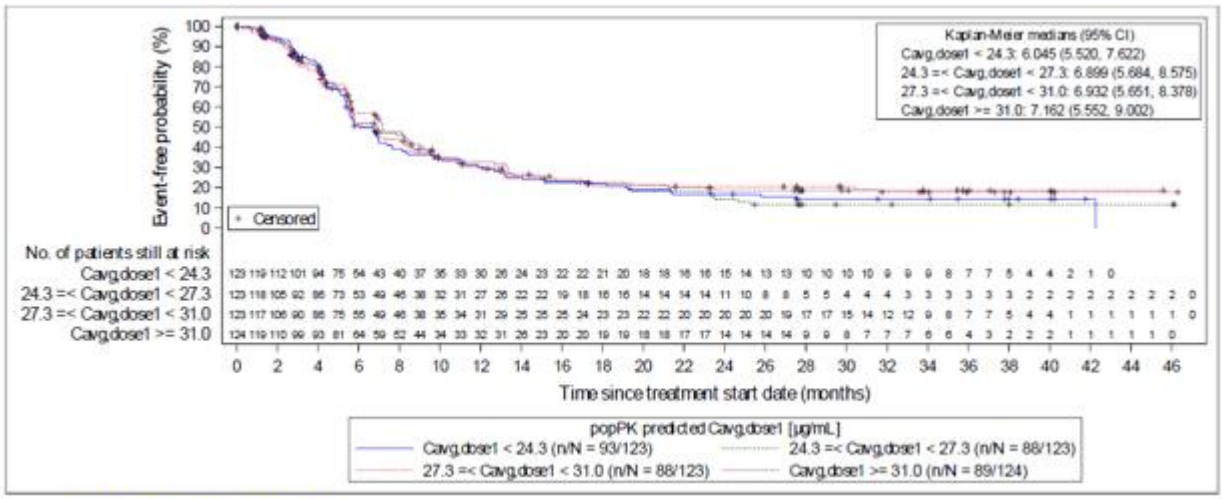


Figure 9: Kaplan-Meier curves of PFS stratified by quartiles of Cavg,dose1 - 1L G/GEJ (1LGCPK-efficacy set)



Source: [ER report: 1L G/GEJ-Figure 4-3]

Cox regression models were also used to evaluate the relationship between the PopPK predicted Cavg,dose1 and OS or PFS. T

Table 9: Estimated median OS stratified by Cavg,dose1 quartiles - 1L G/GEJ(1LGCPK-efficacy set)

Cavg,dose1 quartiles	N	Median exposure (µg/mL)	Number of events	Median OS (months) [95% CI]
Cavg,dose1 < 24.3	123	22.1 (13.8, 24.2)	94	15 (12.2, 19.3)
24.3 ≤ Cavg,dose1 < 27.3	124	25.9 (24.3, 27.3)	89	14.8 (12.3, 19.9)
27.3 ≤ Cavg,dose1 < 31.1	124	28.8 (27.3, 31)	90	17.3 (14.7, 21.3)
Cavg,dose1 ≥ 31.1	124	33.8 (31.1, 70.5)	94	13.6 (11.5, 16.7)
NE-not evaluable Source: Appendix-Table 8.2-11				

Table 10: Estimated median PFS stratified by Cavg,dose1 quartiles - 1L G/GEJ (1LGCPK-efficacy set)

Cavg,dose1 quartiles	N	Median exposure (µg/mL)	Number of events	Median PFS (months) [95% CI]
Cavg,dose1 < 24.3	123	22.1 (13.8, 24.2)	93	6 (5.6, 7.7)
24.3 ≤ Cavg,dose1 < 27.3	123	25.9 (24.3, 27.3)	88	6.9 (5.7, 8.8)
27.3 ≤ Cavg,dose1 < 31.0	123	28.8 (27.3, 31)	88	6.9 (5.7, 8.5)
Cavg,dose1 ≥ 31.0	124	33.7 (31, 70.5)	89	7.2 (5.6, 9.2)
Source: Appendix-Table 8.2-8				

Forest plots illustrated that there is no statistically significant relationship between Cavg,dose1 and the risk of disease progression or death, since the 95% CI of HR of 25th and 75th percentiles versus median Cavg,dose1 crosses the line of null effect.

Figure 10: Estimated effects of significant covariates and Cavg,dose1 in the final Cox model for OS in tislelizumab treated patients - 1L G/GEJ (1LGCPK-efficacy set)

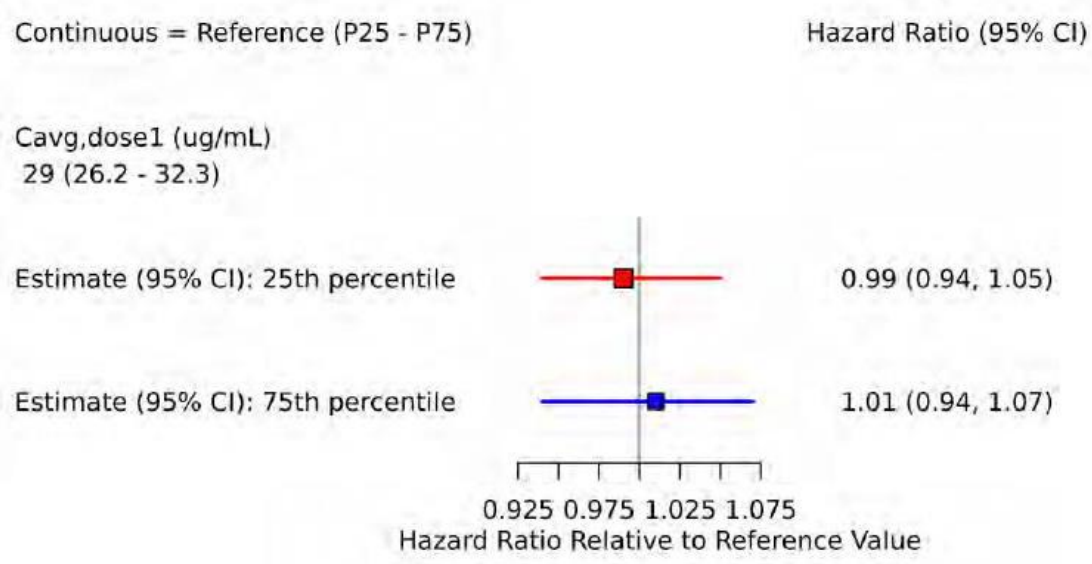
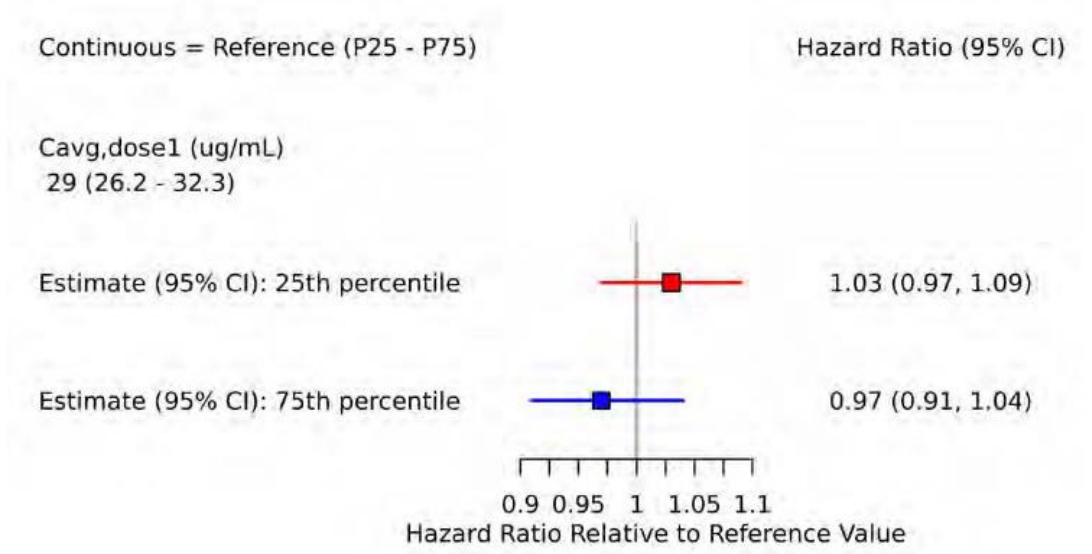


Figure 11: Estimated effects of significant covariates and Cavg,dose1 in the final Cox model for PFS in tislelizumab treated patients - 1L G/GEJ (1LGCPK-efficacy set)

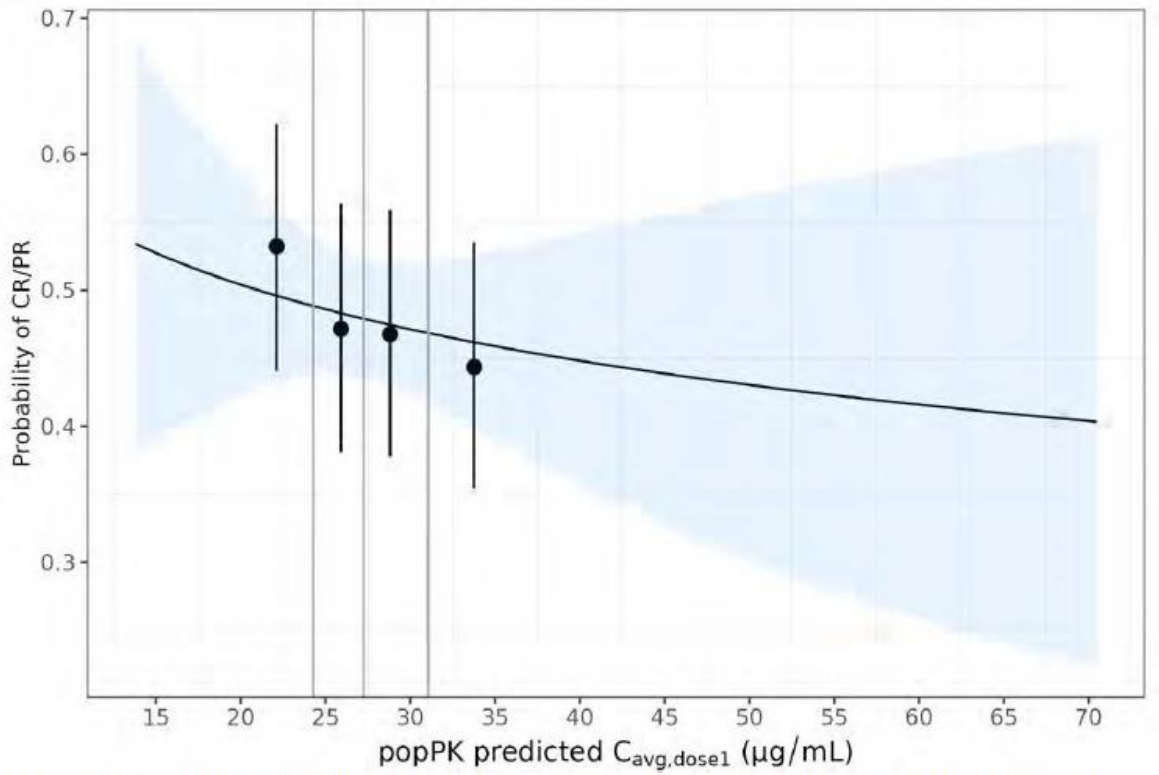


Exposure versus BOR

Based on the summary of PopPK-predicted Cavg,dose1 categorized by confirmed response status, the exposure of tislelizumab was similar between responders and non-responders. In addition, the exposure metrics appeared to be comparable between Asians and non-Asians, and between the regions, irrespective of the responder status.

Logistic regression was further used to evaluate the relationship between exposure and response status. The probability estimates of confirmed BOR being CR/PR versus PopPK predicted Cavg,dose1 were evaluated across the four quartiles of Cavg,dose1. The observed proportions of responders and the model-based probability estimates seemed to be consistent, and both could suggest no change in the probability of confirmed BOR being CR/PR with increased Cavg,dose1.

Figure 12: Predicted probability of confirmed BOR being CR/PR vs. PopPKpredicted Cavg,dose1 - 1L G/GEJ (1LGCPK-efficacy set)



Model is log(p/(1-p)) = intercept + log PopPK predicted Cavg,dose1, where p is the probability of unconfirmed BOR being CR/PR

Boundaries are the 95% CI of the logistic regression model estimation.

The dots are the observed proportions in each PopPK predicted Cavg,dose1 quartile. The 95% CIs for these are based on the Clopper-Pearson method.

Source: Appendix-Figure 8.2-4

Exposure-safety analysis:

The AESI safety endpoints in Study 305 were immune-mediated TEAEs (imAE) and infusion-related reactions (IRR).

Clinically relevant TEAEs safety endpoints were TEAEs with CTCAE grade ≥ 3, TEAEs leading to tislelizumab discontinuation, TEAEs leading to tislelizumab dose modification (i.e. dose interruption, dose delay, and changes in infusion rate), and serious TEAEs.

Immune-mediated TEAEs

Overall, the tislelizumab exposure was similar between subjects with or without any immune-mediated TEAE (Table 11).

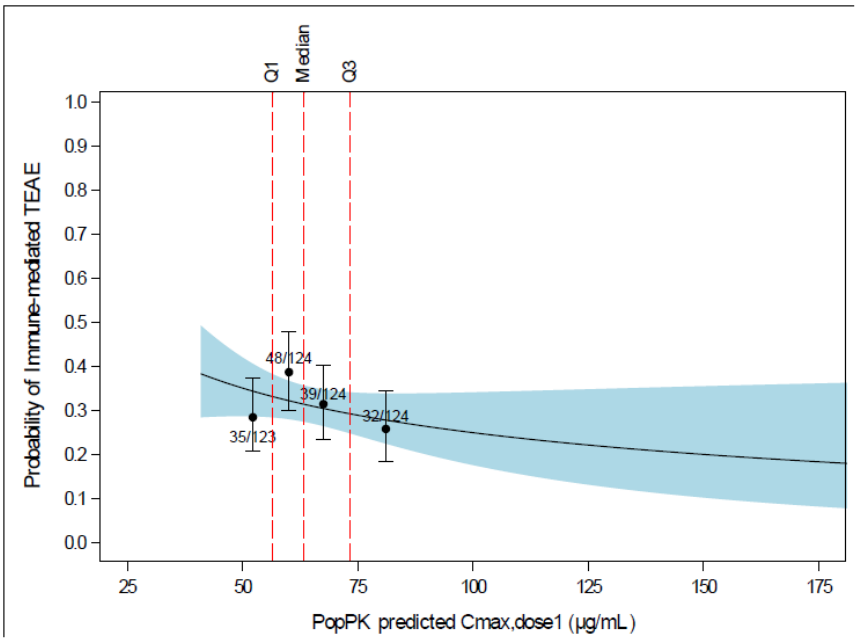
Table 11: PopPK predicted Cmax,dose1 by immune-mediated TEAEs (Yes/No) – 1L G/GEJ (1LGCPK-Safety set)

	Immune-mediated TEAE		
Statistics	**Yes* N=154**	**No N=341**	**All subjects N=495**
popPK predicted Cmax,dose1 [µg/mL]			
n	154	341	495
Mean (SD)	64.4 (10.2)	68.8 (30.7)	67.4 (26.2)
CV%	15.9	44.7	38.9
Geo-mean	63.6	65.8	65.1
CV% geomean	15.4	26.4	23.5
Median	62.6	63.9	63.3
Q1-Q3	56.8-70.2	56.4-74.3	56.6-73.4
Min-Max	45.7-110	40.9-496	40.9-496

n = number of patients
* patients with at least one immune-mediated TEAE
Source: Appendix-Table 8.3-2

To further quantify the relationship between exposure and immune-mediated TEAEs, logistic regression was conducted to estimate the probability of immune-mediated TEAE by exposure, as shown in **Error! Reference source not found.**.

Figure 13: Predicted probability of immune-mediated TEAE vs. PopPK predictedCmax,dose1 - 1L G/GEJ (1LGCPK-Safety set)



Model is log(p/(1-p)) = intercept + log popPK predicted Cmax,dose1, where p is the probability of experiencing at least one immune-mediated TEAE.
Boundaries are the 95% CI of the logistic regression model estimation.
The dots are the observed proportions in each popPK predicted Cmax,dose1 quartile. The 95% CIs for these are based on the Clopper-Pearson method.
Source: Figure 8.3-3

Infusion-related reactions

Overall, the tislelizumab exposure was similar between subjects with or without infusion-related reactions (Table 12).

Table 12: PopPK-predicted Cmax,dose1 by infusion-related reactions (Yes/No) – 1L G/GEJ (1LGCPK-Safety set))

	Infusion-related reaction (IRR)		
Statistics	**Yes* N=33**	**No N=462**	**All subjects N=495**
popPK predicted Cmax,dose1 [µg/mL]			
n	33	462	495
Mean (SD)	69.6 (17.7)	67.2 (26.7)	67.4 (26.2)
CV%	25.4	39.8	38.9
Geo-mean	67.5	65.0	65.1
CV% geomean	25.8	23.3	23.5
Median	67.4	63.1	63.3
Q1-Q3	56.8-80.8	56.6-72.7	56.6-73.4
Min-Max	40.9-110	41.9-496	40.9-496

n = number of patients.
* patients with at least one infusion-related reaction.
Source: Appendix-Table 8.3-6

To further quantify the relationship between exposure and infusion related reactions, logistic regression was conducted to estimate the probability of immune-mediated TEAE by exposure.

TEAE with CTCAE grade ≥ 3

Overall, there was a trend towards slightly higher tislelizumab exposure in subjects with any TEAEs with CTCAE grade ≥ 3 (Table 13**:**) compared to those without.

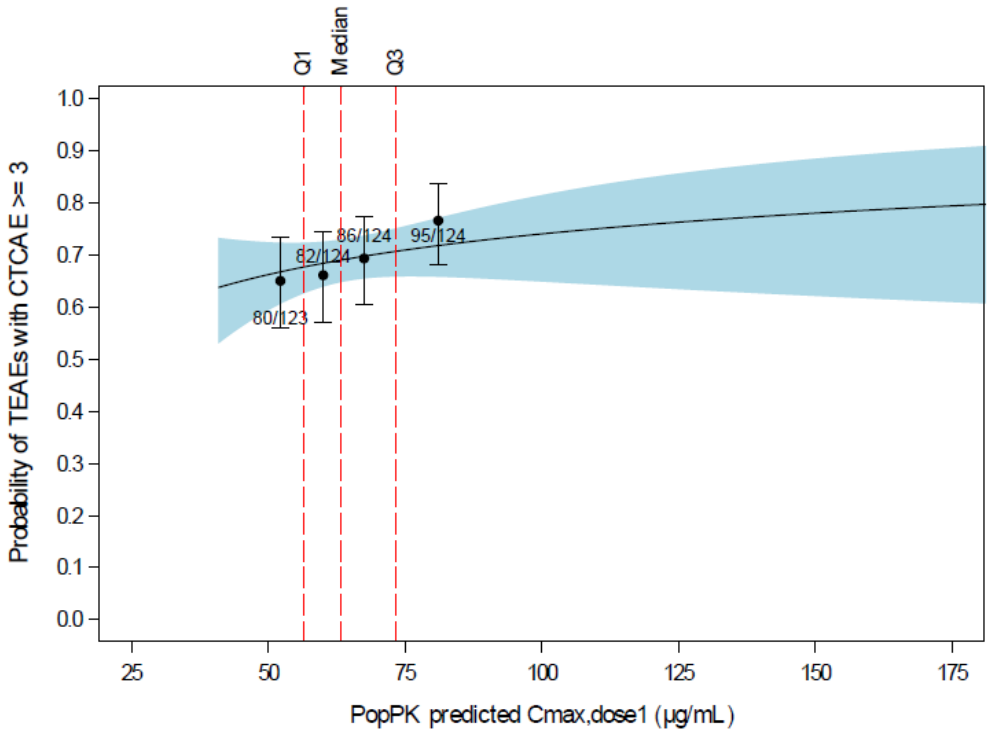
Table 13: PopPK predicted Cmax,dose1 by TEAEs with CTCAE grade ≥ 3 (Yes/No) – 1L G/GEJ (1LGCPK-Safety set)

	TEAE with CTCAE grade >= 3		
Statistics	**Yes* N=343**	**No N=152**	**All subjects N=495**
popPK predicted Cmax,dose1 [µg/mL]			
n	343	152	495
Mean (SD)	68.1 (28.0)	65.8 (21.8)	67.4 (26.2)
CV%	41.1	33.0	38.9
Geo-mean	65.7	63.9	65.1
CV% geomean	24.0	22.3	23.5
Median	63.9	62.1	63.3
Q1-Q3	56.8-74.0	55.6-70.3	56.6-73.4
Min-Max	40.9-496	42.6-279	40.9-496

n = number of patients
* patients with at least one TEAEs with CTCAE ≥ 3
Source: Appendix-Table 8.3-10

To further quantify the relationship between exposure and TEAEs with CTCAE grade ≥ 3, logistic regression was conducted to estimate the probability of TEAEs with CTCAE grade ≥ 3 by exposure, as shown. The results show that there was a positive relationship between exposure and TEAE with CTCAE grade ≥ 3 among subjects treated with tislelizumab.

Figure 14: Logistic regression of probability of TEAE with CTCAE >= 3 vs. popPK predicted Cmax,dose1 - 1L G/GEJ (1LGCPK-Safety set)



Model is log(p/(1-p)) = intercept + log PopPK predicted Cmax,dose1, where p is the probability of experiencing at least one TEAE with CTCAE >= 3.
Boundaries are the 95% CI of the logistic regression model estimation.
The dots are the observed proportions in each PopPK predicted Cmax,dose1 quartile. The 95% CIs for these are based on the Clopper-Pearson method.
Source: Appendix-Figure 8.3-9

Table 14: Predicted probability of experiencing at least one TEAE with CTCAE grade ≥ 3 by PopPK predicted Cmax,dose1 quartile groups - 1L G/GEJ (1LGCPKSafety set)

		TEAE with CTCAE grade ≥ 3	
Cmax,dose1 category (µg/mL)	Median Cmax,dose1 category (µg/mL)	Observed number of events (%) (95% CI)	Model-based probability (%) of an event (95% CI)
<56.6	52.3	80/123 (65.0) (55.9, 73.4)	66.8 (60.6, 72.4)
56.6-<63.3	60.1	82/124 (66.1) (57.1, 74.4)	68.4 (63.9, 72.6)
63.3-<73.4	67.6	86/124 (69.4) (60.4, 77.3)	69.8 (65.5, 73.7)
≥73.4	81.1	95/124 (76.6) (68.2, 83.7)	71.8 (65.8, 77.1)

Source: Table 4-16 Exposure-Response Report

A covariate search was conducted to evaluate the relationship between covariates and TEAEs with CTCAE grade ≥ 3. Other than exposure, none of the assessed covariates (age, weight, sex,

chemotherapy doublet, race, hepatic function, renal function or ECOG) showed a correlation with the probability of experiencing at least one TEAEs with CTCAE grade ≥ 3.

TEAE leading to treatment discontinuation or dose modification of tislelizumab

Tislelizumab exposure was similar between patients with or without any TEAEs leading to tislelizumab discontinuation or TEAEs leading to tislelizumab dose modification (data not shown).

Logistic regression results show that an increase in tislelizumab exposure was not significantly associated with increased risk of TEAEs leading to treatment discontinuation or TEAEs leading to tislelizumab dose modification (data not shown).

Serious TEAE

Overall, the tislelizumab exposure was similar between subjects with or without any serious TEAEs.

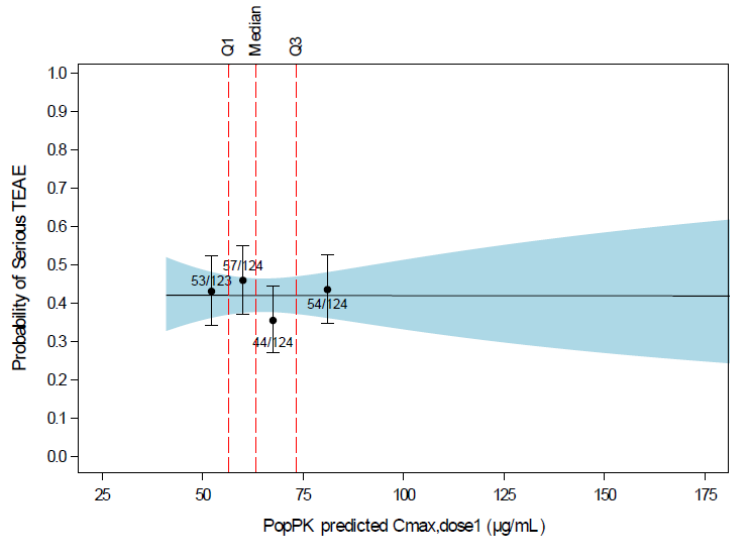
Table 15: PopPK predicted Cmax,dose1 by serious TEAE (Yes/No) – 1L G/GEJ(1LGCPK-Safety set)

	Serious TEAE		
Statistics	**Yes* N=208**	**No N=287**	**All subjects N=495**
popPK predicted Cmax,dose1 [µg/mL]			
n	208	287	495
Mean (SD)	68.1 (33.7)	66.9 (19.1)	67.4 (26.2)
CV%	49.5	28.5	38.9
Geo-mean	65.1	65.1	65.1
CV% geomean	25.8	21.8	23.5
Median	62.5	64.1	63.3
Q1-Q3	56.5-73.6	56.6-72.8	56.6-73.4
Min-Max	40.9-496	41.9-279	40.9-496

n = number of patients.
* patients with at least one serious TEAE

To model relationship between exposure and serious TEAEs, logistic regression was conducted to estimate the probability serious TEAEs of tislelizumab.

Figure 15: Logistic regression of probability of serious TEAE vs. popPK predicted Cmax,dose1 - 1L G/GEJ (1LGCPK-Safety set)



Model is log(p/(1-p)) = intercept + log PopPK predicted Cmax,dose1, where p is the probability of experiencing at least one serious TEAE.
Boundaries are the 95% CI of the logistic regression model estimation.
The dots are the observed proportions in each PopPK predicted Cmax,dose1 quartile. The 95% CIs for these are based on the Clopper-Pearson method.
Source: Appendix Figure 8.3.18

2.3.5. Discussion on clinical pharmacology

Pharmacokinetics

Pharmacokinetics of tislelizumab at the proposed dosing regimen of 200 mg Q3W had already been extensively characterized in previous applications (2L locally advanced or metastatic ESCC, 1L and 2L locally advanced or metastatic NSCLC).

In the pivotal study BGB-A317-305 supporting the current application a limited number of PK samples were collected. These data were used for external validation of the predictive performance and robustness of the previously developed population PK model for Study 305. This approach is generally considered acceptable. However, the initially developed PopPK model (based on NONMEM) was later translated into a Monolix PopPK model using SAEM (Stochastic Approximation Expectation-Maximization) algorithm. The translation of the initial NONMEM model into the Monolix model was based on individual preference of pharmacometricians and, as an additional aspect, potential run time savings when using Monolix. A model qualification report was provided which included an evaluation of the translated Monolix model with regard to convergence of estimated population/individual PK parameters and predicted PK metrics between the Monolix model and the previous NONMEM model. Predictions from the Monolix as compared to the NONMEM model were largely similar. However, differences in the estimates for V2 and V3 were observed. Likewise, deviations from the line of identity were seen in the correlation of the PK parameters V2 and V3. In addition, the accuracy of the predictions for Q2 and Q3 seems to be considerably lower in the Monolix model. Referring to the goodness-of-fit and prediction-corrected visual predictive check plots from the Monolix PopPK model, some deficiencies of model predictions are obvious: Higher concentrations in the early course post last dose are underestimated, while lower concentrations in the later course post last dose are overestimated by the Monolix.

The external validation using the data from Study 305 showed that final Monolix PopPK model was able to adequately describe the observed PK data from Study 305. The simulated steady state exposure of tislelizumab (Cmaxss, Cminss, AUCss) in Study 305 was comparable to the simulated steady state

exposure of tislelizumab in previous studies included in the original PopPK model. Nevertheless, the applicant clarified that any future tislelizumab submissions will use the original final PopPK model developed in NONMEM to conduct external validation or other PopPK modeling activities.

In Study 305, pre- and postdose concentrations of tislelizumab were similar to the concentrations reported in previous studies in which tislelizumab was either administered as monotherapy or in combination with chemotherapy.

PK in special populations

Further simulations based on PK data from Study 305 were conducted in order to evaluate the impact of race and region on pharmacokinetics of tislelizumab. Estimates for Cmin,ss, Cmax,ss, and AUCss tended to be lower in Non-Asian patients and in patients from the rest of the world (RoW), respectively. However, the observed differences were rather small in comparison to the overall variability of tislelizumab exposure and individual exposure values of patients across different regions largely overlap with each other. Differences in PK estimates by race and region are not considered clinically significant.

Pharmacodynamics

Immunogenicity

Of the 470 ADA-evaluable patients in Study 305, 107 (22.8%) patients had treatment-emergent ADA, with 106 (22.6%) having treatment-induced ADA and 1 (0.2%) having treatment-boosted ADA. Persistent ADA were reported in 64 (13.6%) patients and transient ADA in 42 (8.9%) patients. Neutralizing antibodies were detected in 6 (1.3%) patients, with no evidence of altered PK or clinical outcomes.

The analysis of impact of ADA-positive status on PK showed reduced exposure of tislelizumab in ADA-positive patients. Similar tendencies have been observed in other tislelizumab combination therapy studies (e.g. Study 304, 306 and Study 307). Given the generally high variability of tislelizumab exposure and considering that lower concentrations reported for ADA-positive patients were still within the range of overall variability, the clinical relevance of this finding remains questionable.

Here, no impact of ADA on the clinical response could be shown. The potential impact of ADA on clinical efficacy in tislelizumab-treated patients was assessed based on the clinical endpoints of overall survival (OS), progression-free survival (PFS), objective response rate, disease control rate, clinical benefit rate, duration of response, and tumour size. Here, the principal stratum estimand strategy (Bornkamp B et al 2021) was used to assess the potential impact of ADA on the primary efficacy endpoint of OS in the ITT analysis set. The same strategy was used to assess the potential impact of ADA on efficacy endpoints across Phase II studies endpoint. Based on descriptive subgroup analyses, there was no consistent trend for the impact of ADA on OS and PFS. However, accounting for the methodological uncertainties and considering ADA status as a post-randomization event, those analysis should be viewed with caution. Corresponding analyses in the NSCLC studies (Study 304 and Study 307) and ESCC study 306 indicate a trend towards reduced benefit in patients that were found to be ADA positive. In conclusion, it can be agreed that the totality of data presented so far do not allow firm conclusions on a potential clinically relevant impact of ADA-positivity on PK and/or efficacy.

In contrast with findings from previous tislelizumab studies, the rate of serious adverse events was similar in the ADA-positive population as compared to the ADA-negative population in Study 305. No meaningful differences were seen in the frequency of imAEs, IRRs, TEAEs with CTCAE grade ≥ 3 and TEAEs leading to dose modification.

Exposure-response analyses

The final translated Monolix PopPK model was used as basis for analyses of the exposure-efficacy and exposure-safety relationship for tislelizumab. The exposure-efficacy relationship for tislelizumab was explored using efficacy datasets containing data from 495 patients assigned to tislelizumab arm by randomization, who received at least one dose of tislelizumab in combination with platinum and fluoropyrimidine-based chemotherapy, and had PopPK model predicted Cavg,dose1 for exposure-efficacy.

OS, PFS and responder status based on BOR were investigated as efficacy parameters. Safety endpoints included IRRs, imAEs, TEAEs with CTCAE grade ≥ 3, TEAEs leading to tislelizumab treatment discontinuation or dose modification and serious TEAEs.

In the exposure-efficacy analysis, KM plots for OS and PFS stratified by PopPK predicted Cavg,dose1 quartiles did not show any consistent trend and predicted exposures of patients were similar between responders vs non-responders. It is therefore agreed that the results suggest the absence of a relationship between exposure and efficacy within the exposure range evaluated. Further Cox regression model of OS and PFS and logistic regression of unconfirmed BOR being CR/PR suggested no statistically significant relationship between exposure and any evaluated efficacy endpoints.

Exposure-safety analyses revealed that higher tislelizumab exposure correlated with higher rates of patients experiencing TEAE with CTCAE grade ≥ 3. The logistic regression model of TEAE with CTCAE grade ≥ 3 suggested a statistically significant positive relationship with exposure of tislelizumab. No other covariates assessed correlated with this safety endpoint, and exposure still had a significant impact after adjusting for other covariates. However, other analyses indicated that predicted exposures of patients who experienced IRRs, imAEs, TEAEs leading to tislelizumab treatment discontinuation or dose modification and serious TEAEs were similar.

2.3.6. Conclusions on clinical pharmacology

Pharmacokinetics and pharmacodynamics of tislelizumab have been sufficiently characterized. Results from the pivotal study BGB-A317-305 supporting this application for extension of indication are consistent with the analyses provided in previous applications.

2.4. Clinical efficacy

2.4.1. Dose response study

The fixed dose regimen of 200 mg Q3W was selected based on both nonclinical studies and available clinical data obtained from the first-in-human Study 001. The safety and efficacy of the 200 mg Q3W tislelizumab dosing regimen was further verified in patients with multiple malignancies from Study 102 and has been used in all the subsequent tislelizumab clinical studies. The dose selection information for tislelizumab 200 mg Q3W was described in detail in the initial marketing authorization application. No additional dose selection studies or analyses were performed, and there is no new information for the current submission.

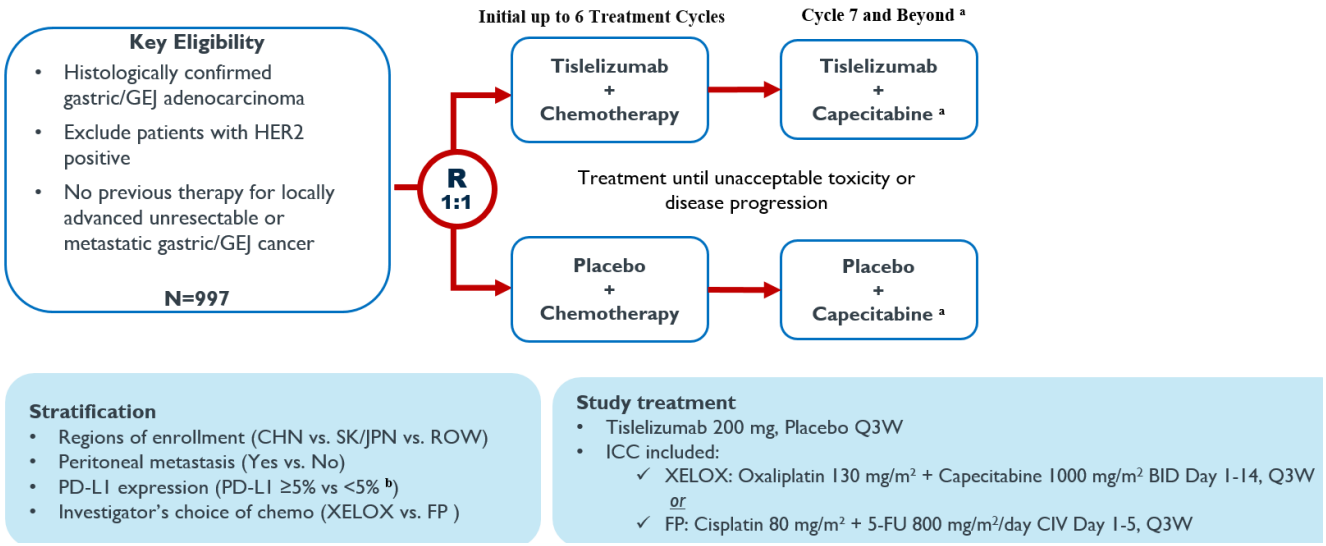
2.4.2. Main study

Title: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Clinical Study Comparing the Efficacy and Safety of Tislelizumab (BGB-A317) plus Platinum and Fluoropyrimidine Versus Placebo plus

Platinum and Fluoropyrimidine as First-Line Treatment in Patients with Locally Advanced Unresectable or Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma - BGB-A317-**305**

Methods

Figure 16: Design Study 305



a The oxaliplatin + capecitabine or cisplatin + 5-FU doublet regimen is administered up to 6 cycles. Capecitabine for oxaliplatin + capecitabine as maintenance therapy is optional.

b PD-L1 score was determined by Tumor Area Positivity (TAP) score using Ventana PD-L1 (SP263) assay

Tumor response was investigator assessed, per RECIST v1.1. Tumor imaging was performed ≤ 28 days before randomization, approximately every 6 weeks during the first 48 weeks and thereafter approximately every 9 weeks.

Regular safety monitoring and the planned interim analysis was performed by an IDMC.

Study participants

Key inclusion criteria (excerpt):

1. Able to provide written informed consent
2. Adult patients
3. Locally advanced unresectable or metastatic gastric or gastroesophageal junction (G/GEJ) cancer and had histologically confirmed adenocarcinoma
4. At least 1 measurable or non-measurable* lesion per RECIST v1.1 as determined by investigator assessment (* implemented with Amendment Version 2.0)
5. No previous systemic therapy for locally advanced unresectable or metastatic G/GEJ cancer. NOTE: Patients could have received prior neoadjuvant or adjuvant therapy as long as it was completed and had no recurrence or disease progression for at least 6 months.
6. Patients had to be able to provide tumor tissues (formalin-fixed paraffin-embedded [FFPE] blocks or approximately 15 [≥ 7 if MSI/MMR and HER2 results were available] freshly cut unstained FFPE

slides) with an associated pathological report. PD-L1 expression was assessed centrally, and patients who had evaluable PD-L1 results were eligible.

7. Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 1
8. Adequate organ function (as defined in the protocol) ≤ 7 days prior to randomization

Key exclusion criteria (excerpt):

1. Patient had squamous cell or undifferentiated or other histological type G/GEJ cancer
2. Active leptomeningeal disease or uncontrolled brain metastasis (patients with asymptomatic and radiologically stable without the need for corticosteroid treatment for ≥ 4 weeks before randomization are eligible).
3. Diagnosed with G/GEJ adenocarcinoma with positive HER2
4. The study excluded patients who had squamous cell or undifferentiated or other histological type G/GEJ cancer; patients who had known HER-2 positive tumours.
5. Uncontrollable pleural effusion, pericardial effusion, or ascites
6. Prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways
7. Active autoimmune diseases or history of autoimmune diseases that may relapse
8. Any condition that requires systemic treatment with either corticosteroids (> 10 mg daily of prednisone or equivalent) or other immunosuppressive medication ≤ 14 days before randomization
9. With history of interstitial lung disease, non-infectious pneumonitis or uncontrolled systemic diseases, including diabetes, hypertension, pulmonary fibrosis, acute lung diseases, etc.
10. With severe chronic or active infections or known history of HIV infection
11. With significant cardiovascular risk factors
12. Administered a live vaccine within 4 weeks before randomization.

Treatments

Tislelizumab

All patients (that were randomized in the tislelizumab + chemotherapy arm) received 200 mg of tislelizumab once every 3 weeks. The first infusion was to be administered over 60 minutes; if well-tolerated, the second infusion was to be administered over 30 minutes.

As a routine precaution, patients were observed for 2 hours after the first 2 infusions in an area with resuscitation equipment and emergency agents.

Tislelizumab (or placebo) could be administered until disease progression, intolerable toxicity, or another treatment discontinuation criterion was met. Treatment beyond the initial RECIST v1.1 defined progression was only permitted if pseudoprogression is suspected and the patient's additional consent for continued treatment beyond initial investigator-assessed progression was obtained.

Chemotherapy

The choice of the standard-of-care chemotherapy regimen (oxaliplatin plus capecitabine or cisplatin plus 5-FU) was determined by the investigator before randomization.

- CapOx

Oxaliplatin: 130 mg/m² via intravenous infusion on Day 1 of each 21-day cycle for up to 6 cycles.

Capecitabine: 1000 mg/m² orally twice daily, for consecutive 14 days of each 21-day for up to 6 cycles and then may be administered as maintenance therapy until disease progression, intolerable toxicity, or another treatment discontinuation criterion is met.

- FP

Cisplatin: 80 mg/m² via intravenous infusion on Day 1 of each 21-day cycle for up to 6 cycles.

5-FU: 800 mg/m2/day via intravenous infusion on Day 1 through Day 5 of each 21-day cycle for up to 6 cycles.

Cross-over between treatment arms was not allowed.

Objectives

Primary Objective

To compare overall survival (**OS**) in patients treated with tislelizumab plus chemotherapy versus patients treated with placebo plus chemotherapy in the PD-L1 Positive and Intent-to-Treat (ITT) Analysis Sets.

Secondary Objectives

- To compare **PFS** per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 as assessed by investigators with tislelizumab plus chemotherapy versus placebo plus chemotherapy in the PD-L1 Positive and ITT Analysis Sets
- To evaluate overall response rate (**ORR**) and duration of response (**DOR**) per RECIST v1.1 as assessed by investigators
- To evaluate **quality of life** using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Gastric Cancer Module QLQ-STO22 (EORTC QLQ-STO22), European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30), and European Quality of Life 5-Dimensions 5-Levels Health Questionnaire (EQ-5D-5L)
- To evaluate disease control rate (**DCR**), clinical benefit rate (**CBR**), and time to response (**TTR**) per RECIST v1.1 as assessed by investigators
- To evaluate the safety and tolerability profile of tislelizumab or placebo plus chemotherapy

Exploratory Objectives

- To evaluate PFS after next line of treatment (PFS2)
- To characterize the pharmacokinetics of tislelizumab
- To determine host immunogenicity to tislelizumab
- To assess predictive, prognostic, and exploratory biomarkers including but not limited to PD-L1 expression, Epstein-Barr virus (EBV) infection, microsatellite instability-high (MSI-H) or mismatch

repair deficient (dMMR) status, genomically stable (GS) or chromosomal instability (CIN), immune-related gene expression profiling, tumor infiltrated lymphocytes (TILs), and tumor mutation burden in tumor tissues and/or blood samples and the association with response to study treatment, mechanisms of resistance, and/or disease status

Outcomes/endpoints

Primary endpoint

The dual primary efficacy endpoints for this study were OS in the PD-L1 Positive and ITT Analysis Sets, defined as time from randomization date to the date of death due to any cause.

Secondary endpoints

- PFS was defined as the time from the randomization date to disease progression or death, whichever occurred first.
- ORR was defined as the number of patients whose BOR was confirmed complete response (CR) or partial response (PR) divided by the number of randomized patients in each arm.
- The duration of response (DOR) was defined as progression/death-event-free time counted from the first objective response date to the first documented radiological disease progression date/or death date, whichever occurred first.
- The DCR was defined as the proportion of patients whose BOR was CR, PR, or stable disease including non-CR/non-PD.
- CBR was defined as the proportion of patients who had CR, PR, or stable disease including non-CR/non-PD of $\geq$ 24 weeks in duration.
- The time to response (TTR) was summarized using descriptive statistics, such as mean, median, and standard deviation. Only patients who had achieved an objective response were included in the analysis of TTR.
- Health-Related Quality of Life was assessed based on descriptive analyses using EORTC QLQ-C30, EORTC QLQ STO22, and EQ-5D-5L questionnaires. Score changes from baseline and least square (LS) mean score changes from baseline to cycle 4 and cycle 6 and time to deterioration were summarized. Time to deterioration was defined as time from randomization to the first occurrence of a decrease of $\geq$ 10 points in GHS/QoL and physical function of the EORTC QLQ-C30, and $\geq$ 10 increase in fatigue of the EORTC QLQ-C30 and in the scores of dysphagia, pain, dietary restrictions, and upper gastrointestinal symptoms of EORTC QLQ-STO22.

Exploratory efficacy endpoints

- Progression-free survival after next line of treatment (PFS2) was defined as the time from the randomization to the first documented disease progression on next-line therapy or death from any cause, whichever occurred first. The first documented progression on next-line treatment was recorded by the investigator.

Biomarker

PD-L1 expression was determined by PD-L1 score assessed by Tumor Area Positivity (TAP) score (previously referred to as Tumor Immune Cell (TIC) score in the protocol), which is defined as the total percentage of the tumor area covered by tumor cells with any membrane staining above background

and tumor-associated immune cells with any staining above background. PD-L1 scores in Study 305 were investigated using the validated Ventana PD-L1 (SP263) assay.

The PD-L1 expression cutoff selection was based on a post-hoc analysis of tumors from patients with gastroesophageal adenocarcinoma (GEA) who were treated with tislelizumab (Study 001). 50 patients from the GC cohort and 27 patients with esophageal adenocarcinoma with evaluable PD-L1 status were included in the analysis using the Ventana PD-L1(SP263) assay. The cutoff of PD-L1 score ≥ 5% was determined as the optimal cutoff based on receiver operating characteristic (ROC) analysis and statistical parameters relative to clinical response including sensitivity/specificity as well as PD-L1 positivity prevalence in Study 001 (49.4%) and pathological feasibility. The PD-L1 assay at the ≥ 5% cutoff was analytically validated for G/GEJ cancer, before it was used in Study 305.

Figure 17: ROC curve for PD-L1 score from BGB-A317-study_001 GEA cohort (N=77)

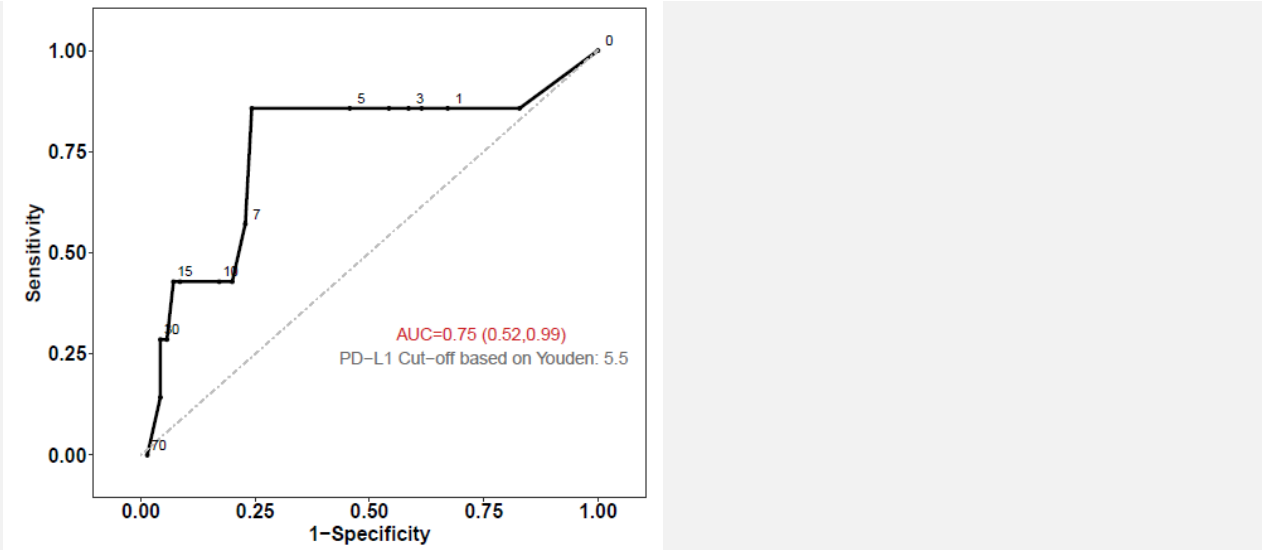


Table 16: Clinical performance with PD-L1 ≥5% cutoff in GEA cohort of BGB-A317-study_001 with an evaluable PD-L1 score (N=77)

PD-L1 score cutoff	Prevalence (n)	Sensitivity	Specificity	PPV	NPV
≥5%	49.4% (38)	85.7%	54.3%	15.8%	97.4%

Sensitivity = No. of confirmed responders in patients with PD-L1 score ≥5% / Total No. of responder
Specificity = No. of non-responders in patients with PD-L1 score <5% / Total No. of non-responder
PPV = Percent of responders within patients with PD-L1 score ≥5%
NPV = Percent of non-responders within patients with PD-L1 score <5%

Table 17: ORR by PD-L1 score ≥5% vs <5% BGB-A317-study_001 GEA cohort (N=77)

Response Category	PD-L1 Score ≥ 5% (N = 38)	PD-L1 Score < 5% (N = 39)
Objective Response Rate (ORR), n (%)	6 (15.8)	1 (2.6)
95% CI	(6.0, 31.3)	(0.1, 13.5)
Data cutoff: 26AUG2020		

Age of tumor tissues for PD-L1 testing

Table 18: Time from biopsy/resection to tissue staining for patients with and without prior (neo)adjuvant systemic therapy (source: Table 5.4 SCE App.1)

Prior Adjuvant/Neoadjuvant Systemic Therapy:Yes

Description	Tisle + Chemo (N = 107)	Placebo + Chemo (N = 100)	Total (N = 207)
Time From Tumor Biopsy/Resection to Tissue Staining (months)			
< 1 month	5 (4.7)	15 (15.0)	20 (9.7)
1-< 6 months	5 (4.7)	7 (7.0)	12 (5.8)
6- < 12 months	4 (3.7)	1 (1.0)	5 (2.4)
12 - < 36 months	71 (66.4)	63 (63.0)	134 (64.7)
>= 36 months	22 (20.6)	14 (14.0)	36 (17.4)
Tissue Type, n (%)			
Archival	107 (100)	99 (99.0)	206 (99.5)
Fresh	0	1 (1.0)	1 (0.5)

Prior Adjuvant/Neoadjuvant Systemic Therapy:No

Description	Tisle + Chemo (N = 394)	Placebo + Chemo (N = 396)	Total (N = 790)
Time From Tumor Biopsy/Resection to Tissue Staining (months)			
< 1 month	270 (68.5)	227 (57.3)	497 (62.9)
1-< 6 months	103 (26.1)	137 (34.6)	240 (30.4)
6- < 12 months	6 (1.5)	7 (1.8)	13 (1.6)
12 - < 36 months	12 (3.0)	16 (4.0)	28 (3.5)
>= 36 months	3 (0.8)	9 (2.3)	12 (1.5)
Tissue Type, n (%)			
Archival	373 (94.7)	377 (95.2)	750 (94.9)
Fresh	21 (5.3)	19 (4.8)	40 (5.1)

Sample size

According to the latest study protocol, the sample size calculation was based on the primary efficacy analyses of OS in the comparison between Arms A and B in the PD-L1 Positive and ITT Analysis Sets. OS was assumed to follow an exponential distribution. A sequential testing procedure was implemented to control overall alpha at 0.025 one-sided. The OS analysis in the PD-L1 Positive Analysis Set was planned to be performed first and OS analysis in the ITT Analysis Set was planned to be carried out only if the OS analysis in the PD-L1 Positive Analysis Set was statistically significant favouring tislelizumab plus chemotherapy arm. Assuming a 50% PD-L1 Positive (PD-L1 score ≥ 5%) prevalence, a total of 928 patients, including approximately 464 (ie, 50%) in the PD-L1 Positive subset, were planned to be enrolled in a 1:1 randomization to observe targeted OS events at the defined time periods (see table below). Assuming a roughly 5% dropout rate, approximately 980 patients were to be enrolled over 24 months at enrollment rates of 17 patients/month in the first 2

months, 34 patients/month in the next 2 months, and 44 patients/month in the last 20 months. The enrollment assumptions, including percentage of PD-L1 Positive patients, were monitored during the enrolment.

Enrollment of patients whose tumors were PD-L1 negative (PD-L1 score < 5%) was planned to be possibly stopped, to ensure that the percentage of PD-L1 Positive (PD-L1 score ≥ 5%) was ≥ 50% of the ITT Analysis Set. The capping was eventually not triggered as the upper limit of 50% of the patients with PD-L1 score < 5% had not been reached. The primary analyses were to be performed when the target number of events in both ITT and PD-L1 Positive Analysis Set were observed. An interim analysis of OS was planned after approximately 70% of the total planned death events had occurred in ITT and PD-L1 Positive Analysis Sets, 538 and 269 events, respectively (see following table).

Table 19: Stopping boundaries of primary analysis of OS:

Analysis Set	Analysis	Time (m)	# Events	p-value[a] (Z score) for Efficacy	p-value[a] (Z score) for Interim Futility	Approximate HR Threshold	Cumulative Prob of Crossing Under H_1
PD-L1+[b]	Interim analysis	30	269	< 0.0072 (>2.45)	> 0.5731 (< -0.18)	0.742	0.47
	Final analysis	48	384	< 0.0228 (> 2.00)	-	0.815	0.80
ITT	Interim analysis	30	538	< 0.0072 (>2.45)	> 0.5384 (< -0.1)	0.810	0.56
	Final analysis	48	768	< 0.0228 (> 2.00)	-	0.866	0.87

a. 1-sided
b. PD-L1+ is 50% of the ITT

Table 20: Hazard Ratio and Median OS assumption, number of events, alpha and power in the primary hypothesis tests.

Analysis Set	HR	Median in Arm A (in months)	Median in Arm B (in months)	# Events	Alpha	Power
PD-L1+	0.75	15.3	11.5	384	0.025	80%
ITT	0.8	14.4	11.5	768	0.025	87%

Change History of the Sample Size in Previous Protocol Amendment

In the original protocol, approximately 640 patients were planned to be enrolled (n=720 in Protocol Amendment 1, prior to inclusion of the first patient), and PFS and OS in the ITT and PD-L1 Positive Analysis Sets were the primary efficacy endpoints (four primary objectives). In Protocol Amendment Version 2.0 (dated 03 April 2020) the objectives and sample size were changed, including an increase in the study sample size (from 720 to 980) and in the number of required death events (from 319 to 384 in the PD-L1 Positive Analysis Set, from 509 to 768 in the ITT Analysis Set), update of HR (from 0.70 to 0.75 in the PD-L1 Positive Analysis Set, from 0.75 to 0.8 in the ITT Analysis Set), and removal of PFS as the primary endpoint.

Randomisation

After completing all screening activities, patients confirmed to be eligible by the investigator were planned to be randomized in a 1:1 ratio to receive either tislelizumab or placebo plus chemotherapy treatment. The choice of chemotherapy regimen must be decided prior to randomization and the interchange of chemotherapy regimen is not permitted during study period.

At randomization, patient enrollment was planned to be stratified by the following factors

- Regions of enrollment: China (including Taiwan) vs. Japan and S. Korea vs. US and Europe and other regions. NOTE: other regions include other western countries/populations.
- PD-L1 expression (positive or negative): PD-L1 positive patients are patients with tumor and immune cell score (TIC score) ≥ 5% using VENTANA PD-L1 (SP263) Cdx Assay*. TIC score is 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.
- Presence of peritoneal metastasis (yes or no)
- Investigator's choice of chemotherapy (oxaliplatin + capecitabine versus cisplatin + 5-FU)

Blinding (masking)

This is a randomized, double-blind, Phase 3 study. Patients were planned to be randomized to receive tislelizumab or matching placebo in a double-blind fashion such that neither the investigator, nor the patient, nor medical or ancillary medical staff, nor the Sponsor or its designees, would know which drug is being administered in addition to chemotherapy.

- Emergency unblinding

Emergency unblinding for AEs may be performed through an Interactive Web Response System (IWRS). All AEs should be evaluated and determined whether they are related to tizlelizumab plus chemotherapy or chemotherapy alone and treatment provided accordingly. Therefore, emergency unblinding should not be required to manage the patient's care. If knowledge of the investigational product is critical to the patient's management and the investigator decides that unblinding is required to manage an adverse reaction (eg, some ≥ Grade 3 irAE or the event of a medical emergency or pregnancy), the investigator should make every effort to contact the Sponsor medical monitor prior to unblinding a patient's treatment assignment unless this could delay emergency treatment of the patient. If a patient's treatment assignment is unblinded due to an emergency treatment, the sponsor must be notified immediately.

- Inadvertent unblinding

Every effort was planned to be made to blind both the patient and the investigator to the identity of tislelizumab or placebo, but the inadvertent unblinding of a patient may occur. If an investigator, site personnel performing assessments, or patient is unblinded, the unblinding was not planned to be sufficient cause (in and of itself) for that patient to be discontinued from study therapy or excluded from any safety or efficacy analyses.

- Unblinding for serious adverse reaction reporting

The sponsor was planned to unblind patients who experience an unexpected serious adverse reaction, for the purpose of reporting to the regulatory authorities. In such a case, the medical monitors will not be informed of the treatment allocation, according to the sponsor's standard procedures

Statistical methods

The dual primary efficacy endpoints for this study were OS in the PD-L1 Positive and ITT Analysis Sets.

Analysis sets

Intent-to-Treat (ITT) analysis set – was planned to include all randomized patients. Patients were planned to be analysed according to their randomized treatment arm.

PD-L1+ analysis set (with tumor and immune cell score [TIC score] ≥ 5% using VENTANA PD-L1 [SP263] Cdx Assay. TIC score is 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) – planned to include all randomized patients whose tumors were PD-L1+. Patients were planned to be analyzed according to their randomized treatment arms.

Per-Protocol (PP) analysis set – planned to include all randomized patients who received at least 1 dose of the assigned study drug and had no major protocol deviations. Major protocol deviations were planned to be determined and documented before the database lock for the primary analyses.

Safety analysis set – planned to include all patients who received at least 1 dose of study drugs.

Multiplicity

OS analysis was planned to be performed in the PD-L1 Positive Analysis Set first. OS analysis in ITT Analysis Set was planned to be performed only if the OS analysis in the PD-L1 Positive Analysis Set was statistically significant favoring tislelizumab plus chemotherapy. There was 1 interim analysis of OS for both efficacy and futility planned. The interim analysis of OS was planned to be performed when approximately 269 deaths in the PD-L1 Positive Analysis Set and 538 deaths in the ITT Analysis Set (70% of the target number of OS events in each analysis set) had been observed. The final analysis of OS was planned to be performed after approximately 384 and 768 death events had been observed in the 2 analysis sets.

Hypothesis testing of the secondary endpoints PFS and ORR in the PD-L1 Positive and ITT Analysis Sets was to be performed at the same time as the interim analysis of OS. Only when the superiority of OS in both PD-L1 Positive and ITT Analysis Sets had been demonstrated, its alpha of 0.025 (1-sided) would be shifted sequentially to the hypothesis testing of the secondary endpoints in order of PFS in the PD-L1 Positive Analysis Set, ORR in the PD-L1 Positive Analysis Set, followed by PFS and ORR in ITT Analysis Set. The hypothesis test would be stopped at the first non-significant endpoint. Nominal p-values were planned to be computed for other efficacy analyses.

Interim analysis and analysis timepoints

There was planned to be one interim analysis of OS using the O'Brien-Fleming boundary approximated by Hwang-Shih-DeCani spending function with the gamma parameter set at -4. The non-binding lower (futility) boundary is defined by Hwang-Shih-DeCani spending function with the gamma parameter set at -12. The interim analysis of OS wasss planned to be performed when approximately 269 deaths in the PD-L1+ analysis set and 538 deaths in the ITT analysis set (70% of the target number of OS events in each analysis set) among the 2 treatment arms have been observed which was estimated to occur approximately 30 months after the first patient is randomized. The final analysis of OS was planned to take place after approximately 384 and 768 death events have been observed in the 2 analysis sets, respectively, which was estimated as 48 months after the first patient is randomized. The boundaries were planned to be updated according to the actual numbers of events in the interim and final analyses, using the above pre-specified alpha spending function.

Primary analysis model and censoring

OS was planned to be defined as time from randomization date to the date of death due to any cause. For patients who were alive by the clinical cutoff date, OS was planned to be censored at the last known alive date. The last known alive date was defined as either the clinical data cutoff date for patients who were still on treatment, or the last available date showing patients alive, or cutoff date, whichever came first for other patients who were alive.

The primary efficacy analyses of OS were to be performed using the stratified log-rank test on the PD-L1 Positive Analysis Set and ITT Analysis Set separately according to the treatment arm and randomization strata (region of enrollment, PD-L1 expression [in ITT Analysis Set only], and presence of peritoneal metastasis) to which patients were assigned at randomization.

The survival distribution of OS was planned to be estimated using the Kaplan-Meier method. The median OS for each treatment group was provided along with the approximate 95% confidence intervals (CIs) using the method of Brookmeyer and Crowley (Brookmeyer and Crowley 1982). The cumulative probability of OS at every 6 months, if estimable, was planned to be calculated for each treatment arm and presented with 2-sided 95% CIs. The CIs were constructed using the standard errors derived from Greenwood's formula (Collett 1994).

The treatment effect was planned to be estimated by fitting a stratified Cox proportional hazard model to the OS times, including the treatment arm as a covariate and the region of enrollment (east Asia versus the rest of the world), PD-L1 expression (for ITT Analysis Set only), and presence of peritoneal metastasis with information obtained via IRT as strata. From this model, the HR of OS was planned to be estimated and presented with a 2-sided 95% CI.

Secondary analyses

PFS assessed by investigators per RECIST v1.1 was planned to be estimated using the Kaplan-Meier (KM) method in the PD-L1+ and ITT analysis set. Data for patients without disease progression or death at the time of analysis was planned to be censored at the time of the last adequate tumor assessment. Data for patients who are lost to follow-up prior to documented disease progression was planned to be censored at the last adequate tumor assessment date when the patient is known to be progression free. Data for patients who start to receive new anticancer therapy was planned to be censored at the last adequate tumor assessment date prior to the introduction of new therapy.

The treatment effect was planned to be estimated by fitting a Cox regression model to the PFS times including treatment arm as a factor and region of enrollment (east Asia versus ROW), PD-L1 expression (only when testing PFS in the ITT analysis set), and presence of peritoneal metastasis as strata. From this model, the hazard ratio (HR) of PFS was planned to be estimated and presented with a2-sided 95% CI.

The null hypotheses of no difference in ORR per RECIST v1.1 assessed by investigators was planned to be tested in a Cochran-Mantel-Haenszel (CMH) test adjusting for pooled stratification factors in the ITT and PD-L1+ analysis sets. Patients with no post-baseline response assessment (for any reason) were planned to be considered non-responders. The 2-sided 95% CIs for the odds ratio in ORR was planned to be calculated, as well as Clopper-Pearson 95% CIs of ORR for each treatment arm.

Results

Participant flow

Figure 18: Study 305 Patient Flow Chart

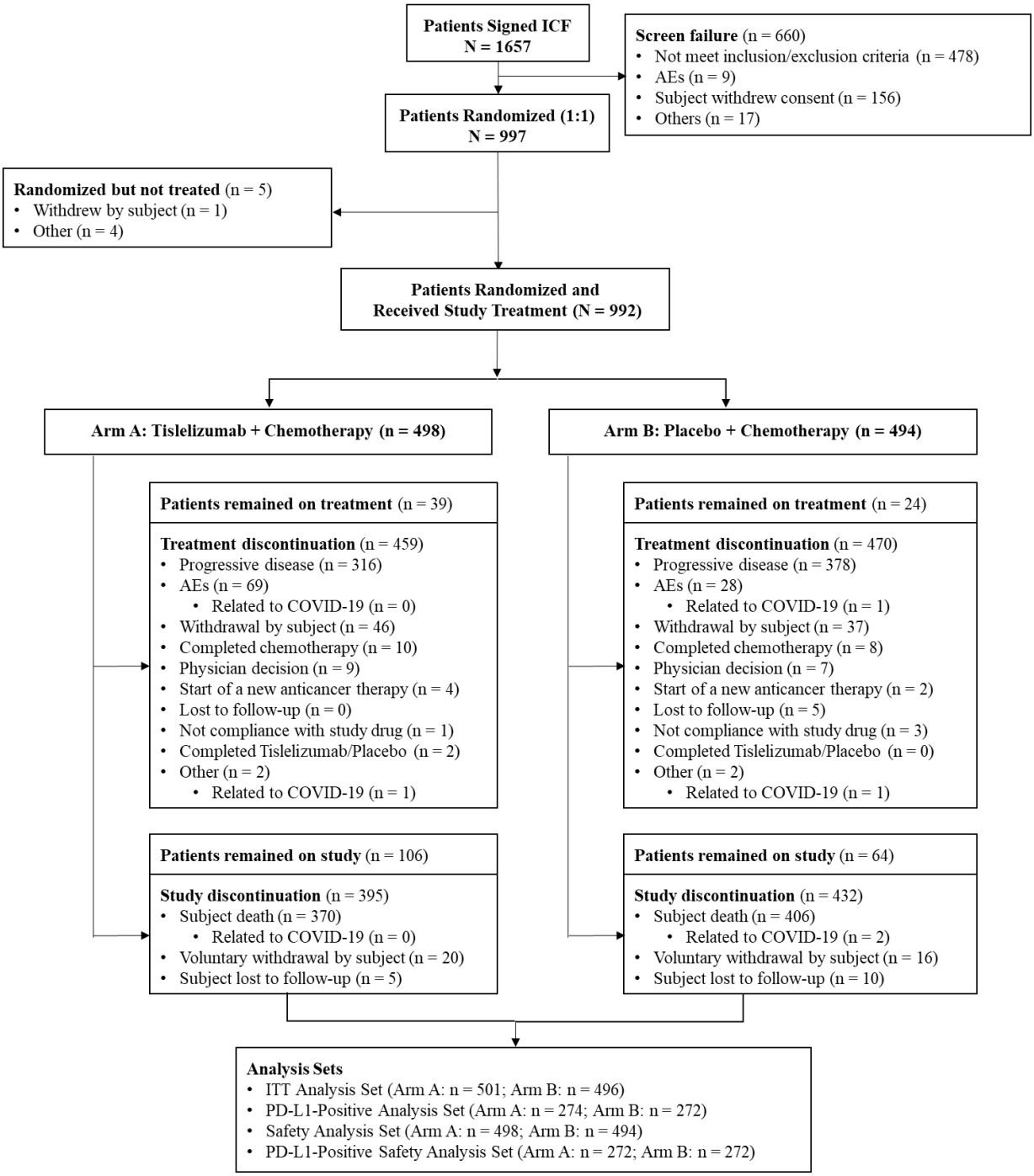


Table 21: Patient Disposition and Reasons for Discontinuation - Study 305 (ITT Analysis Set)

	Tislelizumab + Chemotherapy (N=501) n (%)	Placebo + Chemotherapy (N=496) n (%)	Total (N=997) n (%)
Number of Patients Randomized	**501 (100.0)**	**496 (100.0)**	**997 (100.0)**
Patients Randomized, but Not Treated	**3 (0.6)**	**2 (0.4)**	**5 (0.5)**
Reason for Not Treated			
Withdrawal by Subject	1 (0.2)	0 (0.0)	1 (0.1)
Other	2 (0.4)	2 (0.4)	4 (0.4)
Patients Treated	**498 (99.4)**	**494 (99.6)**	**992 (99.5)**
Patients Discontinued from Treatment or Completed Treatment [a]	459 (91.6)	470 (94.8)	929 (93.2)
Progressive Disease	316 (63.1)	378 (76.2)	694 (69.6)
Radiographic Progression	279 (55.7)	332 (66.9)	611 (61.3)
Clinical Progression	37 (7.4)	46 (9.3)	83 (8.3)
Adverse Event	69 (13.8)	28 (5.6)	97 (9.7)
- Related to COVID-19	0 (0.0)	1 (0.2)	1 (0.1)
Withdrawal by Subject	46 (9.2)	37 (7.5)	83 (8.3)
Completed Chemotherapy	10 (2.0)	8 (1.6)	18 (1.8)
Physician Decision	9 (1.8)	7 (1.4)	16 (1.6)
Start of a New Anticancer Therapy	4 (0.8)	2 (0.4)	6 (0.6)
Lost to Follow-up	0 (0.0)	5 (1.0)	5 (0.5)
Non-Compliance With Study Drug	1 (0.2)	3 (0.6)	4 (0.4)
Completed Tislelizumab/Placebo	2 (0.4)	0 (0.0)	2 (0.2)
Other	2 (0.4)	2 (0.4)	4 (0.4)
- Related to COVID-19	1 (0.2)	1 (0.2)	2 (0.2)
Patients Remained on Treatment	39 (7.8)	24 (4.8)	63 (6.3)
Patients Discontinued from Study	**395 (78.8)**	**432 (87.1)**	**827 (82.9)**
Reason for Discontinuation from Study			
Subject Death	370 (73.9)	406 (81.9)	776 (77.8)
Related to COVID-19	0 (0.0)	2 (0.4)	2 (0.2)
Voluntary Withdrawal by Subject	20 (4.0)	16 (3.2)	36 (3.6)
Subject Lost to Follow-up	5 (1.0)	10 (2.0)	15 (1.5)
Patients Remained in Study	**106 (21.2)**	**64 (12.9)**	**170 (17.1)**
Study Follow-up Duration (months)[b]			
n	501	496	997
Mean (SD)	17.2 (12.05)	15.2 (10.74)	16.2 (11.45)
Median	14.1	12.6	13.2
Q1, Q3	7.4, 26.7	6.9, 21.6	7.1, 24.6
Min, Max	0.1, 50.1	0.3, 46.9	0.1, 50.1
Minimum Study Follow-up Time (months)[c]	24.6	25.0	24.6

Percentages were based on number of patients randomized.
[a] Number of patients discontinued all treatment components, reason for patients discontinued from treatment is the reason for treatment component whichever discontinued last. If tislelizumab and chemotherapy discontinued at the same date, the reason for discontinuation of tislelizumab will be presented.
[b] Study follow-up time is defined as the time from the randomization date to the study discontinuation date (death, consent withdrawal, lost to follow up) or to cutoff date if a patient is still ongoing.
[c] Minimum study follow-up time is defined as a difference between the date of cut-off and the date of last patient randomized.

A total of 660 patient (39.8%) of 1657 screened patients did not meet screening criteria. The most common reason for patients to not satisfy the screening criteria was not meeting the inclusion/exclusion criteria (478 patients [72.4%])

As of the data cutoff, nearly all patients (93.2%) in the ITT analysis set had discontinued study treatment. Disease progression was the most common primary reason for treatment discontinuation in both arms, and this was lower in Arm T+PtF (63.1%) compared with Arm P+PtF (76.2%). A higher proportion of patients in Arm T+PtF discontinued from treatment due to AEs (T+PtF: 13.8% vs. P+PtF: 5.6%).

Recruitment

Study Start Date (first patient randomized): 13 December 2018;
Last patient randomized: 09 February 2021; the study is ongoing; Data Cutoff Date: 28 February 2023
The study is currently being conducted at 141 sites in 13 countries/regions including Mainland China (n=499), Chinese Taiwan (n=17), Japan (n=101), South Korea (n=131), Russia (n=98), the UK (28), France (n=20), Italy (n=18), Poland (n=18), Puerto Rico, Spain (n=45), Turkey (n=17), and the US (n=25). (*n=number of subjects enrolled*)

Conduct of the study

Protocol amendments

The original global protocol for this study was dated 12-Feb-2018. The global protocol was amended a total of 2 times before the data cutoff date. The patients were enrolled after the implementation of Protocol Amendment Version 1.0. When Protocol Amendment Version 2.0 was implemented, 490 patients (50% of the planned sample size) had been enrolled.
Amendment **Version 1.0** (Global, 20-Aug-2018) (excerpt)

Rationale: to incorporate changes based on feedback from Health Authorities, including the US FDA, the EMA, and the Netherlands Medicines Evaluation Board (MEB).

- The alpha allocation approach for the primary endpoint was updated to not include any correlation between the PD-L1 Positive population and the ITT population, as requested by the FDA
    - Adjusted the 1-sided alpha of 0.00275 to 0.0025 for the primary efficacy analyses of PFS in the PD-L1 Positive and ITT Analysis Sets.
    - Adjusted the 1-sided alpha of 0.011 to 0.01 for the primary efficacy analyses of OS in the PD-L1 Positive and ITT Analysis Sets.
- Increase of sample size from 640 to 720 patients to account for dropout and change in alpha allocation approach.
- Added PFS after next line of treatment (PFS2) for the exploratory efficacy analysis.
- Modified the description of exploratory biomarkers.
- Clarified that the patients whose tumors were PD-L1 positive with PD-L1 score $\geq$ 5% using VENTANA PD-L1 (SP263) Assay were considered as PD-L1 positive. PD-L1 score (previously referred to TIC score in protocol) was 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 (TAP score).
- The elderly age limitation (i.e., $\leq$ 75 years of age at the time of voluntarily signing informed consent) was removed from the inclusion criteria.

Amendment **Version 2.0** (Global, 03-Apr-2020) (excerpt)

- Revision of primary study endpoint:
    - Assessment of PFS was moved from primary objective/endpoint to secondary objective/endpoint.

Rationale: Since PFS may not be a suitable surrogate endpoint for OS in trials of PD-1/PD-L1 in first-line treatment of advanced/metastatic GC, OS was considered as the only primary endpoint, in line with CHMP's advice (CHMP SA Letter dated 28Jun18).

    - Sequential testing method was implemented to compare OS of tislelizumab plus chemotherapy versus placebo plus chemotherapy in the PD-L1 Positive Analysis Set first and then in the ITT Analysis Set.

- To account for the update in hazard ratio assumption, primary endpoint and PD-L1 prevalence rate, the statistical calculation of sample size was updated, leading to an increase of the sample size from 720 to 980 patients and of the number of required death events (from 319 to 384 in the PD-L1 Positive Analysis Set, from 509 to 768 in the ITT Analysis Set). The increase in sample size led to an update of the study duration from 43 to 48 months.
- Tumor assessment by blinded independent review committee (BIRC) was removed. Since the second endpoints of DCR, CBR and TTR assessed by BIRC were removed, DCR, CBR, and TTR assessed by investigator were moved from exploratory objectives/endpoints to secondary objectives/endpoints.
- Updated the inclusion criteria to allow patients with non-target lesion only to be enrolled.
- Third-party local laboratory was added as eligible entity to perform an MSI/MMR assessment for patients with unavailable MSI/MMR status, or HER2 test, per the US FDA's request.

Changes in the Planned Analyses

Several post hoc analyses were performed after unblinding (see outcomes and estimations), e.g.:

- To evaluate the impact of treatment discontinuation due to "withdrawal by subject" on the primary analysis of OS in the ITT Analysis Set
- To further evaluate the consistency in treatment effect across regions for secondary endpoints
- During the study conduct after the interim analysis, a few updates or corrections on death and PFS events data in the PD-L1 Positive Analysis Set were made and have all been included in the Study 305 final analysis dataset.

Changes in Study Conduct and Planned Analyses Due to the COVID-19 Pandemic

This study was impacted by the COVID-19 pandemic during the period from January 2020 in Asia and from February 2020 in ROW, up until the data cutoff date (28-Feb-2023). The Sponsor developed robust contingency measures in line with local and global regulatory guidance. Adjustments and/or mitigations were put in place for the study conduct (including visits, procedures, monitoring oversight, and reporting) to minimize the impact of the pandemic and to ensure patient safety and data integrity. Missing or delayed visits and assessments were identified and reported as protocol deviations, and these were flagged by sites as linked to COVID-19 as applicable.

The COVID-19 pandemic did not significantly affect the efficacy results or data quality of the:

- Two patients in Arm P+PtF discontinued the study because of death related to COVID-19; for one patient in Arm P+PtF, this was also classified as an AE of COVID-19 infection leading to discontinuation of treatment.
- A total of 8 patients (0.8%, 4 patients in each arm) had important protocol deviations related to COVID-19 in the ITT Analysis Set; the deviations were related to study assessments and procedures and safety reporting, and none were critical.
- A total of 23 patients (2.3%) experienced $\geq$ 1 missed tumor assessment due to COVID-19 (10 patients (2.0%) in Arm T+PtF and 13 patients (2.6%) in Arm P+PtF); the majority of these missed only assessment, and no patient had $\geq$ 3 missed tumor assessments due to COVID-19.

Because the number of important protocol deviations and discontinuations related to COVID 19 was low, these were considered to have minimal impact on the study efficacy results or conclusions. In support of this, a sensitivity analysis for OS in the ITT analysis set, adjusting for the impact of COVID-19 gave results that were highly consistent with the primary analysis.

Protocol Deviations

In the ITT Analysis Set, 31.4% of patients (30.9% in Arm A and 31.9% in Arm B) were reported with important protocol deviations. The most common categories of important protocol deviations were those of "protocol compliance" (17.8% vs 18.5%), "safety" (8.2% vs 6.9%), and "informed consent" (5.8% vs 5.4% in Arm A vs Arm B, respectively).

A total of 11 patients (1.1%) had critical protocol deviations, i.e. deviations that significantly impact efficacy or safety analyses. Numbers were balanced across treatment arms, see table below.

Table 22: Summary of Critical Protocol Deviations (ITT Analysis Set)

Category Category Subtype	Tislelizumab + Chemotherapy (N = 501) n (%)	Placebo + Chemotherapy (N = 496) n (%)	Total (N = 997) n (%)
Patients With at Least One Critical Protocol Deviation	6 (1.2)	5 (1.0)	11 (1.1)
PROTOCOL COMPLIANCE	6 (1.2)	5 (1.0)	11 (1.1)
INCLUSION / EXCLUSION	2 (0.4)	4 (0.8)	6 (0.6)
PROHIBITED MEDICATION OR TREATMENT	2 (0.4)	0 (0.0)	2 (0.2)
STUDY ASSESSMENTS & PROCEDURES	1 (0.2)	1 (0.2)	2 (0.2)
VISIT COMPLIANCE	1 (0.2)	0 (0.0)	1 (0.1)

Percentages were based on N.
Patients with multiple critical protocol deviations were counted only once in each row category.
Category Subtype 'Prohibited Medication or Treatment' includes both 'Prohibited Medication or Treatment' and 'Prohibitive

Medication or Treatment'.

Baseline data

Table 23: Summary of Demographics and Baseline Characteristics - Study 305 (ITT Analysis Set)

Parameter	Tislelizumab + Chemotherapy (N = 501)	Placebo + Chemotherapy (N = 496)	Total (N = 997)
Age (years)			
Mean (SD)	58.8 (11.07)	59.7 (11.20)	59.3 (11.14)
Median	60.0	61.0	61.0
Q1, Q3	53.0, 66.0	54.0, 68.0	53.0, 67.0
Min, Max	23.0, 86.0	25.0, 86.0	23.0, 86.0
< 65 years	340 (67.9)	313 (63.1)	653 (65.5)
≥ 65 years	161 (32.1)	183 (36.9)	344 (34.5)
Gender, n (%)			
Female	155 (30.9)	150 (30.2)	305 (30.6)
Male	346 (69.1)	346 (69.8)	692 (69.4)
Race, n (%)			
Asian	376 (75.0)	372 (75.0)	748 (75.0)
Chinese	259 (51.7)	258 (52.0)	517 (51.9)

Parameter	Tislelizumab + Chemotherapy (N = 501)	Placebo + Chemotherapy (N = 496)	Total (N = 997)
Korean	67 (13.4)	63 (12.7)	130 (13.0)
Japanese	50 (10.0)	51 (10.3)	101 (10.1)
White	116 (23.2)	107 (21.6)	223 (22.4)
Not Reported	8 (1.6)	16 (3.2)	24 (2.4)
Other	1 (0.2)	0 (0.0)	1 (0.1)
Unknown	0 (0.0)	1 (0.2)	1 (0.1)
Region, n (%)			
East Asia	376 (75.0)	372 (75.0)	748 (75.0)
China (including Taiwan)	259 (51.7)	257 (51.8)	516 (51.8)
Japan	50 (10.0)	51 (10.3)	101 (10.1)
South Korea	67 (13.4)	64 (12.9)	131 (13.1)
Rest of World	125 (25.0)	124 (25.0)	249 (25.0)
US	10 (2.0)	15 (3.0)	25 (2.5)
Europe	115 (23.0)	109 (22.0)	224 (22.5)
Ethnicity, n (%)			
Hispanic or Latino	2 (0.4)	6 (1.2)	8 (0.8)
Not Hispanic or Latino	492 (98.2)	474 (95.6)	966 (96.9)
Not Reported	7 (1.4)	16 (3.2)	23 (2.3)
BMI (kg/m^2)			
Mean (SD)	22.0 (3.84)	22.3 (3.81)	22.2 (3.83)
Median	21.6	21.9	21.7
Q1, Q3	19.3, 24.2	19.6, 24.6	19.5, 24.4
Min, Max	13.6, 38.7	13.8, 36.6	13.6, 38.7
ECOG Status, n (%)			
0	169 (33.7)	154 (31.0)	323 (32.4)
1	332 (66.3)	342 (69.0)	674 (67.6)
Smoking Status, n (%)			
Never	254 (50.7)	257 (51.8)	511 (51.3)
Former	175 (34.9)	179 (36.1)	354 (35.5)
Current	72 (14.4)	60 (12.1)	132 (13.2)
Alcohol Consumption, n (%)			
Never	315 (62.9)	284 (57.3)	599 (60.1)
Former	141 (28.1)	148 (29.8)	289 (29.0)
Current	45 (9.0)	64 (12.9)	109 (10.9)

Table 24: Disease History and Characteristics at Study Entry - Study 305 (ITT Analysis Set)

Parameter	Tislelizumab + Chemotherapy (N = 501)	Placebo + Chemotherapy (N = 496)	Total (N = 997)
Time from Initial Cancer Diagnosis to Study Entry (months) [a]			
n	501	496	997
Mean (SD)	11.0 (27.80)	10.5 (19.91)	10.7 (24.19)
Median	1.5	1.6	1.6
Q1, Q3	0.9, 12.1	0.9, 14.4	0.9, 14.0
Min, Max	0.3, 442.1	0.2, 190.2	0.2, 442.1
Disease Stage at Screening [b, d], n (%)			
Locally Recurrent Disease	0 (0.0)	1 (0.2)	1 (0.1)
Locally Advanced Disease	7 (1.4)	4 (0.8)	11 (1.1)
Metastatic Disease	494 (98.6)	490 (98.8)	984 (98.7)
Primary Location [d], n (%)			
Gastro-Esophageal Junction	96 (19.2)	100 (20.2)	196 (19.7)
Stomach	405 (80.8)	395 (79.6)	800 (80.2)
Number of Metastatic Sites at Study Entry, n (%) [e]			
0-2	335 (66.9)	335 (67.5)	670 (67.2)
≥ 3	166 (33.1)	160 (32.3)	326 (32.7)
Liver Metastases, n (%)			
Yes	190 (37.9)	188 (37.9)	378 (37.9)
No	311 (62.1)	308 (62.1)	619 (62.1)
Presence of Peritoneal Metastasis, n (%)			
Yes	220 (43.9)	214 (43.1)	434 (43.5)
No	281 (56.1)	282 (56.9)	563 (56.5)
Patients with Non-target Lesion Only, n (%)	30 (6.0)	17 (3.4)	47 (4.7)
Histologic Grade, n (%)			
Gx - Grade Cannot Be Assessed	106 (21.2)	119 (24.0)	225 (22.6)
G1 - Well Differentiated	13 (2.6)	23 (4.6)	36 (3.6)
G2 - Moderately Differentiated	101 (20.2)	97 (19.6)	198 (19.9)
G3 - Poorly Differentiated	279 (55.7)	255 (51.4)	534 (53.6)
Unknown	2 (0.4)	2 (0.4)	4 (0.4)
Histologic Type (Lauren Classification), n (%)			
Diffuse-Type	108 (21.6)	105 (21.2)	213 (21.4)
Intestinal-Type	84 (16.8)	88 (17.7)	172 (17.3)
Mixed Type	32 (6.4)	37 (7.5)	69 (6.9)
Unknown	277 (55.3)	266 (53.6)	543 (54.5)
PD-L1 Expression, n (%)			
PD-L1 Score < 5%	227 (45.3)	224 (45.2)	451 (45.2)
PD-L1 Score ≥ 5%	274 (54.7)	272 (54.8)	546 (54.8)
HER2 Status, n (%) [c f]			
Positive	0 (0.0)	1 (0.2)	1 (0.1)
Negative	500 (99.8)	493 (99.4)	993 (99.6)
Equivocal	0 (0.0)	1 (0.2)	1 (0.1)
MSI or MMR Status, n (%)			
MSI-H/dMMR	16 (3.2)	24 (4.8)	40 (4.0)
MSI-L/MSS/pMMR	448 (89.4)	439 (88.5)	887 (89.0)
Unknown	37 (7.4)	33 (6.7)	70 (7.0)
Genomically Stable Type, n (%)			
Yes	7 (1.4)	13 (2.6)	20 (2.0)
No	6 (1.2)	8 (1.6)	14 (1.4)
Not Done	488 (97.4)	475 (95.8)	963 (96.6)
Chromosomal Instability Type, n (%)			
Yes	4 (0.8)	2 (0.4)	6 (0.6)
No	9 (1.8)	9 (1.8)	18 (1.8)
Not Done	488 (97.4)	485 (97.8)	973 (97.6)

Parameter	Tislelizumab + Chemotherapy (N = 501)	Placebo + Chemotherapy (N = 496)	Total (N = 997)
EBV Status, n (%)			
Positive	6 (1.2)	4 (0.8)	10 (1.0)
Negative	54 (10.8)	51 (10.3)	105 (10.5)
Not Done	441 (88.0)	441 (88.9)	882 (88.5)

Percentages were based on N.
Abbreviation: EBV = Epstein-Barr virus; MSI-H = microsatellite instability-high; dMMR = mismatch repair deficient.
Patients who have non-target lesion only were eligible for enrollment in study 305 after Protocol Amendment V2 (03-Apr-2020).
[a] Study Entry date referred to randomization date in this study.
[b] Disease stage rating at screening was based on American Joint Committee on Cancer TNM Staging Classification for Carcinoma of the Stomach and for Carcinoma of the Esophagus and Esophagogastric Junction (8th ed., 2017).
[c] Cases with HER2 3+ overexpression by IHC or HER2 amplification by ISH/FISH (HER2/CEP17 ratio ≥ 2 or an average HER2 copy number ≥ 6.0 signals/cell) are considered positive.
[d] One patient in the placebo + chemotherapy arm did not report primary location and disease stage, as the diagnosis of this patient was updated from gastric adenocarcinoma to be pancreatic cancer after randomization.
[e] One patient in the placebo + chemotherapy arm had metastatic site removed by surgery before study entry.
[f] One patient in each arm had HER2 negative tumor per local lab, but the data was inadvertently removed from EDC.

Table 25: Table Summary of Demographics and Baseline Characteristics PD-L1 Positive Analysis Set

Parameter	Tislelizumab + Chemotherapy (N = 274)	Placebo + Chemotherapy (N = 272)	Total (N = 546)
Age (years)			
n	274	272	546
Mean (SD)	59.8 (10.79)	61.1 (9.87)	60.4 (10.35)
Median	61.0	62.0	62.0
Q1, Q3	54.0, 67.0	55.0, 68.0	54.0, 68.0
Min, Max	23.0, 83.0	30.0, 84.0	23.0, 84.0
< 65 years	175 (63.9)	157 (57.7)	332 (60.8)
>= 65 years	99 (36.1)	115 (42.3)	214 (39.2)
Gender, n (%)			
Female	81 (29.6)	71 (26.1)	152 (27.8)
Male	193 (70.4)	201 (73.9)	394 (72.2)
Race, n (%)			
Asian	202 (73.7)	201 (73.9)	403 (73.8)
Chinese	133 (48.5)	133 (48.9)	266 (48.7)
Japanese	38 (13.9)	35 (12.9)	73 (13.4)
Korean	31 (11.3)	33 (12.1)	64 (11.7)
White	64 (23.4)	62 (22.8)	126 (23.1)
Not Reported	7 (2.6)	8 (2.9)	15 (2.7)
Other	1 (0.4)	0 (0.0)	1 (0.2)
Unknown	0 (0.0)	1 (0.4)	1 (0.2)
Region, n (%)			
East Asia	202 (73.7)	201 (73.9)	403 (73.8)
China (including Taiwan)	133 (48.5)	132 (48.5)	265 (48.5)
Japan	38 (13.9)	35 (12.9)	73 (13.4)
South Korea	31 (11.3)	34 (12.5)	65 (11.9)
Rest of World	72 (26.3)	71 (26.1)	143 (26.2)
US	5 (1.8)	8 (2.9)	13 (2.4)
Europe	67 (24.5)	63 (23.2)	130 (23.8)
Ethnicity, n (%)			
Not Hispanic or Latino	268 (97.8)	264 (97.1)	532 (97.4)
Not Reported	6 (2.2)	8 (2.9)	14 (2.6)

Weight (kg)			
n	274	272	546
Mean (SD)	61.4 (12.84)	62.7 (13.42)	62.0 (13.14)
Median	60.0	61.8	61.0
Q1, Q3	52.2, 69.0	52.0, 71.0	52.0, 70.0
Min, Max	32.1, 112.0	35.5, 111.0	32.1, 112.0
BMI (kg/m^2)			
n	273	271	544
Mean (SD)	22.3 (3.89)	22.6 (3.73)	22.4 (3.81)
Median	21.9	22.4	22.0
Q1, Q3	19.8, 24.5	19.9, 24.8	19.9, 24.6
Min, Max	13.6, 38.7	13.8, 34.3	13.6, 38.7
ECOG Status, n (%)			
0	98 (35.8)	86 (31.6)	184 (33.7)
1	176 (64.2)	186 (68.4)	362 (66.3)
Smoking Status, n (%)			
Never	136 (49.6)	132 (48.5)	268 (49.1)
Former	97 (35.4)	108 (39.7)	205 (37.5)
Current	41 (15.0)	32 (11.8)	73 (13.4)
Alcohol Consumption, n (%)			
Never	170 (62.0)	147 (54.0)	317 (58.1)
Former	75 (27.4)	87 (32.0)	162 (29.7)
Current	29 (10.6)	38 (14.0)	67 (12.3)

Table 26: Table Disease History and Characteristics at Study Entry PD-L1 Positive Analysis Set

Description	Tislelizumab + Chemotherapy (N = 274)	Placebo + Chemotherapy (N = 272)	Total (N = 546)
Time From Initial Cancer Diagnosis to Study Entry (months) [a]			
n	274	272	546
Mean (SD)	8.7 (30.97)	8.0 (18.67)	8.3 (25.57)
Median	1.3	1.4	1.4
Q1, Q3	0.9, 2.6	0.9, 3.2	0.9, 2.8
Min, Max	0.3, 442.1	0.3, 190.2	0.3, 442.1
Disease Stage at Screening, n (%) [b]			
Locally Recurrent Disease	0 (0.0)	1 (0.4)	1 (0.2)
Locally Advanced Disease	4 (1.5)	3 (1.1)	7 (1.3)
Metastatic Disease	270 (98.5)	268 (98.5)	538 (98.5)
Primary Location, n (%)			
Gastro-Esophageal Junction	51 (18.6)	59 (21.7)	110 (20.1)
Stomach	223 (81.4)	213 (78.3)	436 (79.9)
Number of Metastatic Sites at Study Entry, n (%)			
0-2	183 (66.8)	180 (66.2)	363 (66.5)
>=3	91 (33.2)	92 (33.8)	183 (33.5)
Liver Metastases, n (%)			
Yes	121 (44.2)	117 (43.0)	238 (43.6)
No	153 (55.8)	155 (57.0)	308 (56.4)
Presence of Peritoneal Metastasis, n (%)			
Yes	110 (40.1)	107 (39.3)	217 (39.7)
No	164 (59.9)	165 (60.7)	329 (60.3)
Patients With Non-target Lesion Only, n (%)	13 (4.7)	6 (2.2)	19 (3.5)

Histologic Grade, n (%)			
Gx - Grade Cannot Be Assessed	68 (24.8)	66 (24.3)	134 (24.5)
G1 - Well Differentiated	6 (2.2)	11 (4.0)	17 (3.1)
G2 - Moderately Differentiated	55 (20.1)	53 (19.5)	108 (19.8)
G3 - Poorly Differentiated	144 (52.6)	141 (51.8)	285 (52.2)
Unknown	1 (0.4)	1 (0.4)	2 (0.4)
Histologic Type (Lauren Classification), n (%)			
Diffuse-Type	56 (20.4)	56 (20.6)	112 (20.5)
Intestinal-Type	47 (17.2)	51 (18.8)	98 (17.9)
Mixed Type	14 (5.1)	23 (8.5)	37 (6.8)
Unknown	157 (57.3)	142 (52.2)	299 (54.8)
HER2 Status, n (%)			
Negative	274 (100.0)	271 (99.6)	545 (99.8)
Equivocal	0 (0.0)	1 (0.4)	1 (0.2)
MSI or MMR Status, n (%)			
MSI-H/dMMR	11 (4.0)	14 (5.1)	25 (4.6)
MSI-L/MSS/pMMR	245 (89.4)	238 (87.5)	483 (88.5)
Unknown	18 (6.6)	20 (7.4)	38 (7.0)
Genomically Stable Type, n (%)			
Yes	4 (1.5)	9 (3.3)	13 (2.4)
No	2 (0.7)	3 (1.1)	5 (0.9)
Not Done	268 (97.8)	260 (95.6)	528 (96.7)
Chromosomal Instability Type, n (%)			
Yes	1 (0.4)	1 (0.4)	2 (0.4)
No	5 (1.8)	5 (1.8)	10 (1.8)
Not Done	268 (97.8)	266 (97.8)	534 (97.8)

Table 27: Prior Adjuvant/Neo-Adjuvant Anticancer Therapy - Study 305 (ITT Analysis Set)

Description	Tislelizumab + Chemotherapy (N = 501)	Placebo + Chemotherapy (N = 496)	Total (N = 997)
Patients With at Least One Prior Adjuvant/Neo-Adjuvant Systemic Therapy for Cancer, n (%)	**107 (21.4)**	**100 (20.2)**	**207 (20.8)**
Adjuvant	91 (18.2)	94 (19.0)	185 (18.6)
Neo-Adjuvant	33 (6.6)	15 (3.0)	48 (4.8)
Time from End of Last Adjuvant/Neo-Adjuvant Systemic Therapy to Study Entry (months) [a]			
n	107	99	206
Mean (SD)	28.9 (42.66)	24.9 (20.72)	27.0 (33.91)
Median	19.5	18.4	18.6
Q1, Q3	11.2, 30.1	12.9, 28.2	12.2, 28.2
Min, Max	6.0, 408.0	6.0, 134.2	6.0, 408.0
Prior Anticancer Radiotherapy, n (%)	**8 (1.6)**	**7 (1.4)**	**15 (1.5)**
Prior Anticancer Surgery, n (%)	**163 (32.5)**	**165 (33.3)**	**328 (32.9)**
Prior Gastrectomy/Esophagectomy	133 (26.5)	139 (28.0)	272 (27.3)

Numbers analysed

Table 28: Analysis Sets (ITT Analysis Set)

Analysis Set	Tislelizumab + Chemotherapy (N = 501) n (%)	Placebo + Chemotherapy (N = 496) n (%)	Total (N = 997) n (%)
Intent-to-Treat (ITT) Analysis Set [a]	501 (100.0)	496 (100.0)	997 (100.0)
PD-L1 Positive Analysis Set [b]	274 (54.7)	272 (54.8)	546 (54.8)
Safety Analysis Set [c]	498 (99.4)	494 (99.6)	992 (99.5)
PD-L1 Positive Safety Analysis Set [d]	272 (54.3)	272 (54.8)	544 (54.6)
PK Analysis Set [e]	496 (99.0)	NA	496 (49.7)
ADA Analysis Set [f]	470 (93.8)	NA	470 (47.1)

Percentages were based on number of patients randomized in the relevant treatment group.
[a] ITT analysis set includes all randomized patients. The ITT analysis set is grouped based on randomized treatment.
[b] PD-L1 positive analysis set includes all randomized patients with PD-L1 score ≥ 5%.
[c] Safety analysis set includes all patients who received at least one dose of study drugs. The safety analysis sets are based on actual treatment received.
[d] PD-L1 positive safety analysis set includes all patients in the safety analysis set whose PD-L1 score ≥ 5%.
[e] The PK analysis set includes all patients who received at least one dose of tislelizumab per the protocol, for whom any postdose PK data are available.
[f] The ADA analysis set includes all patients who received at least one dose of tislelizumab, have non-missing baseline ADA and at least one post-baseline ADA result.

Outcomes and estimation

The study met both of the primary endpoints (tested sequentially): OS in the PD-L1-positive analysis set (patients with PD-L1 score ≥ 5%) at the interim analysis (data cutoff date: 08-Oct-2021) and OS in the ITT analysis set at the final analysis (data cutoff date: 28-Feb-2023).

Primary endpoint OS

- **OS in the ITT (Final Analysis)**

Study 305 demonstrated a statistically significant improvement in OS with tislelizumab plus chemotherapy vs. placebo plus chemotherapy in the ITT analysis set: the stratified OS HR was 0.80 (95% CI: 0.70, 0.92) with a one-sided p-value of 0.0011 (prespecified boundary p=0.0226).

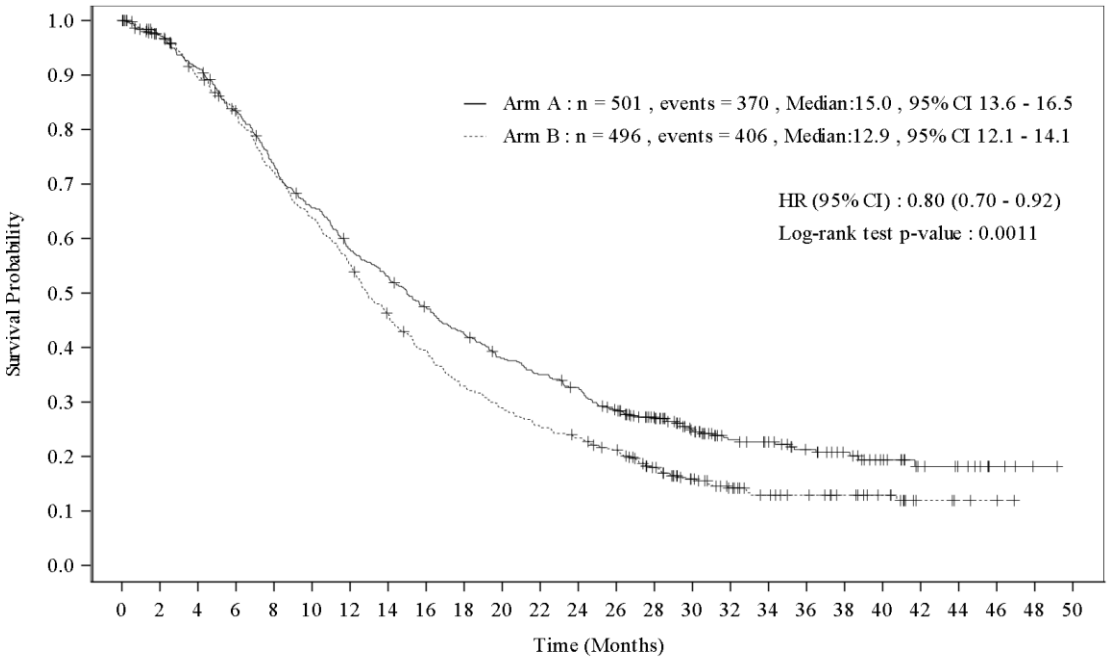
Table 29: Overall Survival - Prim. efficacy analysis for ITT analysis set (Final analysis)

	Tislelizumab + Chemotherapy (N = 501)	Placebo + Chemotherapy (N = 496)
Number of Patients		
Death, n (%)	370 (73.9)	406 (81.9)
Censored, n (%)	131 (26.1)	90 (18.1)
Ongoing Without Event	106 (21.2)	64 (12.9)
Lost to Follow-up	5 (1.0)	10 (2.0)
Withdrew Consent	20 (4.0)	16 (3.2)
One-Sided Stratified Log-Rank Test P-value [a]	0.0011	
Stratified Hazard Ratio (95% CI) [a]	**0.80** (0.70, 0.92)	
Unstratified Hazard Ratio (95% CI) [b]	0.80 (0.69, 0.92)	
Overall Survival (months) (95% CI)		
Median	**15.0** (13.6, 16.5)	**12.9** (12.1, 14.1)
Overall Survival Rate at, % (95% CI)		
18 months	42.4 (38.0, 46.8)	32.9 (28.7, 37.2)

	Tislelizumab + Chemotherapy (N = 501)	Placebo + Chemotherapy (N = 496)
24 months	32.7 (28.5, 36.9)	23.4 (19.7, 27.3)
36 months	21.3 (17.4, 25.5)	12.9 (9.8, 16.4)
Follow-up Time (months) (95% CI)		
Median	32.9 (30.5, 35.2)	32.5 (31.2, 35.0)

Abbreviation: CI = confidence interval; NE = not estimable.
Percentages were based on N.
Medians and other quartiles were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley.
Overall survival rates 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] Primary OS analysis: Stratified by regions (East Asia versus ROW [rest of the world]), PD-L1 expression and presence of peritoneal metastasis.
[b] Unstratified OS sensitivity analysis: Hazard ratio was estimated from Cox model with Arm B (placebo + chemotherapy) as the reference group.

Figure 19: KM Plot of Overall Survival- Study 305 (ITT Analysis Set)



Number of Patients at Risk:

Time:	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50
Arm A	501	477	445	404	355	316	278	254	226	202	179	165	152	130	107	77	59	53	43	31	22	13	10	4	1	0
Arm B	496	472	431	398	344	304	264	218	186	155	136	119	109	96	73	52	39	29	25	20	15	6	3	2	0	0

Sensitivity and supplementary analyses of OS

Table 30: Overview of Sensitivity and Supplementary Analyses for OS – Study 305 (ITT Analysis Set)

Analysis	Summary statistics
Primary analysis (ITT analysis set)	***HR=0.80 (95% CI: 0.70, 0.92)***
Sensitivity analyses	
1. Unstratified OS analysis [a]	HR=0.80 (95% CI: 0.69, 0.92)
2. OS analysis with stratification factors from the eCRF [b]	HR=0.80 (95% CI: 0.69, 0.92)
Supplementary analyses	
1. OS analysis based on Max-Combo method [c]	HR=0.75 (95% CI: 0.62, 0.90)
2. OS analysis accounting for possible non-proportional HR effect based on restricted mean survival time (RMST) method [d]	2.94-month difference in OS RMST (95% CI: 1.07, 4.80)
3. OS analysis adjusted for baseline covariates [e]	HR=0.81 (95% CI: 0.70, 0.93)
4. COVID-19 supplementary analysis [b]	HR=0.81 (95% CI: 0.70, 0.93)

[a] Unstratified OS sensitivity analysis: Hazard ratio was estimated from Cox model

[b] Stratified by regions (East Asia vs. ROW), PD-L1 expression and presence of peritoneal metastasis; HR was estimated from stratified Cox model

[c] A class of WLR tests with weights of FH (0, 0), FH (0, 1), FH (1, 0), and FH (1, 1) were selected for the Max-Combo test. Largest of the absolute value the test statistics was selected while multiplicity was considered using joint asymptotic distribution. FH: Fleming-Harrington

[d] Difference in RMST is calculated as difference of area under the curve from baseline to the minimum of the largest observed time on each of the two treatment groups.

[e] HR was based on stratified Cox regression model including treatment, ECOG PS, liver metastasis, number of metastatic organs (0-2 vs. ≥ 3), prior gastrectomy/esophagectomy (yes vs. no) as covariates, and stratified by region (East Asia vs. ROW) PD-L1 expression and presence of peritoneal metastasis

- **OS in the PD-L1-Positive Analysis Set (PD-L1 ≥5%) at IA**

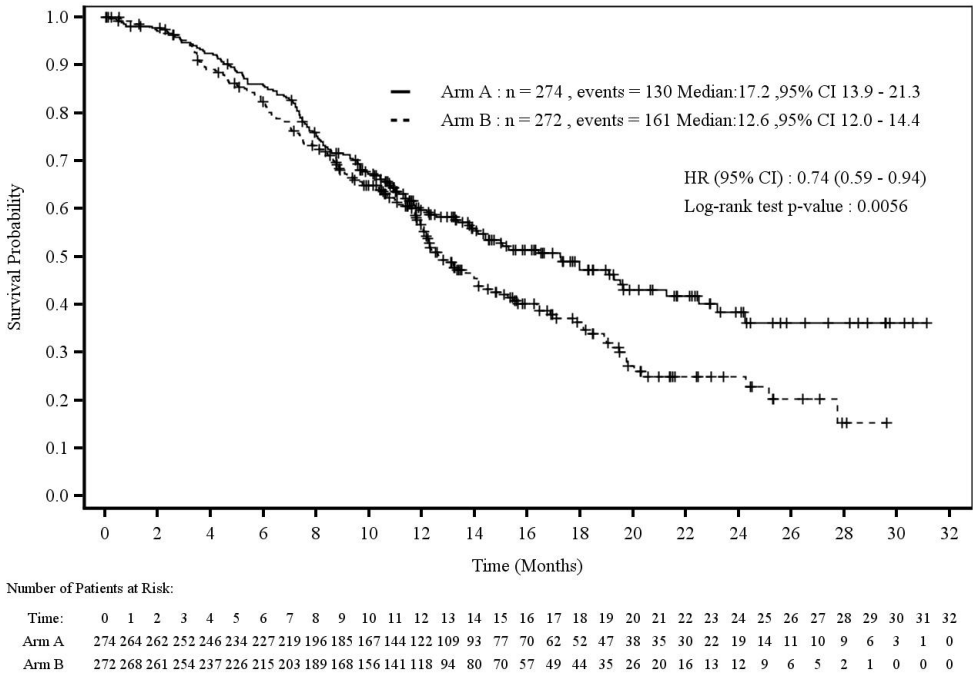
Study 305 demonstrated a statistically significant improvement in OS with tislelizumab plus chemotherapy vs. placebo plus chemotherapy in the PD-L1-Positive Analysis Set (PD-L1 ≥5%) at the interim analysis: the stratified OS HR was 0.74 (95% CI: 0.59, 0.94) with a one-sided p-value of 0.0056 (IA OS boundary of 0.0092).

Table 31: OS in PD-1 positive analysis set at interim analysis

	Primary efficacy analysis for PD-L1-positive analysis set Interim analysis DCO: 08-Oct-2021	
	Tislelizumab + Chemotherapy (N=274)	**Placebo + Chemotherapy (N=272)**
Primary Endpoint		
	Overall Survival (OS)	
Deaths, n (%)	130 (47.4)	161 (59.2)
Median (months) (95% CI)	**17.2** (13.9, 21.3)	**12.6** (12.0, 14.4)
One-Sided Stratified Log-Rank Test[a]	p = 0.0056	
Stratified HR (95% CI) [a]	**0.74** (0.59, 0.94)	

[a] Stratified by region (East Asia vs. ROW) and presence of peritoneal metastasis, and for the ITT analysis by PD-L1 expression (< 5%, ≥ 5%).

Figure 20: KM Plot of Overall Survival (PD-L1-Positive Analysis Set): Interim Analysis



The updated **OS analysis** in the **PD-L1-positive** analysis set based on the **final analysis** showed consistent results:

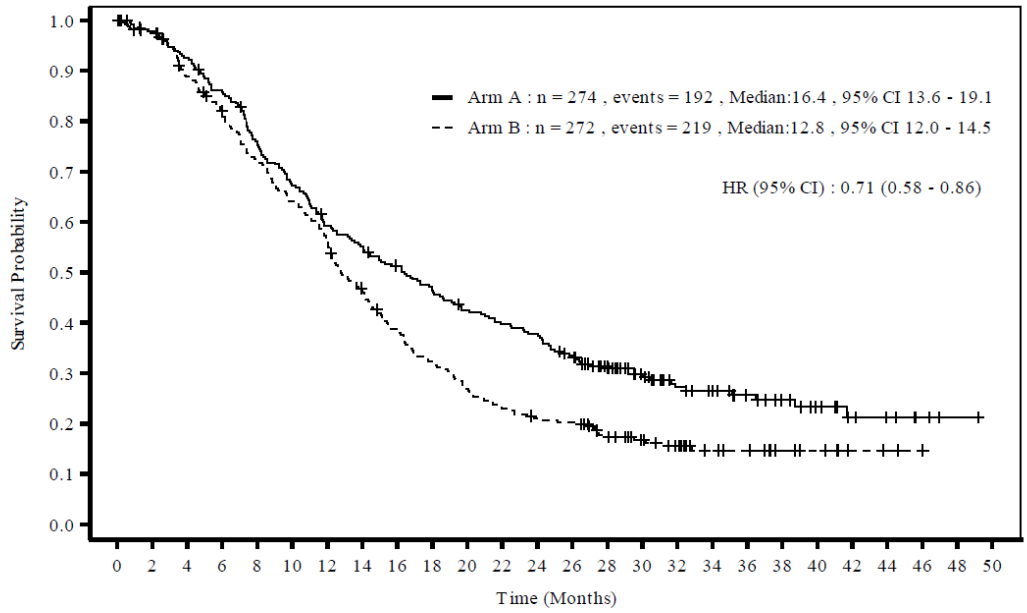
Table 32: *OS in PD-1 positive analysis set at final analysis* (Data cutoff 28 Feb 2023)

	Tislelizumab + chemotherapy (N = 274)	**Placebo + chemotherapy (N = 272)**
	Patients with PD-L1 score ≥ 5%	
Median study follow-up (months)[a]	32.5	32.2
Number of Patients		
Death, n (%)	192 (70.1)	219 (80.5)
Censored, n(%)	82 (29.9)	53 (19.5)
Ongoing Without Event	69 (25.2)	39 (14.3)
Lost to Follow-up	2 (0.7)	5 (1.8)
Withdrew Consent	11 (4.0)	9 (3.3)
OS Median[b] (months) (95% CI)	16.4 (13.6, 19.1)	12.8 (12.0, 14.5)
Hazard ratio[c] (95% CI)	0.71 (0.58, 0.86)	
p-value[c,d]	0.0003[e]	

OS = overall survival; CI = confidence interval; PFS = progression-free survival; ORR = objective response rate.

[a] Median follow-up time was estimated by the reverse Kaplan-Meier method.
[b] Medians were estimated using Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley.
[c] Stratified by regions (east Asia versus US, Europe) and peritoneal metastasis.
[d] One-sided p-value from stratified log-rank test.
[e] Nominal p-value.

Figure 21: KM Plot of Overall Survival (PD-L1 Positive Analysis Set): final analysis



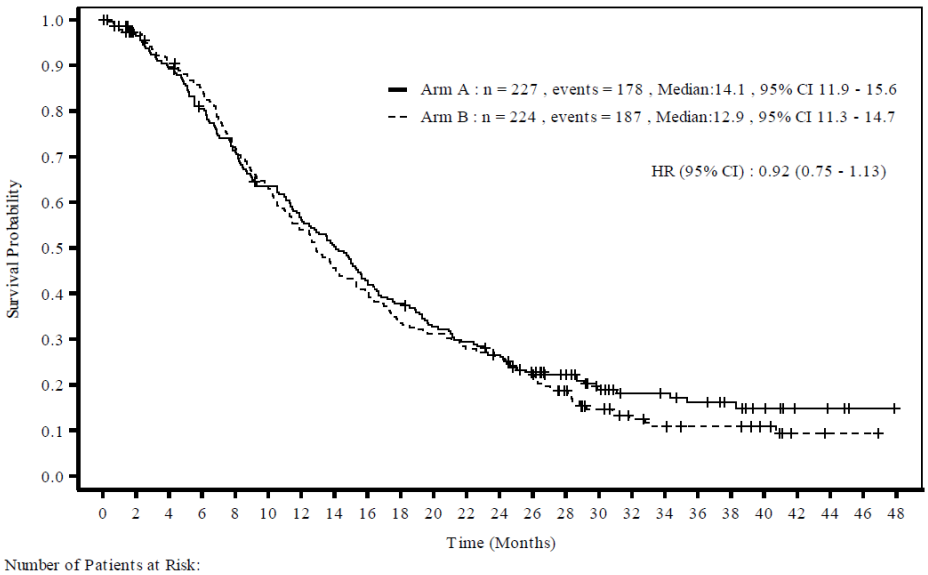
Number of Patients at Risk:

Time:	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50
Arm A	274	263	247	228	199	178	156	145	133	120	109	102	97	84	68	50	38	34	27	19	14	9	7	3	1	0
Arm B	272	261	236	215	190	168	148	120	99	83	69	59	53	51	39	29	23	16	14	9	7	3	2	1	0	0

<u>OS results for patients with **PD-L1 score <5%** at the **final analysis**</u>:

The stratified HR was 0.92 (95% CI: 0.75, 1.13), the median OS was 14.1 months (95% CI: 11.9, 15.6) with tislelizumab plus chemotherapy vs. 12.9 months (95% CI 11.3, 14.7) with placebo plus chemotherapy.

Figure 22: KM Plot for OS for Patients With PD-L1 Score < 5%: final analysis



Number of Patients at Risk:

Time:	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48
Arm A	227	214	198	176	156	138	122	109	93	82	70	63	55	46	39	27	21	19	16	12	8	4	3	1	0
Arm B	224	211	195	183	154	136	116	98	87	72	67	60	56	45	34	23	16	13	11	11	8	3	1	1	0

Secondary endpoints

The primary endpoint OS was met in the ITT analysis at the final analysis, meaning that the sequential formal testing could be then applied to the four predefined secondary endpoints of PFS and ORR in the PD-L1 ≥5% and ITT Analysis Sets. As predefined in SAP, hypothesis testing of the secondary endpoints was planned to be performed using the interim analysis data. The formal testing was conducted in a sequential order of PFS then ORR in the PD L1 positive analysis set followed by PFS then ORR in the ITT analysis, up until the first non-significant endpoint. Since the result for PFS in the PD-L1-positive analysis set was statistically significant but not for ORR at the interim analysis, no further testing was conducted for PFS and ORR in ITT population, and thus the p-values from comparison tests of PFS and ORR in the ITT analysis set are nominal.

Table 33: PFS and ORR in PD-L1-positive analysis set at Interim analysis (excerpt from SCE Table 3)

	Primary efficacy analysis for **PD-L1-positive analysis set (PD-L1 ≥ 5%)** Interim analysis DCO: 08-Oct-2021	
	Tislelizumab + Chemotherapy (N=274)	**Placebo + Chemotherapy (N=272)**
Progression-free survival (PFS)		
Events, n (%)	169 (61.7)	206 (75.7)
Median (months) (95% CI)	**7.2** (5.8, 8.4)	**5.9** (5.6, 7.0)
One-Sided Stratified Log-Rank Test P-value	p<0.0001	
Stratified HR (95% CI) [a]	**0.67** (0.55, 0.83)	
Objective Response Rate (ORR) [b]		
n (%)	138 (**50.4**)	117 (**43.0**)
95% CI [c]	44.3, 56.4	37.1, 49.1
Odds Ratio for ORR (95% CI) [d]	1.36 (0.97, 1.92)	
ORR Diff., % (95% CI) [d]	7.4 (-0.8, 15.6)	
CMH test p-value [e]	0.0764	

[a] Stratified by region (East Asia vs. ROW) and presence of peritoneal metastasis, and for the ITT analysis by PD-L1 expression ((< 5%, ≥ 5%).

[b] ORR is defined as proportion of patients with a confirmed PR or CR per RECIST v1.1.

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

[d] ORR, objective response rate differences and odds ratio between arms calculated using the Cochran-Mantel-Haenszel (CMH) method, stratified by region (East Asia vs. ROW) and presence of peritoneal metastasis

[e] Two-sided CMH test is stratified by regions (East Asia versus ROW), presence of peritoneal metastasis, and for the ITT analysis by PD-L1 expression (< 5%, ≥ 5%)

The results of all efficacy endpoints for the PD-L1-positive analysis set with longer follow-up (based on the final analysis after an additional 17 months follow-up) are consistent with those observed at the interim analysis, please see PD-L1-subgroup analyses below ancillary analyses.

In the following **results of secondary endpoints in the ITT Analysis Set at the final analysis** are presented:

- **PFS**

Table 34: Progression-Free Survival – Study 305 (ITT Analysis Set; final analysis)

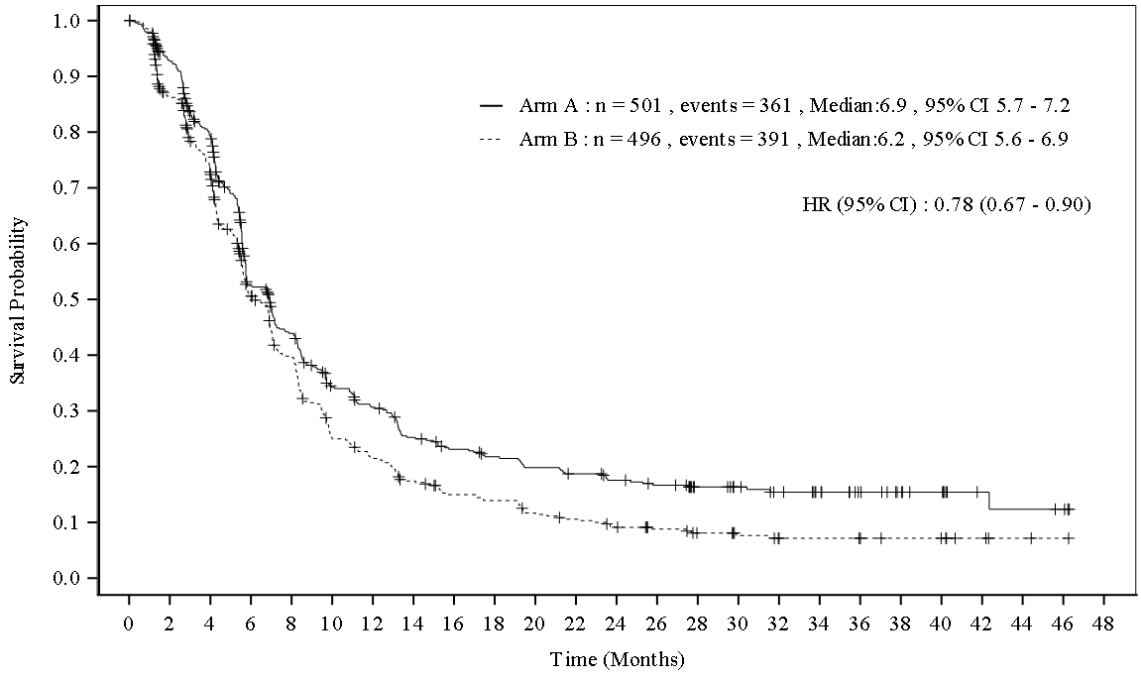
	Tislelizumab + Chemotherapy (N = 501)	**Placebo + Chemotherapy (N = 496)**
Progression Free Survival		
Events, n (%)	361 (72.1)	391 (78.8)
Progressive Disease	311 (62.1)	354 (71.4)
Death	50 (10.0)	37 (7.5)
Censored, n (%)	140 (27.9)	105 (21.2)
No Post-Baseline	15 (3.0)	18 (3.6)
New Anticancer Therapy	38 (7.6)	31 (6.3)
Progressive Disease/Death After > 1 Missed Assessment	22 (4.4)	26 (5.2)
Lost to Follow-up	0 (0.0)	2 (0.4)
Withdrew Consent	5 (1.0)	3 (0.6)
Ongoing Without Event	60 (12.0)	25 (5.0)
Stratified **Hazard Ratio** (95% CI) [a]	**0.78** (0.67, 0.90)	
Unstratified Hazard Ratio (95% CI) [b]	0.78 (0.68, 0.90)	
Progression Free Survival (months) (95% CI)		
Median	**6.9** (5.7, 7.2)	**6.2** (5.6, 6.9)
Progression Free Survival Rate at, % (95% CI)		
12 months	30.7 (26.4, 35.1)	21.5 (17.6, 25.5)
24 months	17.6 (14.0, 21.5)	9.1 (6.5, 12.3)

Medians and other quartiles were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley.
Progression free survival rates were estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula.
[a] Stratified by regions (East Asia versus ROW [rest of the world]), PD-L1 expression and presence of peritoneal metastasis.
[b] Unstratified hazard ratio was estimated from Cox model with Arm B (placebo + chemotherapy) as the reference group.

Sensitivity and supplementary analyses of PFS

- Sensitivity analysis (includes any tumor assessments or deaths after more than one missing visit when deriving PFS): stratified **HR=0.77** (95% CI: 0.67, 0.88), median PFS 6.9 vs 6.3 months
- Supplementary analysis (PFS based on reported data irrespective of the start of a new anticancer therapy): stratified **HR=0.78** (95% CI: 0.68, 0.90), median PFS 6.9 vs 6.1 months

Figure 23: Kaplan-Meier Plot of Progression-Free Survival – Study 305 (ITT Analysis Set; FA)



Number of Patients at Risk:

Time:	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48
Arm A	501	434	361	226	184	136	120	97	86	79	72	67	60	55	41	37	32	27	21	16	12	5	4	3	0
Arm B	496	399	327	211	161	100	85	67	55	51	42	37	31	26	21	16	13	11	10	8	7	4	2	1	0

Arm A = Tislelizumab + Chemotherapy, Arm B = Placebo + Chemotherapy
Cox regression model was stratified by region (East Asia versus ROW), PD-L1 expression and presence of peritoneal metastasis.
'+' = censored.

- **ORR, DCR, CBR, DOR, TTR**

Figure 24: Best overall response, ORR, disease control rate and clinical benefit rate (ITT, FA)

Response Category	Tislelizumab + Chemotherapy (N = 501)		Placebo + Chemotherapy (N = 496)
Best Overall Response (BOR), n (%)			
Complete Response (CR)	19 (3.8)		19 (3.8)
Partial Response (PR)	218 (43.5)		182 (36.7)
Stable Disease (SD)	185 (36.9)		197 (39.7)
Non-CR/Non-PD	28 (5.6)		15 (3.0)
Progressive Disease (PD)	23 (4.6)		55 (11.1)
Not Evaluable [a]	0 (0.0)		2 (0.4)
Not Assessable [b]	28 (5.6)		26 (5.2)
Objective Response Rate (ORR), n (%)	237 (**47.3**)		201 (**40.5**)
95% CI [c]	(42.9, 51.8)		(36.2, 45.0)
Odds Ratio for ORR, (95% CI) [d]		1.33 (1.03, 1.72)	
ORR Difference, % (95% CI) [d]		6.8 (0.8, 12.9)	
Disease Control Rate (DCR), n (%)	450 (**89.8**)		413 (**83.3**)
95% CI [b]	(86.8, 92.3)		(79.7, 86.4)
Clinical Benefit Rate (CBR) [e], n (%)	316 (**63.1**)		292 (**58.9**)
95% CI [b]	(58.7, 67.3)		(54.4, 63.2)

Response Category	Tislelizumab + Chemotherapy (N = 501)	Placebo + Chemotherapy (N = 496)

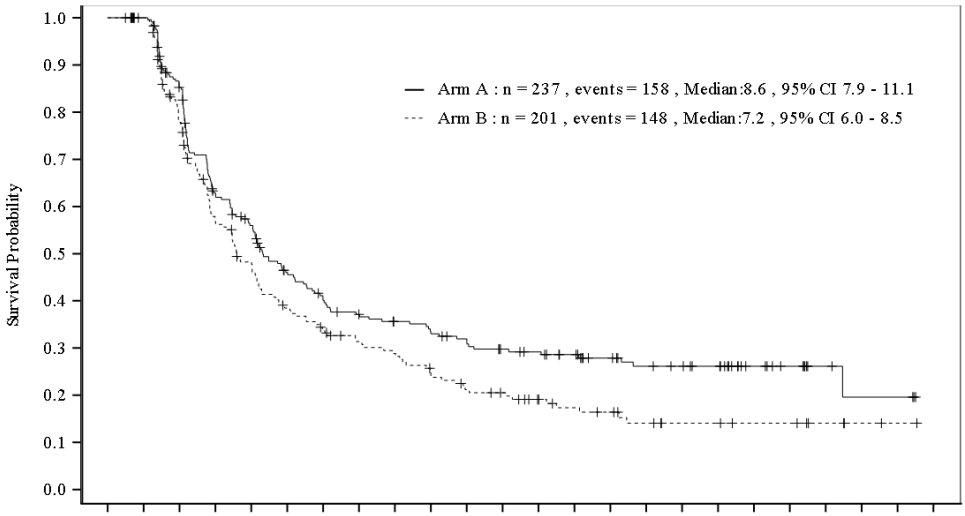
Abbreviation: CI = confidence interval, ORR = CR+PR, DCR = CR+PR+SD (Non-CR/Non-PD), CBR = CR+PR+durable SD (Non-CR/Non-PD).
The percentages of BOR, ORR, DCR and CBR were based on all randomized patients, the percentages of patients with ongoing response were based on responders.
ORR is defined as proportion of number of patients with a **confirmed** PR or CR per RECIST v1.1.
[a] Patients who had ≥ 1 post-baseline tumor assessment, none of which were evaluable for response determination (e.g., not all target lesions captured). Not evaluable is based on RECIST 1.1.
[b] Patients with no post-baseline tumor assessment by the data cutoff, including those who discontinued study (any reason) or died without having any post-baseline tumor assessment.
[c] Exact Clopper-Pearson 2-sided confidence interval.
[d] Objective response rate, objective response rate differences and odds ratios between arms were calculated using the Cochran-Mantel-Haenszel method, stratified by regions (East Asia versus ROW [rest of the world]), PD-L1 expression and presence of peritoneal metastasis.
[e] Clinical benefit rate (CBR) is defined as the proportion of patients who have CR, PR or SD including non-CR/non-PD of ≥ 24 weeks in duration.

Table 35: Duration of Response- Study 305 (ITT Analysis Set; FA)

	Tislelizumab + Chemotherapy (N = 501)	Placebo + Chemotherapy (N = 496)
Number of Responders	**237**	**201**
Duration of Response		
Events, n (%)	158 (66.7)	148 (73.6)
Progressive Disease	146 (61.6)	139 (69.2)
Death	12 (5.1)	9 (4.5)
Censored, n (%)	79 (33.3)	53 (26.4)
New Anticancer Therapy	17 (7.2)	19 (9.5)
Progressive Disease/Death After > 1 Missed Assessment	7 (3.0)	11 (5.5)
Lost to Follow-up	0 (0.0)	1 (0.5)
Withdrew Consent	2 (0.8)	0 (0.0)
Ongoing Without Event	53 (22.4)	22 (10.9)
Duration of Response (Confirmed Responders) (months) (95% CI)		
Median	**8.6** (7.9, 11.1)	**7.2** (6.0, 8.5)

Duration of response analysis included patients with confirmed CR or PR.
Medians and other quartiles were estimated by Kaplan-Meier methodology with 95% CIs estimated using the method of Brookmeyer and Crowley.
Duration of response rates (cumulative probabilities of DOR) were estimated by Kaplan-Meier methodology with 95% CIs estimated using Greenwood's formula.

Figure 25: Kaplan-Meier Plot of Duration of Response – Study 305 (ITT Analysis Set; FA)



Number of Patients at Risk:

Time:	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46
Arm A	237	234	192	138	120	94	81	73	68	64	59	52	49	44	35	30	28	24	14	10	5	3	3	0
Arm B	201	193	146	101	84	66	57	50	46	39	32	29	23	19	17	12	9	9	7	7	4	2	1	0

Arm A = Tislelizumab + Chemotherapy, Arm B = Placebo + Chemotherapy
Only patients who have achieved a confirmed completed or partial response will be included.
'+' = censored.

Time to response: In the ITT analysis set, the median time to response was the same in both arms: 1.4 months (range: 0.9 to 13.4) in Arm T+PtF vs. 1.4 months (range: 1.0 to 17.5) in Arm P+PtF.

- **Health-Related Quality of Life**

Health-Related Quality of Life was assessed in the ITT Analysis Set based on descriptive analyses using EORTC QLQ-C30, the gastric cancer specific stomach module EORTC QLQ STO22, and EQ-5D-5L questionnaires. Completion rates for all 3 questionnaires were similar for both arms at baseline, Cycle 4, and Cycle 6, with adjusted completion rates all above 91% at Cycle 4 and all above 96% at Cycle 6.

Examples of key PRO endpoints are presented below:

Note: Increases in GHS/QoL, physical functioning or EQ-5D-5L scores are improvements.
Increases in scores for symptoms (e.g. fatigue) are deteriorations for EORTC QLQ-C30. Likewise, increases in scores for index score, dysphagia/odynophagia, pain/discomfort, upper gastro-intestinal symptoms, and dietary restrictions are deteriorations for EORTC QLQ-STO22.

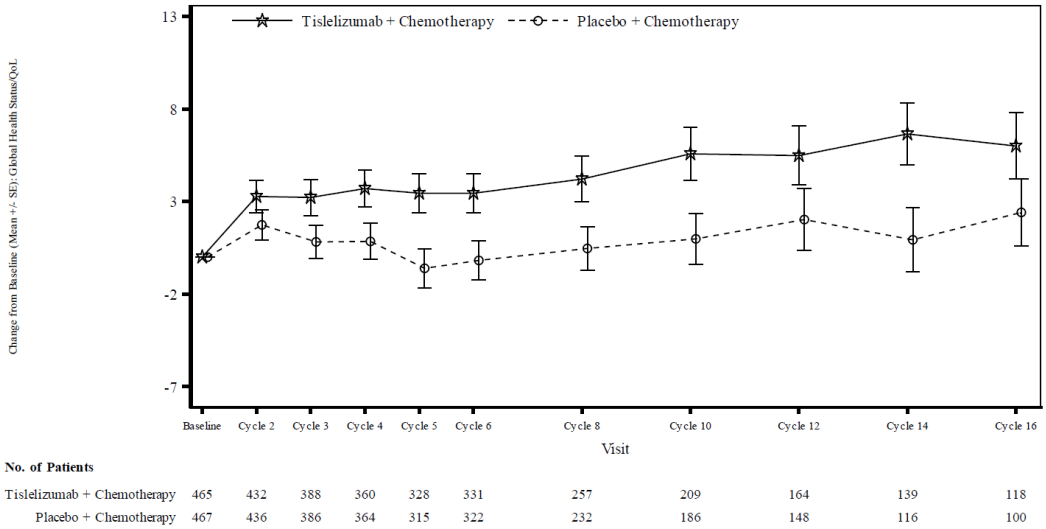
Score Change from Baseline to Cycle 4 and Cycle 6

Table 36: Summary of the mean changes in scores from baseline to Cycle 6 (assessor's table):

Questionnaire/ Parameter - Mean change (standard deviation)	**Tislelizumab + Chemotherapy**	**Placebo + Chemotherapy**
EORTC QLQ-C30		
GHS/QoL	3.4 (19.34)	-0.2 (18.70)
Physical functioning	-0.9 (14.08)	-3.4 (13.48)
Fatigue	-1.0 (21.99)	2.6 (19.32)

EORTC QLQ-STO22		
General gastric cancer symptoms (index score)	-3.0 (11.58)	-1.2 (10.78)
Dysphagia/odynophagia	-3.7 (14.35)	-3.2 (13.37)
Pain/discomfort	-7.9 (19.51)	-4.9 (18.41)
Upper gastrointestinal symptoms	-3.9 (15.58)	-2.8 (16.13)
Dietary restrictions	-2.0 (16.76)	-0.5 (15.81)
EQ-5D-5L		
VAS score	3.0 (16.38)	-0.8 (15.17)

Figure 26: Summary of EORTC QLQ-C30 Scores by Visit ITT Analysis Set – GHS/QoL



LS Mean Change from Baseline

Figure 27: Bar Plot of LS Mean Change from Baseline in EORTC QLQ-C30 Scores (GHS/QoL, physical functioning and fatigue) – Cycle 6 (ITT)

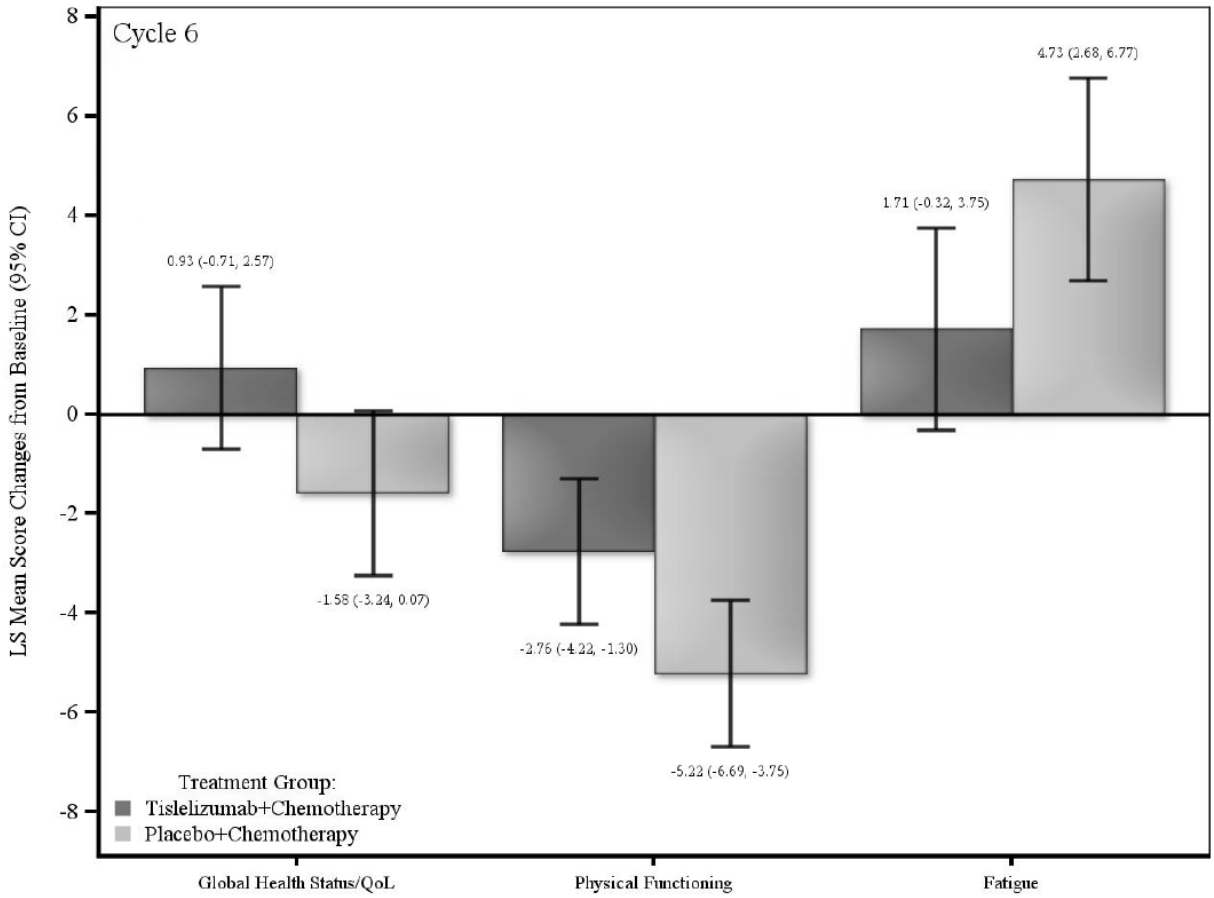
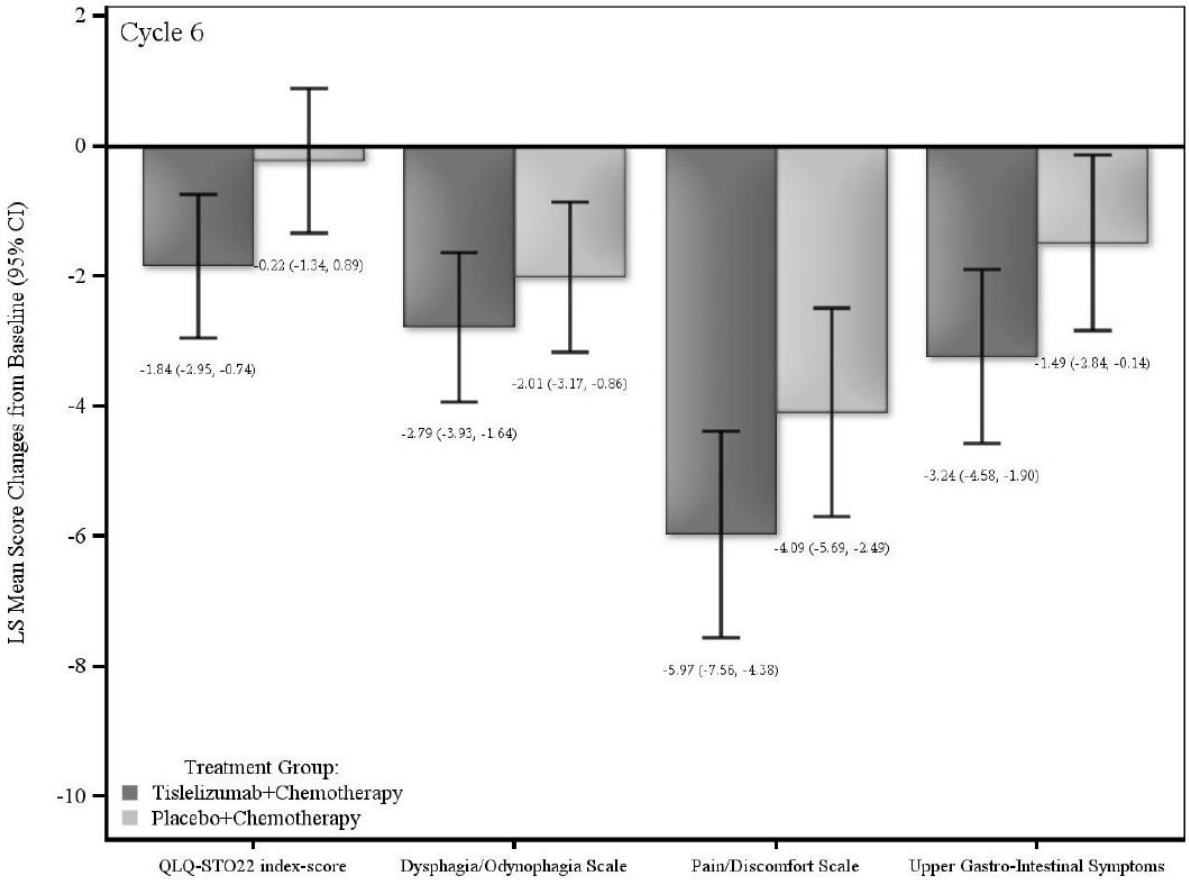


Figure 28: Bar Plot of LS Mean Change from Baseline in EORTC QLQ-STO22 Scores (index score, dysphagia, pain/discomfort, upper GI symptoms) – Cycle 6 (ITT)

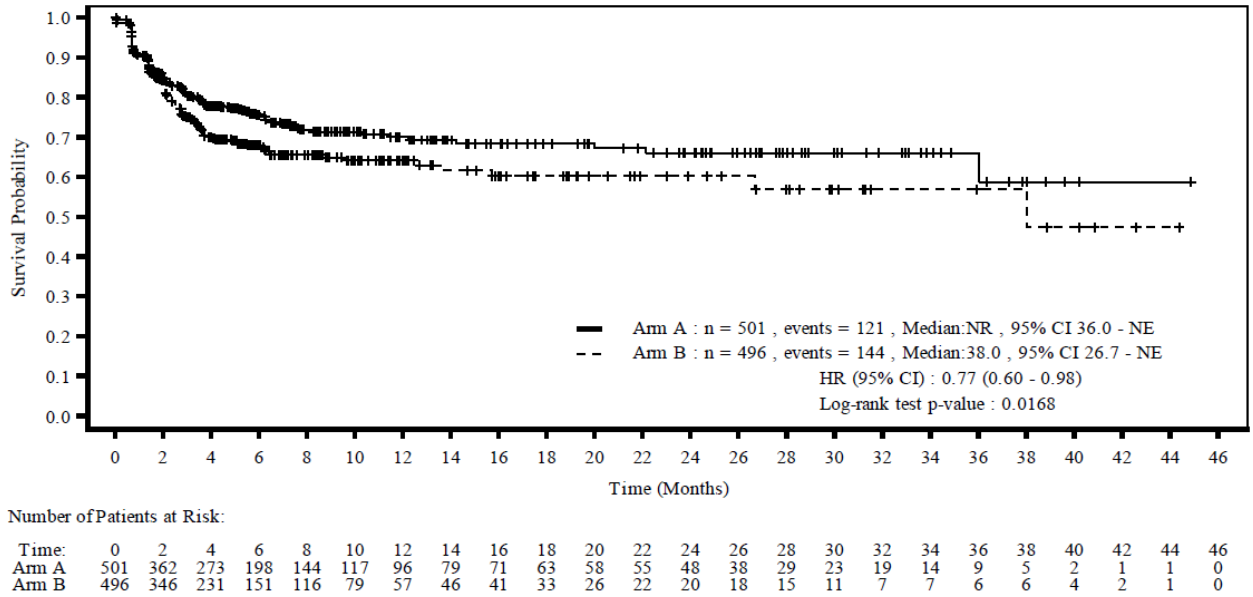


Time to Deterioration

A deterioration event was defined as a ≥ 10-point reduction in mean from baseline in GHS/QoL or physical functioning scale scores, and a ≥ 10-point increase in the symptom scales scores.

The analysis results for the time to deterioration (TTD), indicated by a stratified HR (95% CI), showed that tislelizumab plus chemotherapy treatment was associated with a lower risk for deterioration events in GHS/QoL (0.77 [95% CI: 0.60 to 0.98]), physical functioning (0.72 [95% CI: 0.57 to 0.92]), general gastric cancer symptoms (0.64 [95% CI: 0.45 to 0.92]), pain/discomfort (HR: 0.74 [95% CI: 0.58 to 0.96]) and upper gastrointestinal symptoms (0.73 [95% CI: 0.56 to 0.95]). There were no differences between the arms in risk of deterioration for fatigue (HR=0.83, 95% CI: 0.68, 1.01), dysphagia/odynophagia (HR=0.81; 95% CI:0.54, 1.19), or dietary restrictions (HR=0.96; 95%CI: 0.73, 1.27).

Figure 29: KM Plot of Time to Deterioration of Global Health Status / QoL - EORTC QLQ-C30 (ITT)



Number of Patients at Risk:

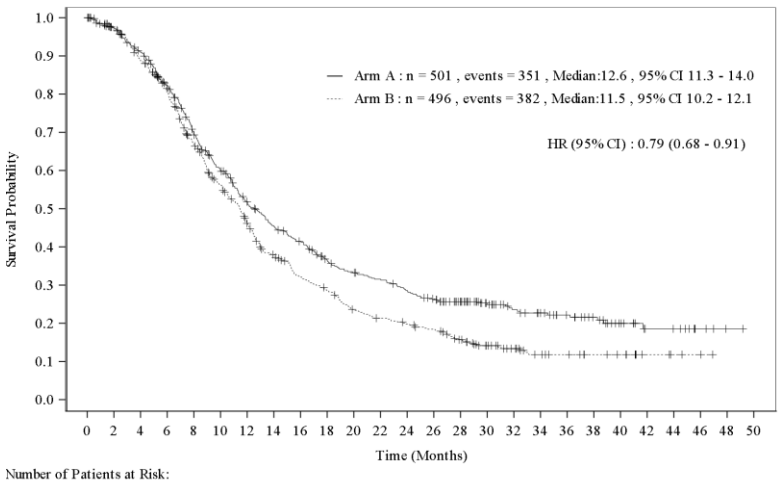
Time:	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46
Arm A	501	362	273	198	144	117	96	79	71	63	58	55	48	38	29	23	19	14	9	5	2	1	1	0
Arm B	496	346	231	151	116	79	57	46	41	33	26	22	20	18	15	11	7	7	6	6	4	2	1	0

Arm A = Tislelizumab + Chemotherapy, Arm B = Placebo + Chemotherapy
Both log-rank and Cox regression model were stratified by regions (east Asia versus ROW [rest of the world]), PD-L1 expression and presence of peritoneal metastasis. The p-value is one sided and is based on the stratified log-rank test.

- **PFS2 (exploratory endpoint)**

Treatment with tislelizumab plus chemotherapy prolonged the time to disease progression or death after next line of treatment compared to placebo plus chemotherapy. As of the data cutoff date, 351 patients (70.1%) in the T+C arm and 382 patients (77.0%) in the P+C arm experienced a PFS2 event. The stratified HR was 0.79 (95% CI: 0.68, 0.91). Median PFS2 was 12.6 (95% CI: 11.3, 14.0) and 11.5 (95% CI: 10.2, 12.1) months in the T+C arm and P+C arm, respectively.

Figure 30: KM Plot of PFS After Next-Line of Treatment (PFS2) - Study 305 (ITT Analysis Set; FA)



Number of Patients at Risk:

Time:	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50
Arm A	501	477	440	391	325	276	232	201	181	154	139	130	117	105	87	65	53	46	38	28	19	11	10	4	1	0
Arm B	496	471	427	380	305	250	200	159	131	115	93	83	76	69	54	40	31	21	18	14	12	6	3	2	0	0

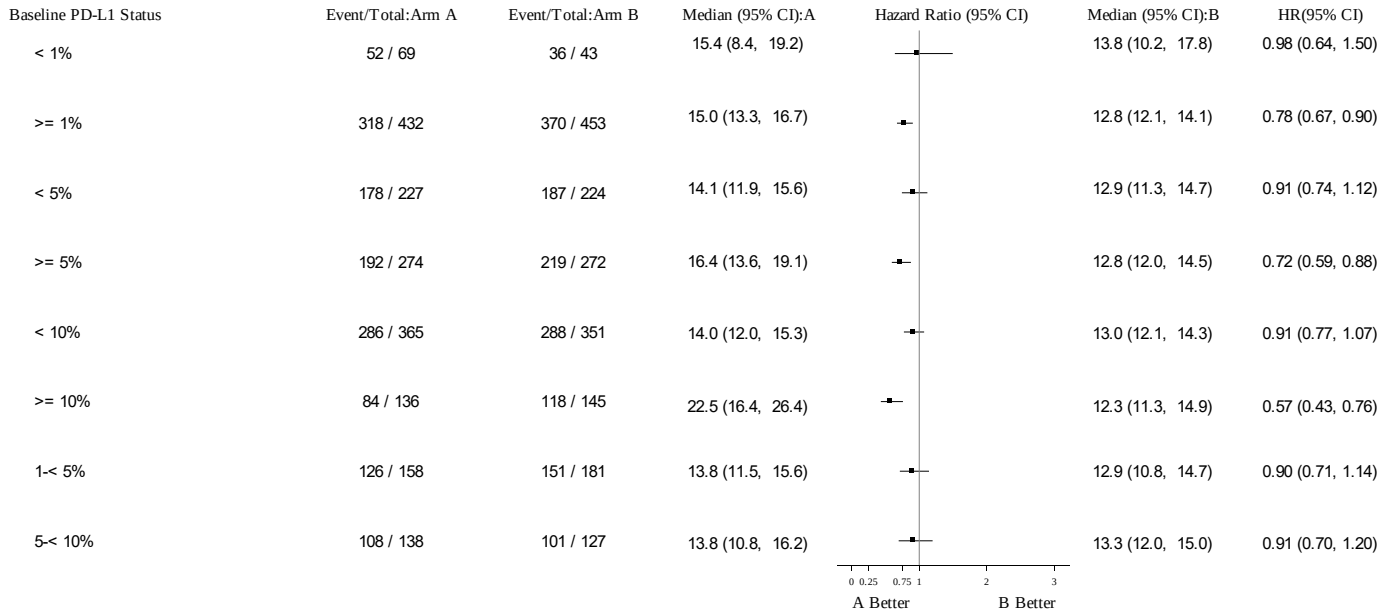
Ancillary analyses

- **PD-L1-subgroup analyses (including additional cutoffs)**

In order to better understand the role of PD-L1 expression, in addition to the protocol-defined 5%, two further cutoff values of baseline PD-L1 score were explored post-hoc: <1%/≥1% and <10%/≥10% (and ranges of 1%-< 5%, 5%- < 10%) for the efficacy endpoints of OS, PFS, and ORR at the final analysis.

Overall Survival

Figure 31: Forest Plot of Overall Survival - PD-L1 Expression Subgroup Analysis

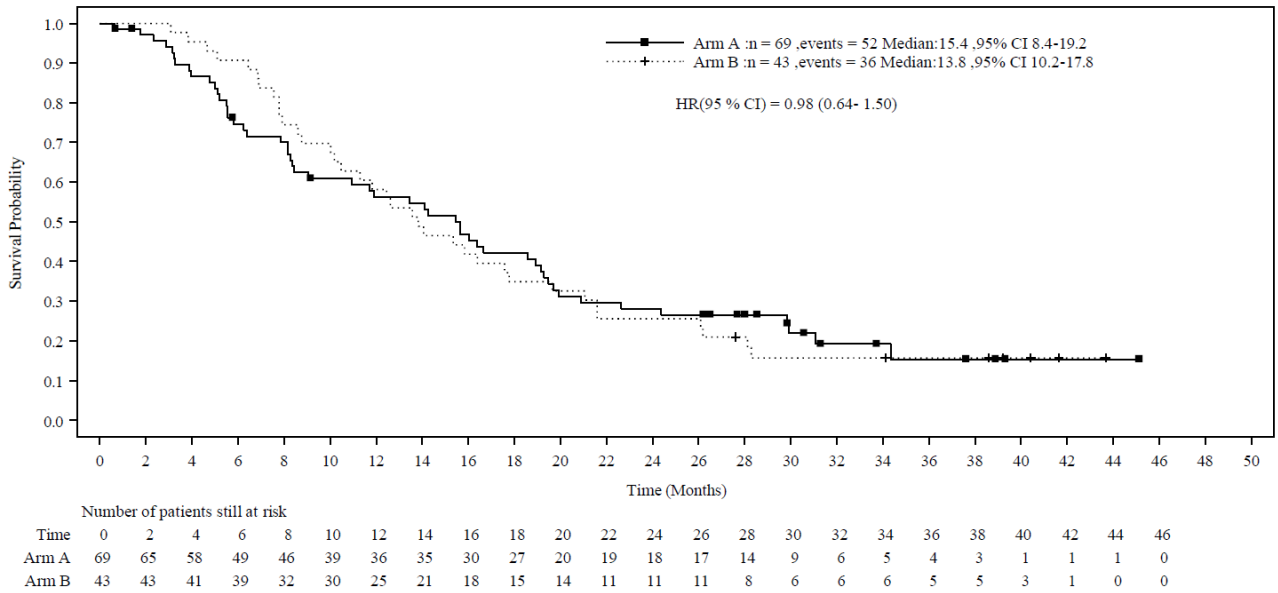


Data cutoff: 28FEB2023. Arm A = Tislelizumab + Chemotherapy, Arm B = Placebo + Chemotherapy
Medians were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley method using log-log transformation.
Hazard ratio and its 95% CI were estimated from unstratified Cox regression model including treatment as covariate.

OS KM curves

PD-L1 1% cutoff

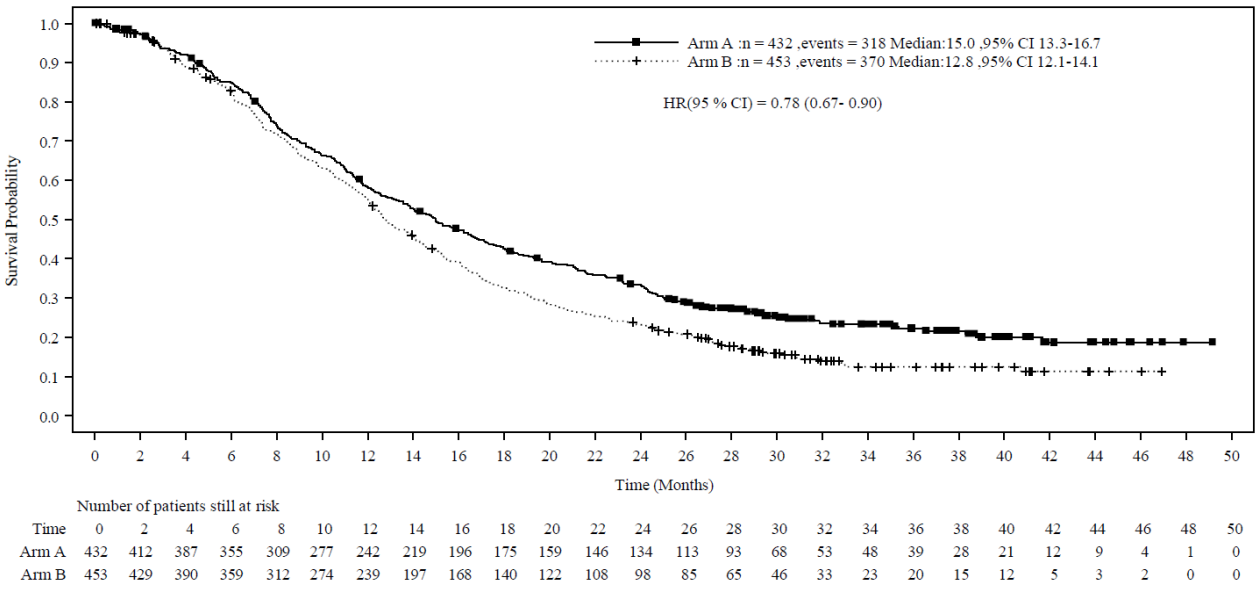
Figure 32: KM Plot of Overall Survival for Patients With PD-L1 Score < 1% (FA)



Number of patients still at risk

Time	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46
Arm A	69	65	58	49	46	39	36	35	30	27	20	19	18	17	14	9	6	5	4	3	1	1	1	0
Arm B	43	43	41	39	32	30	25	21	18	15	14	11	11	11	8	6	6	6	5	5	3	1	0	0

Figure 33: KM Plot of Overall Survival for Patients With PD-L1 Score ≥1% (FA)

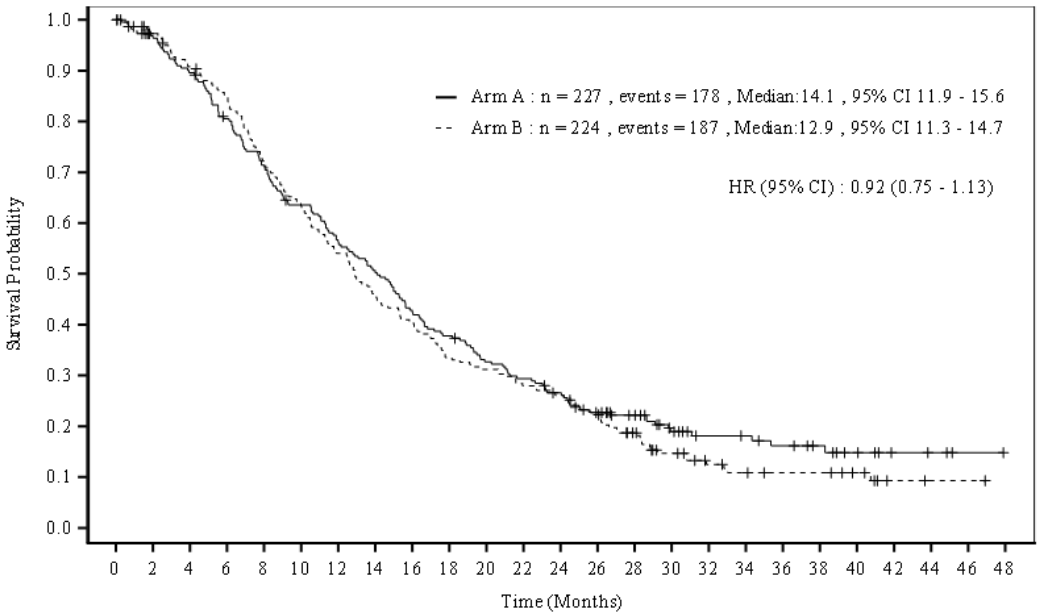


Number of patients still at risk

Time	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50
Arm A	432	412	387	355	309	277	242	219	196	175	159	146	134	113	93	68	53	48	39	28	21	12	9	4	1	0
Arm B	453	429	390	359	312	274	239	197	168	140	122	108	98	85	65	46	33	23	20	15	12	5	3	2	0	0

PD-L1 5% cutoff

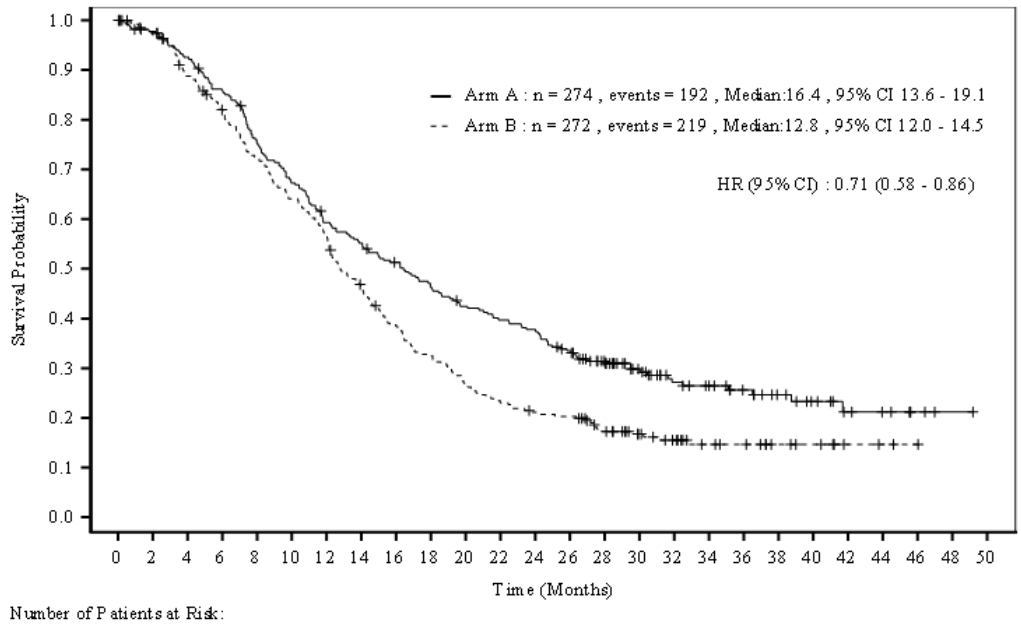
Figure 34: KM Plot of Overall Survival for Patients With PD-L1 Score < 5%; Final Analysis



Number of Patients at Risk:

Time:	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48
Arm A	227	214	198	176	156	138	122	109	93	82	70	63	55	46	39	27	21	19	16	12	8	4	3	1	0
Arm B	224	211	195	183	154	136	116	98	87	72	67	60	56	45	34	23	16	13	11	11	8	3	1	1	0

Figure 35: KM Plot of Overall Survival (PD-L1-Positive Analysis Set: ≥5%); Final Analysis

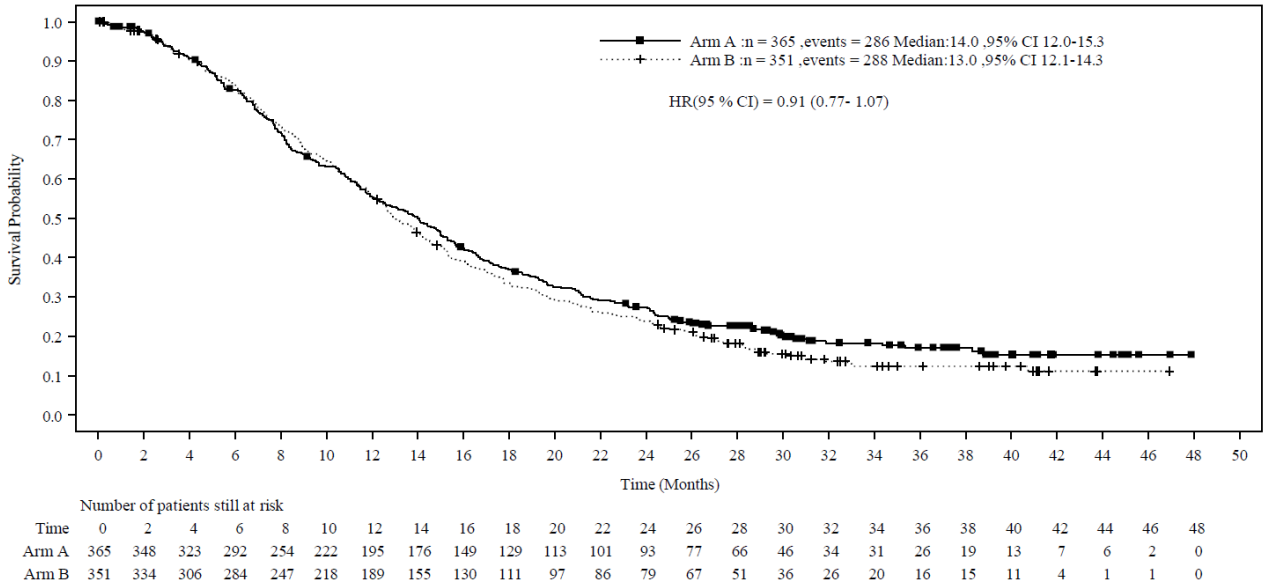


Number of Patients at Risk:

Time:	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50
Arm A	274	263	247	228	199	178	156	145	133	120	109	102	97	84	68	50	38	34	27	19	14	9	7	3	1	0
Arm B	272	261	236	215	190	168	148	120	99	83	69	59	53	51	39	29	23	16	14	9	7	3	2	1	0	0

PD-L1 10% cutoff

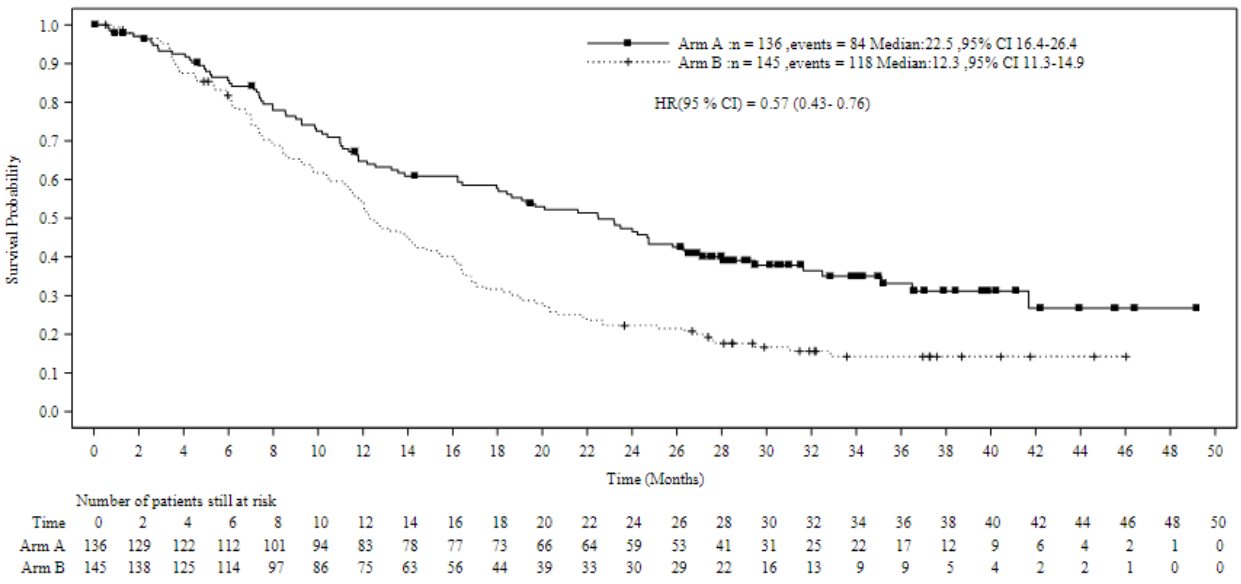
Figure 36: KM Plot of Overall Survival for Patients With PD-L1 Score < 10% (FA)



Number of patients still at risk

Time	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48
Arm A	365	348	323	292	254	222	195	176	149	129	113	101	93	77	66	46	34	31	26	19	13	7	6	2	0
Arm B	351	334	306	284	247	218	189	155	130	111	97	86	79	67	51	36	26	20	16	15	11	4	1	1	0

Figure 37: KM Plot of Overall Survival for Patients With PD-L1 Score ≥10% (FA)



Number of patients still at risk

Time	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50
Arm A	136	129	122	112	101	94	83	78	77	73	66	64	59	53	41	31	25	22	17	12	9	6	4	2	1	0
Arm B	145	138	125	114	97	86	75	63	56	44	39	33	30	29	22	16	13	9	9	5	4	2	2	1	0	0

PD-L1 1-<5% and 5-<10%

Figure 38: KM Plot of Overall Survival for Patients With PD-L1 Score 1-<5% (FA)

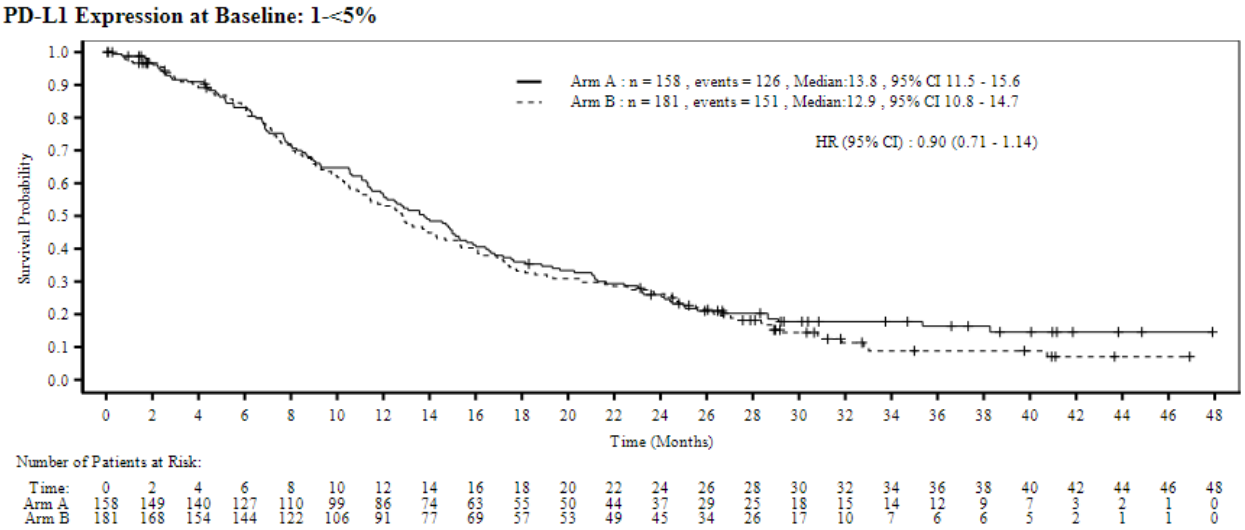
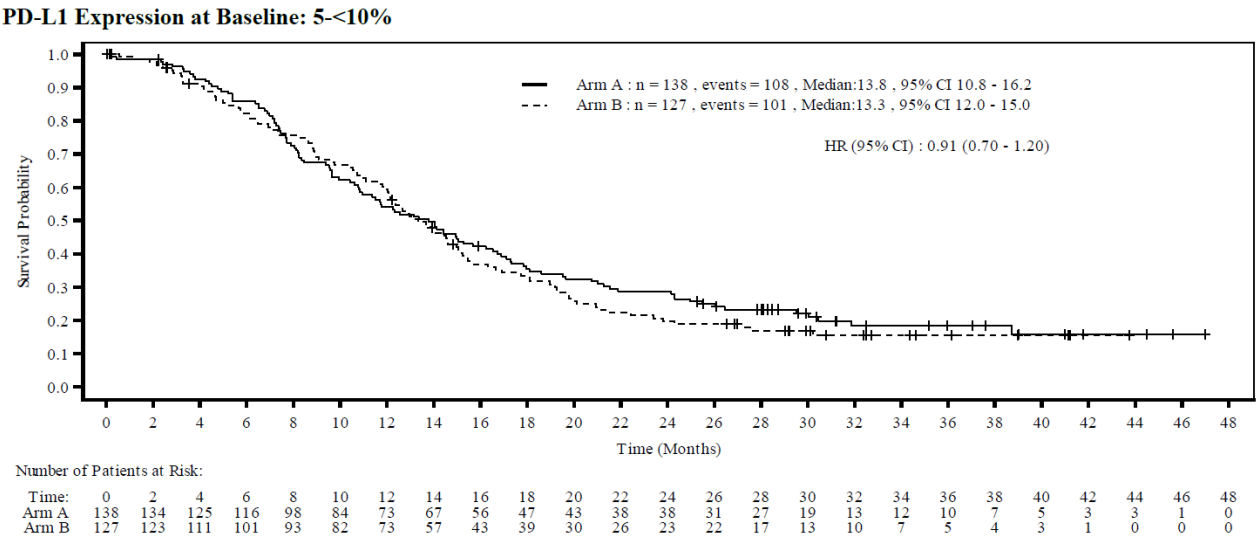


Figure 39: KM Plot of Overall Survival for Patients With PD-L1 Score 5-<10% (FA)



Progression-free survival

Table 37: Progression-Free Survival by PD-L1 5% and additional Cut Offs (FA)

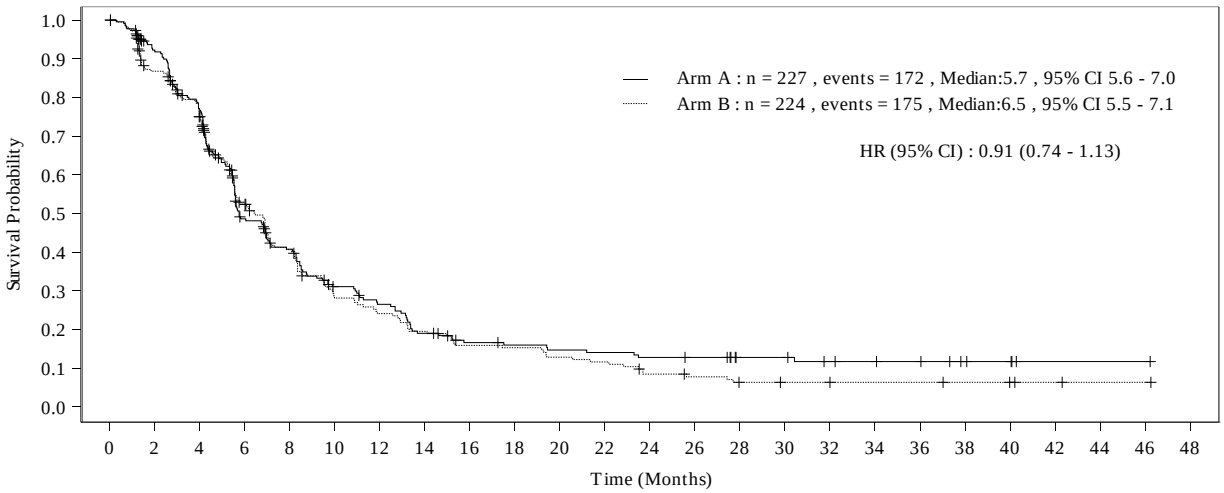
	Median PFS, months (95% CI)		Hazard Ratio (95% CI) [a]
	T+PtF	P+PtF	
ITT analysis set (N=997)	**6.9 (5.7, 7.2)**	**6.2 (5.6, 6.9)**	**0.78 (0.68, 0.90)**
PD-L1 < 1% (N=112)	7.9 (5.6, 9.7)	6.9 (5.6, 15.0)	0.87 (0.54, 1.41)
PD-L1 ≥ 1% (N=885)	6.9 (5.7, 7.2)	5.9 (5.6, 6.9)	0.78 (0.67, 0.91)
PD-L1 < 5% (N=451)	5.7 (5.6, 7.0)	6.5 (5.5, 7.1)	0.92 (0.75, 1.14)
PD-L1 ≥ 5% (n=546)	7.2 (5.8, 8.4)	5.9 (5.6, 7.0)	0.68 (0.56, 0.83)
PD-L1 < 10% (N=716)	5.7 (5.6, 7.0)	6.9 (5.7, 7.1)	0.90 (0.76, 1.06)
PD-L1 ≥ 10% (N=281)	9.0 (7.0, 12.1)	5.7 (4.5, 6.9)	0.56 (0.42, 0.74)

PD-L1 1% -< 5% (N=339)	5.6 (5.1, 6.9)	6.2 (5.5, 7.1)	0.98 (0.78-1.25)
PD-L1 5% -< 10% (N=265)	5.8 (5.6, 7.7)	6.9 (5.7, 8.3)	0.86 (0.65, 1.14)

Medians and other quartiles were estimated by Kaplan-Meier methodology with 95% CIs estimated using the method of Brookmeyer and Crowley.
Progression free survival rates were estimated by Kaplan-Meier methodology with 95% CIs estimated using Greenwood's formula.
a Unstratified HR was estimated from Cox model with Arm B (placebo + chemotherapy) as the reference group.

PD-LI 5% cutoff – PFS KM curves

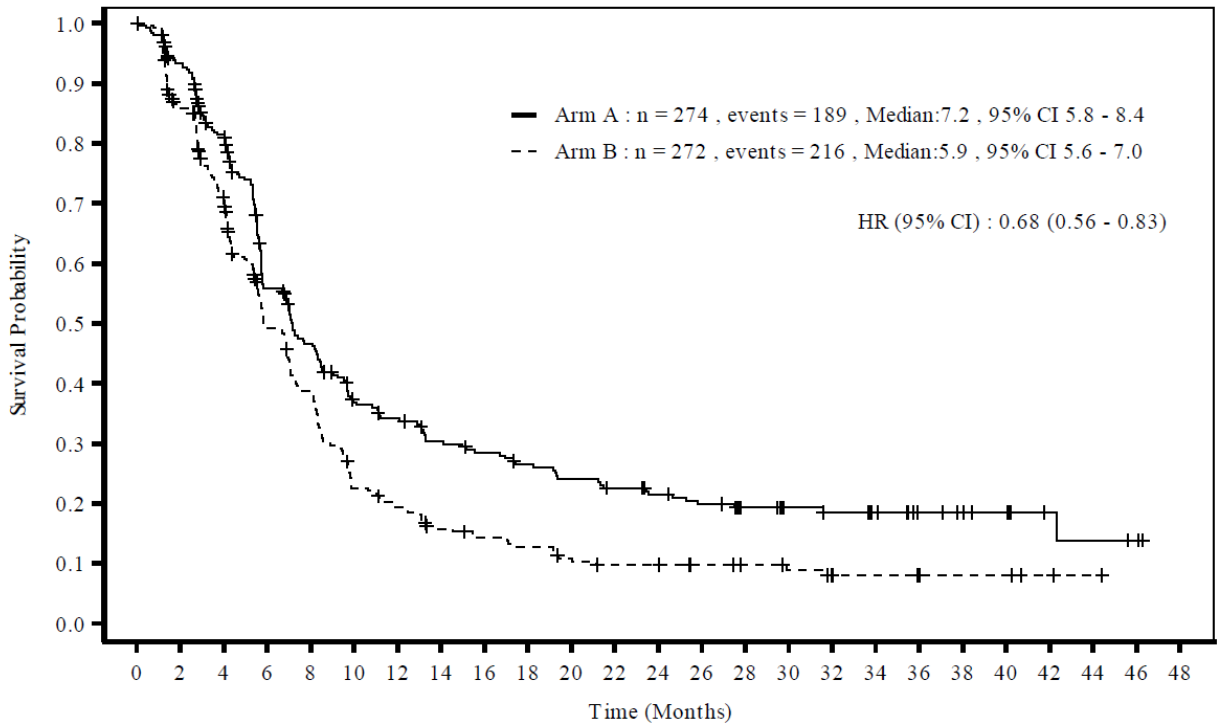
Figure 40: KM Plot of PFS for Patients With PD-L1 Score < 5% (FA)



Number of Patients at Risk:

Time:	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48
Arm A	227	197	161	95	77	55	46	33	27	25	23	22	20	19	13	13	10	9	8	5	4	1	1	1	0
Arm B	224	180	151	97	72	49	42	34	26	25	21	19	13	11	8	6	6	5	5	4	3	2	1	1	0

Figure 41: KM Plot of PFS for Patients With PD-L1 Score ≥5% (FA)



Number of Patients at Risk:

Time:	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48
Arm A	274	237	200	131	107	81	74	64	59	54	49	45	40	36	28	24	22	18	13	11	8	4	3	2	0
Arm B	272	219	176	114	89	51	43	33	29	26	21	18	18	15	13	10	7	6	5	4	4	2	1	0	0

ORR

Table 38: Objective Response Rates by PD-L1 5% and Additional Cut Offs (FA)

	ORR, % [95% CI] [a]		
	T+PtF	**P+PtF**	**Odds Ratio for ORR (95% CI)** [b]
ITT analysis set (N=997)	**47.3 (42.9, 51.8)**	**40.5 (36.2, 45.0)**	**1.33 (1.03, 1.72)**
PD-L1 < 1% (N=112)	44.9 (32.9, 57.4)	34.9 (21.0, 50.9)	1.52 (0.69, 3.34)
PD-L1 ≥ 1% (N=885)	47.7 (42.9, 52.5)	41.1 (36.5, 45.7)	1.31 (1.00, 1.71)
PD-L1 < 5% (N=451)	42.3 (35.8, 49.0)	37.9 (31.6, 44.7)	1.20 (0.82, 1.75)
PD-L1 ≥ 5% (N=546)	51.5 (45.4, 57.5)	42.6 (36.7, 48.8)	1.45 (1.03, 2.04)
PD-L1 < 10% (N=716)	44.9 (39.8, 50.2)	40.7 (35.6, 46.1)	1.19 (0.88, 1.60)
PD-L1 ≥ 10% (N=281)	53.7 (44.9, 62.3)	40.0 (32.0, 48.5)	1.74 (1.08, 2.79)
PD-L1 1% -< 5% (N=339)	41.1 (33.4, 49.2)	38.7 (31.5, 46.2)	1.11 (0.72, 1.71)
PD-L1 5% -< 10% (N=265)	49.3 (40.7, 57.9)	45.7 (36.8, 54.7)	1.16 (0.71, 1.87)

ORR is defined as proportion of number of patients with a confirmed PR or CR per RECIST v1.1
[a] Exact Clopper-Pearson 2-sided confidence interval.
[b] Objective response rate, objective response rate differences and odds ratios between arms were calculated using the Cochran-Mantel-Haenszel method (for ITT analysis this was stratified by regions (East Asia versus ROW [rest of the world]), PD-L1 expression and presence of peritoneal metastasis.

Modeling of OS Based on PD-L1 Score Used as Continuous Variable

To further investigate the impact of baseline PD-L1 expression on treatment effect in terms of the primary OS endpoint, an exploratory modeling approach was applied. The modeling approach used the totality of the data from all patients with available PD-L1 values. This is in contrast to the subgroup analyses presented above, in which the treatment effect was estimated separately within each subgroup and the outcomes were affected by the choice of a particular PD L1 cutoff that dichotomized patients within subgroups of varying sample size and numbers of observed events (and thus led to random variation in the estimated HRs). The modeling approach better utilized the continuous property of PD-L1 expression, by baseline PD-L1 levels as a continuous variable. Of note, only the PD-L1 cutoff of 5% was analytically validated for Study 305; other cutoffs explored were for the purpose of this modeling approach.

The first step of this OS modeling approach was to determine whether a "switch point" exists and if yes, where it locates. The switch point is the PD-L1 level (PD-L1 ≥ switch point) at which the treatment starts to be numerically beneficial; this is what is hereafter referred to as 'switch on'. Below this switch point (PD-L1 < switch point), there is no numerical treatment benefit; this is hereafter referred to as 'switch off'.

The switch point search was performed through multiple stratified Cox models, which included the following covariates:

- PD-L1 low/high categories, where low corresponded to PD-L1 < cut-point, switch off and high corresponded to PD-L1 ≥ cut-point, switch on each observed baseline PD-L1 level with the exception of the lowest one (i.e., 0) defined one candidate cut off.
  Note: 0 was excluded because there was no PD-L1 < 0 subgroup.
- Treatment (tislelizumab + chemotherapy vs. placebo + chemotherapy)
- PD-L1 low/high*treatment interaction

Stratification factors used in the abovementioned Cox models were region (East Asia vs. ROW) and peritoneal metastasis (yes vs. no). Criteria based on the estimated treatment effect in each candidate low PD-L1 subgroup ('switch off') and high PD-L1 subgroup ('switch on') were used to determine the switch point.

The smallest candidate cutoff that yielded:

1. Hazard ratio > 1 for tislelizumab + ICC vs. placebo + ICC in the PD-L1 low subgroup ('switch off')
2. Hazard ratio < 1 for tislelizumab + ICC vs. placebo + ICC in the PD-L1 high subgroup ('switch on')
3. Significant interaction at a reasonable critical value (Z value ⩽ -1.28)

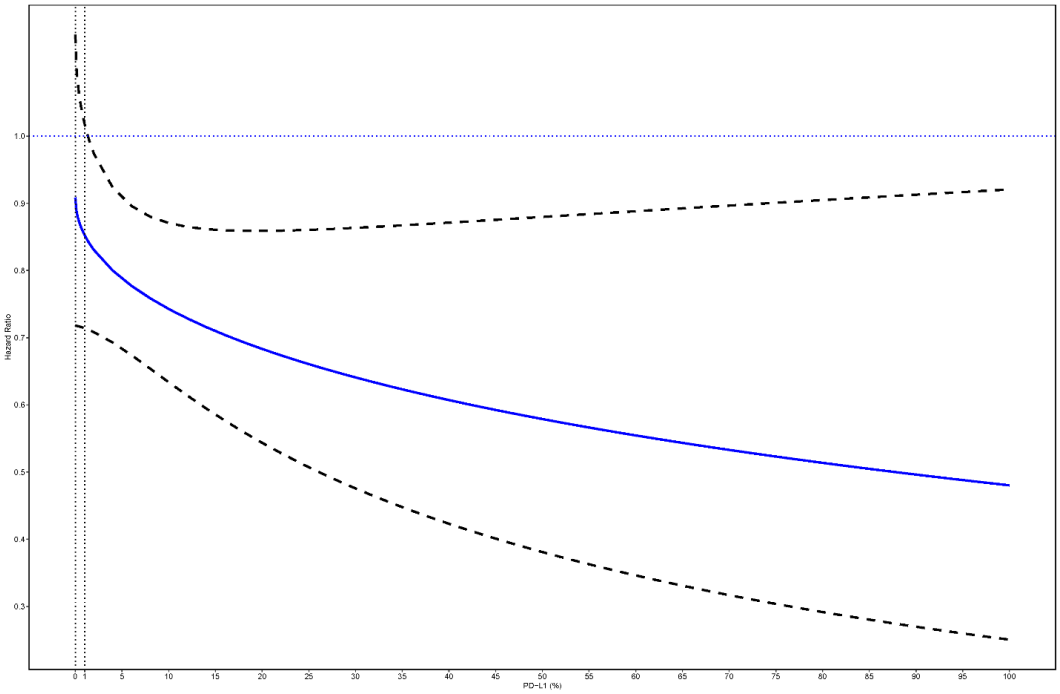
was chosen as the switch point.

The second step was to model the OS hazard ratio in the stratified Cox model as a function of baseline PD-L1 value as a continuous variable. For simplicity, the Box-Cox transformation family including the log transformation was used to transform the skewed distributed continuous PD-L1 level to normal distributed. A grid of power transformation from 0 to 4 with grid size 0.1 was used, and the transformation γ with the least -2 log likelihood was chosen. As no switch point existed based on results from step 1 [see Table 39], the continuous no switch model including covariates of treatment, continuous PD-L1 expression (in terms of VAR=PDL1^γ), and treatment*VAR interaction, was evaluated. Figure 42 shows the final model-based conditional stratified OS HR of the treatment effect as a function of baseline PD-L1 status.

Table 39: Switch point optimization

PD-L1 Level at baseline	Switch off log HR	Switch off Z	Switch on log HR	Interaction log HR	Interaction Z
1	-0.06218	-0.28559	-0.256	-0.19381	-0.83969
2	-0.08003	-0.55308	-0.285	-0.20462	-1.22524
3	-0.11690	-0.93484	-0.291	-0.17424	-1.13780
4	-0.11631	-1.06122	-0.318	-0.20194	-1.38646
5	-0.09531	-0.90674	-0.350	-0.25515	-1.76359
6	-0.11025	-1.26810	-0.503	-0.39308	-2.50848
7	-0.12751	-1.48560	-0.483	-0.35536	-2.23385
8	-0.13212	-1.55170	-0.482	-0.34998	-2.17544
9	-0.10708	-1.27812	-0.579	-0.47212	-2.84620
10	-0.10284	-1.22757	-0.590	-0.48678	-2.93453
11	-0.23376	-2.98287	-0.244	-0.01022	-0.05016
12	-0.24083	-3.07687	-0.203	0.03768	0.18350
13	-0.24486	-3.14217	-0.181	0.06389	0.30469
15	-0.24423	-3.13401	-0.184	0.06001	0.28617
20	-0.21917	-2.85761	-0.382	-0.16281	-0.69757
25	-0.22276	-2.96946	-0.373	-0.15037	-0.53800
30	-0.23146	-3.09777	-0.274	-0.04272	-0.14558
35	-0.22357	-3.01950	-0.430	-0.20632	-0.61063
40	-0.21725	-2.94620	-0.625	-0.40737	-1.10785
50	-0.22118	-3.01531	-0.498	-0.27714	-0.64765
55	-0.22541	-3.07989	-0.532	-0.30695	-0.67070
60	-0.22506	-3.07688	-0.570	-0.34483	-0.72847
70	-0.21541	-2.95177	-1.074	-0.85827	-1.68868
75	-0.21275	-2.91740	-1.205	-0.99237	-1.88833
80	-0.21438	-2.93991	-1.326	-1.11202	-2.11736
85	-0.21743	-2.99329	-1.566	-1.34845	-1.98898
90	-0.21774	-2.99947	-1.703	-1.48486	-2.01508

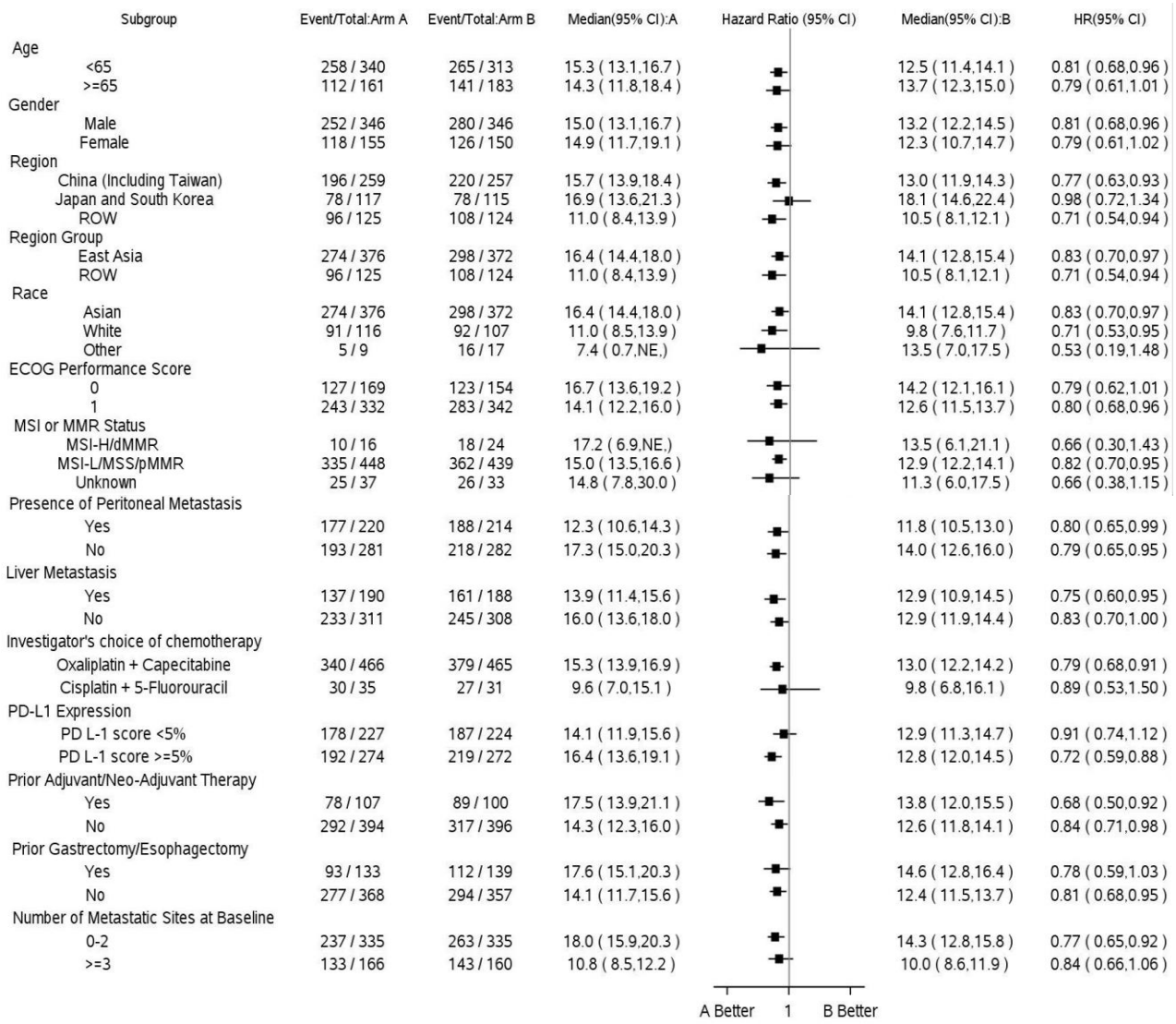
Figure 42: Exploratory Overall Survival Modeling Approach Using Baseline PD-L1 Levels as a Continuous Variable



Based on the final model, when PD-L1=0, VAR=0, the marginal stratified hazard ratio of tislelizumab + chemotherapy vs. placebo + chemotherapy is exp(-0.0743)=0.93. As PD-L1 level increases, the marginal stratified treatment effect hazard ratio also gradually decreases. These results are overall consistent with standard subgroup analyses marginal unstratified treatment effect HRs. The stratified OS HR of treatment condition on baseline PD-L1 level (Figure 42) suggested that the trend in tislelizumab benefit was observed even for PD-L1 level = 0, and the conditional HR decreased in a continuous manner with increasing PD-L1 level. Taken together, for Study 305 data, the modeling approach suggested that no switch point of no benefit vs. certain benefit existed, and a numerical OS treatment benefit can be observed in all patients regardless of PD-L1 levels. RMST results are similar.

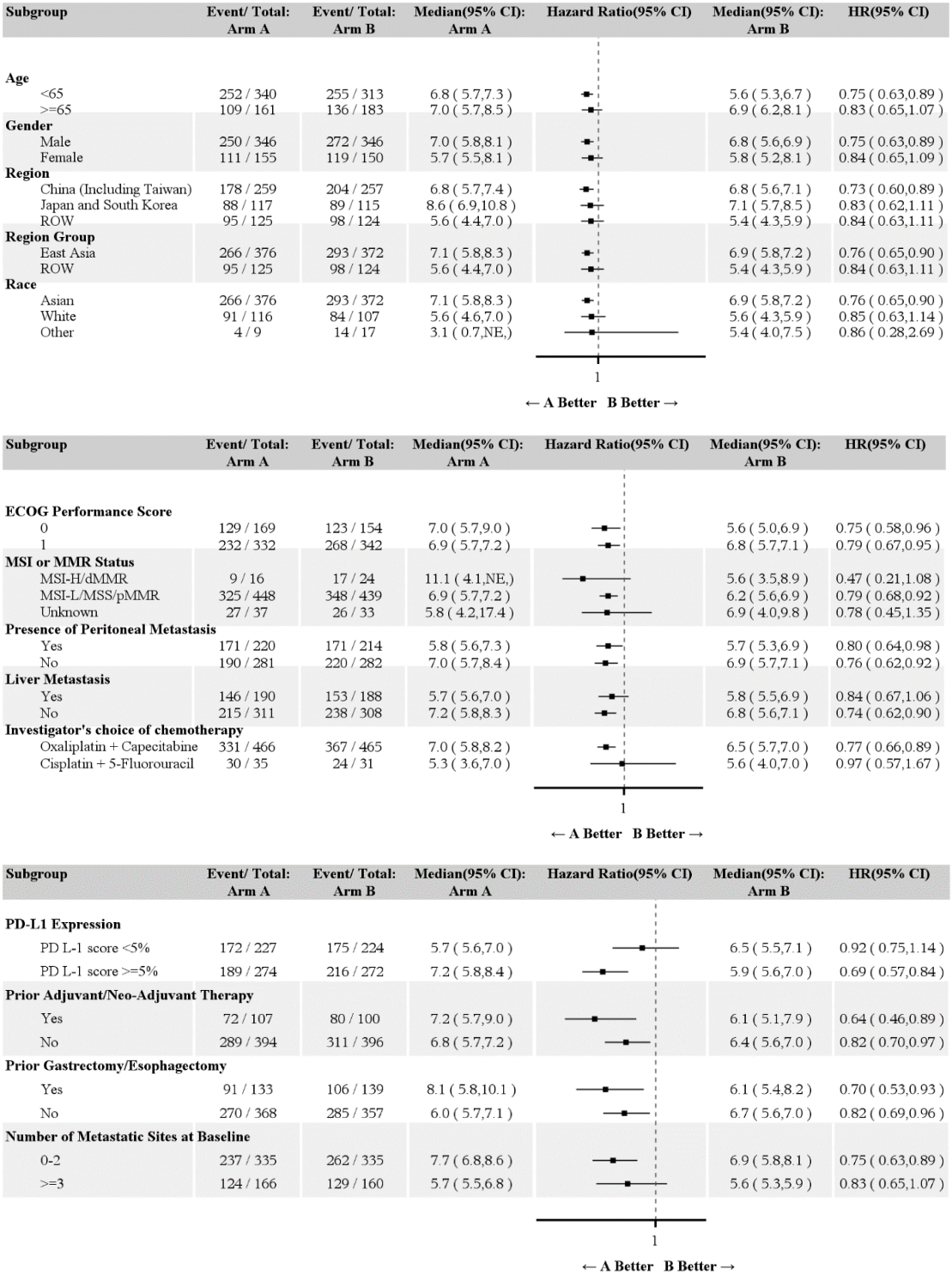
- **Subgroup analyses (predefined)**

Figure 43: Forest Plot of Overall Survival – Subgroup Analysis – Study 305 (ITT Analysis Set)



Abbreviation: CI = confidence interval; NE = not estimable. Arm A = Tislelizumab + Chemotherapy, Arm B = Placebo + Chemotherapy
Any subset with less than 10 patients would not be shown.
Medians were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley method using log-log transformation.
Hazard ratio and its 95% CI were estimated from unstratified Cox regression model including treatment as covariate.
The race subcategory 'Other' includes Not Reported, Unknown and Other.
The range of x-axis for HR is (0, 3), some extreme values greater than 3 is not shown in the plot.

Figure 44: Forest plot of PFS - Subgroup Analysis - Study 305 ITT Analysis Set



Source: ADSL, ADBASE, ADTTE. Data cutoff: 305-28FEB2023. Data extraction: 305-11APR2023.
Abbreviation: CI = confidence interval; NE = not estimable; NR = not reached. Arm A = Tisle + Chemo, Arm B = Placebo + Chemo.
Medians were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley method using log-log transformation.
Hazard ratio and its 95% CI were estimated from unstratified Cox regression model including treatment as covariate.
The race subcategory 'Other' includes Not Reported, Unknown and Other.

Subgroup Analyses by Region

Baseline and disease characteristics in East Asia and in the ROW were generally similar apart from a higher proportion of ECOG PS 1 (70% vs 59%), a lower BMI (21.2 kg/m² vs 24.0 kg/m²), higher proportion of gastric cancer (87% vs 61%), higher rate of prior gastrectomy or esophagectomy (31% vs 18%) and a higher proportion of prior adjuvant systemic therapy (21% vs 11%) in the East Asia vs ROW subgroup.

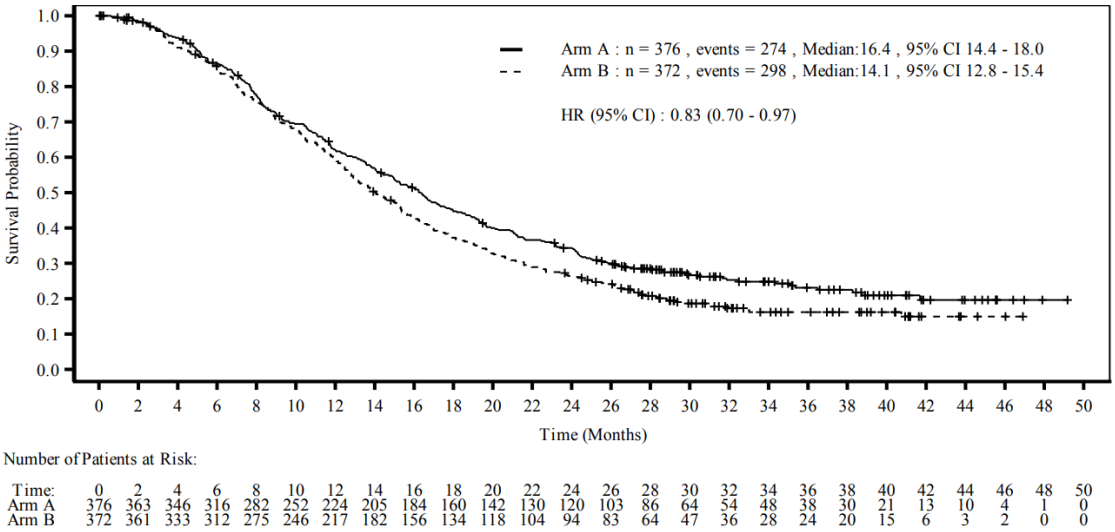
- **OS by region (Asia vs. RoW)**

Table 40: Overall Survival by Regional Subgroups – Study 305 (ITT Analysis Set)

	OS events %		Median OS, months (95% CI)		Hazard Ratio (95% CI) [a]
	T+PtF	P+PtF	T+PtF	P+PtF	
ITT analysis set	**73.9**	**81.9**	**15.0 (13.6, 16.5)**	**12.9 (12.1, 14.1)**	**0.80 (0.69, 0.92)**
East Asia (N=748)	72.9	80.1	16.4 (14.4, 18.0)	14.1 (12.8, 15.4)	0.83 (0.70, 0.97)
ROW (N=249)	76.8	87.1	11.0 (8.4, 13.9)	10.5 (8.1, 12.1)	0.71 (0.54, 0.94)

Medians and other quartiles were estimated by Kaplan-Meier methodology with 95% CIs estimated using the method of Brookmeyer and Crowley.
Overall survival rates were estimated by Kaplan-Meier methodology with 95% CIs estimated using Greenwood's formula.
Median follow-up time was estimated by the reverse Kaplan-Meier methodology.
[a] Unstratified hazard ratio was estimated from Cox model with Arm B (placebo + chemotherapy) as the reference group.

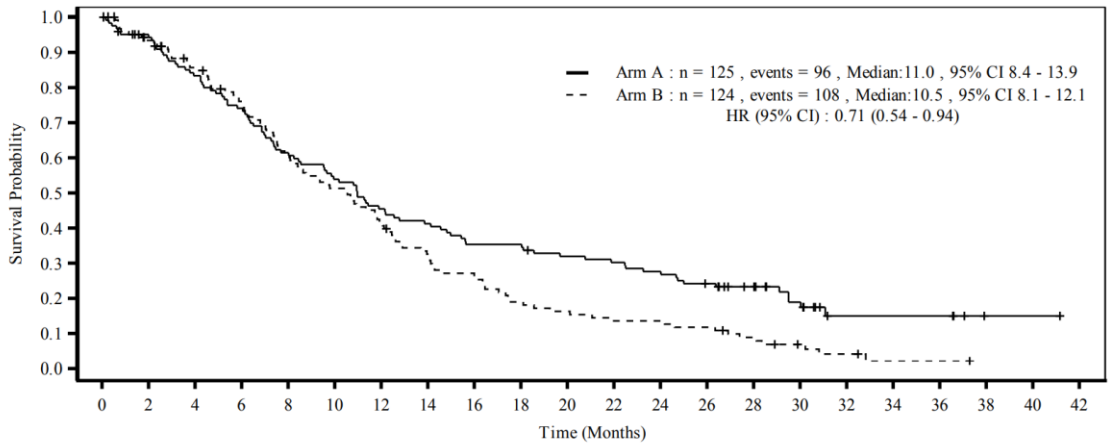
Figure 45: Kaplan-Meier Plot of OS in Region East Asia – Study 305 (ITT Analysis Set)



Number of Patients at Risk:

Time:	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50
Arm A	376	363	346	316	282	252	224	205	184	160	142	130	120	103	86	64	54	48	38	30	21	13	10	4	1	0
Arm B	372	361	333	312	275	246	217	182	156	134	118	104	94	83	64	47	36	28	24	20	15	6	3	2	0	0

Figure 46: Kaplan-Meier Plot of OS in Region ROW– Study 305 (ITT Analysis Set)



Number of Patients at Risk:

Time:	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42
Arm A	125	114	99	88	73	64	54	49	42	42	37	35	32	27	21	13	5	5	5	1	1	0
Arm B	124	111	98	86	69	58	47	36	30	21	18	15	15	13	9	5	3	1	1	0	0	0

Hazard ratio and its 95% CI was estimated from unstratified Cox regression model including treatment as covariate.
'+' = censored.

- **PFS by region (Asia vs. RoW)**

Table 41: PFS by Regional Subgroups – Study 305 (ITT)

	PFS events (%)		Median PFS, months (95% CI)		Hazard Ratio [a] (95% CI)
	T+PtF	P+PtF	T+PtF	P+PtF	
ITT analysis set (N=997)	**72.1**	**78.8**	**6.9 (5.7, 7.2)**	**6.2 (5.6, 6.9)**	**0.78 (0.68, 0.90)**
East Asia (N=748)	70.7	78.8	7.1 (5.8, 8.3)	6.9 (5.8, 7.2)	0.76 (0.64, 0.90)
ROW (N=249)	76.0	79.0	5.6 (4.4, 7.0)	5.4 (4.3, 5.9)	0.84 (0.63, 1.11)

[a] Unstratified hazard ratio was estimated from Cox model with Arm B (placebo + chemotherapy) as the reference group.

- **ORR by region (Asia vs. RoW)**

Table 42: Objective Response Rates by Regional Subgroups – Study 305 (ITT

	ORR, % [95% CI] [a]		Odds Ratio for ORR
	T+PtF	P+PtF	(95% CI) [b]
ITT analysis set (N=997)	**47.3 (42.9, 51.8)**	**40.5 (36.2, 45.0)**	**1.33 (1.03, 1.72)**
East Asia (N=748)	51.1 (45.9, 56.2)	43.5 (38.4, 48.8)	1.35 (1.01, 1.80)
ROW (N=249)	36.0 (27.6, 45.1)	31.5 (23.4, 40.4)	1.23 (0.72, 2.08)

[a] Exact Clopper-Pearson 2-sided confidence interval.
[b] Objective response rate, objective response rate differences and odds ratios between arms were calculated using the unstratified Cochran-Mantel-Haenszel method.

Subsequent systemic anticancer therapies (in overall study population and by region)

Table 43: Post-Treatment Subsequent Anticancer Systemic Therapies - Study 305 (ITT Analysis Set)

Category Preferred Term	Tislelizumab + Chemotherapy (N = 501) n (%)	Placebo + Chemotherapy (N = 496) n (%)
Patients with Any Subsequent Anticancer Systemic Therapy, n (%)	**265 (52.9)**	**294 (59.3)**
Targeted Therapy	150 (29.9)	160 (32.3)
Chemotherapy	251 (50.1)	280 (56.5)
Immunotherapy	62 (12.4)	90 (18.1)
Other Therapies	14 (2.8)	18 (3.6)
1st Subsequent Treatment	**265 (52.9)**	**294 (59.3)**
2nd Subsequent Treatment	**104 (20.8)**	**115 (23.2)**
3rd Subsequent Treatment	**43 (8.6)**	**54 (10.9)**
≥ 4th Subsequent Treatment	**15 (3.0)**	**16 (3.2)**

Table 44: Post-Treatment Subsequent Anticancer Systemic Therapies Study 305 overall + by region

Patients with Any Subsequent Anticancer Systemic Therapy	Tislelizumab + Chemotherapy	Placebo + Chemotherapy	Total
Overall 305 study population (n=997)	**52.9%**	**59.3%**	**56.1%**
ROW (n=249)	37.6%	45.2%	41.4%
East Asia (n=748)	58.0%	64.0%	61.0%
Japan (n=101)	72.0%	82.4%	77.2%

Post-Hoc Exploratory Analyses in the Japan Subgroup

In the Japan and South Korea subgroup, the unstratified OS HR was 0.98 (95% CI: 0.72, 1.34). In patients from Japan (N = 101), the unstratified HR of OS was 1.07 (95% CI: 0.66, 1.74); the median OS was 17.1 months (95% CI: 11.8, 21.6) in Arm T+PtF and 16.8 months (95% CI: 13.9, 22.7) in Arm P+PtF. The baseline demographic factors and disease history characteristics were generally balanced between arms in the Japan subgroup with the exception of ECOG PS=0 (Arm T+PtF: 66.0% vs. Arm P+PtF: 76.5%). There are no additional baseline parameters that could have clearly impacted the results. A higher proportion of patients receiving subsequent anticancer therapies was observed in the Japan subgroup vs the overall ITT population, including targeted therapy, immunotherapy and chemotherapy in line with local guidelines recommending ramucirumab plus paclitaxel as 2L and nivolumab as 3L+ treatment. In addition, the differences in the proportion of patients receiving

subsequent anticancer therapies in Arm P+PtF vs Arm T+PtF were more remarkable in the Japan subgroup than in the overall ITT population. Results of secondary endpoints favoured the T+PtF Arm in the Japan subgroup: unstratified PFS HR 0.68 (95% CI 0.43, 1.06), and ORR 52% in Arm T+PtF vs. 33.3% in Arm P+PtF.

Subgroup Analyses by Primary Tumor Location

Table 45: Overall Survival per Primary Tumor Location (ITT)

	Median OS, months (95% CI)		Hazard Ratio [a] (95% CI)
	T+PtF	P+PtF	
Stomach (n=405)	14.9 (12.8, 6.6)	13.3 (12.5, 14.5)	0.83 (0.71, 0.97)
GEJ (N=96)	15.6 (12.2, 19.7)	10.8 (9.1, 13.1)	0.70 (0.51, 0.97)

[a] Hazard ratio and its 95% CI was estimated from unstratified Cox regression model including treatment as covariate.

The proportion of patients who had the primary tumor location of stomach was higher in the East Asia subgroup than the ROW subgroup (86.6% vs. 61.0%). OS analyses according to primary tumor location (stomach vs GEJ) per region indicated a benefit from addition of tislelizumab to chemotherapy across all subgroups (East Asia: OS HR 0.86 vs 0.64 and ROW: OS HR 0.68 vs 0.76 for stomach vs GEJ, respectively).

Subgroup Analyses in Patients with Locally Advanced/Recurrent Disease

A small proportion of the patients recruited had locally advanced, unresectable disease, as permitted per eligibility criteria (N = 11: Arm T+PtF: N = 7, Arm P+PtF: N = 4). In addition, there was 1 patient in Arm P+PtF who had recurrent disease after prior gastrectomy/esophagectomy and adjuvant therapy.

Determining whether the patients had resectable disease that was suitable for surgery with or without radiotherapy was based on investigators' assessment. The OS HR for patients with locally advanced/recurrent, unresectable disease was 0.21 (95% CI: 0.04, 1.11).

Subgroup Analyses by Age

Table 46: OS subgroup analyses by age

	Median OS, months (95% CI)		Hazard Ratio (95% CI)
	T+PtF	P+PtF	(unstratified)
ITT analysis set (N=997)	**15.0 (13.6, 16.5)**	**12.9 (12.1, 14.1)**	**0.80 (0.69, 0.92)**
Age group			
< 65 years (N=653)	15.3 (13.1, 16.7)	12.5 (11.4, 14.1)	0.81 (0.68, 0.96)
65->75 years (N=287)	16.0 (12.6, 19.7)	13.8 (12.3, 15.4)	0.74 (0.56, 0.97)
≥75 years (N=57)	11.1 (6.9, 15.0)	12.5 (7.3, 16.4)	1.06 (0.58, 1.95)

Subgroup Analyses by Capecitabine Maintenance Treatment (yes/no)

Table 47: OS subgroup analyses by capecitabine maintenance treatment, post-hoc exploratory analysis

	With capecitabine maintenance		Without capecitabine maintenance	
	Tislelizumab + Chemotherapy (N=276)	**Placebo + Chemotherapy (N=250)**	***Tislelizumab + Chemotherapy (N=21)***	***Placebo + Chemotherapy (N=17)***
Primary Endpoint				
Overall Survival (OS)				
Median (months) (95% CI)	21.0 (18.6, 24.1)	18.1 (16.4, 20.3)	16.5 (13.4, 25.0)	15.4 (10.2, 26.1)
Stratified HR (95% CI) [a]	**0.80 (0.66, 0.98)**		**0.85 (0.41, 1.77)**	

Summary of main study

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 48: Summary of Efficacy for trial BGB-A317-305

Title: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Clinical Study Comparing the Efficacy and Safety of Tislelizumab (BGB-A317) plus Platinum and Fluoropyrimidine Versus Placebo plus Platinum and Fluoropyrimidine as First Line Treatment in Patients with Locally Advanced Unresectable or Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma		
Study identifier	BGB-A317-305	
Design	A pivotal global Phase III, double-blinded, placebo-controlled, multicenter, randomized study specifically designed to evaluate the efficacy and safety of tislelizumab in combination with chemotherapy compared with placebo in combination with chemotherapy as first-line treatment in patients with locally advanced unresectable or metastatic G/GEJ adenocarcinoma.	
	Duration of main phase: • Treatment phase: • Safety follow-up • Survival follow-up	 • Until disease progression, intolerable toxicity, or another reason that met the treatment discontinuation criteria • Up to 30 days after last dose • Until death, loss to follow-up, withdrawal of consent, or study completion by the sponsor
	Duration of Run-in phase:	Not applicable
	Duration of Extension phase:	Not applicable
Hypothesis	Superiority	

Treatments groups	Tislelizumab in combination with chemotherapy		Tislelizumab 200 mg every 3 weeks in combination with platinum and fluoropyrimidine-based chemotherapy on a 21-day cycle. Chemotherapy consisted of: • oxaliplatin 130 mg/m² IV on day 1 and capecitabine 1 000 mg/m2 orally twice daily for 14 consecutive days, repeated every 3 weeks. Oxaliplatin was administered for up to 6 cycles and capecitabine was administered as maintenance therapy at investigator's discretion until disease progression, unacceptable toxicity, or another treatment discontinuation criterion is met. or • cisplatin 80 mg/m² IV on day 1, and 5-FU 800 mg/m2/day by continuous IV infusion over 24h daily on days 1 to 5, repeated every 3 weeks. Cisplatin and 5-FU were given for up to 6 cycles. Duration: Study treatment was administered until disease progression, intolerable toxicity, or another reason that met the treatment discontinuation criteria. Number of patients: 501 patients
	Placebo in combination with chemotherapy		Administration of the matched placebo followed the guidance given for tislelizumab. Chemotherapy: Same as above. Duration: Study treatment was administered until disease progression, intolerable toxicity, or another reason that met the treatment discontinuation criteria. Number of patients: 496 patients
Endpoints and definitions	Primary endpoints	• OS in the PD-L1-positive set • OS in the ITT analysis set	Overall survival – defined as the time from the date of randomization to the date of death due to any cause
	Secondary endpoints	• PFS by Investigator	• PFS - defined as the time from the date of randomization to the date of first objectively documented tumour progression, assessed by the investigator per RECIST v1.1 or death, whichever occurs first
		• ORR by Investigator	• ORR - defined as the proportion of patients whose best overall response (BOR) is complete response (CR) or partial response (PR) assessed by the investigator per RECIST v1.1
		• DOR by Investigator	• DOR - defined as the time from the first determination of an objective response until the first documentation of progression assessed by the investigator per RECIST v1.1 or death, whichever comes first
Database lock	Interim analysis DCO: 08-Oct-2021 Final analysis data cutoff date: 28 February 2023		
Results and Analysis			
Analysis description	**Primary Endpoint Analysis - OS**		
Analysis population and time point description	**PD-L1 positive (PD-L1 score ⩾5%) analysis set** Interim analysis DCO: 08-Oct-2021		

Descriptive statistics and estimate variability	Treatment group	Tislelizumab + chemo-therapy	Placebo + chemo-therapy
	Number of patients	N = 274	N = 272
	Median OS (months)	17.2	12.6
	95% CI	13.9, 21.3	12.0, 14.4
Effect estimate per comparison	OS – PD-L1 +	Comparison groups	Tislelizumab + chemo vs chemo
		Stratified Hazard ratio (HR)	0.74
		95% CI	0.59, 0.94
		One-sided stratified log-rank test p-value	0.0056
Analysis population and time point description	**PD-L1 positive (PD-L1 score ⩾5%) analysis set** Final analysis DCO: 28-Feb-2023		
Descriptive statistics and estimate variability	Treatment group	Tislelizumab + chemo-therapy	Placebo + chemo-therapy
	Number of patients	N = 274	N = 272
	Median OS (months)	16.4	12.8
	95% CI	13.6, 19.1	12.0, 14.5
Effect estimate per comparison	OS – PD-L1 +	Comparison groups	Tislelizumab + chemo vs chemo
		Stratified Hazard ratio (HR)	0.71
		95% CI	0.58, 0.86
		One-sided stratified log-rank test p-value	0.0003* *Nominal p-value
Analysis population and time point description	**Intent-to-treat analysis set** Final analysis DCO: 28-Feb-2023		
Descriptive statistics and estimate variability	Treatment group	Tislelizumab + chemo-therapy	Placebo + chemo-therapy
	Number of patients	N = 501	N = 496
	Median OS (months)	15.0	12.9
	95% CI	13.6, 16.5	12.1, 14.1
Effect estimate per comparison	OS - ITT	Comparison groups	Tislelizumab + chemo vs chemo
		Stratified Hazard ratio (HR)	0.80
		95% CI	0.70, 0.92
		One-sided stratified log-rank test p-value	0.0011
Analysis description	**Secondary endpoints efficacy analysis**		

Analysis population and time point description	**PD-L1 positive (PD-L1 score ⩾5%) analysis set** Interim analysis DCO: 08-Oct-2021		
Descriptive statistics and estimate variability	Treatment group	Tislelizumab + chemo-therapy	Placebo + chemo-therapy
	Number of patients	N = 274	N = 272
Progression free survival by investigator	Median PFS (months)	7.2	5.9
	95% CI	5.8, 8.4	5.6, 7.0
Objective Response Rate by investigator	ORR, n	138	117
	ORR (%)	50.4	43.0
	95% CI	44.3, 56.4	37.1, 49.1
Duration of Response by Investigator	Number of responders	138	117
	Median DOR (months)	9.0	7.1
	95% CI	8.2, 19.4	5.7, 8.3
Effect estimate per comparison	PFS	Comparison groups	Tislelizumab + chemo vs chemo
		Stratified Hazard ratio (HR)	0.67
		95% CI	0.55, 0.83
		One-Sided Stratified Log-Rank Test	<0.0001
	ORR	Odds Ratio for ORR	1.36
		95% CI	0.97, 1.92
		ORR Difference, %	7.4
		95% CI	-0.8, 15.6
		CMH test p-value	0.0764
Analysis population and time point description	**PD-L1 positive (PD-L1 score ⩾5%) analysis set** Final analysis DCO: 28-Feb-2023		
Descriptive statistics and estimate variability	Treatment group	Tislelizumab + chemo-therapy	Placebo + chemo-therapy
	Number of patients	N = 274	N = 272
Progression free survival by investigator	Median PFS (months)	7.2	5.9
	95% CI	5.8, 8.4	5.6, 7.0
Objective Response Rate by investigator	ORR, n	141	116
	ORR (%)	51.5	42.6
	95% CI	45.4, 57.5	36.7, 48.8

Duration of Response by Investigator	Number of responders	141	116
	Median DOR (months)	10.0	6.9
	95% CI	8.2, 16.8	5.7, 8.5
Effect estimate per comparison	PFS	Comparison groups	Tislelizumab + chemo vs chemo
		Stratified Hazard ratio (HR)	0.68
		95% CI	0.56, 0.83
	ORR	Odds Ratio for ORR	1.45
		95% CI	1.03, 2.04
		ORR Difference, %	8.9
		95% CI	0.7, 17.0
Analysis population and time point description	**Intent-to-treat analysis set** Final analysis DCO: 28-Feb-2023		
Descriptive statistics and estimate variability	Treatment group	Tislelizumab + chemo-therapy	Placebo + chemo-therapy
	Number of patients	N = 501	N = 496
Progression free survival by investigator	Median PFS (months)	6.9	6.2
	95% CI	5.7, 7.2	5.6, 6.9
Objective Response Rate by investigator	ORR, n	237	201
	ORR (%)	47.3	40.5
	95% CI	42.9, 51.8	36.2, 45.0
Duration of Response by Investigator	Number of responders	237	201
	Median DOR (months)	8.6	7.2
	95% CI	7.9, 11.1	6.0, 8.5
Effect estimate per comparison		Comparison groups	Tislelizumab + chemo vs chemo
	PFS	Stratified Hazard ratio (HR)	0.78
		95% CI	0.67, 0.90
	ORR	Odds Ratio for ORR	1.33
		95% CI	1.03, 1.72
		ORR Difference, %	6.8
		95% CI	0.8, 12.9

Analysis performed across trials (pooled analyses and meta-analysis)

N/A - Since the efficacy for the application is based solely on the results from pivotal Study 305, there are no data for comparison across studies.

Clinical studies in special populations

Table 49: OS subgroup analyses by age

	Median OS, months (95% CI)		Hazard Ratio (95% CI)
	T+PtF	P+PtF	(unstratified)
ITT analysis set (N=997)	**15.0 (13.6, 16.5)**	**12.9 (12.1, 14.1)**	**0.80 (0.69, 0.92)**
Age group			
< 65 years (N=653)	15.3 (13.1, 16.7)	12.5 (11.4, 14.1)	0.81 (0.68, 0.96)
65->75 years (N=287)	16.0 (12.6, 19.7)	13.8 (12.3, 15.4)	0.74 (0.56, 0.97)
≥75 years (N=57)	11.1 (6.9, 15.0)	12.5 (7.3, 16.4)	1.06 (0.58, 1.95)

Supportive studies

Study 001
Study 001 was a Phase IA/B, multi-center, open-label, multiple-dose, dose-escalation, and expansion study of tislelizumab monotherapy in adult patients with advanced solid tumors, including 54 patients with GC. All 54 patients had received prior anticancer therapy, 48.1% had received 2 or more prior therapies. A total of 50 patients received tislelizumab monotherapy at a dose of 5 mg/kg Q3W in the expansion part and were included for efficacy analyses: the ORR was 10% (95% CI: 3.33, 21.81); median DOR was 14.3 months (95% CI: 8.5, NE).

Study 102
Study 102 was a Phase I/II study in patients with advanced solid tumors, including 24 patients with GC tumors and prior systemic treatment; 58% of patients had received ≥ 2 prior regimens. Patients were treated with tislelizumab monotherapy at a flat dose of 200 mg Q3W. The ORR for patients with GC was 16.7% (95% CI: 4.7, 37.4).

Study 205
Study 205 was a Phase II, single-arm, multi-cohort study to investigate tislelizumab in combination with standard chemotherapy as first-line treatment in adults with inoperable, locally advanced or metastatic GC/GEJ or esophageal carcinoma. Fifteen patients were enrolled into the GC/GEJ adenocarcinoma cohort. The ORR was 46.7% (95% CI: 21.27%, 73.41%); the median DOR was not reached (range: 2.99 to 13.11+ months).

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

This application is based on the double-blinded, global Study 305 that randomized 997 participants with previously untreated, HER2-negative, advanced gastric or GEJ adenocarcinoma to receive tislelizumab or placebo in combination with platinum- and fluoropyrimidine-based chemotherapy.

Randomization was stratified by region, chemotherapy option, presence of peritoneal metastasis, and PD-L1 expression (PD-L1 score ≥ 5% vs. PD-L1 score < 5%) which is considered acceptable.

The choice of CAPOX or FP as chemotherapy backbone regimens was determined by the investigator before randomization and is in line with recommended standard of care treatment options. Tislelizumab was applied at the approved dosing regimen of 200 mg IV Q3W. Treatment was administered until disease progression; 11% of patients received treatment with tislelizumab beyond 24 months.

Participants were eligible regardless of their tumour PD-L1 expression level; however, all participants needed to provide tumour tissues for central PD-L1 testing with the Ventana PD-L1 (SP263) assay. PD-L1 expression was determined by a PD-L1 score assessed by Tumour Area Positivity (TAP) score, which is defined as the total percentage of the tumour area covered by tumour cells with any membrane staining above background and tumour-associated immune cells with any staining above background. With amendment 1, PD-L1 positivity was defined as PD-L1 TAP score ≥5%. The PD-L1 expression cutoff selection of 5% was based on a post hoc analysis of tumours from patients with gastroesophageal adenocarcinoma and evaluable PD-L1 status from BGB-A317_Study_001 (n=77). The cutoff of PD-L1 score ≥ 5% was determined as the optimal cutoff based on receiver operating characteristic (ROC) analysis and statistical parameters relative to clinical response including sensitivity/ specificity as well as PD-L1 positivity prevalence in Study 001 and pathological feasibility. The PD-L1 assay was analytically validated at the ≥ 5% cutoff for G/GEJ cancer, before it was used in Study 305; the Applicant provided the analytical validation report with the responses and confirmed that no analytical validation data at other clinical cut-offs than 5% were available.

PD-L1 testing was mostly performed on archival tumour tissue. In patients with prior adjuvant and/or neo-adjuvant systemic therapy (21% of study population), testing was performed on archival tumour tissue in all but one patient, leading to an age of tumour tissue above 3 years in 17% of patients with prior (neo)adjuvant therapy. The reliability of PD-L1 test results regarding analytical long-term stability and to what extent prior chemotherapy might have influenced PD-L1 expression at the time of enrolment were discussed. The PD-L1 expression status between patients who had their tumour biopsies prior to (neo)adjuvant therapy (n=134) and those who had their biopsies after (neo)adjuvant therapy (N=72) were compared. This exploratory analysis showed a similar PD-L1 prevalence (41% vs. 31% with PD-L1 ≥ 5% for patients with sample collection before and after any prior (neo)adjuvant systemic therapy, respectively). In addition, OS outcomes for patients with PD-L1 score ≥ 5% were comparable between these two subgroups. Although these post-hoc analyses are recognized, they are not considered sufficiently informative due to the lack of paired tumour biopsies and small sample size. Lastly, an uncertainty remains that some of the PD-L1 negative patients (for whom PD-L1 status was determined prior to (neo)adjuvant therapy and/or with samples >3 years) might have false negative results. However, although a possible impact of prior (neo)adjuvant therapy on PD-L1 expression cannot be completely excluded nor reliably quantified, this uncertainty is not considered to confound the overall conclusions of the study results.

Baseline characteristics were generally balanced between treatment arms and are overall reflective of patients with advanced gastric /GEJ adenocarcinoma apart from the typical limitations of eligibility criteria that restrict the study population to patients with good performance status (ECOG PS of 0 or 1) and adequate organ function. The majority of participants (68%) were <65 years of age (median age was 61.0 years) and only 6% were enrolled with an age above 75 years. Participants were primarily male (69%), the majority had an ECOG PS of 1 (68%), adenocarcinoma of the stomach (80%) and had not received prior gastrectomy/esophagectomy (73%). Nearly all had metastatic disease (98.7%) including 38% of participants with liver metastases. Most of the patients were enrolled from East Asia (75.0%), the remainder of patients (25.0%) were enrolled from other regions (including US and Europe). A total of 21% of patients received ≥1 prior neo-adjuvant/adjuvant therapy before study entry.

A sample size of n=640 patients was initially planned to ensure sufficient power to demonstrate an effect on either OS or PFS in either the ITT or PD-L1 positive population (four primary objectives). Sample size and objectives were revised in protocol amendments. The first patient was enrolled after the implementation of Protocol Amendment Version 1.0. (Aug-2018) that revised the alpha allocation for the primary endpoints of PFS and OS in the ITT and PD-L1 positive Populations and increased the sample size from 640 to 720 patients. Amendment V2.0 was implemented in April 2020, when 490 patients (50% of the final study population) had been enrolled. At this time, PFS was moved from primary to secondary endpoint, blinded independent review was removed, and a sequential testing method was implemented to compare OS in the PD-L1 Positive Population first and then in the ITT Population; in addition, the sample size was increased to 980 patients.
The revisions in Protocol Amendment V2.0 were based on external results from the KEYNOTE-062 study which were discussed with the Steering Committee. At the time of finalization of Protocol Amendment V2.0, about 21% OS events and 39% PFS events were observed in Study 305. A sensitivity analysis was provided with the test results according to the analysis strategy as defined in the protocol prior to Amendment 2.0. These results indicated that the trial would have met its primary PFS and OS endpoints in the PD-L1+ population, but not in the overall ITT population.
Overall, it is assumed that the reasons for the implemented changes were based on external information and not triggered by knowledge of internal study results, although the study would not have been successful in the overall study population without these modifications.
The overall conduct of the study that was impacted by the COVID-19 pandemic including the reported protocol deviations do not raise concerns regarding the integrity of trial results.

Statistical analysis
The effect of treatment on OS was planned to be tested by means of a stratified logrank-test and estimated through stratified Cox-regression. Region of enrolment (east Asia versus the rest of the world), PD-L1 expression (for ITT Analysis Set only), and presence of peritoneal metastasis with information obtained via IRT were used as strata.
While these methods are appropriate, the Applicant was asked to clarify why the strata do not fully match the strata of randomization. The Applicant explained that given the number of stratification factors and concern that potentially some of the cell would have very few patients, Investigator's choice of chemotherapy (ICC) was not included in the stratified log rank test as pre-specified in the statistical analysis plan. A post-hoc exploratory analysis by including the ICC as one of the stratification factors showed that the conclusion of the key efficacy endpoints result remained unchanged.
OS in the PD-L1 Positive Set first and in the ITT set second were planned to be tested sequentially, followed by a hierarchical strategy for secondary endpoints (i) PFS and (ii) ORR in the PD-L1 Positive Set and (iii) PFS and (iv) ORR in the ITT set. This strategy in principle controls type-I-error; but this strategy was introduced while the study was ongoing and Protocol Amendment 2.0 allocated a higher total one-sided alpha of 0.025 to OS in the PD-L1 Positive Set, as compared to an initially smaller α=0.01 prior to Amendment 2.0 (see above for discussion of protocol amendments).

The censoring rules for PFS have the potential to include informative censoring. In particular, censoring of patients who are known to have progressed after the censoring date, and censoring of patients who start receiving new anticancer treatment may be informative censoring. However, sensitivity analyses were conducted and provided reassurance that PFS results are robust.

Efficacy data and additional analyses

Efficacy results were provided from the interim analysis (IA) of Study 305 (representing the primary OS analysis for the PD-L1-positive analysis set; data cutoff date: 08 Oct 2021) and from the final OS

analysis in the ITT population (data cutoff date: 28 Feb 2023). The **median** duration of study follow-up at the final analysis (FA) was 13.2 months (range: 0.1 to 50.1 months) across both arms.

At the IA, Study 305 demonstrated a statistically significant improvement in OS with tislelizumab plus chemotherapy vs. placebo plus chemotherapy in the PD-L1-Positive Analysis Set (PD-L1 ≥5%): The stratified OS HR was 0.74 (95% CI: 0.59, 0.94) with a one-sided p-value of 0.0056 (IA OS boundary of 0.0092). The study then continued as planned in a blinded manner, and the primary endpoint of OS was also met in the **ITT** population at the final analysis: The stratified **OS HR** was **0.80** (95% CI: 0.70, 0.92) with a one-sided p-value of 0.0011 (prespecified boundary p=0.0226). The median OS was 15.0 (95% CI 13.6, 16.5) vs. 12.9 (95% CI 12.1, 14.1) months for tislelizumab plus chemotherapy arm vs. placebo plus chemotherapy. The efficacy results in the PD-L1-Positive Analysis Set at the time of the final analysis were consistent with those of the IA; at the FA, the stratified OS HR was 0.71 (95% CI: 0.58, 0.86) for patients with PD-L1 ≥5%; the median OS was 16.4 (95% CI 13.6, 19.1) vs. 12.8 (95% CI 12.0, 14.5) months for tislelizumab plus chemotherapy vs. placebo plus chemotherapy.

As per statistical analysis plan, PFS and ORR in the PD-L1 ≥5% and ITT Analysis Sets could be sequentially tested using the interim analysis data when the primary endpoint was met in the ITT population. In this sequence, only the first testing of PFS in the PD-L1-Positive Analysis Set met statistical significance; thus, secondary endpoints of PFS, ORR, DOR and PRO measures in the ITT analysis set were reported descriptively only. In the ITT population, median PFS was 6.9 months vs 6.2 months (PFS HR 0.78; 95% CI 0.67, 0.90), ORR was 47.3% vs. 40.5%, and median DOR 8.6 vs. 7.2 months in favour of the tislelizumab plus chemotherapy arm. Patient-reported health-related quality of life data showed overall no clinically meaningful differences between treatment arms; however, for single items a trend towards a more pronounced improvement or reduced deterioration was observed in patients who were treated with tislelizumab plus chemotherapy compared with those who were treated with placebo plus chemotherapy. For the exploratory endpoint of PFS2 the HR was 0.79 (95% CI: 0.68, 0.91), median PFS2 was 12.6 vs. 11.5 months in favour of the tislelizumab plus chemotherapy arm.

Further information on how the blind was maintained after the interim analysis was requested. It was clarified that prior to IA of Study 305, an interim analysis data integrity plan was implemented after consultation with FDA which included the scenario that the OS endpoint would be met in PD-L1+ analysis set only but not in the ITT analysis set. According to the plan, patient-level unblinding was restricted to a designate filing team within the Sponsor, all the other sponsor and site staff, investigators and patients remained blinded to the study aggregated results until the complete unblinding after the final analysis. After IA the IDMC informed the Sponsor that the first primary endpoint in the PD-L1+ analysis set was met. This was also communicated to the investigators and via a press release also highlighting that "the study will continue as a double-blinded study" and "additional follow-up would be needed to assess OS benefits in the intention-to-treat (ITT) population". This is acknowledged; however, even if the individual blind might have been maintained despite differences in the safety profile, the impact of communicating a significant OS benefit in PD-L1 expressors at interim remains unclear. Since the indication is eventually restricted to patients with PD-L1 expression above 5% and an OS benefit was demonstrated in this subgroup at interim, the respective uncertainty is not critical.

Efficacy by PD-L1 expression

Results in the overall study population of patients with GEJ/gastric cancer showed a moderate benefit for the addition of tislelizumab to standard 1L chemotherapy across all endpoints. This benefit was more pronounced in the predefined PD-L1-Positive Analysis Set (PD-L1 score ≥ 5%, representing 55% of the study population), indicating that the treatment effect in the overall population is driven by a PD-L1 positive subpopulation. With the aim to better understand the impact of PD-L1 expression on

efficacy outcomes, results of exploratory analysis evaluating additional cutoff values (PD-L1 1% and 10%) were provided.

These data showed the largest benefit (unstratified OS HR 0.57, 95% CI 0.43 0.76) for patients whose tumours express PD-L1 ≥10% (representing 28% of study population). Results of complementary negative subgroups suggest no benefit for the small subgroup of PD-L1 <1% (OS HR 0.98) and only a marginal benefit for the subgroups of PD-L1 <5% and PD-L1 <10% (both OS HR 0.91) as well as for the disjoint subgroups of PD-L1 1-<5% (OS HR 0.90) and PD-L1 5-<10% (OS HR 0.91). OS KM plots for the subgroup of patients with PD-L1 <10% and PD-L1 5-<10% are separating only slightly after 12 and 15 months. PFS results by PD-L1 subgroups show similar results with only small improvements for patients with PD-L1 <10% (PFS HR 0.9), and PD-L1 5-<10% (PFS HR 0.86), but a clear benefit for patients whose tumours express PD-L1 ≥10% (PFS HR 0.56; 95% CI 0.42, 0.74). Exploratory modelling data supported the increased treatment effect of tislelizumab with higher PD-L1 scores. While exploratory post-hoc modelling should be interpreted with caution, this exercise supports the above considerations. Of note, across a range of PD-L1 switch points the value 10% provides the largest interaction test statistic, suggesting that numerical differences in estimated treatment effect between patients below and above this cut-off are strongest at 10%. The model does not suggest a detrimental effect with any cutoff, but it doesn't alleviate concerns on small effects with low PD-L1 expression. The relevance of benefits and risks need to be considered.

In summary, the subgroup analyses of the pivotal study indicated an association between efficacy outcomes and of PD-L1 expression levels with a most pronounced benefit for the subpopulation with PD-L1 ≥10%. Expression status was centrally assessed in all patients with a validated assay and are considered credible. Subgroup results are biologically plausible, and a correlation of PD-L1 status with efficacy is established in this indication leading to restricted indications also for other checkpoint inhibitors (i.e. there is external replication). Thus, a true heterogeneous treatment effect across different PD-L1 expression subgroups is supported by the considerations outlined in the CHMP guideline on the investigation of subgroups in confirmatory clinical trials. In view of the additional toxicity of tislelizumab in the combination treatment, the B/R balance is not considered favourable in the overall study population. PD-L1 score of 5% was prespecified as stratification factor in the study design and OS in the PD-L1 positive population (defined as PD-L1 ≥5%) was evaluated as primary endpoint. The stratified OS HR in the prespecified PD-L1 positive population with PD-L1 ≥5% is 0.71 (95% CI 0.58, 0.86) vs. OS HR 0.92 (95% CI 0.75, 1.13) in patients with PD-L1 score <5%.
The indication was therefore restricted to subjects whose tumors express PD-L1 with a score of ≥ 5%. The following indication wording was agreed on: *"Tevimbra, in combination with platinum and fluoropyrimidine-based chemotherapy, is indicated for the first-line treatment of adult patients with HER-2-negative locally advanced unresectable or metastatic gastric or gastroesophageal junction (G/GEJ) adenocarcinoma whose tumours express PD-L1 with a tumour area positivity (TAP) score ⩾ 5% (see section 5.1)."*

Discussion of other subgroup results

Most of the participants were enrolled in East Asia (75%). Subgroup analyses by region showed a similar treatment effect of tislelizumab in combination with chemotherapy (OS HR 0.83 vs 0.71, PFS HR 0.76 vs. 0.84, odds ratio for ORR 1.35 vs. 1.23) for East Asia vs. Rest of the World (ROW), respectively, but median OS, PFS and ORR were improved for Asian participants in both treatment arms. A lower proportion of patients in the ROW subgroup received subsequent anticancer systemic therapies compared to the East Asia subgroup (41% vs. 61%).

An even higher proportion of Japanese patients (77%) received subsequent anticancer therapies with more pronounced differences between treatment arms (Arm T+PtF: 72% vs. Arm P+PtF: 82%) which

could have confounded the OS results in the Japan subgroup as highlighted by the MAH (OS HR 1.07, 95% CI: 0.66, 1.74 in patients from Japan). Results of secondary endpoints favoured the T+PtF Arm in the Japan subgroup: unstratified PFS HR 0.68 (95% CI 0.43, 1.06), and ORR 52% in Arm T+PtF vs. 33.3% in Arm P+PtF.

As regard chemotherapy options, the majority of patients received oxaliplatin plus capecitabine (93.4%), compared with cisplatin plus 5-FU (6.6%). The subgroup results for patients who received cisplatin plus 5-FU showed lower median OS results in both treatment arms (9.6 and 9.8 months, respectively) and a less favourable OS HR of 0.89 (95% CI 0.53, 1.50) as compared to patients treated with oxaliplatin plus capecitabine (median OS 15.3 and 13.0 months, OS HR 0.79; 95% CI 0.68, 0.91). Interpretation of results in the cisplatin/5-FU subgroup is however hampered by the small sample size and wide confidence interval and there is no obvious biological rationale to expect a different treatment effect of tislelizumab by chemotherapy regimen.

In Study 305, for those patients randomized to receive 6 cycles of oxaliplatin plus capecitabine, capecitabine could optionally be continued as maintenance therapy for those who experienced a complete response, partial response, or stable disease, according to investigators' judgement. The majority of patients (n=526) received capecitabine maintenance, only a few patients (n=38) did not; this distribution was balanced across treatment arms. A post-hoc exploratory analysis indicated similar treatment effects (OS HR 0.80 and 0.85 for patients with and without capecitabine maintenance), although interpretation is limited by the small subgroup size for patients not receiving maintenance therapy and uncertainties in comparing patient groups defined by an intercurrent (post-randomization) event.

Subgroup analyses by age did not indicate a differential treatment effect for patients younger or older than 65 years; however, in the small subgroup of patients in the age group ≥ 75 years (n=57), the OS analysis raised uncertainties on a potential lack of benefit of adding tislelizumab in these elderly patients (OS HR 1.06; 95% CI 0.58, 1.95; median 0S 11.1 for tislelizumab plus chemo vs. 12.5 months for placebo plus chemo). But the size of study patients in the age group beyond 75 years is too small to draw definitive conclusions.

2.4.4. Conclusions on the clinical efficacy

Study 305 demonstrated a statistically significant overall survival improvement for tislelizumab in addition to standard chemotherapy in the 1L treatment of patients with GEJ/gastric cancer in the PD-L1 positive population (defined as PD-L1 ≥5%) and the overall study population. The OS results were supported by secondary endpoints.
However, the benefit was driven by subjects whose tumours express higher PD-L1 scores leading to a restriction of the indication to patients whose tumours express PD-L1 with a TAP score of ≥ 5%.

2.5. Clinical safety

Introduction

The safety data supporting this application are primarily derived from the pivotal Phase III Study 305. The data from all tislelizumab-treated patients at the final analysis (FA) (data cutoff date 28-Feb-2023) in Study 305 is the primary source of data supporting the safety of tislelizumab in combination with platinum- and fluoropyrimidine-containing chemotherapy as first-line treatment in locally advanced unresectable or metastatic G/GEJ cancer patients.

Study 305 is a global, multicenter, randomized, double-blind, placebo-controlled study, evaluating the efficacy and safety of tislelizumab (at the approved registrational dosing regimen for Tevimbra, i.e., 200 mg administered IV Q3W) in combination with platinum- and fluoropyrimidine-based chemotherapy compared to the efficacy and safety of placebo in combination with platinum and fluoropyrimidine-based chemotherapy in patients with locally advanced unresectable or metastatic G/GEJ adenocarcinoma.

For the abbreviations used in this document, please see List of Abbreviations.

Table 50: Overview of pivotal phase III Study 305

Study number/ Status	Study design	Patient population	Treatment regimen	N	Safety assessments	Data cutoff date
305 Ongoing	Phase III randomized, double-blinded, placebo-controlled, global study to compare the efficacy and safety of tislelizumab plus chemotherapy versus placebo plus chemotherapy	Patients with histologically confirmed, locally advanced unresectable or metastatic G/GEJ cancer, with no previous systemic therapy for respective indication	Tislelizumab 200 mg IV Q3W or matched placebo in combination with fluoropyrimidine- (capecitabine[b] or 5-FU[c]) and platinum- (oxaliplatin[d] or cisplatin[e]) based chemotherapy	Study 305 safety set: 992 (T+PtF[a]: 498, P+PtF[a]: 494) PD-L1-positive safety set: 544 (T+PtF[a]: 272, P+PtF[a]: 272)	Incidence and severity of AEs according to NCI-CTCAE v5.0 Changes in vital signs, physical findings, ECG, ECOG PS, ophthalmologic findings, pulmonary function, and clinical laboratory results	28-Feb-2023 (final analysis)

[a] T+PtF: tislelizumab in combination with capecitabine plus oxaliplatin or 5-FU plus cisplatin, P+PtF: placebo in combination with capecitabine plus oxaliplatin or 5-FU plus cisplatin.
[b] 1000 mg/m^2 orally twice daily, from the morning of Day 1 to the evening of Day 14 OR from the evening of Day 1 to the morning of Day 15 of each 21-day cycle, for up to 6 cycles; continuation post Cycle 6 was optional.
[c] 800 mg/m^2/day IV on Day 1 through Day 5 of each 21-day cycle, for up to 6 cycles.
[d] 130 mg/m^2 IV on Day 1 of each 21-day cycle, for up to 6 cycles.
[e] 80 mg/m^2 IV on Day 1 of each 21-day cycle, for up to 6 cycles.
Source: [Study 305 FA CSR]

The safety evaluation is additionally supported by integrated safety data from patients across 7 studies (N = 1534), including patients who were treated with tislelizumab monotherapy across various tumor types and received the recommended dose or an equivalent dose (200 mg Q3W), as well as by safety data from patients who received tislelizumab in combination with various chemotherapies and in various indications.

Safety data are presented side-by-side in tables for the following populations:

- **Study 305 safety set** (N = 992) includes all patients from Study 305 who received at least one dose of tislelizumab/placebo in combination with chemotherapy. This patient population is representative of the targeted population of patients with locally advanced unresectable or metastatic G/GEJ cancer.
- **Tislelizumab monotherapy pool** (N = 1534) includes patients with various tumor types who received tislelizumab monotherapy at 200 mg Q3W; pooling of 7 studies (Study 001, Study 102, Study 203, Study 204, Study 208, Study 302 and Study 303).
- **Tislelizumab combination therapy pool** (N = 1336) includes all patients who received tislelizumab 200 mg Q3W in combination with various chemotherapies and in various indications in Study 206, Study 304, **pivotal Study 305**, Study 306, and Study 307.

Of the studies included in the Tislelizumab monotherapy pool, Studies 001, 102, 203, 204, 208, and 302 have now been completed, and Study 303 is ongoing. This submission is based on the data cutoff dates provided in **Table 51** for the monotherapy pool and presented below.

Table 51: Studies providing supporting safety data for tislelizumab monotherapy

	Monotherapy studies						
	001	**102**	**208**	**204**	**203**	**302**	**303**
Phase	I[1]	I/II	II	II	II	III	III
Disease type	ST (CRC, NSCLC, MM, cuSCC, UM, GC, PC, OC, UC, HNSCC, RCC, TNBC, HCC, ESCC, MCC, CC, GIST, sarcoma, or other tumors with known MSI-H or dMMR)	ST (NSCLC, MM, GC, ESCC, OC, UC, HNSCC, RCC, TNBC, CRC, SCNEC or other tumors with known MSI-H or dMMR, NPC, Child-Pugh Class A HCC)	Previously treated, unresectable HCC	UC	R/R cHL	Advanced unresectable/ metastatic ESCC	Locally advanced or metastatic (squamous or nonsquamous NSCLC)
Study design	Phase I, open-label, multiple-dose, dose-escalation and expansion study investigating the safety, tolerability, PK, and antitumor activity of tislelizumab in patients with advanced tumors.	Phase I/II multicenter, open-label, study in Chinese patients with advanced solid tumors. The Phase I portion assessed safety, tolerability, PK characteristics, preliminary antitumor activity, and confirmed the MTD, if any, and/or RP2D of tislelizumab. The Phase II portion was conducted as an indication-expansion study to further assess the safety, PK, and preliminary efficacy in patients with malignant solid tumors, including cohorts in patients with NSCLC.	Phase II, open-label, global study investigating the efficacy, safety, and PK of tislelizumab in patients with previously treated HCC.	Phase II single-arm, multicenter study to evaluate the efficacy and safety of tislelizumab in patients with PD-L1 high, locally advanced or metastatic urothelial carcinoma who had progressed during or following a platinum-containing regimen	Phase II open-label, multicenter, single-arm study to evaluate the efficacy of tislelizumab therapy in adult patients with R/R cHL.	Phase III randomized, controlled, open-label, global study comparing the efficacy of tislelizumab vs. chemotherapy as second-line treatment in patients with recurrent, advanced, unresectable or metastatic ESCC.	Phase III, randomized, open-label, multicenter study in adult patients with histologically confirmed, locally advanced or metastatic NSCLC (squamous or nonsquamous) who had disease progression during or after a platinum-containing regimen to investigate the efficacy and safety of tislelizumab compared with docetaxel.
Phase	I[1]	I/II	II	II	II	III	III
Participating countries	Australia; New Zealand; USA; South Korea; China (including Taiwan)	China	China (including Taiwan); Germany, Spain, France, UK, Italy, and Poland	China, Korea	China	China (including Taiwan), Belgium, Spain, France, UK, Italy, Japan, Korea, USA, Germany	China, Bulgaria, Brazil, Lithuania Mexico, New Zealand, Poland, Russia, Slovakia, Turkey
Tislelizumab dose regimen	200 mg Q3W[2]	200mg Q3W, 200mg W1D1, W5+D1 Q3W[3] (PK sub-study)	200 mg Q3W	200 mg Q3W	200 mg Q3W	200 mg Q3W	Tislelizumab 200 mg iv Q3W
Patients in Safety Set (N)	13	300 (24 GC)	249	113	70	255 in Tislelizumab arm	534 in Tislelizumab arm
Data cutoff date	26-Aug-2020 (Final CSR data cutoff)	31-May-2020 (Final CSR data cutoff)	30-Jun-2021 (Interim CSR data cutoff)	16-Sep-2019 (Interim CSR data cutoff)	02-Nov-2020 (Final CSR data cutoff)	01-Dec-2020 (Final CSR data cutoff)	15-Jul-2021 (Interim CSR data cutoff)

[1] Study 001 is a two-stage study consisting of a Phase IA component for dose escalation and dose-finding, and a Phase IB component for indication expansion.
[2] In Study 001, other dose regimens (0.5/2/5/10 mg/kg Q2W, 2/5 mg/kg Q2W/Q3W and, 5 mg/kg Q3W) were also tested, but only the approved dose of 200 mg Q3W was included in the monotherapy pool.
[3] In Study 102, the dose of 200mg W1D1, W5+D1 Q3W means dosing with 200 mg on Day 1 with interval of 4 weeks for Cycle 1 and 3 weeks for cycles thereafter.
CC: cholangiocarcinoma; cHL: classical Hodgkin Lymphoma; CRC: Colorectal cancer; cuSCC: Squamous cell carcinoma; dMMR: deficient Mismatch Repair; ESCC: Esophageal carcinoma; GC: Gastric cancer; GIST: gastrointestinal stromal tumor; HCC: Hepatocellular carcinoma; HNSCC: Head and neck squamous cell carcinoma; MCC: Merkel-cell carcinoma; MM: Melanoma; MSI-H: Microsatellite Instability – High; NPC: Nasopharyngeal cancer; NSQ- NSCLC: nonsquamous- non-small cell lung cancer; NSCLC: Non-small cell lung cancer; OC: Ovarian Cancer; PC: Pancreatic cancer; RCC: Renal cell carcinoma; R/R: Relapsed or Refractory; SCNEC: Small cell neuroendocrine carcinoma; SQ-NSCLC: squamous-non-small cell lung cancer; ST: Advanced solid tumor; TNBC: Triple negative breast cancer; UC: Urothelial carcinoma; UM: Uveal melanoma.
Source: [Study 001], [Study 102], [Study 208], [Study 204], [Study 203], [Study 302], [Study 303]

Table 52: Studies providing supporting safety data for tislelizumab in combination with chemotherapy including pivotal Study 305

	Study 206	Study 304	Study 305	Study 306	Study 307
Phase	**Phase II**	**Phase III**	**Phase III**	**Phase III**	**Phase III**
Disease type	NSCLC, SCLC	Non-squamous NSCLC	First-line locally advanced unresectable or metastatic gastric/gastroesophageal junction adenocarcinoma	First-line recurrent or metastatic ESCC	Squamous NSCLC
Study design	Multi-cohort, open-label, study of tislelizumab in combination with standard chemotherapy as first-line treatment in patients with locally advanced or metastatic lung cancer.	Randomized, open-label, multicenter study comparing the efficacy and safety of tislelizumab combined with platinum (cisplatin or carboplatin) and pemetrexed versus platinum (cisplatin or carboplatin) and pemetrexed alone as first-line treatment in patients with Stage IIIB or IV nonsquamous NSCLC.	Phase III randomized, double-blinded, placebo-controlled, global study to compare the efficacy and safety of tislelizumab versus chemotherapy	Randomized, double-blind, placebo-controlled, multicenter, study to evaluate the efficacy and safety of tislelizumab in combination with chemotherapy as first-line treatment in patients with unresectable, locally advanced recurrent or metastatic esophageal squamous cell carcinoma	Randomized, open-label, multicenter study comparing the efficacy and safety of tislelizumab combined with carboplatin and either paclitaxel or nab-paclitaxel versus paclitaxel plus carboplatin alone as first-line treatment in patients with untreated Stage IIIB or IV squamous NSCLC.
Participating countries	China	China	Mainland China, Chinese Taiwan, Japan, South Korea, the United Kingdom, Russia, France, Italy, Poland, Puerto Rico, Spain, Turkey, and the United States (US)	Asia (Chinese Taiwan, Japan, Korea, Mainland China), Europe (Belgium, Czech Republic, France, Germany, Italy, Poland, Romania, Russia, Spain, the United Kingdom), Northern America (the United States) and Oceania (Australia)	China
Tislelizumab dose regimen	200 mg Q3W	200 mg Q3W	200 mg Q3W	200 mg Q3W	200 mg Q3W
Chemotherapy	Platinum-containing doublet chemotherapy as per histology[a]	Cisplatin[b] or carboplatin[b] and pemetrexed[b]	Fluoropyrimidine-(capecitabine[e] or 5-FU[f]) and platinum- (oxaliplatin[g] or cisplatin[h]) based chemotherapy	Platinum-containing chemotherapy doublet (cisplatin or oxaliplatin) with fluoropyrimidine (capecitabine or 5-FU) or paclitaxel[d].	T+PC[c]: Paclitaxel and carboplatin; T+nPC[c]: Nab-paclitaxel and carboplatin[c]
Safety Set (N) in tislelizumab arm	54	222	498	324	238
Data cutoff date	31-Dec-2019 (Final CSR data cutoff)	26-Oct-2020 (Final CSR data cutoff)	28-Feb-2023 (Final analysis CSR data cutoff)	28-Feb-2022 (Interim CSR data cutoff)	30-Sep-2020 (Final CSR data cutoff)

[a] NSQ cohort: pemetrexed 500 mg/m^2 iv and cisplatin 75 mg/m^2/day iv (or carboplatin area under the curve [AUC] 5) up to 4 cycles. Maintenance treatment of pemetrexed (500 mg/m^2 iv on Day 1 of each 21-day cycle) until progressive disease for patients whose disease had not progressed after 4 cycles of platinum-containing doublet chemotherapy. SQ-A cohort: paclitaxel 175 mg/m^2 iv and cisplatin 75 mg/m^2/day iv (or carboplatin AUC 5) on Day 1 of each 21-day cycle (4-6 cycles); SQ-B cohort: gemcitabine 1250 mg/m^2 iv on Day 1 and Day 8, and cisplatin 75 mg/m^2/day iv (or carboplatin AUC 5) on Day 1 of each 21-day cycle (4-6 cycles). SCLC cohort: etoposide 100 mg/m^2 on Days 1, 2, and 3; cisplatin 75 mg/m^2/day iv (or carboplatin AUC 5) on Day 1 of each 21-day cycle (4-6 cycles).
[b] Cisplatin 75 mg/m^2 or Carboplatin AUC 5, pemetrexed 500 mg/m^2 (4-6 cycles). Maintenance treatment of pemetrexed 500 mg/m^2
[c] T+PC: Paclitaxel 175 mg/m^2 D1 Q3W, Carboplatin AUC 5 D1 Q3W (4-6 cycles); T+nPC: Nab-paclitaxel 100 mg/m^2 D1, 8, 15 Q3W, Carboplatin AUC 5 D1 Q3W (4-6 cycles)
[d] Cisplatin: 60-80 mg/m^2 iv or Oxaliplatin: 130 mg/m^2 iv D1 every 3 weeks, 5-FU: 750-800 mg/m^2 D1-5 every 3 weeks iv, Capecitabine: 1000 mg/m^2 on D1-14 of each cycle oral bid, Paclitaxel: 175 mg/m^2 on Day 1 every 3 weeks iv.
[e] Capecitabine:1000 mg/m^2 orally twice daily, from the morning of Day 1 to the evening of Day 14 OR from the evening of Day 1 to the morning of Day 15 of each 21-day cycle, for up to 6 cycles; continuation post Cycle 6 was optional.
[f] 5-FU: 800 mg/m^2/day IV on Day 1 through Day 5 of each 21-day cycle, for up to 6 cycles.
[g] Oxaliplatin:130 mg/m^2 IV on Day 1 of each 21-day cycle, for up to 6 cycles.
[h] Cisplatin: 80 mg/m^2 IV on Day 1 of each 21-day cycle, for up to 6 cycles.
Source: [Study 206], [Study 304 Addendum], [Study 305], [Study 306], [Study 307 Addendum]

Patient exposure

The duration of exposure and number of cycles received during the study treatment period were summarized with descriptive statistics and by categories for study treatment overall, as well as for Tislelizumab/Placebo drug for Study 305 and the Tislelizumab monotherapy pool.

Exposure to Tislelizumab in Study 305

Table 53: Duration of exposure to Tislelizumab and overall summary of cycles (Safety Set)

	Study 305 All patients		Tislelizumab monotherapy pool
	T+PtF	P+PtF	
	N=498	N=494	N=1534
Total number of patients receiving study drug - n (%)	498 (100.0)	494 (100.0)	1534 (100.0)
Duration of exposure (months)			
Mean (SD)	9.71 (9.689)	8.28 (8.418)	8.58 (9.650)
Median	5.91	5.65	4.17
Q1-Q3	3.32-11.89	3.02-9.82	2.07-11.04
Min-Max	0.1-47.0	0.3-46.9	0.2-43.3
Duration of exposure (categories) - n (%)			
< 1 month	27 (5.4)	23 (4.7)	117 (7.6)
1 - < 3 months	87 (17.5)	100 (20.2)	515 (33.6)
3 - < 6 months	139 (27.9)	140 (28.3)	276 (18.0)
6 - < 12 months	122 (24.5)	143 (28.9)	258 (16.8)
12 - < 18 months	42 (8.4)	36 (7.3)	117 (7.6)
18 - < 24 months	21 (4.2)	19 (3.8)	83 (5.4)
≥ 24 months	60 (12.0)	33 (6.7)	168 (11.0)
Number of cycles received			
Mean (SD)	13.1 (13.13)	11.2 (11.44)	12.0 (13.30)
Median	8.0	8.0	6.0
Q1-Q3	4.0-16.0	4.0-13.0	3.0-16.0
Min-Max	1-67	1-68	1-62
Number of cycles received (categories) - n (%)			
1 - < 4 cycles	86 (17.3)	96 (19.4)	514 (33.5)
4 - < 8 cycles	136 (27.3)	142 (28.7)	354 (23.1)
8 - < 12 cycles	102 (20.5)	102 (20.6)	175 (11.4)
12 - < 18 cycles	59 (11.8)	73 (14.8)	133 (8.7)
18 - < 36 cycles	68 (13.7)	54 (10.9)	212 (13.8)
≥ 36 cycles	47 (9.4)	27 (5.5)	146 (9.5)

Data cutoff for Study 305: 28-Feb-2023
Data cutoff for Tislelizumab Monotherapy Pool: Study 001-26-Aug-2020, Study 102-31-May-2020, Study 203-02- Nov-2020, Study 204-16-Sep-2019, Study 208-30-Jun-2021, Study 302-01-Dec-2020, and Study 303-15-Jul-2021

Exposure to chemotherapy in Study 305

Table 54: Duration of exposure to chemotherapy and overall summary of cycles (Safety Set)

	Tislelizumab + Chemotherapy (N = 498)				Placebo + Chemotherapy (N = 494)			
	Oxaliplatin + Capecitabine		Cisplatin + 5-FU		Oxaliplatin + Capecitabine		Cisplatin + 5-FU	
	Oxaliplatin (N = 463)	Capecitabine (N = 453)	Cisplatin (N = 35)	5-FU (N = 35)	Oxaliplatin (N = 463)	Capecitabine (N = 450)	Cisplatin (N = 31)	5-FU (N = 31)
Duration of Treatment (month) [a]								
Mean (SD)	3.8 (1.29)	9.3 (9.07)	3.5 (1.30)	3.5 (1.33)	3.7 (1.30)	8.1 (8.15)	3.8 (1.36)	3.9 (1.21)
Median	4.2	5.8	4.1	4.2	4.2	5.6	4.3	4.3
Min, Max	0.1, 8.0	0.3, 45.5	0.3, 5.3	0.3, 5.3	0.3, 6.9	0.2, 44.6	0.7, 5.0	0.7, 5.1
Duration of Treatment, n (%)								
< 3 months	108 (23.3)	96 (21.2)	10 (28.6)	11 (31.4)	125 (27.0)	114 (25.3)	6 (19.4)	5 (16.1)
3 to < 6 months	348 (75.2)	136 (30.0)	25 (71.4)	24 (68.6)	332 (71.7)	131 (29.1)	25 (80.6)	26 (83.9)
6 to < 9 months	7 (1.5)	75 (16.6)	0 (0.0)	0 (0.0)	6 (1.3)	81 (18.0)	0 (0.0)	0 (0.0)
9 to < 12 months	0 (0.0)	40 (8.8)	0 (0.0)	0 (0.0)	0 (0.0)	46 (10.2)	0 (0.0)	0 (0.0)
12 to < 24 months	0 (0.0)	56 (12.4)	0 (0.0)	0 (0.0)	0 (0.0)	50 (11.1)	0 (0.0)	0 (0.0)
>= 24 months	0 (0.0)	50 (11.0)	0 (0.0)	0 (0.0)	0 (0.0)	28 (6.2)	0 (0.0)	0 (0.0)
Total Number of Doses Taken								
Mean (SD)	5.0 (1.57)	340.3 (341.21)	4.8 (1.71)	4.8 (1.73)	4.9 (1.62)	295.5 (308.78)	4.9 (1.74)	5.0 (1.49)
Median	6.0	217.0	6.0	6.0	6.0	199.5	6.0	6.0
Min, Max	1.0, 7.0	2.0, 1732.0	1.0, 6.0	1.0, 6.0	1.0, 7.0	1.0, 1748.0	1.0, 6.0	1.0, 6.0
Number of Cycles, n (%)								
1	23 (5.0)	21 (4.6)	3 (8.6)	3 (8.6)	21 (4.5)	19 (4.2)	3 (9.7)	1 (3.2)
2	36 (7.8)	35 (7.7)	1 (2.9)	1 (2.9)	51 (11.0)	47 (10.4)	2 (6.5)	3 (9.7)
3	23 (5.0)	18 (4.0)	5 (14.3)	6 (17.1)	24 (5.2)	22 (4.9)	1 (3.2)	1 (3.2)
4	50 (10.8)	39 (8.6)	2 (5.7)	1 (2.9)	43 (9.3)	37 (8.2)	2 (6.5)	2 (6.5)
5	31 (6.7)	19 (4.2)	3 (8.6)	3 (8.6)	45 (9.7)	32 (7.1)	4 (12.9)	6 (19.4)
6	299 (64.6)	45 (9.9)	21 (60.0)	21 (60.0)	278 (60.0)	43 (9.6)	19 (61.3)	18 (58.1)
1-6	462 (99.8)	177 (39.1)	35 (100.0)	35 (100.0)	462 (99.8)	200 (44.4)	31 (100.0)	31 (100.0)
7-12	1 (0.2)	138 (30.5)	0 (0.0)	0 (0.0)	1 (0.2)	132 (29.3)	0 (0.0)	0 (0.0)
13-18	0 (0.0)	51 (11.3)	0 (0.0)	0 (0.0)	0 (0.0)	55 (12.2)	0 (0.0)	0 (0.0)
19-24	0 (0.0)	23 (5.1)	0 (0.0)	0 (0.0)	0 (0.0)	18 (4.0)	0 (0.0)	0 (0.0)
25-30	0 (0.0)	12 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	12 (2.7)	0 (0.0)	0 (0.0)
>30	0 (0.0)	52 (11.5)	0 (0.0)	0 (0.0)	0 (0.0)	33 (7.3)	0 (0.0)	0 (0.0)

Total Cumulative Dose (mg/m^2) per Patient [b]								
Mean (SD)	611.1 (195.67)	291070.6 (287191.58)	369.3 (133.85)	18202.6 (6965.02)	594.6 (200.78)	250046.0 (248228.58)	361.2 (132.43)	18239.2 (5847.97)
Median	666.3	193257.8	421.6	20938.7	660.0	172220.9	403.3	19451.6
Min, Max	99.3, 927.5	1631.5, 1703579.1	75.3, 486.5	3002.9, 24323.3	126.6, 818.1	1017.1, 1805968.9	79.0, 493.4	4008.3, 24670.3
Actual Dose Intensity (mg/m^2/cycle) per Patient [c]								
Mean (SD)	114.0 (16.76)	21724.0 (4979.67)	72.9 (9.84)	3556.5 (565.50)	113.9 (16.21)	21554.2 (4925.49)	68.4 (11.74)	3294.9 (589.13)
Median	118.5	22033.2	76.0	3770.2	117.0	22112.2	70.5	3391.5
Min, Max	60.9, 134.5	1631.5, 30042.3	46.4, 84.7	1904.6, 4234.6	47.6, 138.7	1017.1, 30149.7	31.0, 86.2	1635.2, 4016.1
Relative Dose Intensity (%) [d]								
Mean (SD)	87.7 (12.89)	77.6 (17.78)	91.2 (12.30)	88.9 (14.14)	87.6 (12.47)	77.0 (17.59)	85.5 (14.67)	82.4 (14.73)
Median	91.1	78.7	95.0	94.3	90.0	79.0	88.1	84.8
Min, Max	46.9, 103.5	5.8, 107.3	58.1, 105.9	47.6, 105.9	36.6, 106.7	3.6, 107.7	38.7, 107.7	40.9, 100.4

Source: ADSL, ADEXSUM. Data cutoff: 28FEB2023. Data extraction: 11APR2023.
Percentages were based on N.
Dose Modification includes dose delay, dose interruption, dose reduction and infusion rate decreased for chemotherapy.
Dose Interruption means infusion interruption for intravenous administration, means actual dose missing for capecitabine which is taken orally BID.
[a] Duration of treatment is defined as (last dose date of exposure – first dose date + 1)/30.4375. For patients whose treatments are on-going, cutoff date is considered as 'last dose date of exposure'; for patients who discontinue the treatment, 'last date of exposure'
= min (cutoff date, death date, last dose date + 20) for oxaliplatin and cisplatin
= min (cutoff date, death date, last dose date + 7) for capecitabine
= min (cutoff date, death date, last dose date + 16) for 5-FU.
[b] Total cumulative doses per patient is the sum of all actual dosages per administration at all visits prior to the cutoff date per patient. For 5-FU, 5 days' infusion at one visit will be counted as one dose. For capecitabine, one dose refers to the dose received at one time, and the scheduled doses for capecitabine is twice daily.
[c] Actual Dose Intensity (mg/m2/cycle) = 21 × (total cumulative dose (mg) / BSA) divided by ((last dose date up to cutoff + 21 – first dose date) for oxaliplatin and cisplatin; (last dose date + 8 – first dose date) for capecitabine, (last dose date + 17 – first dose date) for 5-FU); baseline weights are used to derive BSA, unless the weights changes from the baseline weights (or the newly referred body weight) at the visit are greater than 10%.
[d] Relative Dose Intensity = Dose Intensity/protocol specified planned dose intensity, which for cisplatin is 80 mg/m^2/cycle; for oxaliplatin is 130 mg/m^2/cycle; for 5-FU is 4000 mg/m^2/cycle; for capecitabine is 28000 mg/m^2/cycle.
unblind/bgb_a317/bgb_a317_305/fa_2023/dev/pgm/tlfs/t-ex-c-i.sas 26JUN2023 01:30 t-29-ex-i-c-i.rtf

Exposure to tislelizumab doses in study 305, monotherapy pool and combination therapy pool

Table 55: Exposure to tislelizumab doses

	305 Tisle + Chemo - All N=498	Tisle monotherapy 200 mg Q3W N=1534	Tisle combination therapy N=1336
Total number of subjects - n(%)	498 (100.0)	1534 (100.0)	1336 (100.0)
Cumulative dose (mg)			
Mean (SD)	2613.99 (2626.276)	2390.29 (2657.269)	2592.42 (2225.509)
Median	1600.00	1200.00	1800.00
Q1-Q3	800.00-3200.00	600.00-3200.00	1000.00-3600.00
Min-Max	200.0-13400.0	200.0-12400.0	200.0-13400.0
Dose intensity (mg/week)			
Mean (SD)	62.40 (5.401)	64.71 (4.206)	61.52 (6.090)
Median	64.03	66.57	63.31
Q1-Q3	60.22-66.67	64.22-66.67	58.71-66.37
Min-Max	38.4-68.9	30.8-71.8	23.1-71.8
Relative dose intensity (%)			
Mean (SD)	93.60 (8.102)	97.06 (6.309)	92.28 (9.135)
Median	96.04	99.86	94.97
Q1-Q3	90.32-100.00	96.33-100.00	88.07-99.55
Min-Max	57.5-103.3	46.2-107.7	34.7-107.7
Relative dose intensity (categories) - n(%)			
<=75	23 (4.6)	32 (2.1)	81 (6.1)
>75 - 90	97 (19.5)	121 (7.9)	314 (23.5)
>90 - 110	378 (75.9)	1381 (90.0)	941 (70.4)

Patients disposition and reasons for discontinuation in study 305

Table 56: Patient Disposition (Safety Set)

Disposition/Reason	305 Tisle + Chemo - All N=498 n (%)	305 Placebo + Chemo - All N=494 n (%)	Tisle monotherapy 200 mg Q3W N=1534 n (%)
Treatment ongoing #	39 (7.8)	24 (4.9)	147 (9.6)
Discontinued from treatment	459 (92.2)	470 (95.1)	1387 (90.4)
Reason for discontinuation			
Disease Progression	279 (56.0)	332 (67.2)	866 (56.5)
Adverse Event	69 (13.9)	28 (5.7)	160 (10.4)
Withdrawal by Subject	46 (9.2)	37 (7.5)	70 (4.6)
Symptomatic Deterioration	37 (7.4)	46 (9.3)	56 (3.7)
Completed Chemotherapy	10 (2.0)	8 (1.6)	0
Investigator Decision	9 (1.8)	7 (1.4)	19 (1.2)
Start of a New Anti Cancer Therapy	4 (0.8)	2 (0.4)	0
Completed Tislelizumab/Placebo	2 (0.4)	0	0
Other	2 (0.4)	2 (0.4)	51 (3.3)
Non-Compliance with Study Drug	1 (0.2)	3 (0.6)	2 (0.1)
Death	0	0	30 (2.0)
Loss Of Clinical Benefit	0	0	121 (7.9)
Lost to Follow-Up	0	5 (1.0)	3 (0.2)
Protocol Deviation	0	0	2 (0.1)
Study Terminated by Sponsor	0	0	7 (0.5)
Discontinued from study	392 (78.7)	430 (87.0)	1207 (78.7)
Reason for discontinuation			
Death	370 (74.3)	404 (81.8)	1035 (67.5)
Withdrawal by Subject	17 (3.4)	16 (3.2)	40 (2.6)
Lost to Follow-Up	5 (1.0)	10 (2.0)	24 (1.6)
Other	0	0	41 (2.7)
Study Terminated by Sponsor	0	0	67 (4.4)

Disposition/Reason	305 Tisle + Chemo - All N=498 n (%)	305 Placebo + Chemo - All N=494 n (%)	Tisle monotherapy 200 mg Q3W N=1534 n (%)
Data cutoff for Study 305: 28FEB2023. Data cutoff for Tisle monotherapy: Study 001-26AUG2020, Study 102-31MAY2020, Study 203-02NOV2020, Study 204-16SEP2019, Study 208-30JUN2021, Study 302-01DEC2020, Study 303-15JUL2021. #Ongoing at the time of the respective study data cutoff date. Clinical Progression and Clinical Progressive Disease are reported as Symptomatic Deterioration, Radiographic Progression, Radiographic Progressive Disease and Progressive Disease are reported as Disease Progression, Physician Decision is reported as Investigator Decision, Withdraw Consent(in Study 001 & Study 102), Withdrawal of Informed Consent(in Study 204) and Patient Withdraw Consent (in Study 203) are reported as Withdrawal by Subject, Concurrent Antineoplastic Therapy is reported as Protocol Deviation. Loss of clinical benefit was originally collected in Study 303(included in the tisle monotherapy pool) as the explanation of the 'Other' reason. For subjects who discontinued from study treatment due to 'other' and specified as 'death' in CRF are counted as reason='death'.			

Adverse event

All TEAEs discussed in the following sections are treatment-emergent unless otherwise specified. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. All AE data were analyzed according to MedDRA Version 26.0 for AEs and for ADRs.

Since different studies have different TEAE definitions, a harmonized TEAE definition was used for analysis of safety parameters for the safety pools as well as the pivotal Study 305.

A treatment-emergent AE (TEAE) is defined as an AE that had an onset date or a worsening in severity from baseline (pre-treatment) on or after the first dose of study treatment up to 30 days after the last dose of study treatment or initiation of new anticancer therapy, whichever occurred first. TEAEs also included all imAEs identified as per a programmatic algorithmic approach, recorded up to 90 days after the last dose of the study treatment regardless of whether or not the patient started a new anticancer therapy. It should be noted that this differs from the Study 305 CSR analyses where imAEs starting beyond the 30-day time window after the last dose of study treatment were not considered as a TEAE.

As long as an AE met the criteria from the TEAE definition above, a same AE, defined as any consecutive records with the same Preferred Term (PT) was considered as a TEAE until its last record, even if it worsened outside of the treatment emergent period.

Safety data were summarized by number and percentage of patients having at least one TEAE, having at least one TEAE in each primary System Organ Class (SOC) and for each preferred term using MedDRA coding. A patient with multiple occurrences of a TEAE was counted only once in the respective TEAE category. A patient with multiple CTCAE grades for the same PT was summarized under the maximum CTCAE grade recorded for the event. TEAE with missing CTCAE grade were included in the "All grades" column of the summary tables.

Adverse event summary

Table 57: Overview of treatment-emergent adverse events (Safety Set)

Category	Study 305 All patients		Tislelizumab monotherapy pool N=1534 n (%)
	T+PtF N=498 n (%)	P+PtF N=494 n (%)	
TEAEs	495 (99.4)	486 (98.4)	1479 (96.4)
Treatment-related	483 (97.0)	476 (96.4)	1137 (74.1)
Tislelizumab/placebo-related	324 (65.1)	262 (53.0)	1137 (74.1)

Chemotherapy-related	479 (96.2)	475 (96.2)	NA
TEAEs with grade ≥3	346 (69.5)	324 (65.6)	693 (45.2)
Treatment-related	270 (54.2)	246 (49.8)	259 (16.9)
Tislelizumab/placebo-related	135 (27.1)	94 (19.0)	259 (16.9)
Chemotherapy-related	245 (49.2)	241 (48.8)	NA
Serious TEAEs	211 (42.4)	178 (36.0)	533 (34.7)
Treatment-related	115 (23.1)	72 (14.6)	181 (11.8)
Tislelizumab/placebo-related	85 (17.1)	38 (7.7)	181 (11.8)
Chemotherapy-related	89 (17.9)	67 (13.6)	NA
Fatal serious TEAEs	47 (9.4)	42 (8.5)	128 (8.3)
Treatment-related	11 (2.2)	4 (0.8)	17 (1.1)
Tislelizumab/placebo-related	9 (1.8)	4 (0.8)	17 (1.1)
Chemotherapy-related	10 (2.0)	3 (0.6)	NA
TEAEs leading to any treatment discontinuation	115 (23.1)	67 (13.6)	199 (13.0)
Leading to Tislelizumab/placebo discontinuation	79 (15.9)	36 (7.3)	199 (13.0)
Tislelizumab/placebo-related	41 (8.2)	6 (1.2)	87 (5.7)
Chemotherapy-related	22 (4.4)	6 (1.2)	NA
Leading to Chemotherapy discontinuation	105 (21.1)	62 (12.6)	NA
Tislelizumab/placebo-related	37 (7.4)	9 (1.8)	NA
Chemotherapy-related	57 (11.4)	38 (7.7)	NA
TEAEs leading to any treatment modification	381 (76.5)	375 (75.9)	417 (27.2)
Leading to Tislelizumab/placebo modification	244 (49.0)	239 (48.4)	417 (27.2)
Tislelizumab/placebo-related	111 (22.3)	103 (20.9)	252 (16.4)
Chemotherapy-related	188 (37.8)	190 (38.5)	NA
Leading to chemotherapy modification	378 (75.9)	372 (75.3)	NA
Tislelizumab/placebo-related	144 (28.9)	132 (26.7)	NA
Chemotherapy-related	347 (69.7)	350 (70.9)	NA
Immune-mediated TEAEs	154 (30.9)	58 (11.7)	506 (33.0)
Infusion-Related Reaction	33 (6.6)	15 (3.0)	44 (2.9)

- Data cutoff for Study 305: 28FEB2023
- Data cutoff for Tisle monotherapy: Study 001-26AUG2020, Study 102-31MAY2020, Study 203-02NOV2020, Study 204-16SEP2019, Study 208-30JUN2021, Study 302-01DEC2020, Study 303-15JUL2021
NA : Not applicable. Numbers (n) represent counts of patients.
A patient with multiple grades for an AE is only counted under the maximum grade.
The types of dose modification include dose delay, dose interruption, dose reduction, dose frequency change and infusion rate decreased for chemotherapy, dose delay, dose interruption, dose frequency change
and infusion rate decreased for
tislelizumab/placebo. MedDRA Version 26.0,
CTCAE v5.0 for 305 and v4.03 for monotherapy pool.

Most common Adverse Events

The most common **TEAEs by SOC** (≥ 30% in any group) in the Study 305 safety set in the Tislelizumab+Chemotherapy and Placebo+Chemotherapy arm respectively include gastrointestinal disorders (85.9% vs. 82.4%), investigations (73.9% vs.73.1%), metabolism and nutrition disorders (64.7% vs. 64.4%), general disorders and administration site conditions (63.3% vs. 52.2%), blood and lymphatic system disorders (52.6% vs. 52.8%), nervous system disorders (48.6% vs. 52.4%), skin and subcutaneous tissue disorders (39.4% vs. 31.8%), and infections and infestations (30.7% vs. 21.7%). These events primarily represented Grade 1 (mild) or Grade 2 (moderate) events.

Table 58: Treatment-emergent adverse events by System Organ Class, all grades and grade ≥ 3 (Safety Set)

	Study 305 All patients					
	T+PtF N=498		**P+PtF N=494**		**Tislelizumab monotherapy pool N=1534**	
System organ class	**All grades n (%)**	**Grade ≥3 n (%)**	**All grades n (%)**	**Grade ≥3 n (%)**	**All grades n (%)**	**Grade ≥3 n (%)**
Number of patients with at	495 (99.4)	346 (69.5)	486 (98.4)	324 (65.6)	1479 (96.4)	693 (45.2)

	Study 305 All patients					
	T+PtF N=498		P+PtF N=494		Tislelizumab monotherapy pool N=1534	
System organ class	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)
least one event						
Gastrointestinal disorders	428 (85.9)	97 (19.5)	407 (82.4)	83 (16.8)	703 (45.8)	122 (8.0)
Investigations	368 (73.9)	142 (28.5)	361 (73.1)	138 (27.9)	916 (59.7)	180 (11.7)
Metabolism and nutrition disorders	322 (64.7)	63 (12.7)	318 (64.4)	47 (9.5)	680 (44.3)	138 (9.0)
General disorders and administration site conditions	315 (63.3)	49 (9.8)	258 (52.2)	39 (7.9)	665 (43.4)	79 (5.1)
Blood and lymphatic system disorders	262 (52.6)	90 (18.1)	261 (52.8)	99 (20.0)	519 (33.8)	99 (6.5)
Nervous system disorders	242 (48.6)	17 (3.4)	259 (52.4)	14 (2.8)	214 (14.0)	40 (2.6)
Skin and subcutaneous tissue disorders	196 (39.4)	21 (4.2)	157 (31.8)	11 (2.2)	377 (24.6)	16 (1.0)
Infections and infestations	153 (30.7)	43 (8.6)	107 (21.7)	24 (4.9)	492 (32.1)	133 (8.7)
Respiratory, thoracic and mediastinal disorders	138 (27.7)	20 (4.0)	123 (24.9)	11 (2.2)	584 (38.1)	102 (6.6)
Musculoskeletal and connective tissue disorders	105 (21.1)	8 (1.6)	115 (23.3)	5 (1.0)	422 (27.5)	33 (2.2)
Endocrine disorders	76 (15.3)	2 (0.4)	21 (4.3)	0	265 (17.3)	5 (0.3)
Eye disorders	71 (14.3)	3 (0.6)	65 (13.2)	2 (0.4)	131 (8.5)	6 (0.4)
Psychiatric disorders	65 (13.1)	0	66 (13.4)	2 (0.4)	128 (8.3)	3 (0.2)
Hepatobiliary disorders	44 (8.8)	25 (5.0)	38 (7.7)	12 (2.4)	107 (7.0)	47 (3.1)
Vascular disorders	40 (8.0)	9 (1.8)	68 (13.8)	14 (2.8)	122 (8.0)	44 (2.9)
Cardiac disorders	38 (7.6)	6 (1.2)	25 (5.1)	7 (1.4)	147 (9.6)	30 (2.0)
Renal and urinary disorders	37 (7.4)	12 (2.4)	31 (6.3)	6 (1.2)	166 (10.8)	19 (1.2)
Injury, poisoning and procedural complications	34 (6.8)	4 (0.8)	27 (5.5)	5 (1.0)	83 (5.4)	16 (1.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	15 (3.0)	7 (1.4)	14 (2.8)	9 (1.8)	95 (6.2)	26 (1.7)
Immune system disorders	13 (2.6)	3 (0.6)	10 (2.0)	5 (1.0)	14 (0.9)	2 (0.1)
Reproductive system and breast disorders	10 (2.0)	0	9 (1.8)	0	30 (2.0)	1 (0.1)
Ear and labyrinth disorders	6 (1.2)	0	17 (3.4)	1 (0.2)	25 (1.6)	2 (0.1)
Product issues	0	0	0	0	2 (0.1)	1 (0.1)

- Data cutoff for Study 305: 28FEB2023
- Data cutoff for Tisle monotherapy: Study 001-26AUG2020, Study 102-31MAY2020, Study 203-02NOV2020, Study 204-16SEP2019, Study 208-30JUN2021,Study 302-01DEC2020, Study 303-15JUL2021

Numbers (n) represent counts of patients.

A patient with multiple grades for an AE is only counted under the maximum grade. MedDRA Version 26.0, CTCAE v5.0 for Study 305 study and v4.03 for monotherapy pool. Source: [SCS Appendix 1-Table 3.1-4]

Source: Summary of Clinical Safety Table 11

The most frequently occurring treatment emergent adverse events **by PT** (≥ 30% in any group) in the study 305 safety set were nausea, decreased appetite, anaemia, vomiting, platelet count decreased, neutrophil count decreased, and aspartate aminotransferase increased.

Table 59: Treatment-emergent adverse events (at least 10% in any group in the all grades column) by Preferred Term, all grades and grade ≥ 3 (Safety Set)

	Study 305 All patients					
	T+PtF N=498		P+PtF N=494		Tislelizumab monotherapy pool N=1534	
Preferred terms	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)
Number of patients with at least one event	495 (99.4)	346 (69.5)	486 (98.4)	324 (65.6)	1479 (96.4)	693 (45.2)
Nausea	251 (50.4)	14 (2.8)	239 (48.4)	11 (2.2)	155 (10.1)	3 (0.2)
Decreased appetite	205 (41.2)	19 (3.8)	209 (42.3)	18 (3.6)	230 (15.0)	17 (1.1)
Anaemia	197 (39.6)	40 (8.0)	209 (42.3)	53 (10.7)	429 (28.0)	76 (5.0)
Vomiting	180 (36.1)	12 (2.4)	179 (36.2)	13 (2.6)	123 (8.0)	9 (0.6)
Platelet count decreased	177 (35.5)	57 (11.4)	188 (38.1)	59 (11.9)	93 (6.1)	13 (0.8)
Neutrophil count decreased	168 (33.7)	59 (11.8)	163 (33.0)	58 (11.7)	68 (4.4)	12 (0.8)
Aspartate aminotransferase increased	156 (31.3)	17 (3.4)	150 (30.4)	5 (1.0)	327 (21.3)	40 (2.6)
Diarrhoea	135 (27.1)	14 (2.8)	144 (29.1)	11 (2.2)	145 (9.5)	12 (0.8)
Alanine aminotransferase increased	122 (24.5)	11 (2.2)	105 (21.3)	5 (1.0)	303 (19.8)	24 (1.6)
White blood cell count decreased	119 (23.9)	15 (3.0)	135 (27.3)	8 (1.6)	104 (6.8)	8 (0.5)
Weight decreased	108 (21.7)	8 (1.6)	99 (20.0)	2 (0.4)	228 (14.9)	10 (0.7)
Peripheral sensory neuropathy	106 (21.3)	1 (0.2)	118 (23.9)	3 (0.6)	6 (0.4)	0
Pyrexia	100 (20.1)	8 (1.6)	71 (14.4)	3 (0.6)	242 (15.8)	5 (0.3)
Asthenia	97 (19.5)	13 (2.6)	85 (17.2)	13 (2.6)	162 (10.6)	14 (0.9)
Palmar-plantar erythrodysaesthesia syndrome	95 (19.1)	15 (3.0)	94 (19.0)	11 (2.2)	4 (0.3)	0
Constipation	87 (17.5)	1 (0.2)	103 (20.9)	1 (0.2)	193 (12.6)	1 (0.1)
Fatigue	87 (17.5)	12 (2.4)	73 (14.8)	8 (1.6)	134 (8.7)	10 (0.7)
Hypoalbuminaemia	87 (17.5)	4 (0.8)	92 (18.6)	2 (0.4)	181 (11.8)	4 (0.3)
Hypokalaemia	81 (16.3)	21 (4.2)	57 (11.5)	15 (3.0)	116 (7.6)	25 (1.6)
Blood bilirubin increased	77 (15.5)	12 (2.4)	74 (15.0)	7 (1.4)	157 (10.2)	22 (1.4)
Abdominal pain	76 (15.3)	6 (1.2)	81 (16.4)	6 (1.2)	79 (5.1)	8 (0.5)
Neutropenia	75 (15.1)	33 (6.6)	82 (16.6)	34 (6.9)	28 (1.8)	10 (0.7)
Hypoaesthesia	70 (14.1)	1 (0.2)	69 (14.0)	0	21 (1.4)	0
Hypothyroidism	64 (12.9)	1 (0.2)	13 (2.6)	0	199 (13.0)	1 (0.1)
Thrombocytopenia	64 (12.9)	16 (3.2)	59 (11.9)	15 (3.0)	51 (3.3)	4 (0.3)
Abdominal distension	50 (10.0)	0	53 (10.7)	0	57 (3.7)	2 (0.1)
Abdominal pain upper	50 (10.0)	3 (0.6)	55 (11.1)	1 (0.2)	55 (3.6)	4 (0.3)
Pruritus	50 (10.0)	1 (0.2)	15 (3.0)	0	157 (10.2)	0
Insomnia	47 (9.4)	0	53 (10.7)	1 (0.2)	95 (6.2)	1 (0.1)
Cough	23 (4.6)	0	31 (6.3)	0	249 (16.2)	5 (0.3)

- Data cutoff for Study 305: 28FEB2023
- Data cutoff for Tisle monotherapy: Study 001-26AUG2020, Study 102-31MAY2020, Study 203-02NOV2020, Study 204-16SEP2019, Study 208-30JUN2021, Study 302-01DEC2020, Study 303-15JUL2021

Numbers (n) represent counts of patients.

A patient with multiple grades for an AE is only counted under the maximum grade. MedDRA Version 26.0, CTCAE v5.0 for Study 305 study and v4.03 for monotherapy pool.

Table60: Treatment-emergent adverse events by System Organ Class and Preferred Term (first five Preferred Terms in each System Organ Class), all grades and grade ≥ 3 (Safety Set)

Primary system organ class Preferred term	305 Tisle + Chemo - All N=498 n (%)		305 Placebo + Chemo - All N=494 n (%)		Tisle monotherapy 200 mg Q3W N=1534 n (%)		Tisle combination therapy N=1336 n (%)	
	All grades n (%)	Grade >=3 n (%)	All grades n (%)	Grade >=3 n (%)	All grades n (%)	Grade >=3 n (%)	All grades n (%)	Grade >=3 n (%)
Number of subjects with at least one event	495 (99.4)	346 (69.5)	486 (98.4)	324 (65.6)	1479 (96.4)	693 (45.2)	1331 (99.6)	1008 (75.4)
Blood and lymphatic system disorders	262 (52.6)	90 (18.1)	261 (52.8)	99 (20.0)	519 (33.8)	99 (6.5)	965 (72.2)	401 (30.0)
Anaemia	197 (39.6)	40 (8.0)	209 (42.3)	53 (10.7)	429 (28.0)	76 (5.0)	842 (63.0)	178 (13.3)
Neutropenia	75 (15.1)	33 (6.6)	82 (16.6)	34 (6.9)	28 (1.8)	10 (0.7)	323 (24.2)	186 (13.9)
Thrombocytopenia	64 (12.9)	16 (3.2)	59 (11.9)	15 (3.0)	51 (3.3)	4 (0.3)	255 (19.1)	74 (5.5)
Leukopenia	45 (9.0)	7 (1.4)	45 (9.1)	7 (1.4)	48 (3.1)	4 (0.3)	276 (20.7)	89 (6.7)
Lymphopenia	12 (2.4)	1 (0.2)	4 (0.8)	1 (0.2)	14 (0.9)	2 (0.1)	26 (1.9)	4 (0.3)
Cardiac disorders	38 (7.6)	6 (1.2)	25 (5.1)	7 (1.4)	147 (9.6)	30 (2.0)	154 (11.5)	18 (1.3)
Sinus bradycardia	9 (1.8)	0	0	0	2 (0.1)	0	16 (1.2)	0
Myocarditis	4 (0.8)	1 (0.2)	1 (0.2)	0	7 (0.5)	1 (0.1)	13 (1.0)	5 (0.4)
Tachycardia	4 (0.8)	0	2 (0.4)	0	12 (0.8)	0	5 (0.4)	0
Angina pectoris	3 (0.6)	1 (0.2)	1 (0.2)	0	4 (0.3)	0	3 (0.2)	1 (0.1)
Cardiac failure	3 (0.6)	2 (0.4)	1 (0.2)	0	7 (0.5)	3 (0.2)	5 (0.4)	3 (0.2)
Ear and labyrinth disorders	6 (1.2)	0	17 (3.4)	1 (0.2)	25 (1.6)	2 (0.1)	28 (2.1)	0
Tinnitus	3 (0.6)	0	4 (0.8)	0	8 (0.5)	0	12 (0.9)	0
Deafness	2 (0.4)	0	0	0	2 (0.1)	0	4 (0.3)	0
Vertigo	1 (0.2)	0	6 (1.2)	0	9 (0.6)	2 (0.1)	6 (0.4)	0
Deafness unilateral	0	0	1 (0.2)	0	0	0	1 (0.1)	0
Ear disorder	0	0	1 (0.2)	0	0	0	0	0
Endocrine disorders	76 (15.3)	2 (0.4)	21 (4.3)	0	265 (17.3)	5 (0.3)	222 (16.6)	9 (0.7)
Hypothyroidism	64 (12.9)	1 (0.2)	13 (2.6)	0	199 (13.0)	1 (0.1)	169 (12.6)	1 (0.1)
Hyperthyroidism	13 (2.6)	0	2 (0.4)	0	61 (4.0)	0	46 (3.4)	0
Adrenal insufficiency	3 (0.6)	1 (0.2)	2 (0.4)	0	4 (0.3)	1 (0.1)	9 (0.7)	5 (0.4)
Hypopituitarism	2 (0.4)	0	0	0	1 (0.1)	0	5 (0.4)	1 (0.1)
Thyroid disorder	2 (0.4)	0	1 (0.2)	0	1 (0.1)	0	6 (0.4)	0
Eye disorders	71 (14.3)	3 (0.6)	65 (13.2)	2 (0.4)	131 (8.5)	6 (0.4)	131 (9.8)	8 (0.6)
Cataract	17 (3.4)	0	22 (4.5)	1 (0.2)	28 (1.8)	3 (0.2)	25 (1.9)	3 (0.2)
Dry eye	10 (2.0)	0	9 (1.8)	0	13 (0.8)	0	18 (1.3)	0
Vision blurred	8 (1.6)	0	6 (1.2)	1 (0.2)	22 (1.4)	0	17 (1.3)	0
Blepharitis	5 (1.0)	0	1 (0.2)	0	3 (0.2)	0	7 (0.5)	0
Lacrimation	5 (1.0)	0	2 (0.4)	0	6 (0.4)	0	7 (0.5)	0
Gastrointestinal disorders	428 (85.9)	97 (19.5)	407 (82.4)	83 (16.8)	703 (45.8)	122 (8.0)	1050 (78.6)	189 (14.1)
Nausea	251 (50.4)	14 (2.8)	239 (48.4)	11 (2.2)	155 (10.1)	3 (0.2)	587 (43.9)	26 (1.9)
Vomiting	180 (36.1)	12 (2.4)	179 (36.2)	13 (2.6)	123 (8.0)	9 (0.6)	383 (28.7)	20 (1.5)
Diarrhoea	135 (27.1)	14 (2.8)	144 (29.1)	11 (2.2)	145 (9.5)	12 (0.8)	301 (22.5)	31 (2.3)
Constipation	87 (17.5)	1 (0.2)	103 (20.9)	1 (0.2)	193 (12.6)	1 (0.1)	327 (24.5)	1 (0.1)
Abdominal pain	76 (15.3)	6 (1.2)	81 (16.4)	6 (1.2)	79 (5.1)	8 (0.5)	120 (9.0)	6 (0.4)
General disorders and administration site conditions	315 (63.3)	49 (9.8)	258 (52.2)	39 (7.9)	665 (43.4)	79 (5.1)	830 (62.1)	105 (7.9)
Pyrexia	100 (20.1)	8 (1.6)	71 (14.4)	3 (0.6)	242 (15.8)	5 (0.3)	254 (19.0)	9 (0.7)
Asthenia	97 (19.5)	13 (2.6)	85 (17.2)	13 (2.6)	162 (10.6)	14 (0.9)	259 (19.4)	23 (1.7)
Fatigue	87 (17.5)	12 (2.4)	73 (14.8)	8 (1.6)	134 (8.7)	10 (0.7)	173 (12.9)	31 (2.3)
Oedema peripheral	41 (8.2)	0	38 (7.7)	2 (0.4)	66 (4.3)	4 (0.3)	82 (6.1)	0
Malaise	37 (7.4)	2 (0.4)	41 (8.3)	0	88 (5.7)	8 (0.5)	170 (12.7)	14 (1.0)
Hepatobiliary disorders	44 (8.8)	25 (5.0)	38 (7.7)	12 (2.4)	107 (7.0)	47 (3.1)	90 (6.7)	41 (3.1)
Hepatic function abnormal	12 (2.4)	3 (0.6)	11 (2.2)	1 (0.2)	20 (1.3)	7 (0.5)	30 (2.2)	7 (0.5)
Cholangitis	6 (1.2)	4 (0.8)	1 (0.2)	1 (0.2)	0	0	6 (0.4)	4 (0.3)
Hyperbilirubinaemia	6 (1.2)	0	8 (1.6)	1 (0.2)	13 (0.8)	2 (0.1)	11 (0.8)	0
Immune-mediated hepatitis	5 (1.0)	5 (1.0)	1 (0.2)	1 (0.2)	7 (0.5)	5 (0.3)	11 (0.8)	11 (0.8)
Jaundice cholestatic	3 (0.6)	3 (0.6)	4 (0.8)	3 (0.6)	4 (0.3)	3 (0.2)	3 (0.2)	3 (0.2)

Primary system organ class Preferred term	305 Tisle + Chemo - All N=498 n (%)		305 Placebo + Chemo - All N=494 n (%)		Tisle monotherapy 200 mg Q3W N=1534 n (%)		Tisle combination therapy N=1336 n (%)	
	All grades n (%)	Grade >=3 n (%)	All grades n (%)	Grade >=3 n (%)	All grades n (%)	Grade >=3 n (%)	All grades n (%)	Grade >=3 n (%)
Immune system disorders	13 (2.6)	3 (0.6)	10 (2.0)	5 (1.0)	14 (0.9)	2 (0.1)	26 (1.9)	8 (0.6)
Drug hypersensitivity	8 (1.6)	1 (0.2)	3 (0.6)	0	2 (0.1)	0	15 (1.1)	4 (0.3)
Anaphylactic reaction	2 (0.4)	2 (0.4)	3 (0.6)	3 (0.6)	1 (0.1)	1 (0.1)	2 (0.1)	2 (0.1)
Food allergy	2 (0.4)	0	0	0	0	0	2 (0.1)	0
Contrast media allergy	1 (0.2)	0	2 (0.4)	0	6 (0.4)	1 (0.1)	2 (0.1)	0
Haemophagocytic lymphohistiocytosis	1 (0.2)	0	0	0	0	0	1 (0.1)	0
Infections and infestations	153 (30.7)	43 (8.6)	107 (21.7)	24 (4.9)	492 (32.1)	133 (8.7)	457 (34.2)	122 (9.1)
Pneumonia	30 (6.0)	9 (1.8)	27 (5.5)	14 (2.8)	152 (9.9)	74 (4.8)	147 (11.0)	53 (4.0)
Upper respiratory tract infection	24 (4.8)	3 (0.6)	13 (2.6)	0	140 (9.1)	12 (0.8)	107 (8.0)	12 (0.9)
COVID-19	22 (4.4)	2 (0.4)	16 (3.2)	1 (0.2)	4 (0.3)	2 (0.1)	25 (1.9)	2 (0.1)
Conjunctivitis	11 (2.2)	0	8 (1.6)	0	19 (1.2)	0	27 (2.0)	0
Nasopharyngitis	11 (2.2)	0	5 (1.0)	0	40 (2.6)	0	29 (2.2)	0
Injury, poisoning and procedural complications	34 (6.8)	4 (0.8)	27 (5.5)	5 (1.0)	83 (5.4)	16 (1.0)	100 (7.5)	13 (1.0)
Procedural pain	4 (0.8)	0	2 (0.4)	0	7 (0.5)	0	8 (0.6)	0
Contusion	2 (0.4)	0	2 (0.4)	0	6 (0.4)	0	8 (0.6)	0
Fall	2 (0.4)	0	3 (0.6)	0	5 (0.3)	2 (0.1)	5 (0.4)	0
Fracture	2 (0.4)	0	0	0	1 (0.1)	0	3 (0.2)	0
Skin laceration	2 (0.4)	0	1 (0.2)	0	0	0	2 (0.1)	0
Investigations	368 (73.9)	142 (28.5)	361 (73.1)	138 (27.9)	916 (59.7)	180 (11.7)	1110 (83.1)	533 (39.9)
Platelet count decreased	177 (35.5)	57 (11.4)	188 (38.1)	59 (11.9)	93 (6.1)	13 (0.8)	480 (35.9)	115 (8.6)
Neutrophil count decreased	168 (33.7)	59 (11.8)	163 (33.0)	58 (11.7)	68 (4.4)	12 (0.8)	658 (49.3)	360 (26.9)
Aspartate aminotransferase increased	156 (31.3)	17 (3.4)	150 (30.4)	5 (1.0)	327 (21.3)	40 (2.6)	424 (31.7)	32 (2.4)
Alanine aminotransferase increased	122 (24.5)	11 (2.2)	105 (21.3)	5 (1.0)	303 (19.8)	24 (1.6)	408 (30.5)	32 (2.4)
White blood cell count decreased	119 (23.9)	15 (3.0)	135 (27.3)	8 (1.6)	104 (6.8)	8 (0.5)	596 (44.6)	148 (11.1)
Metabolism and nutrition disorders	322 (64.7)	63 (12.7)	318 (64.4)	47 (9.5)	680 (44.3)	138 (9.0)	921 (68.9)	190 (14.2)
Decreased appetite	205 (41.2)	19 (3.8)	209 (42.3)	18 (3.6)	230 (15.0)	17 (1.1)	559 (41.8)	44 (3.3)
Hypoalbuminaemia	87 (17.5)	4 (0.8)	92 (18.6)	2 (0.4)	181 (11.8)	4 (0.3)	261 (19.5)	5 (0.4)
Hypokalaemia	81 (16.3)	21 (4.2)	57 (11.5)	15 (3.0)	116 (7.6)	25 (1.6)	224 (16.8)	57 (4.3)
Hyponatraemia	36 (7.2)	8 (1.6)	32 (6.5)	5 (1.0)	136 (8.9)	41 (2.7)	200 (15.0)	54 (4.0)
Hypoproteinaemia	22 (4.4)	0	25 (5.1)	2 (0.4)	52 (3.4)	0	82 (6.1)	0
Musculoskeletal and connective tissue disorders	105 (21.1)	8 (1.6)	115 (23.3)	5 (1.0)	422 (27.5)	33 (2.2)	435 (32.6)	22 (1.6)
Back pain	33 (6.6)	3 (0.6)	40 (8.1)	1 (0.2)	114 (7.4)	7 (0.5)	115 (8.6)	4 (0.3)
Arthralgia	22 (4.4)	0	22 (4.5)	0	138 (9.0)	4 (0.3)	129 (9.7)	1 (0.1)
Pain in extremity	18 (3.6)	0	21 (4.3)	0	60 (3.9)	3 (0.2)	123 (9.2)	3 (0.2)
Myalgia	14 (2.8)	0	17 (3.4)	0	26 (1.7)	0	61 (4.6)	3 (0.2)
Muscular weakness	6 (1.2)	0	9 (1.8)	2 (0.4)	21 (1.4)	7 (0.5)	31 (2.3)	2 (0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	15 (3.0)	7 (1.4)	14 (2.8)	9 (1.8)	95 (6.2)	26 (1.7)	62 (4.6)	14 (1.0)
Tumour haemorrhage	5 (1.0)	2 (0.4)	4 (0.8)	4 (0.8)	2 (0.1)	2 (0.1)	6 (0.4)	3 (0.2)
Cancer pain	3 (0.6)	1 (0.2)	1 (0.2)	0	46 (3.0)	6 (0.4)	24 (1.8)	3 (0.2)
Pyogenic granuloma	2 (0.4)	0	0	0	0	0	2 (0.1)	0
Iris neoplasm	1 (0.2)	0	0	0	0	0	1 (0.1)	0
Malignant pleural	1 (0.2)	1 (0.2)	0	0	0	0	1 (0.1)	1 (0.1)

Primary system organ class Preferred term	305 Tisle + Chemo - All N=498 n (%)		305 Placebo + Chemo - All N=494 n (%)		Tisle monotherapy 200 mg Q3W N=1534 n (%)		Tisle combination therapy N=1336 n (%)	
	All grades n (%)	Grade >=3 n (%)	All grades n (%)	Grade >=3 n (%)	All grades n (%)	Grade >=3 n (%)	All grades n (%)	Grade >=3 n (%)
Nervous system disorders	242 (48.6)	17 (3.4)	259 (52.4)	14 (2.8)	214 (14.0)	40 (2.6)	578 (43.3)	53 (4.0)
Peripheral sensory neuropathy	106 (21.3)	1 (0.2)	118 (23.9)	3 (0.6)	6 (0.4)	0	192 (14.4)	12 (0.9)
Hypoaesthesia	70 (14.1)	1 (0.2)	69 (14.0)	0	21 (1.4)	0	156 (11.7)	2 (0.1)
Dizziness	40 (8.0)	1 (0.2)	42 (8.5)	1 (0.2)	60 (3.9)	2 (0.1)	106 (7.9)	4 (0.3)
Dysgeusia	25 (5.0)	0	18 (3.6)	0	8 (0.5)	0	39 (2.9)	0
Headache	20 (4.0)	0	18 (3.6)	0	52 (3.4)	4 (0.3)	58 (4.3)	1 (0.1)
Product issues	0	0	0	0	2 (0.1)	1 (0.1)	1 (0.1)	0
Device occlusion	0	0	0	0	1 (0.1)	1 (0.1)	0	0
Thrombosis in device	0	0	0	0	1 (0.1)	0	1 (0.1)	0
Psychiatric disorders	65 (13.1)	0	66 (13.4)	2 (0.4)	128 (8.3)	3 (0.2)	173 (12.9)	4 (0.3)
Insomnia	47 (9.4)	0	53 (10.7)	1 (0.2)	95 (6.2)	1 (0.1)	126 (9.4)	0
Anxiety	4 (0.8)	0	3 (0.6)	0	16 (1.0)	0	11 (0.8)	0
Frigophobia	3 (0.6)	0	0	0	0	0	3 (0.2)	0
Depression	2 (0.4)	0	5 (1.0)	0	11 (0.7)	1 (0.1)	6 (0.4)	1 (0.1)
Adjustment disorder	1 (0.2)	0	0	0	0	0	1 (0.1)	0
Renal and urinary disorders	37 (7.4)	12 (2.4)	31 (6.3)	6 (1.2)	166 (10.8)	19 (1.2)	115 (8.6)	22 (1.6)
Acute kidney injury	8 (1.6)	6 (1.2)	4 (0.8)	4 (0.8)	3 (0.2)	2 (0.1)	19 (1.4)	10 (0.7)
Proteinuria	7 (1.4)	0	4 (0.8)	0	88 (5.7)	4 (0.3)	19 (1.4)	0
Dysuria	4 (0.8)	0	6 (1.2)	0	10 (0.7)	0	11 (0.8)	0
Renal failure	3 (0.6)	2 (0.4)	1 (0.2)	1 (0.2)	8 (0.5)	4 (0.3)	4 (0.3)	2 (0.1)
Urinary retention	3 (0.6)	1 (0.2)	4 (0.8)	0	3 (0.2)	0	5 (0.4)	1 (0.1)
Reproductive system and breast disorders	10 (2.0)	0	9 (1.8)	0	30 (2.0)	1 (0.1)	32 (2.4)	2 (0.1)
Acquired hydrocele	1 (0.2)	0	0	0	2 (0.1)	0	2 (0.1)	0
Benign prostatic hyperplasia	1 (0.2)	0	1 (0.2)	0	7 (0.5)	0	8 (0.6)	1 (0.1)
Gynaecomastia	1 (0.2)	0	1 (0.2)	0	0	0	4 (0.3)	0
Menstruation irregular	1 (0.2)	0	1 (0.2)	0	0	0	1 (0.1)	0
Pelvic fluid collection	1 (0.2)	0	0	0	2 (0.1)	1 (0.1)	3 (0.2)	0
Respiratory, thoracic and mediastinal disorders	138 (27.7)	20 (4.0)	123 (24.9)	11 (2.2)	584 (38.1)	102 (6.6)	547 (40.9)	83 (6.2)
Dyspnoea	29 (5.8)	2 (0.4)	32 (6.5)	1 (0.2)	119 (7.8)	21 (1.4)	111 (8.3)	11 (0.8)
Productive cough	28 (5.6)	0	20 (4.0)	0	77 (5.0)	3 (0.2)	97 (7.3)	1 (0.1)
Cough	23 (4.6)	0	31 (6.3)	0	249 (16.2)	5 (0.3)	155 (11.6)	4 (0.3)
Hiccups	20 (4.0)	1 (0.2)	17 (3.4)	0	7 (0.5)	0	53 (4.0)	1 (0.1)
Pneumonitis	15 (3.0)	4 (0.8)	0	0	51 (3.3)	16 (1.0)	84 (6.3)	23 (1.7)
Skin and subcutaneous tissue disorders	196 (39.4)	21 (4.2)	157 (31.8)	11 (2.2)	377 (24.6)	16 (1.0)	623 (46.6)	51 (3.8)
Palmar-plantar erythrodysaesthesia syndrome	95 (19.1)	15 (3.0)	94 (19.0)	11 (2.2)	4 (0.3)	0	108 (8.1)	18 (1.3)
Pruritus	50 (10.0)	1 (0.2)	15 (3.0)	0	157 (10.2)	0	130 (9.7)	3 (0.2)
Rash	41 (8.2)	0	17 (3.4)	0	138 (9.0)	6 (0.4)	176 (13.2)	15 (1.1)
Skin hyperpigmentation	20 (4.0)	0	14 (2.8)	0	0	0	25 (1.9)	0
Rash maculo-papular	13 (2.6)	2 (0.4)	5 (1.0)	0	20 (1.3)	1 (0.1)	25 (1.9)	3 (0.2)
Vascular disorders	40 (8.0)	9 (1.8)	68 (13.8)	14 (2.8)	122 (8.0)	44 (2.9)	146 (10.9)	30 (2.2)
Hypertension	12 (2.4)	7 (1.4)	23 (4.7)	7 (1.4)	70 (4.6)	32 (2.1)	49 (3.7)	18 (1.3)
Hypotension	9 (1.8)	0	7 (1.4)	2 (0.4)	22 (1.4)	4 (0.3)	30 (2.2)	5 (0.4)
Vascular pain	5 (1.0)	0	8 (1.6)	0	0	0	6 (0.4)	0
Phlebitis	4 (0.8)	0	5 (1.0)	0	3 (0.2)	0	14 (1.0)	0
Venous thrombosis limb	3 (0.6)	0	1 (0.2)	0	4 (0.3)	1 (0.1)	13 (1.0)	1 (0.1)

Table 61: Treatment-emergent adverse events by maximum grade (Safety Set)

Maximum grade	Study 305 T+PtF N=498 n (%)	Study 305 +PtF N=494 n (%)	Tislelizumab monotherapy pool 200 mg Q3W N=1534 n (%)	Tislelizumab combination therapy pool N=1336 n (%)
Number of subjects with at least one event	495 (99.4)	486 (98.4)	1479 (96.4)	1331 (99.6)
Grade 1	16 (3.2)	20 (4.0)	206 (13.4)	33 (2.5)
Grade 2	133 (26.7)	142 (28.7)	580 (37.8)	290 (21.7)
Grade 3	263 (52.8)	249 (50.4)	472 (30.8)	676 (50.6)
Grade 4	36 (7.2)	33 (6.7)	93 (6.1)	238 (17.8)
Grade 5	47 (9.4)	42 (8.5)	128 (8.3)	94 (7.0)
Missing	0	0	0	0

- Data cutoff for 305: 28FEB2023
- Data cutoff for Tisle monotherapy: 001-26AUG2020, 102-31MAY2020, 203-02NOV2020, 204-16SEP2019, 208-30JUN2021,
302-01DEC2020, 303-15JUL2021
- Data cutoff for Tisle combination therapy: 206-31DEC2019, 304-26OCT2020, 305-28FEB2023, 306-28FEB2022, 307-30SEP2020
Numbers (n) represent counts of subjects.
A subject with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version 26.0, CTCAE version v4.03 for all studies (from either tisle monotherapy or combination therapy)
except for studies 304/305/307: version v5.

Given the scales used for the causality assessment of AEs are different in the studies forming part of the Tislelizumab monotherapy pool, for SCS analyses purposes, treatment-related AEs were defined as:

- Adverse event noted by the investigator as related, definitely related, probably related, possibly related, or with missing causal relationship in Studies 102, 203, and 204 for the Tislelizumab monotherapy pool.
- Adverse event noted by the investigator as related to study drug or with missing causal relationship in Studies 001, 208, 302, and 303 for the Tislelizumab monotherapy pool.

Table 62: Treatment-emergent adverse events (incidence ≥ 10% in the T+PtF group) all grades and grade ≥ 3 related to any component of study treatment by Preferred Term (Safety Set)

	305 Tisle + Chemo - All N=498		305 Placebo + Chemo - All N=494		Tisle monotherapy 200 mg Q3W N=1534		Tisle combination therapy N=1336	
Preferred terms	All grades n (%)	Grade >=3 n (%)	All grades n (%)	Grade >=3 n (%)	All grades n (%)	Grade >=3 n (%)	All grades n (%)	Grade >=3 n (%)
Number of subjects with at least one event	483 (97.0)	270 (54.2)	476 (96.4)	246 (49.8)	1137 (74.1)	259 (16.9)	1308 (97.9)	872 (65.3)
Nausea	237 (47.6)	13 (2.6)	232 (47.0)	9 (1.8)	65 (4.2)	1 (0.1)	548 (41.0)	23 (1.7)
Decreased appetite	182 (36.5)	14 (2.8)	185 (37.4)	16 (3.2)	91 (5.9)	3 (0.2)	488 (36.5)	29 (2.2)
Platelet count decreased	175 (35.1)	56 (11.2)	183 (37.0)	57 (11.5)	49 (3.2)	4 (0.3)	473 (35.4)	113 (8.5)
Neutrophil count decreased	168 (33.7)	59 (11.8)	160 (32.4)	57 (11.5)	45 (2.9)	6 (0.4)	655 (49.0)	359 (26.9)
Vomiting	161 (32.3)	11 (2.2)	162 (32.8)	12 (2.4)	35 (2.3)	1 (0.1)	334 (25.0)	17 (1.3)
Anaemia	158 (31.7)	25 (5.0)	163 (33.0)	37 (7.5)	158 (10.3)	21 (1.4)	755 (56.5)	144 (10.8)
Aspartate aminotransferase increased	146 (29.3)	13 (2.6)	137 (27.7)	4 (0.8)	234 (15.3)	22 (1.4)	389 (29.1)	26 (1.9)
White blood cell count decreased	119 (23.9)	15 (3.0)	134 (27.1)	8 (1.6)	75 (4.9)	4 (0.3)	595 (44.5)	146 (10.9)
Alanine aminotransferase	113 (22.7)	8 (1.6)	97 (19.6)	4 (0.8)	228 (14.9)	16 (1.0)	374 (28.0)	29 (2.2)
Diarrhoea	111 (22.3)	12 (2.4)	126 (25.5)	11 (2.2)	71 (4.6)	6 (0.4)	211 (15.8)	22 (1.6)
Peripheral sensory neuropathy	106 (21.3)	1 (0.2)	116 (23.5)	3 (0.6)	2 (0.1)	0	190 (14.2)	12 (0.9)
Palmar-plantar erythrodysaesthesia syndrome	95 (19.1)	15 (3.0)	93 (18.8)	10 (2.0)	3 (0.2)	0	108 (8.1)	18 (1.3)
Asthenia	76 (15.3)	10 (2.0)	71 (14.4)	7 (1.4)	85 (5.5)	1 (0.1)	217 (16.2)	16 (1.2)
Fatigue	75 (15.1)	9 (1.8)	61 (12.3)	6 (1.2)	77 (5.0)	3 (0.2)	145 (10.9)	24 (1.8)
Neutropenia	74 (14.9)	33 (6.6)	80 (16.2)	34 (6.9)	22 (1.4)	7 (0.5)	321 (24.0)	185 (13.8)
Hypoaesthesia	69 (13.9)	1 (0.2)	67 (13.6)	0	7 (0.5)	0	146 (10.9)	2 (0.1)
Blood bilirubin increased	61 (12.2)	7 (1.4)	58 (11.7)	3 (0.6)	102 (6.6)	6 (0.4)	163 (12.2)	8 (0.6)
Thrombocytopenia	60 (12.0)	15 (3.0)	56 (11.3)	14 (2.8)	30 (2.0)	1 (0.1)	247 (18.5)	73 (5.5)
Weight decreased	58 (11.6)	0	54 (10.9)	0	33 (2.2)	2 (0.1)	125 (9.4)	3 (0.2)
Hypothyroidism	57 (11.4)	1 (0.2)	13 (2.6)	0	184 (12.0)	1 (0.1)	158 (11.8)	1 (0.1)

Source: Summary of Clinical Safety Appendix 2, excerpt from Comb_Table 1.3-4

Table 63: Treatment-emergent adverse events (incidence ≥ 5% in the T+PtF group) all grades and grade ≥ 3 related to tislelizumab/placebo by Preferred Term (Safety Set)

	305 Tisle + Chemo - All _N=498_		305 Placebo + Chemo - All _N=494_		Tisle monotherapy 200 mg Q3W _N=1534_		Tisle combination therapy _N=1336_	
	All grades	Grade >=3	All grades	Grade >=3	All grades	Grade >=3	All grades	Grade >=3
Preferred Terms	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Number of subjects with at least one event	324 (65.1)	135 (27.1)	262 (53.0)	94 (19.0)	1137 (74.1)	259 (16.9)	997 (74.6)	418 (31.3)
Hypothyroidism	56 (11.2)	1 (0.2)	13 (2.6)	0	184 (12.0)	1 (0.1)	156 (11.7)	1 (0.1)
Aspartate aminotransferase increased	53 (10.6)	11 (2.2)	51 (10.3)	2 (0.4)	234 (15.3)	22 (1.4)	193 (14.4)	21 (1.6)
Nausea	53 (10.6)	1 (0.2)	49 (9.9)	3 (0.6)	65 (4.2)	1 (0.1)	117 (8.8)	5 (0.4)
Anaemia	51 (10.2)	6 (1.2)	52 (10.5)	10 (2.0)	158 (10.3)	21 (1.4)	240 (18.0)	44 (3.3)
Platelet count decreased	46 (9.2)	16 (3.2)	45 (9.1)	19 (3.8)	49 (3.2)	4 (0.3)	150 (11.2)	35 (2.6)
Neutrophil count decreased	45 (9.0)	15 (3.0)	39 (7.9)	10 (2.0)	45 (2.9)	6 (0.4)	168 (12.6)	81 (6.1)
Decreased appetite	43 (8.6)	4 (0.8)	39 (7.9)	3 (0.6)	91 (5.9)	3 (0.2)	142 (10.6)	9 (0.7)
Alanine aminotransferase increased	42 (8.4)	7 (1.4)	37 (7.5)	3 (0.6)	228 (14.9)	16 (1.0)	193 (14.4)	21 (1.6)
Fatigue	33 (6.6)	5 (1.0)	31 (6.3)	2 (0.4)	77 (5.0)	3 (0.2)	65 (4.9)	13 (1.0)
Pruritus	32 (6.4)	1 (0.2)	5 (1.0)	0	114 (7.4)	0	78 (5.8)	2 (0.1)
Asthenia	31 (6.2)	5 (1.0)	31 (6.3)	5 (1.0)	85 (5.5)	1 (0.1)	95 (7.1)	6 (0.4)
White blood cell count decreased	30 (6.0)	2 (0.4)	35 (7.1)	2 (0.4)	75 (4.9)	4 (0.3)	154 (11.5)	42 (3.1)
Vomiting	29 (5.8)	1 (0.2)	33 (6.7)	4 (0.8)	35 (2.3)	1 (0.1)	69 (5.2)	3 (0.2)
Diarrhoea	27 (5.4)	3 (0.6)	38 (7.7)	6 (1.2)	71 (4.6)	6 (0.4)	68 (5.1)	9 (0.7)
Rash	25 (5.0)	0	7 (1.4)	0	110 (7.2)	4 (0.3)	130 (9.7)	15 (1.1)

Table 64: Treatment-emergent adverse events (incidence ≥ 10% in the T+PtF group) all grades and grade ≥ 3 related to chemotherapy by Preferred Term (Safety Set)

	305 Tisle + Chemo - All N=498		305 Placebo + Chemo - All N=494		Tisle combination therapy N=1336	
Preferred Terms	All grades n (%)	Grade >=3 n (%)	All grades n (%)	Grade >=3 n (%)	All grades n (%)	Grade >=3 n (%)
Number of subjects with at least one event	479 (96.2)	245 (49.2)	475 (96.2)	241 (48.8)	1301 (97.4)	820 (61.4)
Nausea	235 (47.2)	13 (2.6)	230 (46.6)	9 (1.8)	541 (40.5)	22 (1.6)
Decreased appetite	178 (35.7)	13 (2.6)	185 (37.4)	16 (3.2)	477 (35.7)	27 (2.0)
Platelet count decreased	175 (35.1)	56 (11.2)	181 (36.6)	57 (11.5)	470 (35.2)	112 (8.4)
Neutrophil count decreased	168 (33.7)	59 (11.8)	160 (32.4)	57 (11.5)	653 (48.9)	358 (26.8)
Vomiting	160 (32.1)	11 (2.2)	162 (32.8)	12 (2.4)	331 (24.8)	16 (1.2)
Anaemia	156 (31.3)	24 (4.8)	163 (33.0)	37 (7.5)	749 (56.1)	140 (10.5)
Aspartate aminotransferase increased	142 (28.5)	11 (2.2)	136 (27.5)	4 (0.8)	367 (27.5)	18 (1.3)
White blood cell count decreased	119 (23.9)	15 (3.0)	134 (27.1)	8 (1.6)	593 (44.4)	146 (10.9)
Alanine aminotransferase increased	109 (21.9)	5 (1.0)	96 (19.4)	3 (0.6)	353 (26.4)	21 (1.6)
Diarrhoea	108 (21.7)	11 (2.2)	124 (25.1)	10 (2.0)	198 (14.8)	19 (1.4)
Peripheral sensory neuropathy	106 (21.3)	1 (0.2)	115 (23.3)	3 (0.6)	189 (14.1)	12 (0.9)
Palmar-plantar erythrodysaesthesia syndrome	95 (19.1)	15 (3.0)	93 (18.8)	10 (2.0)	108 (8.1)	18 (1.3)
Neutropenia	74 (14.9)	33 (6.6)	80 (16.2)	34 (6.9)	318 (23.8)	184 (13.8)
Asthenia	72 (14.5)	10 (2.0)	70 (14.2)	7 (1.4)	209 (15.6)	16 (1.2)
Fatigue	68 (13.7)	6 (1.2)	59 (11.9)	5 (1.0)	133 (10.0)	19 (1.4)
Hypoaesthesia	68 (13.7)	1 (0.2)	67 (13.6)	0	143 (10.7)	2 (0.1)
Thrombocytopenia	60 (12.0)	15 (3.0)	56 (11.3)	14 (2.8)	244 (18.3)	71 (5.3)
Blood bilirubin increased	58 (11.6)	6 (1.2)	57 (11.5)	2 (0.4)	144 (10.8)	6 (0.4)
Weight decreased	57 (11.4)	0	54 (10.9)	0	122 (9.1)	3 (0.2)
Leukopenia	44 (8.8)	6 (1.2)	44 (8.9)	7 (1.4)	272 (20.4)	86 (6.4)

Source: Summary of Clinical Safety Appendix 2, excerpt from Comb_Table 3.1-7.1

Serious adverse event/death/other significant events

Serious Adverse Events (SAEs)

Table 65: Serious TEAEs (at least 1% in any group) by Preferred Term (Safety Set)

Preferred terms	Study 305 All patients		Tislelizumab monotherapy pool
	T+PtF N=498 n (%)	P+PtF N=494 n (%)	N=1534 n (%)
Any preferred term	211 (42.4)	178 (36.0)	533 (34.7)
Platelet count decreased	16 (3.2)	17 (3.4)	4 (0.3)
Pneumonia	12 (2.4)	14 (2.8)	79 (5.1)
Death	10 (2.0)	5 (1.0)	16 (1.0)
Decreased appetite	7 (1.4)	5 (1.0)	11 (0.7)
Vomiting	7 (1.4)	5 (1.0)	8 (0.5)
Cholangitis	6 (1.2)	1 (0.2)	0
Diarrhoea	6 (1.2)	4 (0.8)	5 (0.3)
Gastric haemorrhage	6 (1.2)	1 (0.2)	3 (0.2)
Gastrointestinal haemorrhage	6 (1.2)	2 (0.4)	2 (0.1)
General physical health deterioration	6 (1.2)	7 (1.4)	10 (0.7)
Pyrexia	6 (1.2)	6 (1.2)	15 (1.0)
Sepsis	6 (1.2)	2 (0.4)	5 (0.3)
Ascites	5 (1.0)	5 (1.0)	11 (0.7)
Aspartate aminotransferase increased	5 (1.0)	1 (0.2)	8 (0.5)
Ileus	5 (1.0)	4 (0.8)	1 (0.1)
Immune-mediated hepatitis	5 (1.0)	1 (0.2)	4 (0.3)
Pneumonitis	5 (1.0)	0	24 (1.6)
Pulmonary embolism	5 (1.0)	4 (0.8)	8 (0.5)
Acute kidney injury	4 (0.8)	2 (0.4)	2 (0.1)
Anaemia	4 (0.8)	10 (2.0)	4 (0.3)
Nausea	4 (0.8)	5 (1.0)	4 (0.3)
Upper gastrointestinal haemorrhage	4 (0.8)	7 (1.4)	14 (0.9)
Dysphagia	2 (0.4)	3 (0.6)	16 (1.0)
Dyspnoea	0	0	16 (1.0)
Obstruction gastric	1 (0.2)	5 (1.0)	1 (0.1)

Data cutoff for Study 305: 28FEB2023
Data cutoff for Tisle monotherapy: Study 001-26AUG2020, Study 102-31MAY2020, Study 203-02NOV2020, Study 204-16SEP2019, Study 208-30JUN2021, Study 302-01DEC2020, Study 303-15JUL2021
Numbers (n) represent counts of patients. MedDRA Version 26.0.

Drug-related Serious Adverse Events (SAEs)

Table 66: Serious TEAEs (incidence ≥ 0.5% in the T+PtF group) related to any component of study treatment by Preferred Term (Safety Set)

Preferred terms	305 Tisle + Chemo - All N=498 n (%)	305 Placebo + Chemo - All N=494 n (%)	Tisle monotherapy 200 mg Q3W N=1534 n (%)	Tisle combination therapy N=1336 n (%)
Any preferred term	115 (23.1)	72 (14.6)	181 (11.8)	338 (25.3)
Platelet count decreased	16 (3.2)	17 (3.4)	4 (0.3)	26 (1.9)
Vomiting	6 (1.2)	5 (1.0)	4 (0.3)	12 (0.9)
Decreased appetite	5 (1.0)	4 (0.8)	2 (0.1)	11 (0.8)
Diarrhoea	5 (1.0)	4 (0.8)	5 (0.3)	12 (0.9)
Immune-mediated hepatitis	5 (1.0)	1 (0.2)	4 (0.3)	10 (0.7)
Pneumonitis	5 (1.0)	0	23 (1.5)	38 (2.8)
Anaemia	4 (0.8)	7 (1.4)	2 (0.1)	16 (1.2)
Aspartate aminotransferase increased	4 (0.8)	1 (0.2)	6 (0.4)	11 (0.8)
Death	4 (0.8)	0	2 (0.1)	5 (0.4)
Nausea	4 (0.8)	3 (0.6)	3 (0.2)	9 (0.7)
Acute kidney injury	3 (0.6)	2 (0.4)	0	8 (0.6)
Alanine aminotransferase increased	3 (0.6)	0	5 (0.3)	9 (0.7)
Colitis	3 (0.6)	3 (0.6)	1 (0.1)	8 (0.6)
Hepatic function abnormal	3 (0.6)	0	2 (0.1)	7 (0.5)
Sepsis	3 (0.6)	0	0	3 (0.2)

Table 67: Serious TEAEs (incidence ≥ 0.5% in the T+PtF group) related to tislelizumab/placebo by Preferred Term (Safety Set)

Preferred terms	305 Tisle + Chemo - All N=498 n (%)	305 Placebo + Chemo - All N=494 n (%)	Tisle monotherapy 200 mg Q3W N=1534 n (%)	Tisle combination therapy N=1336 n (%)
Any preferred term	85 (17.1)	38 (7.7)	181 (11.8)	243 (18.2)
Platelet count decreased	9 (1.8)	8 (1.6)	4 (0.3)	12 (0.9)
Immune-mediated hepatitis	5 (1.0)	1 (0.2)	4 (0.3)	10 (0.7)
Pneumonitis	5 (1.0)	0	23 (1.5)	38 (2.8)
Aspartate aminotransferase increased	4 (0.8)	0	6 (0.4)	11 (0.8)
Death	4 (0.8)	0	2 (0.1)	5 (0.4)
Alanine aminotransferase increased	3 (0.6)	0	5 (0.3)	9 (0.7)
Colitis	3 (0.6)	1 (0.2)	1 (0.1)	7 (0.5)
Decreased appetite	3 (0.6)	0	2 (0.1)	5 (0.4)
Diarrhoea	3 (0.6)	3 (0.6)	5 (0.3)	9 (0.7)

Table 68: Serious TEAEs (incidence ≥ 0.5% in the T+PtF group) related to any component of chemotherapy by Preferred Term (Safety Set)

Preferred terms	305 Tisle + Chemo - All N=498 n (%)	305 Placebo + Chemo - All N=494 n (%)	Tisle combination therapy N=1336 n (%)
Any preferred term	89 (17.9)	67 (13.6)	246 (18.4)
Platelet count decreased	16 (3.2)	17 (3.4)	26 (1.9)
Vomiting	6 (1.2)	5 (1.0)	11 (0.8)
Diarrhoea	5 (1.0)	3 (0.6)	11 (0.8)
Anaemia	4 (0.8)	7 (1.4)	15 (1.1)
Decreased appetite	4 (0.8)	4 (0.8)	9 (0.7)
Nausea	4 (0.8)	3 (0.6)	8 (0.6)
Acute kidney injury	3 (0.6)	2 (0.4)	7 (0.5)
Aspartate aminotransferase increased	3 (0.6)	1 (0.2)	7 (0.5)
Death	3 (0.6)	0	4 (0.3)
Hepatic function abnormal	3 (0.6)	0	6 (0.4)
Sepsis	3 (0.6)	0	3 (0.2)

Deaths

Table 69: On-treatment deaths by Preferred Term (Safety Set)

Category Preferred term	Study 305 All patients T+PtF N=498 n (%)	 P+PtF N=494 n (%)	Tislelizumab monotherapy pool N=1534 n (%)
Number of patients who died	42 (8.4)	35 (7.1)	120 (7.8)
Adverse event	19 (3.8)	14 (2.8)	48 (3.1)
Death[1]	8 (1.6)	2 (0.4)	9 (0.6)
Sepsis	3 (0.6)	1 (0.2)	0
Pulmonary embolism	2 (0.4)	1 (0.2)	2 (0.1)
Respiratory failure	2 (0.4)	0	4 (0.3)
Colitis	1 (0.2)	0	0
Pneumonia bacterial	1 (0.2)	0	0
Shock haemorrhagic	1 (0.2)	0	0
Subdural haematoma	1 (0.2)	1 (0.2)	0
Sudden death	1 (0.2)	0	1 (0.1)
Arteriosclerosis	0	1 (0.2)	0
Brain herniation	0	1 (0.2)	0
COVID-19	0	1 (0.2)	0
Cardiopulmonary failure	0	1 (0.2)	1 (0.1)
Cerebrovascular accident	0	1 (0.2)	0
Completed suicide	0	1 (0.2)	0
Hepatic failure	0	1 (0.2)	1 (0.1)
Left ventricular failure	0	1 (0.2)	0
Peritonitis	0	1 (0.2)	0
Disease under study	23 (4.6)	21 (4.3)	69 (4.5)
General physical health deterioration	6 (1.2)	5 (1.0)	7 (0.5)
Gastric haemorrhage	3 (0.6)	0	0
Missing[2]	3 (0.6)	4 (0.8)	15 (1.0)
Death	2 (0.4)	3 (0.6)	5 (0.3)
Gastrointestinal haemorrhage	2 (0.4)	0	0
Ascites	1 (0.2)	0	1 (0.1)
Cachexia	1 (0.2)	0	1 (0.1)
Hypovolaemic shock	1 (0.2)	0	0
Metastases to meninges	1 (0.2)	0	0
Obstruction gastric	1 (0.2)	1 (0.2)	0
Renal failure	1 (0.2)	0	0
Sepsis	1 (0.2)	0	1 (0.1)
Chest discomfort	0	1 (0.2)	0
Failure to thrive	0	1 (0.2)	0
Multiple organ dysfunction syndrome	0	2 (0.4)	6 (0.4)
Pneumonia aspiration	0	1 (0.2)	0
Pulmonary embolism	0	1 (0.2)	0
Pulmonary tumour thrombotic microangiopathy	0	1 (0.2)	0
Upper gastrointestinal haemorrhage	0	1 (0.2)	4 (0.3)

- Data cutoff for 305: 28FEB2023
- Data cutoff for Tisle monotherapy: Study 001-26AUG2020, Study 102-31MAY2020, Study 203-02NOV2020, Study 204-16SEP2019, Study 208-30JUN2021, Study 302-01DEC2020, Study 303-15JUL2021

Deaths occuring during the study treatment and up to 30 days after the last dose are summarized in this table.
MedDRA Version 26.0.
Note: All on-treatment deaths reported in Study 305 are included this table. For deaths reported only in the monotherapy pool for 'adverse event' or 'disease under study', refer to [SCS Appendix 1-Table 3.1-12].
[1]Death was reported as a PT when the cause of death could not be determined.
[2]No fatal AE was reported, as the death occurred after initiation of a new anticancer therapy in Study 305 and for various reasons in the Tislelizumab monotherapy pool.
Source: [SCS Appendix 1-Table 3.1-12]

Other significant events - Adverse Events of Special Interest (AESI)

Immune-mediated adverse events as identified by the programmatic algorithmic approach are of special interest in this study, plus all infusion-related reactions.

Immune-Mediated Adverse Events

Immune-mediated AEs (imAEs) were identified based on a pre-defined programmatic algorithmic approach that ensures consistency in the retrieval, selection, and classification of cases over time. The process is based on lists of terms with narrow and broad scope. The narrow component comprises terms for which the immune-mediated aetiology is specified in the PT and that are always considered imAEs. The broad component is comprised of terms that are known or possible imAEs, and that are considered imAEs when any of the following additional criteria are met:

- Treatment of the AEs with systemic steroids or other immunosuppressants
- For AE falling into the categories of hyperthyroidism/hypothyroidism/thyroiditis, AE treated with anti-thyroid/thyroid supplement therapy
- For AE falling into diabetes mellitus category, treatment of the AE with insulin
- Investigator assessment as imAE/AESI in the CRF (as defined in the protocol/CRF in each study)
- Investigator causality assessment as related, possibly related to any study drug
- Action taken with any study drug as drug interruption (e.g. dose/drug delay, dose/drug interrupted, interruption, dose frequency change, infusion interrupted)/discontinuation

All AEs for which the PT fell either into the narrow list or the broad list combined with at least one of the additional criteria were defined as imAEs if they occurred on or after the first dose of the study treatment and up to 90 days after the last dose of the study treatment or start of the crossover period (for studies allowing crossover), whichever occurred first.

ImAEs were recorded up to 90 days after the last dose of tislelizumab or placebo, regardless of whether or not the patient started a new anticancer therapy. The imAEs were defined as followed:

- **Immune-mediated hepatitis**, defined as hepatic inflammation without clear alternative etiology and requiring use of corticosteroids, has been reported in patients treated with PD-1 inhibitors, including fatal cases.
- **Immune-mediated nephritis**, defined as renal dysfunction in the absence of a clear alternative etiology and requiring the use of corticosteroids, has been reported in patients treated with PD-1 inhibitors.
- **Immune-mediated pneumonitis**, defined as pulmonary inflammation in the absence of a clear alternative etiology and requiring the use of corticosteroids, has been reported in patients treated with PD-1 inhibitors.
- **Immune-mediated colitis**, frequently associated with diarrhea, defined as requiring use of corticosteroids and with no clear alternative etiology, has been reported in patients treated with PD-1 inhibitors.
- **Immune-mediated skin reactions**, including rash or dermatitis, have been reported in patients receiving PD-1 inhibitors.

  Cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported in patients treated with anti-PD-1/PD-L1 antibodies.
- **Immune-mediated endocrinopathies**, including thyroid disorders, adrenal insufficiency, and hypophysitis, which may require supportive treatment depending on the specific endocrine disorder have been reported with tislelizumab. Type 1 diabetes mellitus has been reported in patients treated with PD-1 inhibitors including diabetic ketoacidosis.

- **Other clinically important imAEs** reported in less than 1% of patients receiving tislelizumab in clinical studies and included myositis, myocarditis, arthritis, polymyalgia rheumatica, rhabdomyolysis, pericarditis, musculoskeletal, pancreatitis, ocular events, and others.

Table 70: Overview of immune-mediated treatment-emergent adverse events (Safety Set)

imAE category :Overall	305 Tisle+Chemo-All (N=498)	305 Placebo+Chemo-All (N=494)	Tisle monotherapy 200 mg Q3W (N=1534)	Tisle combination therapy (N=1336)
	n(%)	n(%)	n(%)	n(%)
Number of subjects with at least one imTEAEs	154 (30.9)	58 (11.7)	506 (33.0)	507 (37.9)
Cumulative incidence proportions (95% CI) (%) at:				
3 months	16.7 (13.5,20.1)	6.5 (4.5,8.9)	21.6 (19.6,23.7)	22.2 (20.0,24.4)
6 months	24.5 (20.8,28.4)	8.7 (6.4,11.4)	27.2 (25.0,29.4)	29.8 (27.4,32.3)
12 months	29.3 (25.4,33.4)	10.9 (8.4,13.9)	30.8 (28.5,33.1)	35.8 (33.2,38.4)
Maximum grade				
Grade 3	34 (6.8)	9 (1.8)	59 (3.8)	92 (6.9)
Grade 4	3 (0.6)	1 (0.2)	12 (0.8)	13 (1.0)
Grade 5	1 (0.2)	0 (0.0)	1 (0.1)	7 (0.5)
Serious imTEAEs	37 (7.4)	9 (1.8)	89 (5.8)	117 (8.8)
imTEAE leading to any study drug discontinuation	22 (4.4)	1 (0.2)	51 (3.3)	80 (6.0)
imTEAE leading to Tislelizumab/placebo discontinuation	21 (4.2)	1 (0.2)	51 (3.3)	74 (5.5)
imTEAE leading to any study drug modification	46 (9.2)	15 (3.0)	95 (6.2)	167 (12.5)
imTEAE leading to Tislelizumab/placebo dose modification	33 (6.6)	8 (1.6)	95 (6.2)	143 (10.7)
imTEAE leading to death	1 (0.2)	0 (0.0)	1 (0.1)	7 (0.5)

- Data cutoff for 305: 28FEB2023
- Data cutoff for Tisle monotherapy: 001-26AUG2020, 102-31MAY2020, 203-02NOV2020, 204-16SEP2019, 208-30JUN2021, 302-01DEC2020, 303-15JUL2021
- Data cutoff for Tisle combination therapy: 206-31DEC2019, 304-26OCT2020, 305-28FEB2023, 306-28FEB2022, 307-30SEP2020
Numbers (n) represent counts of subjects.
Dose modification included dose/infusion interruption, dose delay, dose frequency change and infusion rate decreased, and in addition dose
reduction for chemotherapy. ImTEAE leading to more than one drug action will be counted in the respective action taken categories.
MedDRA version 26.0, CTCAE version v4.03 for all studies (from either tisle monotherapy or combination therapy)
except for studies 304/305/307: version v5.0 Case retrieval Sheet version released 20230825.
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Table 71: Overview of immune-mediated treatment-emergent adverse events by category (Safety Set)

	Study 305	All patients	Tislelizumab
	T+PtF	P+PtF	monotherapy pool
	N=498	N=494	N=1534
imAE category	n (%)	n (%)	n (%)
Number of patients with at least one imTEAEs	154 (30.9)	58 (11.7)	506 (33.0)
Immune-mediated endocrinopathies (hypothyroidism)	63 (12.7)	15 (3.0)	214 (14.0)
Immune-mediated skin adverse reaction	53 (10.6)	15 (3.0)	173 (11.3)
Immune-mediated pneumonitis	19 (3.8)	2 (0.4)	84 (5.5)
Immune-mediated endocrinopathies (hyperthyroidism)	16 (3.2)	5 (1.0)	72 (4.7)
Immune-mediated hepatitis	10 (2.0)	2 (0.4)	16 (1.0)
Immune-mediated endocrinopathies (diabetes mellitus)	8 (1.6)	1 (0.2)	10 (0.7)
Immune-mediated colitis	6 (1.2)	10 (2.0)	7 (0.5)
Other immune-mediated reactions (musculoskeletal)	5 (1.0)	0 (0.0)	10 (0.7)
Immune-mediated myocarditis/pericarditis	4 (0.8)	1 (0.2)	12 (0.8)
Immune-mediated myositis/rhabdomyolysis	3 (0.6)	2 (0.4)	14 (0.9)
Immune-mediated endocrinopathies (adrenal insufficiency)	3 (0.6)	2 (0.4)	8 (0.5)
Immune-mediated endocrinopathies (thyroiditis)	3 (0.6)	2 (0.4)	18 (1.2)
Immune-mediated nephritis and renal dysfunction	3 (0.6)	0 (0.0)	4 (0.3)
Immune-mediated endocrinopathies (hypophysitis)	2 (0.4)	1 (0.2)	3 (0.2)
Other immune-mediated reactions (pancreatitis)	2 (0.4)	1 (0.2)	3 (0.2)
Other immune-mediated reactions (other)	2 (0.4)	5 (1.0)	1 (0.1)
Other immune-mediated reactions (CNS)	1 (0.2)	0 (0.0)	0 (0.0)
Other immune-mediated reactions (blood dyscrasias)	1 (0.2)	0 (0.0)	0 (0.0)
Other immune-mediated reactions (ocular)	0 (0.0)	0 (0.0)	2 (0.1)

- Data cutoff for Study 305: 28FEB2023

- Data cutoff for Tisle monotherapy: Study 001-26AUG2020, Study 102-31MAY2020, Study 203-02NOV2020, Study 204-16SEP2019, Study 208-30JUN2021, Study 302-01DEC2020, Study 303-15JUL2021

Numbers (n) represent counts of patients.

MedDRA Version 26.0, CTCAE v5.0 for Study 305 study and v4.03 for monotherapy pool. Case retrieval Sheet version released 25-Aug-2023.

Table 72: Immune-mediated treatment-emergent adverse events by category and grade/seriousness/discontinuation in the T+PtF group (Assessor's Table)

	Study 305 All Patients - T+PtF (N = 498) n (%)						
Category	**Any Grade**	**Grade 3**	**Grade 4**	**Grade 5**	**Serious**	**Leading to any study drug dis-continuation**	**Leading to death**
Patients with at least one immune-mediated TEAE	**154 (30.9)**	**34 (6.8)**	**3 (0.6)**	**1 (0.2)**	**37 (7.4)**	**22 (4.4)**	**1 (0.2)**
Immune-mediated endocrinopathies (hypothyroidism)	63 (12.7)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)
Immune-mediated skin adverse reaction	53 (10.6)	4 (0.8)	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.2)	0 (0.0)
Immune-mediated pneumonitis	19 (3.8)	4 (0.8)	0 (0.0)	0 (0.0)	7 (1.4)	6 (1.2)	0 (0.0)
Immune-mediated endocrinopathies (hyperthyroidism)	16 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Immune-mediated hepatitis	10 (2.0)	10 (2.0)	0 (0.0)	0 (0.0)	6 (1.2)	3 (0.6)	0 (0.0)
Immune-mediated endocrinopathies (diabetes mellitus)	8 (1.6)	4 (0.8)	2 (0.4)	0 (0.0)	5 (1.0)	1 (0.2)	0 (0.0)
Immune-mediated colitis	6 (1.2)	2 (0.4)	0 (0.0)	1 (0.2)	5 (1.0)	5 (1.0)	1 (0.2)
Other immune-mediated reactions (musculoskeletal)	5 (1.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Immune-mediated myocarditis/pericarditis	4 (0.8)	1 (0.2)	1 (0.2)	0 (0.0)	2 (0.4)	1 (0.2)	0 (0.0)
Immune-mediated myositis/rhabdomyolysis	3 (0.6)	2 (0.4)	0 (0.0)	0 (0.0)	3 (0.6)	1 (0.2)	0 (0.0)
Immune-mediated endocrinopathies (adrenal insufficiency)	3 (0.6)	1 (0.2)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)
Immune-mediated endocrinopathies (thyroiditis)	3 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Immune-mediated nephritis and renal dysfunction	3 (0.6)	2 (0.4)	0 (0.0)	0 (0.0)	3 (0.6)	2 (0.4)	0 (0.0)
Immune-mediated endocrinopathies (hypophysitis)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other immune-mediated reactions (pancreatitis)	2 (0.4)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Other immune-mediated reactions (other)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other immune-mediated reactions (CNS)	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Other immune-mediated reactions (blood dyscrasias)	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)
Other immune-mediated reactions (ocular)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

- Data cutoff for 305: 28FEB2023
- Data cutoff for Tisle monotherapy: 001-26AUG2020, 102-31MAY2020, 203-02NOV2020, 204-16SEP2019, 208-30JUN2021, 302-01DEC2020, 303-15JUL2021
- Data cutoff for Tisle combination therapy: 206-31DEC2019, 304-26OCT2020, 305-28FEB2023, 306-28FEB2022, 307-30SEP2020

Numbers (n) represent counts of subjects.
Dose modification included dose/infusion interruption, dose delay, dose frequency change and infusion rate decreased, and in addition dose reduction for chemotherapy. ImTEAE leading to more than one drug action will be counted in the respective action taken categories.
MedDRA version 26.0, CTCAE version v4.03 for all studies (from either tisle monotherapy or combination therapy) except for studies 304/305/307: version v5.0 Case retrieval Sheet version released 20230825.

Table 73: Outcomes of immune-mediated treatment-emergent adverse events by category (Assessor's Table)

Category	Study 305 All Patients - T+PtF (N = 498) n (%)					
	Total number of events in the category	Resolved n (%)	Recovering/ resolving n (%)	Not recovered/ resolved n (%)	Fatal n (%)	Unknown n (%)
Immune-mediated endocrinopathies (hypothyroidism)	77	26 (33.8)	5 (6.5)	45 (58.4)	0	1 (1.3)
Immune-mediated skin adverse reaction	66	45 (68.2)	3 (4.5)	16 (24.2)	0	2 (3.0)
Immune-mediated pneumonitis	19	10 (52.6)	0	9 (47.4)	0	0
Immune-mediated endocrinopathies (hyperthyroidism)	17	11 (64.7)	2 (11.8)	4 (23.5)	0	0
Immune-mediated hepatitis	10	8 (80.0)	0	1 (10.0)	0	1 (10.0)
Immune-mediated endocrinopathies (diabetes mellitus)	9	2 (22.2)	3 (33.3)	4 (44.4)	0	0
Immune-mediated colitis	7	5 (71.4)	0	1 (14.3)	1 (14.3)	0
Other immune-mediated reactions (musculoskeletal)	5	2 (40.0)	1 (20.0)	2 (40.0)	0	0
Immune-mediated myocarditis/pericarditis	4	3 (75.0)	0	1 (25.0)	0	0
Immune-mediated myositis/rhabdomyolysis	3	3 (100)	0	0	0	0
Immune-mediated endocrinopathies (adrenal insufficiency)	3	1 (33.3)	1 (33.3)	1 (33.3)	0	0
Immune-mediated endocrinopathies (thyroiditis)	3	2 (66.7)	0	1 (33.3)	0	0
Immune-mediated nephritis and renal dysfunction	3	2 (66.7)	0	1 (33.3)	0	0
Immune-mediated endocrinopathies (hypophysitis)	2	0	0	1 (50.0)	0	1 (50.0)
Other immune-mediated reactions (pancreatitis)	2	2 (100.0)	0	0	0	0
Other immune-mediated reactions (other)	2	2 (100.0)	0	0	0	0
Other immune-mediated reactions (CNS)	1	1 (100.0)	0	0	0	0
Other immune-mediated reactions (blood dyscrasias)	1	0	0	1 (100.0)	0	0
Other immune-mediated reactions (ocular)	0	0	0	0	0	0

Resolved included both 'Recovered/Resolved' or 'Recovered/Resolved with sequelae'. For 102 part of Tisle monotherapy, "worsen" has been categorized in "Not recovered/not resolved".(a) Recovered from a category of imAE only if all events in the category were recovered. Percentage is calculated based on the number of subjects with at least one event (b)time from the first dosing date to first onset date of imAE in the category. (c)time from the onset date to AE end date, unknown AE end date was censored at earliest date of end of study, death, or data cutoff. Median, Q1 and Q3 were estimated by Kaplan-Meier method.(d) '+' = Censored. (e) Time from AE onset date to AE stop date available by cutoff date, and with outcome reported as 'Recovered/Resolved' or 'Recovered/Resolved with sequelae'. Mean, median, Q1 and Q3 were calculated descriptively. Case Retrieval Strategy version released 20230825.

Infusion-Related Reactions

An infusion-related reaction (IRR) was defined as any event matching the narrow scope of a "infusion-related reactions" Company Medical Query (CMQ) and occurring on the same day as any study drug administration intravenously.

Table 74: Infusion-related reactions (treatment-emergent, T+PtF and P+PtF groups) by Preferred Term and maximum grade (Safety Set)

	305 Tisle + Chemo - All N=498				305 Placebo + Chemo - All N=494			
Preferred Term	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Number of subjects with at least one TEAE	33 (6.6)	5 (1.0)	0	0	15 (3.0)	3 (0.6)	0	0
Chills	15 (3.0)	2 (0.4)	0	0	2 (0.4)	0	0	0
Drug hypersensitivity	7 (1.4)	1 (0.2)	0	0	3 (0.6)	0	0	0
Rash	6 (1.2)	0	0	0	1 (0.2)	0	0	0
Anaphylactic reaction	2 (0.4)	2 (0.4)	0	0	2 (0.4)	2 (0.4)	0	0
Urticaria	2 (0.4)	0	0	0	1 (0.2)	0	0	0
Corneal oedema	1 (0.2)	0	0	0	0	0	0	0
Face oedema	1 (0.2)	0	0	0	0	0	0	0
Rhinitis allergic	1 (0.2)	0	0	0	3 (0.6)	0	0	0
Anaphylactic shock	0	0	0	0	1 (0.2)	1 (0.2)	0	0
Eyelid oedema	0	0	0	0	1 (0.2)	0	0	0
Infusion related reaction	0	0	0	0	0	0	0	0
Laryngeal oedema	0	0	0	0	1 (0.2)	0	0	0
Pruritus allergic	0	0	0	0	1 (0.2)	0	0	0
Rash erythematous	0	0	0	0	0	0	0	0
Rash pruritic	0	0	0	0	0	0	0	0
Swelling face	0	0	0	0	0	0	0	0

Adverse drug reactions

The following data were used for ADR determination:

- Pivotal Study 305
- The Tislelizumab monotherapy safety pool, where statistics were reported for the tislelizumab-containing arm only
- The Tislelizumab combination therapy safety pool, where statistics were reported for the tislelizumab-containing arm only. The combination therapy pool includes pooled safety data from Study 305 and Studies BGB-A317-206, BGB-A317-304, BGB-A317-306, and BGB-A317-307 (hereafter referred to as Studies 206, 304, 306, and 307, respectively), enrolling patients with various tumor types who received tislelizumab in combination with various regimens of chemotherapy, which were utilized to support ADR determination for the combination treatment.

Therefore, the changes included in section 4.8 of the current procedure II/06 represent the most updated safety pool and a consolidated version that includes also the changes from II/03. It is clarified that in the Summary of Clinical Safety, all the patients from the BGB-A317-206 study are included in the combination pool, when in the SmPC, only the NSCLC patients from this study are included (i.e., the 17 patients from the SCLC cohort are excluded since they were not included in the SmPC for the procedure II/08).

As a result of the updated safety pool, several ADRs frequencies were updated as follows:

Sjögren's syndrome-uncommon

Hyperthyroidism-to common

Adrenal insufficiency-to uncommon

Hypophysitis-to uncommon

Hyperglycaemia-to common

Encephalitis-to Rare

Guillain-Barre syndrome-to Rare

Myasthenia gravis-to rare

Uveitis-to uncommon

Pericarditis-to rare

Dyspnoea-to common

Pneumonitis-to common

Stomatitis-to very common.

Pancreatitis-to common

Vitiligo-uncommon

Severe skin reactions-to rare

Pyrexia-to very common

Arthralgia-to common

Blood alkaline phosphatase increased-to common

Blood creatinine increased-to common

Tables supporting the updates made in section 4.8 of the SmPC are presented below.

Adverse drug reaction candidates include two types of events, namely prequalified candidate ADRs and other candidate ADRs identified through numerical screening rules.

Prequalified ADR candidates were identified using the eCRS as well as using identified imAE from the data. These were events suspected to be related to the drug based on the known mechanism of action, previous experience collected with the drug, drugs in the same class, any event included in the European Medicines Agency (EMA) Designated Medical Event (DME) list, or imAE flag indicating if there was at least 1 patient with imAE identified for the MedDRA category of interest.

Other ADR candidates are events for which an excess versus comparator was observed. These were identified using a numerical screening rule i.e. algorithmically, based on all TEAEs (for more details see Summary of Clinical Safety). The numerical screening criteria were evaluated in the randomized period subset of each study at MedDRA SOC, HLGT, HLT, and PT level.

All ADR candidates (both prequalified ADRs and ADR candidates identified via the numerical screening rule) underwent a medical review using the Bradford Hill criteria to assess the plausibility of a causal association between tislelizumab and the candidate ADRs. These criteria included event severity, temporal relationship, pharmacological action, and the safety profile of other drugs with similar mechanism of action.

An immune-mediated ADR was defined as any PT flagged as ADR and reported as an imAE in at least one patient of the pivotal study, monotherapy, or combination therapy pool. All imADRs analyses reported TEAEs frequencies for each imAE category.

The ADRs of the tislelizumab combination therapy pool presented in section 4.8 of the SmPC are based on 1319 patients with non-small cell lung cancer (NSCLC), gastric or gastroesophageal junction (G/GEJ) adenocarcinoma and esophageal squamous cell carcinoma (OSCC) that have been treated with tislelizumab + chemotherapy in Studies 206, 304, 307, 305 and 306.

Table 75: Adverse Drug Reactions by SOC, ADR and Frequency Category (Safety Analysis Set)

	Tisle monotherapy N = 1534			Tisle combination therapy N = 1319		
System Organ Class ADR	**All Grades n (%)**	**Grade 3/4 n (%)**	**Frequency Category (All Grades)**	**All Grades n (%)**	**Grade 3/4 n (%)**	**Frequency Category (All Grades)**
Patients With Any Adverse Drug Reaction	1355 (88.3)	435 (28.4)		1295 (98.2)	870 (66.0)	
Infections and infestations	159 (10.4)	67 (4.4)		155 (11.8)	50 (3.8)	
Pneumonia [a]	159 (10.4)	67 (4.4)	Very common	155 (11.8)	50 (3.8)	Very common
Blood and lymphatic system disorders	603 (39.3)	122 (8.0)		1114 (84.5)	661 (50.1)	
Anaemia [b]	457 (29.8)	78 (5.1)	Very common	839 (63.6)	175 (13.3)	Very common
Thrombocytopenia [c]	138 (9.0)	16 (1.0)	Common	644 (48.8)	175 (13.3)	Very common
Neutropenia [d]	90 (5.9)	22 (1.4)	Common	865 (65.6)	506 (38.4)	Very common
Lymphopenia [e]	70 (4.6)	19 (1.2)	Common	132 (10.0)	33 (2.5)	Very common
Immune system disorders	0 (0.0)	0 (0.0)		2 (0.2)	0 (0.0)	
Sjogren's syndrome [f]	0 (0.0)	0 (0.0)	-	2 (0.2)	0 (0.0)	Uncommon
Endocrine disorders	304 (19.8)	4 (0.3)		253 (19.2)	8 (0.6)	
Hypothyroidism [g]	221 (14.4)	1 (0.1)	Very common	186 (14.1)	1 (0.1)	Very common
Hyperthyroidism [h]	94 (6.1)	0 (0.0)	Common	85 (6.4)	0 (0.0)	Common
Thyroiditis [i]	18 (1.2)	0 (0.0)	Common	6 (0.5)	1 (0.1)	Uncommon
Adrenal insufficiency [j]	7 (0.5)	3 (0.2)	Uncommon	9 (0.7)	5 (0.4)	Uncommon
Hypophysitis [k]	1 (0.1)	0 (0.0)	Rare	5 (0.4)	1 (0.1)	Uncommon
Metabolism and nutrition disorders	332 (21.6)	87 (5.7)		422 (32.0)	116 (8.8)	
Hyperglycaemia [l]	149 (9.7)	22 (1.4)	Common	128 (9.7)	10 (0.8)	Common
Hyponatraemia [m]	146 (9.5)	44 (2.9)	Common	204 (15.5)	52 (3.9)	Very common
Hypokalaemia [n]	121 (7.9)	25 (1.6)	Common	227 (17.2)	58 (4.4)	Very common
Diabetes mellitus [o]	14 (0.9)	5 (0.3)	Uncommon	18 (1.4)	11 (0.8)	Common
Nervous system disorders	0 (0.0)	0 (0.0)		3 (0.2)	3 (0.2)	
Encephalitis [p]	0 (0.0)	0 (0.0)	-	1 (0.1)	1 (0.1)	Rare
Guillain-Barre syndrome [q]	0 (0.0)	0 (0.0)	-	1 (0.1)	1 (0.1)	Rare
Myasthenia Gravis [r]	0 (0.0)	0 (0.0)	-	1 (0.1)	1 (0.1)	Rare
Eye disorders	4 (0.3)	0 (0.0)		3 (0.2)	1 (0.1)	
Uveitis [s]	4 (0.3)	0 (0.0)	Uncommon	3 (0.2)	1 (0.1)	Uncommon
Cardiac disorders	13 (0.8)	4 (0.3)		16 (1.2)	4 (0.3)	
Myocarditis [t]	12 (0.8)	4 (0.3)	Uncommon	15 (1.1)	3 (0.2)	Common
Pericarditis [u]	1 (0.1)	0 (0.0)	Rare	1 (0.1)	1 (0.1)	Rare
Vascular disorders	81 (5.3)	35 (2.3)		62 (4.7)	21 (1.6)	
Hypertension [v]	81 (5.3)	35 (2.3)	Common	62 (4.7)	21 (1.6)	Common
Respiratory, thoracic and mediastinal disorders	391 (25.5)	52 (3.4)		309 (23.4)	39 (3.0)	

	Tisle monotherapy N = 1534			Tisle combination therapy N = 1319		
System Organ Class ADR	**All Grades n (%)**	**Grade 3/4 n (%)**	**Frequency Category (All Grades)**	**All Grades n (%)**	**Grade 3/4 n (%)**	**Frequency Category (All Grades)**
Cough [w]	249 (16.2)	5 (0.3)	Very common	150 (11.4)	4 (0.3)	Very common
Dyspnoea [x]	119 (7.8)	20 (1.3)	Common	111 (8.4)	9 (0.7)	Common
Pneumonitis [y]	84 (5.5)	30 (2.0)	Common	105 (8.0)	26 (2.0)	Common
Gastrointestinal disorders	314 (20.5)	31 (2.0)		784 (59.4)	95 (7.2)	
Nausea [z]	155 (10.1)	3 (0.2)	Very common	580 (44.0)	25 (1.9)	Very common
Diarrhoea [aa]	146 (9.5)	12 (0.8)	Common	300 (22.7)	31 (2.4)	Very common
Stomatitis [bb]	48 (3.1)	5 (0.3)	Common	149 (11.3)	22 (1.7)	Very common
Pancreatitis [cc]	16 (1.0)	10 (0.7)	Common	47 (3.6)	16 (1.2)	Common
Colitis [dd]	8 (0.5)	2 (0.1)	Uncommon	16 (1.2)	8 (0.6)	Common
Hepatobiliary disorders	43 (2.8)	19 (1.2)		55 (4.2)	26 (2.0)	
Hepatitis [ee]	43 (2.8)	19 (1.2)	Common	55 (4.2)	26 (2.0)	Common
Skin and subcutaneous tissue disorders	342 (22.3)	14 (0.9)		361 (27.4)	37 (2.8)	
Rash [ff]	224 (14.6)	13 (0.8)	Very common	275 (20.8)	34 (2.6)	Very common
Pruritus [gg]	157 (10.2)	0 (0.0)	Very common	127 (9.6)	3 (0.2)	Common
Vitiligo [hh]	11 (0.7)	0 (0.0)	Uncommon	4 (0.3)	0 (0.0)	Uncommon
Severe skin reaction [ii]	3 (0.2)	1 (0.1)	Uncommon	1 (0.1)	0 (0.0)	Rare
Musculoskeletal and connective tissue disorders	176 (11.5)	9 (0.6)		188 (14.3)	7 (0.5)	
Arthralgia [jj]	138 (9.0)	4 (0.3)	Common	128 (9.7)	1 (0.1)	Common
Myalgia [kk]	26 (1.7)	0 (0.0)	Common	61 (4.6)	3 (0.2)	Common
Myositis [ll]	14 (0.9)	4 (0.3)	Uncommon	7 (0.5)	3 (0.2)	Uncommon
Arthritis [mm]	11 (0.7)	2 (0.1)	Uncommon	15 (1.1)	3 (0.2)	Common
Renal and urinary disorders	4 (0.3)	1 (0.1)		5 (0.4)	2 (0.2)	
Nephritis [nn]	4 (0.3)	1 (0.1)	Uncommon	5 (0.4)	2 (0.2)	Uncommon
General disorders and administration site conditions	607 (39.6)	48 (3.1)		874 (66.3)	102 (7.7)	
Fatigue [oo]	367 (23.9)	31 (2.0)	Very common	568 (43.1)	66 (5.0)	Very common
Pyrexia [pp]	243 (15.8)	5 (0.3)	Very common	249 (18.9)	9 (0.7)	Very common
Decreased appetite [qq]	230 (15.0)	16 (1.0)	Very common	551 (41.8)	44 (3.3)	Very common
Investigations	560 (36.5)	82 (5.3)		634 (48.1)	63 (4.8)	
Aspartate aminotransferase increased [rr]	327 (21.3)	40 (2.6)	Very common	418 (31.7)	32 (2.4)	Very common
Alanine aminotransferase increased [ss]	303 (19.8)	24 (1.6)	Very common	401 (30.4)	32 (2.4)	Very common
Blood bilirubin increased [tt]	187 (12.2)	32 (2.1)	Very common	207 (15.7)	16 (1.2)	Very common
Blood alkaline phosphatase increased [uu]	115 (7.5)	17 (1.1)	Common	93 (7.1)	4 (0.3)	Common
Blood creatinine increased [vv]	86 (5.6)	2 (0.1)	Common	123 (9.3)	3 (0.2)	Common
Injury, poisoning and procedural complications	44 (2.9)	2 (0.1)		86 (6.5)	10 (0.8)	
Infusion related reaction [ww]	44 (2.9)	2 (0.1)	Common	86 (6.5)	10 (0.8)	Common

Source: ADSL, ADADR. Data cutoff: 001-26AUG2020, 102-31MAY2020, 203-02NOV2020, 204-16SEP2019, 208-30JUN2021, 302-01DEC2020, 303-15JUL2021, 206-31DEC2019, 304-26OCT2020, 305-28FEB2023, 306-

28FEB2022, 307-30SEP2020. Data extraction: 001-26AUG2020, 102-30JUN2020, 203-09NOV2020, 204-16OCT2019, 208-04AUG2021, 302-15JAN2021, 303-22OCT2021, 206-13JUL2020, 304-23FEB2021, 305-11APR2023, 306-06APR2022, 307-20FEB2021.
The Tisle combination therapy pool includes NSCLC patients from Study 206, and patients from the Tislelizumab + chemotherapy arm(s) in Study 304, 307, 305 and 306.
Patients with multiple events for a given ADR and system organ class were counted only once for the ADR and system organ class, respectively.
Frequency categories were defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000).
Adverse events were classified based on MedDRA version 26.0.
a. Pneumonia includes Lower respiratory tract infection, Lower respiratory tract infection bacterial, Pneumocystis jirovecii pneumonia, Pneumonia, Pneumonia bacterial, Pneumonia fungal, Pneumonia staphylococcal, Pneumonia viral.
b. Anaemia includes Anaemia, Haemoglobin decreased.
c. Thrombocytopenia includes Immune thrombocytopenia, Platelet count decreased, Thrombocytopenia.
d. Neutropenia includes Neutropenia, Neutrophil count decreased.
e. Lymphopenia includes Lymphocyte count decreased, Lymphocyte percentage decreased, Lymphopenia.
f. Sjogren's syndrome includes Sjogren's syndrome.
g. Hypothyroidism includes Central hypothyroidism, Hypothyroidism, Primary hypothyroidism, Thyroxine decreased, Thyroxine free decreased, Tri-iodothyronine decreased, Tri-iodothyronine free decreased.
h. Hyperthyroidism includes Blood thyroid stimulating hormone decreased, Hyperthyroidism, Thyroxine free increased, Thyroxine increased, Tri-iodothyronine free increased, Tri-iodothyronine increased.
i. Thyroiditis includes Autoimmune thyroiditis, Thyroiditis, Thyroiditis subacute.
j. Adrenal insufficiency includes Adrenal insufficiency, Glucocorticoid deficiency, Immune-mediated adrenal insufficiency, Secondary adrenocortical insufficiency.
k. Hypophysitis includes Hypopituitarism.
l. Hyperglycaemia includes Blood glucose increased, Hyperglycaemia.
m. Hyponatraemia includes Blood sodium decreased, Hyponatraemia.
n. Hypokalaemia includes Blood potassium decreased, Hypokalaemia.
o. Diabetes mellitus includes Diabetes mellitus, Diabetic ketoacidosis, Latent autoimmune diabetes in adults, Type 1 diabetes mellitus.
p. Encephalitis includes Immune-mediated encephalitis.
q. Guillain-Barre syndrome includes Guillain-Barre syndrome.
r. Myasthenia Gravis includes Myasthenia gravis.
s. Uveitis includes Chorioretinitis, Iridocyclitis, Iritis, Uveitis.
t. Myocarditis includes Autoimmune myocarditis, Immune-mediated myocarditis, Myocarditis.
u. Pericarditis includes Pericarditis.
v. Hypertension includes Blood pressure increased, Essential hypertension, Hypertension.
w. Cough includes Cough.
x. Dyspnoea includes Dyspnoea.
y. Pneumonitis includes Immune-mediated lung disease, Interstitial lung disease, Organising pneumonia, Pneumonitis.
z. Nausea includes Nausea.
aa. Diarrhoea includes Diarrhoea, Frequent bowel movements.
bb. Stomatitis includes Aphthous ulcer, Mouth ulceration, Oral mucosa erosion, Stomatitis.
cc. Pancreatitis includes Amylase increased, Lipase increased, Pancreatitis, Pancreatitis acute.
dd. Colitis includes Colitis, Immune-mediated enterocolitis.
ee. Hepatitis includes Autoimmune hepatitis, Drug-induced liver injury, Hepatic function abnormal, Hepatitis, Hepatotoxicity, Immune-mediated hepatitis, Liver injury.

ff. Rash includes Acute febrile neutrophilic dermatosis, Dermatitis, Dermatitis acneiform, Dermatitis allergic, Drug eruption, Eczema, Erythema, Erythema nodosum, Hand dermatitis, Immune-mediated dermatitis, Lichenoid keratosis, Pemphigoid, Psoriasis, Rash, Rash erythematous, Rash follicular, Rash macular, Rash maculo-papular, Rash papular, Rash pruritic, Rash pustular, Skin exfoliation, Urticaria.
gg. Pruritus includes Pruritus.
hh. Vitiligo includes Leukoderma, Skin depigmentation, Skin hypopigmentation, Vitiligo.
ii. Severe skin reaction includes Erythema multiforme.
jj. Arthralgia includes Arthralgia.
kk. Myalgia includes Myalgia.
ll. Myositis includes Immune-mediated myositis, Myositis, Rhabdomyolysis.
mm. Arthritis includes Arthritis, Immune-mediated arthritis, Polyarthritis.
nn. Nephritis includes Focal segmental glomerulosclerosis, Immune-mediated nephritis, Nephritis, Tubulointerstitial nephritis.
oo. Fatigue includes Asthenia, Fatigue, Lethargy, Malaise.
pp. Pyrexia includes Body temperature increased, Pyrexia.
qq. Decreased appetite includes Decreased appetite.
rr. Aspartate aminotransferase increased includes Aspartate aminotransferase increased.
ss. Alanine aminotransferase increased includes Alanine aminotransferase increased.
tt. Blood bilirubin increased includes Bilirubin conjugated increased, Blood bilirubin increased, Blood bilirubin unconjugated increased, Hyperbilirubinaemia.
uu. Blood alkaline phosphatase increased includes Blood alkaline phosphatase increased.
vv. Blood creatinine increased includes Blood creatinine increased.
ww. Infusion related reaction includes Anaphylactic reaction, Chills, Corneal oedema, Dermatitis allergic, Drug eruption, Drug hypersensitivity, Face oedema, Gingival swelling, Infusion related reaction, Laryngeal oedema, Lip oedema, Lip swelling, Mouth swelling, Pruritus allergic, Rash, Rash erythematous, Rash pruritic, Rhinitis allergic, Swelling face, Tongue oedema, Type I hypersensitivity, Urticaria.

Laboratory findings

The summaries included all assessments available for the laboratory parameter collected during the on-treatment period (up to 30 days of the last dose of any study drug) from all sources (local or central laboratory, when available).

Laboratory parameters that were graded in NCI-CTCAE (v5.0 for Study 305, v4.03 for the Tislelizumab monotherapy pool) were summarized by shifts from baseline CTCAE grades to maximum post-baseline grades.

Hematology

Table 76: Worst post-baseline hematology abnormalities based on CTC grades (Safety Set)

	Study 305 All patients				Tislelizumab monotherapy pool	
	T+PtF N=498		P+PtF N=494		N=1534	
	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Hemoglobin decrease	461 (92.6)	45 (9.0)	448 (90.7)	47 (9.5)	1067 (69.6)	75 (4.9)
Hemoglobin increase	6 (1.2)	0	5 (1.0)	0	66 (4.3)	2 (0.1)
Leukocytes decrease	291 (58.4)	28 (5.6)	308 (62.3)	25 (5.1)	274 (17.9)	14 (0.9)
Lymphocytes decrease	312 (62.7)	70 (14.1)	288 (58.3)	53 (10.7)	867 (56.5)	178 (11.6)
Lymphocytes increase	13 (2.6)	0	8 (1.6)	0	29 (1.9)	1 (0.1)
Neutrophils decrease	309 (62.0)	86 (17.3)	305 (61.7)	88 (17.8)	186 (12.1)	29 (1.9)
Platelets decrease	336 (67.5)	64 (12.9)	336 (68.0)	63 (12.8)	301 (19.6)	18 (1.2)

- Data cutoff for Study 305: 28FEB2023
- Data cutoff for Tisle monotherapy: Study 001-26AUG2020, Study 102-31MAY2020, Study 203-02NOV2020, Study 204-16SEP2019, Study 208-30JUN2021, Study 302-01DEC2020, Study 303-15JUL2021

Numbers (n) represent counts of patients. 'All grades' represents patients with any Grade 1, 2, 3 or 4 post-baseline.
Only on-treatment assessment up to 30 days after last dose of study treatment are included.
Grades based on CTCAE version v5.0 for Study 305 study and v4.03 for monotherapy pool.
Source: [SCS Appendix 1-Table 1.4-1]

Source: Summary of Clinical Safety Table 19

Clinical Chemistry

Table 77: Worst post-baseline chemistry abnormalities based on CTC grades (Safety Set)

	Study 305 All patients				Tislelizumab monotherapy pool	
	T+PtF N=498		P+PtF N=494		N=1534	
	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Alanine aminotransferase increase	225 (45.2)	25 (5.0)	195 (39.5)	11 (2.2)	549 (35.8)	34 (2.2)
Albumin decrease	349 (70.1)	6 (1.2)	338 (68.4)	8 (1.6)	684 (44.6)	10 (0.7)
Alkaline phosphatase increase	183 (36.7)	5 (1.0)	186 (37.7)	10 (2.0)	699 (45.6)	39 (2.5)
Aspartate aminotransferase increase	326 (65.5)	28 (5.6)	304 (61.5)	15 (3.0)	632 (41.2)	51 (3.3)
Bilirubin increase	194 (39.0)	17 (3.4)	190 (38.5)	20 (4.0)	319 (20.8)	34 (2.2)
Creatine kinase increase	135 (27.1)	14 (2.8)	118 (23.9)	9 (1.8)	260 (16.9)	25 (1.6)
Creatinine increase	91 (18.3)	12 (2.4)	71 (14.4)	7 (1.4)	282 (18.4)	13 (0.8)
Glucose decrease	77 (15.5)	1 (0.2)	74 (15.0)	1 (0.2)	153 (10.0)	8 (0.5)
Glucose increase	335 (67.3)	0	319 (64.6)	0	972 (63.4)	74 (4.8)
Potassium decrease	181 (36.3)	49 (9.8)	161 (32.6)	39 (7.9)	254 (16.6)	38 (2.5)
Potassium increase	80 (16.1)	6 (1.2)	89 (18.0)	8 (1.6)	169 (11.0)	13 (0.8)
Sodium decrease	258 (51.8)	37 (7.4)	231 (46.8)	32 (6.5)	623 (40.6)	93 (6.1)
Sodium increase	44 (8.8)	2 (0.4)	49 (9.9)	3 (0.6)	118 (7.7)	1 (0.1)

- Data cutoff for Study 305: 28FEB2023
- Data cutoff for Tisle monotherapy: Study 001-26AUG2020, Study 102-31MAY2020, Study 203-02NOV2020, Study 204-16SEP2019, Study 208-30JUN2021, Study 302-01DEC2020, Study 303-15JUL2021

Numbers (n) represent counts of patients. 'All grades' represents patients with any Grade 1, 2, 3 or 4 post-baseline.
Only on-treatment assessment up to 30 days after last dose of study treatment are included.
Grades based on CTCAE version v5.0 for Study 305 study and v4.03 for monotherapy pool.
Source: [SCS Appendix 1-Table 1.4-2]

Source: Summary of Clinical Safety Table 20

Liver Enzymes

When analyzing potential Hy's law cases by laboratory value with the criteria of ALT/AST > 3 x ULN and bilirubin > 2 x ULN, and alkaline phosphatase < 2 x ULN, all postbaseline laboratory data were used regardless of the relative timing of the laboratory tests. It should be noted that this differs from the Study 305 CSR analysis of potential Hy's law cases where ALT/AST elevation, bilirubin elevation, and ALP < 2 x ULN needed to be within 3 days of each other to qualify as a potential Hy's law case.

Of the patients with ALT or AST ≤ ULN at baseline, 4 patients (0.8%) in the T+PtF group and 4 patients (0.8%) in the P+PtF group met the biochemical criteria (ALT or AST > 3 x ULN and bilirubin > 2 x ULN without ALP ≥ 2 x ULN) for Hy's law.

Of the patients with ALT or AST > ULN at baseline, 1 patient in the T+PtF group met the biochemical criteria for Hy's law post-baseline.

According to the applicant, all these cases were subsequently reviewed. After medical review of the cases in the T+PtF group, none of these was considered as a Hy's law case.

Electrocardiograms

Table 78: Abnormal Post-Baseline ECG Results (Safety Analysis Set)

QTcF Interval (msec)	Tislelizumab + Chemotherapy (N = 498) n (%)	Placebo + Chemotherapy (N = 494) n (%)
Patients with both baseline and at least one post-baseline measure	272 (54.6)	271 (54.9)
Increase of > 30 msec [a]	29 (10.7)	32 (11.8)
Increase of > 60 msec [a]	6 (2.2)	8 (3.0)
Patients with at least one post-baseline measure	272 (54.6)	271 (54.9)
Value of > 450 msec [b]	18 (6.6)	17 (6.3)
Value of > 480 msec [b]	2 (0.7)	2 (0.7)
Value of > 500 msec [b]	5 (1.8)	2 (0.7)

Source: ADSL, ADEG. Data cutoff: 28FEB2023. Data extraction: 11APR2023.
Abbreviations: QTcF, QTc Fridericia.
ECG results came from local lab.
Patients were counted in each applicable category.
Percentages were based on N except for [a] and [b] .
[a] The denominator was the number of patients with both baseline and at least one post-baseline measure.
[b] The denominator was the number of patients with at least one post-baseline measure.
unblind/bgb_a317/bgb_a317_305/fa_2023/dev/pgm/tlfs/t-ecg-abn-i.sas 26JUN2023 01:32 t-71-ecg-abn-i.rtf

Source: Clinical Study Report Body (BGB-A317-305: DCO28Feb2023)

Immunogenicity

For information on the immunogenicity of tislelizumab, please see Section 2.3.3.

Among ADA-evaluable patients receiving 200 mg once every 3 weeks, the following rates of adverse events (AEs) have been observed for the ADA-positive population compared to the ADA-negative population, respectively: Grade ≥3 AEs 51.7% vs. 41.2%, serious adverse events (SAEs) 37.9% vs. 31.0%, AEs leading to tislelizumab treatment discontinuation 12.1% vs 10.7% (for monotherapy); Grade ≥ 3 AEs 78.5% vs. 74.5%, SAEs 44.7% vs. 41.5%, AEs leading to tislelizumab treatment discontinuation 14.4% vs 13.8% (for combination therapy).

Thyroid Laboratory Tests

Table 79: Summary of thyroids laboratory tests (Safety set)

	305 Tisle + Chemo - All N=498 n (%)	305 Placebo + Chemo - All N=494 n (%)	305 Tisle + Chemo - PD-L1+ N=272 n (%)	305 Placebo + Chemo - PD-L1+ N=272 n (%)	Tisle monotherapy 200 mg Q3W N=1534 n (%)
No of patients with baseline and post-baseline assessment	424 (85.1)	427 (86.4)	232 (85.3)	233 (85.7)	1263 (82.3)
Post-baseline TSH>ULN and T4<LLN *	53 (12.5)	9 (2.1)	27 (11.6)	4 (1.7)	172 (13.6)
- Baseline TSH and T4 within normal range	42 (9.9)	5 (1.2)	22 (9.5)	3 (1.3)	99 (7.8)
Post-baseline TSH<LLN and T4>ULN *	16 (3.8)	5 (1.2)	11 (4.7)	2 (0.9)	83 (6.6)
- Baseline TSH and T4 within normal range	14 (3.3)	2 (0.5)	9 (3.9)	1 (0.4)	63 (5.0)

Source: Summary of Clinical Safety Appendix 1_Table 4.2-3

Safety in special populations

To assess differences in the safety profile between specific subgroups of patients, the overview of TEAEs, all grades, grade ≥ 3 TEAEs regardless of relationship were repeated for the following subgroups:

Age

Table 80: Overview of treatment-emergent adverse events by age (Safety Set)

	305 Tisle + Chemo - All N=498			305 Placebo + Chemo - All N=494			Tisle monotherapy 200 mg Q3W N=1534			Tisle combination therapy N=1336		
	<65 years N=337 n (%)	>= 65 and < 75 years N=133 n (%)	>=75 years N=28 n (%)	<65 years N=312 n (%)	>= 65 and < 75 years N=153 n (%)	>=75 years N=29 n (%)	<65 years N=1034 n (%)	>= 65 and < 75 years N=435 n (%)	>=75 years N=65 n (%)	<65 years N=861 n (%)	>= 65 and < 75 years N=430 n (%)	>=75 years N=45 n (%)
TEAEs	335(99.4)	132(99.2)	28(100)	308(98.7)	150(98.0)	28(96.6)	996(96.3)	419(96.3)	64(98.5)	857(99.5)	429(99.8)	45(100)
Treatment-related	327(97.0)	129(97.0)	27(96.4)	301(96.5)	149(97.4)	26(89.7)	771(74.6)	325(74.7)	41(63.1)	841(97.7)	424(98.6)	43(95.6)
Tislelizumab/placebo-related	211(62.6)	92(69.2)	21(75.0)	163(52.2)	83(54.2)	16(55.2)	771(74.6)	325(74.7)	41(63.1)	620(72.0)	345(80.2)	32(71.1)
Chemotherapy-related	326(96.7)	127(95.5)	26(92.9)	300(96.2)	149(97.4)	26(89.7)	NA	NA	NA	837(97.2)	422(98.1)	42(93.3)
TEAEs with grade >=3	229(68.0)	98(73.7)	19(67.9)	196(62.8)	110(71.9)	18(62.1)	444(42.9)	217(49.9)	32(49.2)	636(73.9)	342(79.5)	30(66.7)
Treatment-related	166(49.3)	88(66.2)	16(57.1)	150(48.1)	84(54.9)	12(41.4)	163(15.8)	89(20.5)	7(10.8)	530(61.6)	316(73.5)	26(57.8)
Tislelizumab/placebo-related	77(22.8)	48(36.1)	10(35.7)	57(18.3)	30(19.6)	7(24.1)	163(15.8)	89(20.5)	7(10.8)	233(27.1)	171(39.8)	14(31.1)
Chemotherapy-related	153(45.4)	78(58.6)	14(50.0)	147(47.1)	82(53.6)	12(41.4)	NA	NA	NA	508(59.0)	288(67.0)	24(53.3)
Serious TEAEs	135(40.1)	58(43.6)	18(64.3)	103(33.0)	63(41.2)	12(41.4)	345(33.4)	161(37.0)	27(41.5)	339(39.4)	207(48.1)	28(62.2)
Treatment-related	67(19.9)	36(27.1)	12(42.9)	44(14.1)	25(16.3)	3(10.3)	116(11.2)	58(13.3)	7(10.8)	178(20.7)	142(33.0)	18(40.0)
Tislelizumab/placebo-related	50(14.8)	27(20.3)	8(28.6)	25(8.0)	11(7.2)	2(6.9)	116(11.2)	58(13.3)	7(10.8)	125(14.5)	107(24.9)	11(24.4)
Chemotherapy-related	53(15.7)	26(19.5)	10(35.7)	39(12.5)	25(16.3)	3(10.3)	NA	NA	NA	128(14.9)	103(24.0)	15(33.3)
Fatal serious TEAEs	30(8.9)	14(10.5)	3(10.7)	23(7.4)	16(10.5)	3(10.3)	81(7.8)	40(9.2)	7(10.8)	54(6.3)	35(8.1)	5(11.1)
Treatment-related	8(2.4)	3(2.3)	0	3(1.0)	1(0.7)	0	11(1.1)	5(1.1)	1(1.5)	15(1.7)	11(2.6)	0
Tislelizumab/placebo-related	7(2.1)	2(1.5)	0	3(1.0)	1(0.7)	0	11(1.1)	5(1.1)	1(1.5)	13(1.5)	10(2.3)	0
Chemotherapy-related	8(2.4)	2(1.5)	0	3(1.0)	0	0	NA	NA	NA	11(1.3)	7(1.6)	0
TEAEs leading to any treatment discontinuation	68(20.2)	39(29.3)	8(28.6)	36(11.5)	27(17.6)	4(13.8)	119(11.5)	70(16.1)	10(15.4)	211(24.5)	141(32.8)	13(28.9)
Leading to Tislelizumab/placebo discontinuation	42(12.5)	31(23.3)	6(21.4)	17(5.4)	15(9.8)	4(13.8)	119(11.5)	70(16.1)	10(15.4)	106(12.3)	80(18.6)	8(17.8)
Tislelizumab/placebo-related	21(6.2)	16(12.0)	4(14.3)	5(1.6)	0	1(3.4)	44(4.3)	38(8.7)	5(7.7)	68(7.9)	55(12.8)	6(13.3)
Chemotherapy-related	13(3.9)	8(6.0)	1(3.6)	3(1.0)	2(1.3)	1(3.4)	NA	NA	NA	36(4.2)	22(5.1)	1(2.2)
Leading to Chemotherapy discontinuation	62(18.4)	36(27.1)	7(25.0)	33(10.6)	25(16.3)	4(13.8)	NA	NA	NA	180(20.9)	124(28.8)	12(26.7)
Tislelizumab/placebo-related	17(5.0)	16(12.0)	4(14.3)	6(1.9)	2(1.3)	1(3.4)	NA	NA	NA	57(6.6)	47(10.9)	5(11.1)
Chemotherapy-related	37(11.0)	17(12.8)	3(10.7)	22(7.1)	15(9.8)	1(3.4)	NA	NA	NA	137(15.9)	85(19.8)	7(15.6)
TEAEs leading to any treatment modification	255(75.7)	105(78.9)	21(75.0)	230(73.7)	122(79.7)	23(79.3)	263(25.4)	128(29.4)	26(40.0)	635(73.8)	339(78.8)	34(75.6)
Leading to Tislelizumab/placebo modification	152(45.1)	76(57.1)	16(57.1)	147(47.1)	76(49.7)	16(55.2)	263(25.4)	128(29.4)	26(40.0)	455(52.8)	256(59.5)	28(62.2)
Tislelizumab/placebo-related	63(18.7)	38(28.6)	10(35.7)	66(21.2)	28(18.3)	9(31.0)	162(15.7)	77(17.7)	13(20.0)	228(26.5)	154(35.8)	14(31.1)
Chemotherapy-related	113(33.5)	63(47.4)	12(42.9)	118(37.8)	61(39.9)	11(37.9)	NA	NA	NA	344(40.0)	197(45.8)	20(44.4)
Leading to Chemotherapy modification	254(75.4)	103(77.4)	21(75.0)	229(73.4)	120(78.4)	23(79.3)	NA	NA	NA	608(70.6)	327(76.0)	34(75.6)
Tislelizumab/placebo-related	91(27.0)	42(31.6)	11(39.3)	86(27.6)	38(24.8)	8(27.6)	NA	NA	NA	233(27.1)	144(33.5)	13(28.9)
Chemotherapy-related	232(68.8)	96(72.2)	19(67.9)	212(67.9)	117(76.5)	21(72.4)	NA	NA	NA	557(64.7)	298(69.3)	31(68.9)
Immune-mediated TEAEs	94(27.9)	51(38.3)	9(32.1)	34(10.9)	22(14.4)	2(6.9)	337(32.6)	150(34.5)	19(29.2)	312(36.2)	179(41.6)	16(35.6)
Infusion-Related Reaction	27(8.0)	6(4.5)	0	10(3.2)	5(3.3)	0	31(3.0)	11(2.5)	2(3.1)	62(7.2)	24(5.6)	0

Source: Summary of Clinical Safety Appendix 2 Comb_Table 5.1-1

Gender

Table 81: Overview of treatment-emergent adverse events by gender (Safety Set)

	305 Tisle + Chemo - All N=498		305 Placebo + Chemo - All N=494		Tisle monotherapy 200 mg Q3W N=1534		Tisle combination therapy N=1336	
	Female N=155 n (%)	Male N=343 n (%)	Female N=149 n (%)	Male N=345 n (%)	Female N=346 n (%)	Male N=1188 n (%)	Female N=288 n (%)	Male N=1048 n (%)
TEAEs	154(99.4)	341(99.4)	148(99.3)	338(98.0)	336(97.1)	1143(96.2)	287(99.7)	1044(99.6)
Treatment-related	150(96.8)	333(97.1)	144(96.6)	332(96.2)	261(75.4)	876(73.7)	281(97.6)	1027(98.0)
Tislelizumab/placebo-related	98(63.2)	226(65.9)	80(53.7)	182(52.8)	261(75.4)	876(73.7)	208(72.2)	789(75.3)
Chemotherapy-related	148(95.5)	331(96.5)	144(96.6)	331(95.9)	NA	NA	279(96.9)	1022(97.5)
TEAEs with grade >=3	116(74.8)	230(67.1)	110(73.8)	214(62.0)	148(42.8)	545(45.9)	219(76.0)	789(75.3)
Treatment-related	96(61.9)	174(50.7)	89(59.7)	157(45.5)	49(14.2)	210(17.7)	194(67.4)	678(64.7)
Tislelizumab/placebo-related	50(32.3)	85(24.8)	29(19.5)	65(18.8)	49(14.2)	210(17.7)	93(32.3)	325(31.0)
Chemotherapy-related	87(56.1)	158(46.1)	88(59.1)	153(44.3)	NA	NA	182(63.2)	638(60.9)
Serious TEAEs	65(41.9)	146(42.6)	61(40.9)	117(33.9)	104(30.1)	429(36.1)	113(39.2)	461(44.0)
Treatment-related	38(24.5)	77(22.4)	30(20.1)	42(12.2)	34(9.8)	147(12.4)	72(25.0)	266(25.4)
Tislelizumab/placebo-related	29(18.7)	56(16.3)	12(8.1)	26(7.5)	34(9.8)	147(12.4)	50(17.4)	193(18.4)
Chemotherapy-related	30(19.4)	59(17.2)	29(19.5)	38(11.0)	NA	NA	53(18.4)	193(18.4)
Fatal serious TEAEs	16(10.3)	31(9.0)	19(12.8)	23(6.7)	26(7.5)	102(8.6)	20(6.9)	74(7.1)
Treatment-related	3(1.9)	8(2.3)	3(2.0)	1(0.3)	3(0.9)	14(1.2)	5(1.7)	21(2.0)
Tislelizumab/placebo-related	2(1.3)	7(2.0)	3(2.0)	1(0.3)	3(0.9)	14(1.2)	4(1.4)	19(1.8)
Chemotherapy-related	2(1.3)	8(2.3)	3(2.0)	0	NA	NA	3(1.0)	15(1.4)
TEAEs leading to any treatment discontinuation	28(18.1)	87(25.4)	28(18.8)	39(11.3)	34(9.8)	165(13.9)	70(24.3)	295(28.1)
Leading to Tislelizumab/placebo discontinuation	21(13.5)	58(16.9)	17(11.4)	19(5.5)	34(9.8)	165(13.9)	34(11.8)	160(15.3)
Tislelizumab/placebo-related	13(8.4)	28(8.2)	6(4.0)	0	16(4.6)	71(6.0)	24(8.3)	105(10.0)
Chemotherapy-related	7(4.5)	15(4.4)	5(3.4)	1(0.3)	NA	NA	12(4.2)	47(4.5)
Leading to Chemotherapy discontinuation	24(15.5)	81(23.6)	24(16.1)	38(11.0)	NA	NA	59(20.5)	257(24.5)
Tislelizumab/placebo-related	11(7.1)	26(7.6)	5(3.4)	4(1.2)	NA	NA	23(8.0)	86(8.2)
Chemotherapy-related	12(7.7)	45(13.1)	17(11.4)	21(6.1)	NA	NA	44(15.3)	185(17.7)
TEAEs leading to any treatment modification	127(81.9)	254(74.1)	124(83.2)	251(72.8)	95(27.5)	322(27.1)	228(79.2)	780(74.4)
Leading to Tislelizumab/placebo modification	87(56.1)	157(45.8)	88(59.1)	151(43.8)	95(27.5)	322(27.1)	168(58.3)	571(54.5)
Tislelizumab/placebo-related	39(25.2)	72(21.0)	36(24.2)	67(19.4)	56(16.2)	196(16.5)	87(30.2)	309(29.5)
Chemotherapy-related	74(47.7)	114(33.2)	79(53.0)	111(32.2)	NA	NA	132(45.8)	429(40.9)
Leading to Chemotherapy modification	127(81.9)	251(73.2)	123(82.6)	249(72.2)	NA	NA	222(77.1)	747(71.3)
Tislelizumab/placebo-related	51(32.9)	93(27.1)	42(28.2)	90(26.1)	NA	NA	87(30.2)	303(28.9)
Chemotherapy-related	119(76.8)	228(66.5)	116(77.9)	234(67.8)	NA	NA	206(71.5)	680(64.9)
Immune-mediated TEAEs	48(31.0)	106(30.9)	18(12.1)	40(11.6)	123(35.5)	383(32.2)	103(35.8)	404(38.5)
Infusion-Related Reaction	12(7.7)	21(6.1)	11(7.4)	4(1.2)	12(3.5)	32(2.7)	25(8.7)	61(5.8)

Source: Summary of Clinical Safety Appendix 2 Table Comb_5.1-2

Hepatic function

Table 82: Overview of treatment-emergent adverse events by hepatic function (Safety Set)

	305 Tisle + Chemo - All N=498			305 Placebo + Chemo - All N=494			Tisle monotherapy 200 mg Q3W N=1534			Tisle combination therapy N=1336		
	Normal N=418 n (%)	Impairment N=80 n (%)	Missing N=0 n (%)	Normal N=415 n (%)	Impairment N=76 n (%)	Missing N=3 n (%)	Normal N=1243 n (%)	Impairment N=285 n (%)	Missing N=6 n (%)	Normal N=1192 n (%)	Impairment N=144 n (%)	Missing N=0 n (%)
TEAEs	416(99.5)	79(98.8)	0	408(98.3)	75(98.7)	3(100)	1199(96.5)	274(96.1)	6(100)	1188(99.7)	143(99.3)	0
Treatment-related	406(97.1)	77(96.3)	0	402(96.9)	71(93.4)	3(100)	942(75.8)	191(67.0)	4(66.7)	1168(98.0)	140(97.2)	0
Tislelizumab/placebo-related	273(65.3)	51(63.8)	0	221(53.3)	38(50.0)	3(100)	942(75.8)	191(67.0)	4(66.7)	898(75.3)	99(68.8)	0
Chemotherapy-related	404(96.7)	75(93.8)	0	401(96.6)	71(93.4)	3(100)	NA	NA	NA	1163(97.6)	138(95.8)	0
TEAEs with grade >=3	289(69.1)	57(71.3)	0	273(65.8)	49(64.5)	2(66.7)	545(43.8)	145(50.9)	3(50.0)	904(75.8)	104(72.2)	0
Treatment-related	228(54.5)	42(52.5)	0	207(49.9)	37(48.7)	2(66.7)	208(16.7)	50(17.5)	1(16.7)	789(66.2)	83(57.6)	0
Tislelizumab/placebo-related	114(27.3)	21(26.3)	0	80(19.3)	12(15.8)	2(66.7)	208(16.7)	50(17.5)	1(16.7)	375(31.5)	43(29.9)	0
Chemotherapy-related	205(49.0)	40(50.0)	0	202(48.7)	37(48.7)	2(66.7)	NA	NA	NA	740(62.1)	80(55.6)	0
Serious TEAEs	174(41.6)	37(46.3)	0	153(36.9)	25(32.9)	0	420(33.8)	111(38.9)	2(33.3)	512(43.0)	62(43.1)	0
Treatment-related	95(22.7)	20(25.0)	0	61(14.7)	11(14.5)	0	149(12.0)	31(10.9)	1(16.7)	301(25.3)	37(25.7)	0
Tislelizumab/placebo-related	71(17.0)	14(17.5)	0	30(7.2)	8(10.5)	0	149(12.0)	31(10.9)	1(16.7)	218(18.3)	25(17.4)	0
Chemotherapy-related	71(17.0)	18(22.5)	0	58(14.0)	9(11.8)	0	NA	NA	NA	215(18.0)	31(21.5)	0
Fatal serious TEAEs	40(9.6)	7(8.8)	0	37(8.9)	5(6.6)	0	85(6.8)	42(14.7)	1(16.7)	85(7.1)	9(6.3)	0
Treatment-related	11(2.6)	0	0	4(1.0)	0	0	10(0.8)	6(2.1)	1(16.7)	26(2.2)	0	0
Tislelizumab/placebo-related	9(2.2)	0	0	4(1.0)	0	0	10(0.8)	6(2.1)	1(16.7)	23(1.9)	0	0
Chemotherapy-related	10(2.4)	0	0	3(0.7)	0	0	NA	NA	NA	18(1.5)	0	0
TEAEs leading to any treatment discontinuation	97(23.2)	18(22.5)	0	57(13.7)	10(13.2)	0	160(12.9)	36(12.6)	3(50.0)	329(27.6)	36(25.0)	0
Leading to Tislelizumab/placebo discontinuation	66(15.8)	13(16.3)	0	31(7.5)	5(6.6)	0	160(12.9)	36(12.6)	3(50.0)	173(14.5)	21(14.6)	0
Tislelizumab/placebo-related	34(8.1)	7(8.8)	0	4(1.0)	2(2.6)	0	77(6.2)	9(3.2)	1(16.7)	116(9.7)	13(9.0)	0
Chemotherapy-related	19(4.5)	3(3.8)	0	5(1.2)	1(1.3)	0	NA	NA	NA	52(4.4)	7(4.9)	0
Leading to Chemotherapy discontinuation	87(20.8)	18(22.5)	0	53(12.8)	9(11.8)	0	NA	NA	NA	283(23.7)	33(22.9)	0
Tislelizumab/placebo-related	30(7.2)	7(8.8)	0	8(1.9)	1(1.3)	0	NA	NA	NA	96(8.1)	13(9.0)	0
Chemotherapy-related	51(12.2)	6(7.5)	0	32(7.7)	6(7.9)	0	NA	NA	NA	210(17.6)	19(13.2)	0
TEAEs leading to any treatment modification	320(76.6)	61(76.3)	0	314(75.7)	59(77.6)	2(66.7)	325(26.1)	90(31.6)	2(33.3)	905(75.9)	103(71.5)	0
Leading to Tislelizumab/placebo modification	202(48.3)	42(52.5)	0	202(48.7)	35(46.1)	2(66.7)	325(26.1)	90(31.6)	2(33.3)	668(56.0)	71(49.3)	0
Tislelizumab/placebo-related	93(22.2)	18(22.5)	0	90(21.7)	11(14.5)	2(66.7)	202(16.3)	49(17.2)	1(16.7)	358(30.0)	38(26.4)	0
Chemotherapy-related	158(37.8)	30(37.5)	0	163(39.3)	25(32.9)	2(66.7)	NA	NA	NA	507(42.5)	54(37.5)	0
Leading to Chemotherapy modification	317(75.8)	61(76.3)	0	311(74.9)	59(77.6)	2(66.7)	NA	NA	NA	869(72.9)	100(69.4)	0
Tislelizumab/placebo-related	116(27.8)	28(35.0)	0	115(27.7)	15(19.7)	2(66.7)	NA	NA	NA	344(28.9)	46(31.9)	0
Chemotherapy-related	292(69.9)	55(68.8)	0	294(70.8)	54(71.1)	2(66.7)	NA	NA	NA	796(66.8)	90(62.5)	0
Immune-mediated TEAEs	130(31.1)	24(30.0)	0	44(10.6)	14(18.4)	0	422(34.0)	82(28.8)	2(33.3)	467(39.2)	40(27.8)	0
Infusion-Related Reaction	27(6.5)	6(7.5)	0	12(2.9)	3(3.9)	0	35(2.8)	9(3.2)	0	74(6.2)	12(8.3)	0

Source: Summary of Clinical Safety Appendix 2 Table Comb_5.1-3

Renal function

Table 83: Overview of treatment-emergent adverse events by renal function (Safety Set)

	305 Tisle + Chemo - All N=498			305 Placebo + Chemo - All N=494			Tisle monotherapy 200 mg Q3W N=1534			Tisle combination therapy N=1336		
	Normal N=333 n (%)	Impairment N=165 n (%)	Missing N=0 n (%)	Normal N=329 n (%)	Impairment N=164 n (%)	Missing N=1 n (%)	Normal N=944 n (%)	Impairment N=590 n (%)	Missing N=0 n (%)	Normal N=929 n (%)	Impairment N=400 n (%)	Missing N=7 n (%)
TEAEs	330(99.1)	165(100)	0	323(98.2)	162(98.8)	1(100)	908(96.2)	571(96.8)	0	924(99.5)	400(100)	7(100)
Treatment-related	322(96.7)	161(97.6)	0	318(96.7)	157(95.7)	1(100)	689(73.0)	448(75.9)	0	909(97.8)	392(98.0)	7(100)
Tislelizumab/placebo-related	210(63.1)	114(69.1)	0	169(51.4)	92(56.1)	1(100)	689(73.0)	448(75.9)	0	685(73.7)	307(76.8)	5(71.4)
Chemotherapy-related	320(96.1)	159(96.4)	0	317(96.4)	157(95.7)	1(100)	NA	NA	NA	904(97.3)	390(97.5)	7(100)
TEAEs with grade >=3	227(68.2)	119(72.1)	0	206(62.6)	117(71.3)	1(100)	420(44.5)	273(46.3)	0	699(75.2)	303(75.8)	6(85.7)
Treatment-related	173(52.0)	97(58.8)	0	159(48.3)	86(52.4)	1(100)	162(17.2)	97(16.4)	0	604(65.0)	262(65.5)	6(85.7)
Tislelizumab/placebo-related	81(24.3)	54(32.7)	0	58(17.6)	35(21.3)	1(100)	162(17.2)	97(16.4)	0	287(30.9)	128(32.0)	3(42.9)
Chemotherapy-related	161(48.3)	84(50.9)	0	156(47.4)	84(51.2)	1(100)	NA	NA	NA	574(61.8)	240(60.0)	6(85.7)
Serious TEAEs	142(42.6)	69(41.8)	0	109(33.1)	69(42.1)	0	328(34.7)	205(34.7)	0	401(43.2)	169(42.3)	4(57.1)
Treatment-related	77(23.1)	38(23.0)	0	47(14.3)	25(15.2)	0	109(11.5)	72(12.2)	0	235(25.3)	99(24.8)	4(57.1)
Tislelizumab/placebo-related	55(16.5)	30(18.2)	0	25(7.6)	13(7.9)	0	109(11.5)	72(12.2)	0	164(17.7)	75(18.8)	4(57.1)
Chemotherapy-related	62(18.6)	27(16.4)	0	43(13.1)	24(14.6)	0	NA	NA	NA	176(18.9)	67(16.8)	3(42.9)
Fatal serious TEAEs	33(9.9)	14(8.5)	0	22(6.7)	20(12.2)	0	82(8.7)	46(7.8)	0	58(6.2)	36(9.0)	0
Treatment-related	9(2.7)	2(1.2)	0	3(0.9)	1(0.6)	0	11(1.2)	6(1.0)	0	17(1.8)	9(2.3)	0
Tislelizumab/placebo-related	8(2.4)	1(0.6)	0	3(0.9)	1(0.6)	0	11(1.2)	6(1.0)	0	15(1.6)	8(2.0)	0
Chemotherapy-related	8(2.4)	2(1.2)	0	2(0.6)	1(0.6)	0	NA	NA	NA	13(1.4)	5(1.3)	0
TEAEs leading to any treatment discontinuation	69(20.7)	46(27.9)	0	37(11.2)	30(18.3)	0	122(12.9)	77(13.1)	0	239(25.7)	123(30.8)	3(42.9)
Leading to Tislelizumab/placebo discontinuation	49(14.7)	30(18.2)	0	17(5.2)	19(11.6)	0	122(12.9)	77(13.1)	0	125(13.5)	66(16.5)	3(42.9)
Tislelizumab/placebo-related	24(7.2)	17(10.3)	0	4(1.2)	2(1.2)	0	51(5.4)	36(6.1)	0	82(8.8)	44(11.0)	3(42.9)
Chemotherapy-related	17(5.1)	5(3.0)	0	4(1.2)	2(1.2)	0	NA	NA	NA	43(4.6)	15(3.8)	1(14.3)
Leading to Chemotherapy discontinuation	63(18.9)	42(25.5)	0	34(10.3)	28(17.1)	0	NA	NA	NA	205(22.1)	111(27.8)	0
Tislelizumab/placebo-related	20(6.0)	17(10.3)	0	5(1.5)	4(2.4)	0	NA	NA	NA	65(7.0)	44(11.0)	0
Chemotherapy-related	36(10.8)	21(12.7)	0	25(7.6)	13(7.9)	0	NA	NA	NA	157(16.9)	72(18.0)	0
TEAEs leading to any treatment modification	251(75.4)	130(78.8)	0	255(77.5)	119(72.6)	1(100)	236(25.0)	181(30.7)	0	692(74.5)	310(77.5)	6(85.7)
Leading to Tislelizumab/placebo modification	153(45.9)	91(55.2)	0	162(49.2)	76(46.3)	1(100)	236(25.0)	181(30.7)	0	506(54.5)	228(57.0)	5(71.4)
Tislelizumab/placebo-related	66(19.8)	45(27.3)	0	64(19.5)	38(23.2)	1(100)	139(14.7)	113(19.2)	0	276(29.7)	119(29.8)	1(14.3)
Chemotherapy-related	119(35.7)	69(41.8)	0	129(39.2)	60(36.6)	1(100)	NA	NA	NA	388(41.8)	168(42.0)	5(71.4)
Leading to Chemotherapy modification	250(75.1)	128(77.6)	0	252(76.6)	119(72.6)	1(100)	NA	NA	NA	670(72.1)	293(73.3)	6(85.7)
Tislelizumab/placebo-related	93(27.9)	51(30.9)	0	87(26.4)	44(26.8)	1(100)	NA	NA	NA	275(29.6)	111(27.8)	4(57.1)
Chemotherapy-related	232(69.7)	115(69.7)	0	237(72.0)	112(68.3)	1(100)	NA	NA	NA	612(65.9)	269(67.3)	5(71.4)
Immune-mediated TEAEs	105(31.5)	49(29.7)	0	39(11.9)	19(11.6)	0	295(31.3)	211(35.8)	0	346(37.2)	157(39.3)	4(57.1)
Infusion-Related Reaction	26(7.8)	7(4.2)	0	13(4.0)	2(1.2)	0	32(3.4)	12(2.0)	0	67(7.2)	19(4.8)	0

Source: Summary of Clinical Safety Appendix 2 Comb_Table 5.1-4

Race/ethnicity

Table 84: Overview of treatment-emergent adverse events by race (Safety Set)

	305 Tisle + Chemo - All N=498			305 Placebo + Chemo - All N=494			Tisle monotherapy 200 mg Q3W N=1534			Tisle combination therapy N=1336		
	Asian N=375 n (%)	White N=114 n (%)	Other N=9 n (%)	Asian N=370 n (%)	White N=107 n (%)	Other N=17 n (%)	Asian N=1234 n (%)	White N=252 n (%)	Other N=48 n (%)	Asian N=1130 n (%)	White N=193 n (%)	Other N=13 n (%)
TEAEs	374(99.7)	112(98.2)	9(100)	366(98.9)	103(96.3)	17(100)	1189(96.4)	243(96.4)	47(97.9)	1127(99.7)	191(99.0)	13(100)
Treatment-related	366(97.6)	108(94.7)	9(100)	360(97.3)	99(92.5)	17(100)	942(76.3)	167(66.3)	28(58.3)	1113(98.5)	182(94.3)	13(100)
Tislelizumab/placebo-related	240(64.0)	76(66.7)	8(88.9)	189(51.1)	63(58.9)	10(58.8)	942(76.3)	167(66.3)	28(58.3)	856(75.8)	130(67.4)	11(84.6)
Chemotherapy-related	366(97.6)	105(92.1)	8(88.9)	360(97.3)	98(91.6)	17(100)	NA	NA	NA	1110(98.2)	179(92.7)	12(92.3)
TEAEs with grade >=3	260(69.3)	78(68.4)	8(88.9)	236(63.8)	75(70.1)	13(76.5)	540(43.8)	126(50.0)	27(56.3)	860(76.1)	136(70.5)	12(92.3)
Treatment-related	209(55.7)	53(46.5)	8(88.9)	185(50.0)	52(48.6)	9(52.9)	224(18.2)	31(12.3)	4(8.3)	763(67.5)	99(51.3)	10(76.9)
Tislelizumab/placebo-related	97(25.9)	33(28.9)	5(55.6)	65(17.6)	25(23.4)	4(23.5)	224(18.2)	31(12.3)	4(8.3)	354(31.3)	57(29.5)	7(53.8)
Chemotherapy-related	196(52.3)	44(38.6)	5(55.6)	181(48.9)	51(47.7)	9(52.9)	NA	NA	NA	728(64.4)	85(44.0)	7(53.8)
Serious TEAEs	157(41.9)	46(40.4)	8(88.9)	125(33.8)	44(41.1)	9(52.9)	427(34.6)	86(34.1)	20(41.7)	476(42.1)	86(44.6)	12(92.3)
Treatment-related	98(26.1)	11(9.6)	6(66.7)	55(14.9)	14(13.1)	3(17.6)	163(13.2)	17(6.7)	1(2.1)	299(26.5)	31(16.1)	8(61.5)
Tislelizumab/placebo-related	72(19.2)	8(7.0)	5(55.6)	29(7.8)	8(7.5)	1(5.9)	163(13.2)	17(6.7)	1(2.1)	215(19.0)	21(10.9)	7(53.8)
Chemotherapy-related	79(21.1)	7(6.1)	3(33.3)	53(14.3)	12(11.2)	2(11.8)	NA	NA	NA	220(19.5)	22(11.4)	4(30.8)
Fatal serious TEAEs	26(6.9)	19(16.7)	2(22.2)	21(5.7)	19(17.8)	2(11.8)	89(7.2)	31(12.3)	8(16.7)	64(5.7)	27(14.0)	3(23.1)
Treatment-related	9(2.4)	1(0.9)	1(11.1)	3(0.8)	1(0.9)	0	15(1.2)	1(0.4)	1(2.1)	23(2.0)	2(1.0)	1(7.7)
Tislelizumab/placebo-related	8(2.1)	0	1(11.1)	3(0.8)	1(0.9)	0	15(1.2)	1(0.4)	1(2.1)	21(1.9)	1(0.5)	1(7.7)
Chemotherapy-related	8(2.1)	1(0.9)	1(11.1)	3(0.8)	0	0	NA	NA	NA	16(1.4)	1(0.5)	1(7.7)
TEAEs leading to any treatment discontinuation	79(21.1)	31(27.2)	5(55.6)	45(12.2)	17(15.9)	5(29.4)	157(12.7)	34(13.5)	8(16.7)	294(26.0)	63(32.6)	8(61.5)
Leading to Tislelizumab/placebo discontinuation	48(12.8)	26(22.8)	5(55.6)	17(4.6)	15(14.0)	4(23.5)	157(12.7)	34(13.5)	8(16.7)	148(13.1)	39(20.2)	7(53.8)
Tislelizumab/placebo-related	30(8.0)	7(6.1)	4(44.4)	5(1.4)	1(0.9)	0	75(6.1)	9(3.6)	3(6.3)	108(9.6)	15(7.8)	6(46.2)
Chemotherapy-related	22(5.9)	0	0	4(1.1)	1(0.9)	1(5.9)	NA	NA	NA	55(4.9)	3(1.6)	1(7.7)
Leading to Chemotherapy discontinuation	74(19.7)	27(23.7)	4(44.4)	42(11.4)	16(15.0)	4(23.5)	NA	NA	NA	251(22.2)	58(30.1)	7(53.8)
Tislelizumab/placebo-related	30(8.0)	4(3.5)	3(33.3)	6(1.6)	3(2.8)	0	NA	NA	NA	94(8.3)	11(5.7)	4(30.8)
Chemotherapy-related	50(13.3)	7(6.1)	0	31(8.4)	5(4.7)	2(11.8)	NA	NA	NA	196(17.3)	32(16.6)	1(7.7)
TEAEs leading to any treatment modification	306(81.6)	69(60.5)	6(66.7)	294(79.5)	70(65.4)	11(64.7)	326(26.4)	77(30.6)	14(29.2)	869(76.9)	130(67.4)	9(69.2)
Leading to Tislelizumab/placebo modification	193(51.5)	48(42.1)	3(33.3)	180(48.6)	54(50.5)	5(29.4)	326(26.4)	77(30.6)	14(29.2)	641(56.7)	95(49.2)	3(23.1)
Tislelizumab/placebo-related	91(24.3)	19(16.7)	1(11.1)	78(21.1)	24(22.4)	1(5.9)	208(16.9)	38(15.1)	6(12.5)	356(31.5)	39(20.2)	1(7.7)
Chemotherapy-related	153(40.8)	33(28.9)	2(22.2)	147(39.7)	40(37.4)	3(17.6)	NA	NA	NA	496(43.9)	63(32.6)	2(15.4)
Leading to Chemotherapy modification	305(81.3)	68(59.6)	5(55.6)	293(79.2)	68(63.6)	11(64.7)	NA	NA	NA	834(73.8)	127(65.8)	8(61.5)
Tislelizumab/placebo-related	121(32.3)	22(19.3)	1(11.1)	100(27.0)	29(27.1)	3(17.6)	NA	NA	NA	347(30.7)	41(21.2)	2(15.4)
Chemotherapy-related	289(77.1)	54(47.4)	4(44.4)	280(75.7)	59(55.1)	11(64.7)	NA	NA	NA	775(68.6)	105(54.4)	6(46.2)
Immune-mediated TEAEs	126(33.6)	23(20.2)	5(55.6)	43(11.6)	12(11.2)	3(17.6)	419(34.0)	77(30.6)	10(20.8)	455(40.3)	46(23.8)	6(46.2)
Infusion-Related Reaction	30(8.0)	3(2.6)	0	14(3.8)	0	1(5.9)	33(2.7)	9(3.6)	2(4.2)	79(7.0)	7(3.6)	0

Source: Summary of Clinical Safety Appendix 2 Comb_Table 5.1-5

ECOG status

Table 85: Overview of treatment-emergent adverse events by ECOG status (Safety Set)

	305 Tisle + Chemo - All N=498		305 Placebo + Chemo - All N=494		Tisle monotherapy 200 mg Q3W N=1534		Tisle combination therapy N=1336	
	0 N=169 n (%)	1 N=329 n (%)	0 N=154 n (%)	1 N=340 n (%)	0 N=499 n (%)	1 N=1035 n (%)	0 N=393 n (%)	1 N=943 n (%)
TEAEs	168(99.4)	327(99.4)	151(98.1)	335(98.5)	478(95.8)	1001(96.7)	392(99.7)	939(99.6)
Treatment-related	164(97.0)	319(97.0)	151(98.1)	325(95.6)	374(74.9)	763(73.7)	385(98.0)	923(97.9)
Tislelizumab/placebo-related	112(66.3)	212(64.4)	81(52.6)	181(53.2)	374(74.9)	763(73.7)	288(73.3)	709(75.2)
Chemotherapy-related	163(96.4)	316(96.0)	151(98.1)	324(95.3)	NA	NA	382(97.2)	919(97.5)
TEAEs with grade >=3	111(65.7)	235(71.4)	97(63.0)	227(66.8)	208(41.7)	485(46.9)	289(73.5)	719(76.2)
Treatment-related	88(52.1)	182(55.3)	68(44.2)	178(52.4)	75(15.0)	184(17.8)	248(63.1)	624(66.2)
Tislelizumab/placebo-related	44(26.0)	91(27.7)	30(19.5)	64(18.8)	75(15.0)	184(17.8)	114(29.0)	304(32.2)
Chemotherapy-related	79(46.7)	166(50.5)	66(42.9)	175(51.5)	NA	NA	230(58.5)	590(62.6)
Serious TEAEs	67(39.6)	144(43.8)	50(32.5)	128(37.6)	156(31.3)	377(36.4)	162(41.2)	412(43.7)
Treatment-related	37(21.9)	78(23.7)	17(11.0)	55(16.2)	56(11.2)	125(12.1)	95(24.2)	243(25.8)
Tislelizumab/placebo-related	24(14.2)	61(18.5)	11(7.1)	27(7.9)	56(11.2)	125(12.1)	65(16.5)	178(18.9)
Chemotherapy-related	32(18.9)	57(17.3)	14(9.1)	53(15.6)	NA	NA	72(18.3)	174(18.5)
Fatal serious TEAEs	13(7.7)	34(10.3)	10(6.5)	32(9.4)	31(6.2)	97(9.4)	27(6.9)	67(7.1)
Treatment-related	4(2.4)	7(2.1)	0	4(1.2)	5(1.0)	12(1.2)	9(2.3)	17(1.8)
Tislelizumab/placebo-related	3(1.8)	6(1.8)	0	4(1.2)	5(1.0)	12(1.2)	8(2.0)	15(1.6)
Chemotherapy-related	4(2.4)	6(1.8)	0	3(0.9)	NA	NA	8(2.0)	10(1.1)
TEAEs leading to any treatment discontinuation	37(21.9)	78(23.7)	20(13.0)	47(13.8)	55(11.0)	144(13.9)	99(25.2)	266(28.2)
Leading to Tislelizumab/placebo discontinuation	25(14.8)	54(16.4)	9(5.8)	27(7.9)	55(11.0)	144(13.9)	49(12.5)	145(15.4)
Tislelizumab/placebo-related	16(9.5)	25(7.6)	2(1.3)	4(1.2)	31(6.2)	56(5.4)	31(7.9)	98(10.4)
Chemotherapy-related	8(4.7)	14(4.3)	0	6(1.8)	NA	NA	18(4.6)	41(4.3)
Leading to Chemotherapy discontinuation	34(20.1)	71(21.6)	17(11.0)	45(13.2)	NA	NA	90(22.9)	226(24.0)
Tislelizumab/placebo-related	14(8.3)	23(7.0)	3(1.9)	6(1.8)	NA	NA	28(7.1)	81(8.6)
Chemotherapy-related	20(11.8)	37(11.2)	12(7.8)	26(7.6)	NA	NA	67(17.0)	162(17.2)
TEAEs leading to any treatment modification	121(71.6)	260(79.0)	107(69.5)	268(78.8)	128(25.7)	289(27.9)	297(75.6)	711(75.4)
Leading to Tislelizumab/placebo modification	74(43.8)	170(51.7)	71(46.1)	168(49.4)	128(25.7)	289(27.9)	213(54.2)	526(55.8)
Tislelizumab/placebo-related	37(21.9)	74(22.5)	31(20.1)	72(21.2)	79(15.8)	173(16.7)	108(27.5)	288(30.5)
Chemotherapy-related	58(34.3)	130(39.5)	52(33.8)	138(40.6)	NA	NA	155(39.4)	406(43.1)
Leading to Chemotherapy modification	120(71.0)	258(78.4)	105(68.2)	267(78.5)	NA	NA	289(73.5)	680(72.1)
Tislelizumab/placebo-related	47(27.8)	97(29.5)	39(25.3)	93(27.4)	NA	NA	103(26.2)	287(30.4)
Chemotherapy-related	110(65.1)	237(72.0)	97(63.0)	253(74.4)	NA	NA	265(67.4)	621(65.9)
Immune-mediated TEAEs	55(32.5)	99(30.1)	22(14.3)	36(10.6)	176(35.3)	330(31.9)	142(36.1)	365(38.7)
Infusion-Related Reaction	9(5.3)	24(7.3)	5(3.2)	10(2.9)	23(4.6)	21(2.0)	23(5.9)	63(6.7)

Source: Summary of Clinical Safety Appendix 2 Comb_Table 5.1-6

Geographical region

Table 86: Treatment-emergent adverse events, all grades, by geographical region and Preferred Term (Safety Set)

	East Asia		Rest of world	
	T+PtF N=375	P+PtF N=370	T+PtF N=123	P+PtF N=124
Preferred Terms	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Number of patients with at least one event	374 (99.7)	366 (98.9)	121 (98.4)	120 (96.8)
TEAEs reported more frequently (≥ 10%) in T+PtF group East Asia vs. ROW region				
Platelet count decreased	168 (44.8)	181 (48.9)	9 (7.3)	7 (5.6)
Aspartate aminotransferase increased	147 (39.2)	143 (38.6)	9 (7.3)	7 (5.6)
Vomiting	155 (41.3)	143 (38.6)	25 (20.3)	36 (29.0)
Neutrophil count decreased	156 (41.6)	154 (41.6)	12 (9.8)	9 (7.3)
White blood cell count decreased	117 (31.2)	128 (34.6)	2 (1.6)	7 (5.6)
Alanine aminotransferase increased	115 (30.7)	99 (26.8)	7 (5.7)	6 (4.8)
Hypoalbuminaemia	83 (22.1)	82 (22.2)	4 (3.3)	10 (8.1)
Blood bilirubin increased	74 (19.7)	68 (18.4)	3 (2.4)	6 (4.8)
Weight decreased	94 (25.1)	80 (21.6)	14 (11.4)	19 (15.3)
Hypoaesthesia	67 (17.9)	67 (18.1)	3 (2.4)	2 (1.6)
Decreased appetite	169 (45.1)	165 (44.6)	36 (29.3)	44 (35.5)
Pyrexia	90 (24.0)	60 (16.2)	10 (8.1)	19 (15.3)
Palmar-plantar erythrodysaesthesia syndrome	83 (22.1)	86 (23.2)	12 (9.8)	8 (6.5)
TEAEs reported more frequently (≥ 10%) in T+PtF group ROW vs. East Asia region				
Asthenia	53 (14.1)	43 (11.6)	44 (35.8)	42 (33.9)
Fatigue	53 (14.1)	43 (11.6)	34 (27.6)	30 (24.2)
Neutropenia	38 (10.1)	38 (10.3)	37 (30.1)	44 (35.5)

Data cutoff for Study 305: 28-Feb-2023
Numbers (n) represent counts of patients.
A patient with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA Version 26.0.
Source: [SCS Appendix 1-Table 5.1-14]
Source: Summary of Clinical Safety Table 22

Table 87: Overview of treatment-emergent adverse events by geographical region (Safety Set)

	305 Tisle + Chemo - All N=498		305 Placebo + Chemo - All N=494		Tisle monotherapy 200 mg Q3W N=1534		Tisle combination therapy N=1336	
	East Asia N=375 n (%)	ROW N=123 n (%)	East Asia N=370 n (%)	ROW N=124 n (%)	East Asia N=1229 n (%)	ROW N=305 n (%)	East Asia N=1130 n (%)	ROW N=206 n (%)
TEAEs	374(99.7)	121(98.4)	366(98.9)	120(96.8)	1184(96.3)	295(96.7)	1127(99.7)	204(99.0)
Treatment-related	366(97.6)	117(95.1)	360(97.3)	116(93.5)	938(76.3)	199(65.2)	1113(98.5)	195(94.7)
Tislelizumab/placebo-related	240(64.0)	84(68.3)	189(51.1)	73(58.9)	938(76.3)	199(65.2)	856(75.8)	141(68.4)
Chemotherapy-related	366(97.6)	113(91.9)	360(97.3)	115(92.7)	NA	NA	1110(98.2)	191(92.7)
TEAEs with grade >=3	260(69.3)	86(69.9)	236(63.8)	88(71.0)	538(43.8)	155(50.8)	860(76.1)	148(71.8)
Treatment-related	209(55.7)	61(49.6)	185(50.0)	61(49.2)	223(18.1)	36(11.8)	763(67.5)	109(52.9)
Tislelizumab/placebo-related	97(25.9)	38(30.9)	65(17.6)	29(23.4)	223(18.1)	36(11.8)	354(31.3)	64(31.1)
Chemotherapy-related	196(52.3)	49(39.8)	181(48.9)	60(48.4)	NA	NA	728(64.4)	92(44.7)
Serious TEAEs	157(41.9)	54(43.9)	125(33.8)	53(42.7)	425(34.6)	108(35.4)	476(42.1)	98(47.6)
Treatment-related	98(26.1)	17(13.8)	55(14.9)	17(13.7)	162(13.2)	19(6.2)	299(26.5)	39(18.9)
Tislelizumab/placebo-related	72(19.2)	13(10.6)	29(7.8)	9(7.3)	162(13.2)	19(6.2)	215(19.0)	28(13.6)
Chemotherapy-related	79(21.1)	10(8.1)	53(14.3)	14(11.3)	NA	NA	220(19.5)	26(12.6)
Fatal serious TEAEs	26(6.9)	21(17.1)	21(5.7)	21(16.9)	89(7.2)	39(12.8)	64(5.7)	30(14.6)
Treatment-related	9(2.4)	2(1.6)	3(0.8)	1(0.8)	15(1.2)	2(0.7)	23(2.0)	3(1.5)
Tislelizumab/placebo-related	8(2.1)	1(0.8)	3(0.8)	1(0.8)	15(1.2)	2(0.7)	21(1.9)	2(1.0)
Chemotherapy-related	8(2.1)	2(1.6)	3(0.8)	0	NA	NA	16(1.4)	2(1.0)
TEAEs leading to any treatment discontinuation	79(21.1)	36(29.3)	45(12.2)	22(17.7)	157(12.8)	42(13.8)	294(26.0)	71(34.5)
Leading to Tislelizumab/placebo discontinuation	48(12.8)	31(25.2)	17(4.6)	19(15.3)	157(12.8)	42(13.8)	148(13.1)	46(22.3)
Tislelizumab/placebo-related	30(8.0)	11(8.9)	5(1.4)	1(0.8)	75(6.1)	12(3.9)	108(9.6)	21(10.2)
Chemotherapy-related	22(5.9)	0	4(1.1)	2(1.6)	NA	NA	55(4.9)	4(1.9)
Leading to Chemotherapy discontinuation	74(19.7)	31(25.2)	42(11.4)	20(16.1)	NA	NA	251(22.2)	65(31.6)
Tislelizumab/placebo-related	30(8.0)	7(5.7)	6(1.6)	3(2.4)	NA	NA	94(8.3)	15(7.3)
Chemotherapy-related	50(13.3)	7(5.7)	31(8.4)	7(5.6)	NA	NA	196(17.3)	33(16.0)
TEAEs leading to any treatment modification	306(81.6)	75(61.0)	294(79.5)	81(65.3)	326(26.5)	91(29.8)	869(76.9)	139(67.5)
Leading to Tislelizumab/placebo modification	193(51.5)	51(41.5)	180(48.6)	59(47.6)	326(26.5)	91(29.8)	641(56.7)	98(47.6)
Tislelizumab/placebo-related	91(24.3)	20(16.3)	78(21.1)	25(20.2)	208(16.9)	44(14.4)	356(31.5)	40(19.4)
Chemotherapy-related	153(40.8)	35(28.5)	147(39.7)	43(34.7)	NA	NA	496(43.9)	65(31.6)
Leading to Chemotherapy modification	305(81.3)	73(59.3)	293(79.2)	79(63.7)	NA	NA	834(73.8)	135(65.5)
Tislelizumab/placebo-related	121(32.3)	23(18.7)	100(27.0)	32(25.8)	NA	NA	347(30.7)	43(20.9)
Chemotherapy-related	289(77.1)	58(47.2)	280(75.7)	70(56.5)	NA	NA	775(68.6)	111(53.9)
Immune-mediated TEAEs	126(33.6)	28(22.8)	43(11.6)	15(12.1)	418(34.0)	88(28.9)	455(40.3)	52(25.2)
Infusion-Related Reaction	30(8.0)	3(2.4)	14(3.8)	1(0.8)	33(2.7)	11(3.6)	79(7.0)	7(3.4)

Safety related to drug-drug interactions and other interactions

No new information on drug interactions for tislelizumab has been generated in support of this application.

Discontinuation due to adverse events

Table 88: Treatment-emergent adverse events (incidence ≥ 0.5% in the T+PtF group) all grades and grade ≥ 3 leading to discontinuation of any component of study treatment by Preferred Term (Safety Set)

	305 Tisle + Chemo - All N=498		305 Placebo + Chemo - All N=494		Tisle monotherapy 200 mg Q3W N=1534		Tisle combination therapy N=1336	
Preferred terms	All grades n (%)	Grade >=3 n (%)	All grades n (%)	Grade >=3 n (%)	All grades n (%)	Grade >=3 n (%)	All grades n (%)	Grade >=3 n (%)
Number of subjects with at least one event	73 (14.7)	61 (12.2)	37 (7.5)	33 (6.7)	199 (13.0)	162 (10.6)	145 (10.9)	103 (7.7)
Death	6 (1.2)	6 (1.2)	2 (0.4)	2 (0.4)	9 (0.6)	9 (0.6)	6 (0.4)	6 (0.4)
Fatigue	4 (0.8)	3 (0.6)	0	0	1 (0.1)	1 (0.1)	8 (0.6)	5 (0.4)
Gastrointestinal haemorrhage	3 (0.6)	3 (0.6)	0	0	2 (0.1)	2 (0.1)	3 (0.2)	3 (0.2)
Pneumonitis	3 (0.6)	2 (0.4)	0	0	14 (0.9)	9 (0.6)	11 (0.8)	5 (0.4)

Table 89: Treatment-emergent adverse events (incidence ≥ 0.5% in any group all grades column) all grades and grade ≥ 3 leading to tislelizumab/placebo discontinuation by Preferred Term (Safety Set)

	Study 305 All patients					
	T+PtF N=498		**P+PtF N=494**		**Tislelizumab monotherapy pool N=1534**	
Preferred Terms	**All grades n (%)**	**Grade ≥3 n (%)**	**All grades n (%)**	**Grade ≥3 n (%)**	**All grades n (%)**	**Grade ≥3 n (%)**
Number of patients with at least one event	79 (15.9)	63 (12.7)	36 (7.3)	32 (6.5)	199 (13.0)	162 (10.6)
Death	6 (1.2)	6 (1.2)	2 (0.4)	2 (0.4)	9 (0.6)	9 (0.6)
Pneumonitis	5 (1.0)	3 (0.6)	0	0	14 (0.9)	9 (0.6)
Fatigue	4 (0.8)	3 (0.6)	0	0	1 (0.1)	1 (0.1)
Ascites	3 (0.6)	3 (0.6)	0	0	3 (0.2)	3 (0.2)
Colitis	3 (0.6)	1 (0.2)	1 (0.2)	0	0	0
Immune-mediated hepatitis	3 (0.6)	3 (0.6)	0	0	0	0
General physical health deterioration	2 (0.4)	2 (0.4)	3 (0.6)	3 (0.6)	5 (0.3)	4 (0.3)
Interstitial lung disease	1 (0.2)	0	0	0	7 (0.5)	6 (0.4)
Pneumonia	1 (0.2)	0	2 (0.4)	2 (0.4)	18 (1.2)	15 (1.0)
Immune-mediated lung disease	0	0	0	0	9 (0.6)	4 (0.3)
Upper gastrointestinal haemorrhage	0	0	2 (0.4)	1 (0.2)	8 (0.5)	8 (0.5)

- Data cutoff for Study 305: 28FEB2023
- Data cutoff for Tisle monotherapy: Study 001-26AUG2020, Study 102-31MAY2020, Study 203-02NOV2020, Study 204-16SEP2019, Study 208-30JUN2021, Study 302-01DEC2020, Study 303-15JUL2021

Numbers (n) represent counts of patients.

A patient with multiple grades for an AE is only counted under the maximum grade.
Events are sorted by decreasing frequency of all grades PT in the T+PtF column in the Study 305 All patients population
MedDRA Version 26.0, CTCAE v5.0 for Study 305 study and v4.03 for monotherapy pool.
Source: [SCS Appendix 1-Table 3.1-17]
Source: Summary of Clinical Safety Table 15

Table 90: Treatment-emergent adverse events (incidence ≥ 0.5% in the T+PtF group) all grades and grade ≥ 3 leading to discontinuation of any chemotherapy component by Preferred Term (Safety Set)

	305 Tisle + Chemo - All N=498		305 Placebo + Chemo - All N=494		Tisle combination therapy N=1336	
Preferred Terms	All grades n (%)	Grade >=3 n (%)	All grades n (%)	Grade >=3 n (%)	All grades n (%)	Grade >=3 n (%)
Number of subjects with at least one event	105 (21.1)	69 (13.9)	62 (12.6)	46 (9.3)	316 (23.7)	184 (13.8)
Death	6 (1.2)	6 (1.2)	2 (0.4)	2 (0.4)	8 (0.6)	8 (0.6)
Peripheral sensory neuropathy	5 (1.0)	0	2 (0.4)	0	29 (2.2)	10 (0.7)
Platelet count decreased	5 (1.0)	2 (0.4)	7 (1.4)	4 (0.8)	12 (0.9)	8 (0.6)
Dyspnoea	4 (0.8)	0	1 (0.2)	1 (0.2)	6 (0.4)	1 (0.1)
Fatigue	4 (0.8)	3 (0.6)	0	0	9 (0.7)	4 (0.3)
Pneumonitis	4 (0.8)	2 (0.4)	0	0	17 (1.3)	11 (0.8)
Blood bilirubin increased	3 (0.6)	2 (0.4)	0	0	3 (0.2)	2 (0.1)
Gastrointestinal haemorrhage	3 (0.6)	3 (0.6)	0	0	4 (0.3)	4 (0.3)
Nausea	3 (0.6)	0	0	0	6 (0.4)	1 (0.1)
Neutrophil count decreased	3 (0.6)	3 (0.6)	5 (1.0)	4 (0.8)	13 (1.0)	11 (0.8)
Palmar-plantar erythrodysaesthesia syndrome	3 (0.6)	1 (0.2)	2 (0.4)	0	4 (0.3)	1 (0.1)
Pruritus	3 (0.6)	0	0	0	4 (0.3)	0
Thrombocytopenia	3 (0.6)	2 (0.4)	2 (0.4)	1 (0.2)	19 (1.4)	13 (1.0)

Source: Summary of Clinical Safety Appendix 2 Comb_Table 3.1-17.1

Post marketing experience

Tislelizumab has received marketing authorization in China for various indications and recently (13-Sep-2023) in the EU as monotherapy for the treatment of adult patients with unresectable, locally advanced or metastatic esophageal squamous cell carcinoma (ESCC) after prior platinum-based chemotherapy.

The first marketing authorization for tislelizumab was granted in China on 26-Dec-2019; this has been followed by a series of subsequent marketing authorizations. As of 25-Dec- 2022, there is a cumulative total exposure of approximately 109,466.6 patient-years (1,313,599 patient-months) based on the treatment cycle of Q3W.

As of the current time of reporting for this SCS submission, safety data reported from ongoing clinical trials and ongoing monitoring of post-marketing reports have not resulted in the identification of any new safety signals that would result in a change of the positive overall benefit-risk profile of tislelizumab.

2.5.1. Discussion on clinical safety

The safety data set (data cut-off date: 28 February 2023) to support this extension of indication for Tislelizumab in patients with locally advanced unresectable or metastatic G/GEJ adenocarcinoma is based on a global, multicenter, randomized, double-blind, placebo-controlled study (Study 305), evaluating the efficacy and safety of Tislelizumab (200 mg administered IV Q3W) in combination with platinum- and fluoropyrimidine-based chemotherapy compared to the efficacy and safety of placebo in combination with platinum and fluoropyrimidine-based chemotherapy. In total, safety data of 992 patients from this pivotal study are available. Thereof, 498 patients were included in the Tislelizumab+Chemotherapy arm and 494 patients in the Placebo+Chemotherapy arm. In addition, in total 544 patients included in study 305 were PD-L1 positive (patients with a PD-L1 score ≥ 5%). Thereof, 272 patients positive for PD-L1 were included in both the Tislelizumab+Chemotherapy arm and in the Placebo+Chemotherapy arm.

In addition, data from a Tislelizumab monotherapy pool (n=1534) and from a Tislelizumab combination therapy pool (n=1336) were considered as supportive, since differences in the included studies' design, patient populations, tumour types, previous therapy (first- or second-line) etc. are substantial, precluding a direct comparison to data from Study 305. It is clarified that in the Summary of Clinical Safety, all the patients from the BGB-A317-206 study are included in the combination pool, when in the SmPC, only the NSCLC patients from this study are included (i.e., the 17 patients from the SCLC cohort are excluded since they were not included in the SmPC for the procedure II/08).

However, in principle, this amount of safety data can be considered adequate to describe the toxicity profile of Tislelizumab (200 mg Q3W).

In the pivotal study 305, the demographics and baseline disease characteristics as well as the disease history were more or less balanced between the Tislelizumab+Chemotherapy arm and the Placebo+Chemotherapy arm and were overall representative of the target population.

At the time of the data cut-off, only a small number of patients in pivotal Study 305 remained on treatment (7.8% in the Tislelizumab+Chemotherapy arm vs. in the 4.9% Placebo+Chemotherapy arm).

The median **duration of exposure** (Tislelizumab+Chemotherapy: 5.91 months vs. Placebo+Chemotherapy: 5.65 months) and the median number of cycles (Tislelizumab+Chemotherapy: 8.0 cycles vs. Placebo+Chemotherapy: 8.0 cycles), were comparable between both study arms and was slightly higher compared to the Tislelizumab monotherapy pool (4.17 months; 6.0 cycles). The proportion of patients who received Tislelizumab or Placebo for a duration of 12 month or longer was higher in the Tislelizumab+Chemotherapy arm (24.6%) compared to the Placebo+Chemotherapy arm (17.8%). The duration of exposure in the Tislelizumab monotherapy pool (24.0%) was similar to the Tislelizumab+Chemotherapy arm in study 305. No relevant differences were observed in the median actual dose intensity and the relative dose intensity of Tislelizumab or Placebo comparing the treatment arms (Tislelizumab plus Chemotherapy arm vs. Placebo plus Chemotherapy arm: 192.1 mg/cycle vs. 192.5 mg/cycle and 96% vs. 96.25%).

The median actual dose and median relative dose intensity of administered chemotherapy components Oxaliplatin+Capecitabine was comparable between both treatment arms (ADI for Tislelizumab+Chemotherapy and Placebo+Chemotherapy respectively: Oxaliplatin: 118.5 mg/m²/cycle and 117.0 mg/m²/cycle; Capecitabine: 22033.2 mg/m²/cycle and 22112.2 mg/m²/cycle and RDI for Tislelizumab+Chemotherapy and Placebo+Chemotherapy respectively: Oxaliplatin: 91.1 % and 90.0%; Capecitabine: 78.7% and 79.0%). In contrast a numerically difference in the median actual dose and median relative dose was observed for the chemotherapy components Cisplatin+5-FU between the Tislelizumab+Chemotherapy arm and Placebo+Chemotherapy arm. The intensity was in generally lower in the Placebo+Chemotherapy arm compared to the Tislelizumab+Chemotherapy arm for both, the median actual dose (Cisplatin: 70.5 mg/m2/cycle; 5-FU: 3391.5 mg/m2/cycle and Cisplatin: 76.0

mg/m2/cycle, 5-FU: 3770.2 mg/m2/cycle, respectively) and the median relative dose (Cisplatin: 88.1 %, 5-FU: 84.8% and Cisplatin: 95.0 %, 5-FU: 94.3%, respectively). However, the impact of this difference is considered to be low. In addition, as the number of participants treated with Cisplatin+5-FU was quite small, the results should be interpreted with caution and it is considered unlikely that this observed difference has a major impact on the overall safety results of study 305.

At the data cut-off date (28-Feb-2023), a total of 92.2% of patients in the Tislelizumab+Chemotherapy arm (T+PtF) vs. 95.1% of patients in the Placebo+Chemotherapy arm (P+PtF) in the Study 305 safety set discontinued study treatment. The most common **reasons for discontinuation** of treatment in study 305 were disease progression (T+PtF: 56.0% vs. P+PtF: 67.2%), adverse events (T+PtF: 13.9% vs. P+PtF: 5.7%), withdrawal by subjects (T+PtF: 9.2% vs. P+PtF: 7.5%), and symptomatic deterioration (T+PtF: 7.4% vs. P+PtF: 9.3%). A total of 78.7% of patients in the Tislelizumab+Chemotherapy arm vs. 87.0% of patients in the Placebo+Chemotherapy arm in the Study 305 safety set discontinued from the study. The most common reason for discontinuation was death (T+PtF: 74.3% vs. P+PtF: 81.8%).

The **Adverse Event Summary** demonstrated similar incidences of TEAEs in the Placebo+Chemotherapy arm (96%) and the Tislelizumab+Chemotherapy arm (97%). Less treatment-related AEs were observed in the Tislelizumab monotherapy pool (74.1%) compared to both arms in study 305. However, this observation is not unexpected and can be attributed to the chemotherapy, and is also reflected in the other TEAE categories. TEAEs Grade ≥ 3 were overall similar in the Tislelizumab+Chemotherapy arm (69.5%) and the Placebo+Chemotherapy arm (65.6%) and lower in Tislelizumab monotherapy pool (45.2%). Serious AEs were reported more frequently in the Tislelizumab+Chemotherapy arm (42.4%) compared to the Placebo+Chemotherapy arm (36%) and the Tislelizumab monotherapy pool (34.7%). The fatal serious TEAEs reported can be considered overall as similar in all groups, although the incidences of the fatal serious TEAEs were slightly lower in Placebo+Chemotherapy arm (8.5%) and Tislelizumab monotherapy pool (8.3%) compared to the Tislelizumab+Chemotherapy arm (9.4%). In addition, the immune mediated AEs and infusion related reactions were higher in the Tislelizumab+Chemotherapy arm (imTEAEs: 30.9%; IRR: 6.6%) compared to the Placebo+Chemotherapy arm (imTEAEs:11.7%; IRR:3.0%) as expected, since imTEAEs and IRR are typical AEs for monoclonal antibodies.

Considering the PD-L1-positive (patients with a PD-L1 score ≥ 5%) safety set, it appears consistent with those for the Study 305 safety set. No clinical meaningful differences between the Study 305 safety set compared to the PD-L1-positive safety set has been observed.

The most frequently occurring **treatment emergent adverse events by PT** (≥ 30% in any group) in the study 305 safety set were nausea (T+PtF:50.4% ;P+PtF:48.4%), decreased appetite (T+PtF:41.2%; P+PtF:42.3%), anaemia (T+PtF:39.6%; P+PtF:42.3%), vomiting (T+PtF:36.1%; P+PtF:36.2%), platelet count decreased (T+PtF:35.5%; P+PtF:38.1%), neutrophil count decreased (T+PtF:33.7%; P+PtF:33.0%), and aspartate aminotransferase increased (T+PtF:31.3%; P+PtF:30.4%). The frequency was more or less comparable between both study arms. The incidence of the above mentioned most common TEAEs by PT was mostly quite lower in the Tislelizumab monotherapy pool. The TEAE events reported were manly grade 2 and 3 and more or less comparable between both study arms.

The number of patients with at least one **TEAE event for all grades related to Tislelizumab or Placebo** were lowest for the Placebo+Chemotherapy arm (53.0%) in study 305, highest for Tislelizumab monotherapy pool (74.1%) and Tislelizumab combination therapy pool (74.6%) and the incidence for the Tislelizumab+Chemotherapy arm (65.1%) of study 305 was in between.

The most common Tislelizumab related AEs in Study 305 (incidence ≥5% in the Tislelizumab+Chemotherapy arm) were hypothyroidism (11.2%), aspartate aminotransferase increase

(10.6%), nausea (10.6%), anaemia (10.2%) and platelet count decrease (9.2%). Most of the most common Tislelizumab related AEs in Study 305 were overall similar between the two treatment arms. A higher incidence for hypothyroidism and (11.2% vs. 2.6%), pruritus (6.4% vs 1.0%) and rash (5.0% vs 1.4%) were reported in the Tislelizumab+Chemotherapy arm compared to the Placebo+Chemotherapy arm.

In Study 305, **serious TEAEs** were reported with a higher incidence in the Tislelizumab+Chemotherapy arm (42.4%) compared to the Placebo+Chemotherapy arm (36.0%). In the Tislelizumab monotherapy pool (34.7%) an incidence similar to the Placebo+Chemotherapy arm (36.0%) in study 305 has been reported. Higher incidences in the Tislelizumab+Chemotherapy arm compared to the Placebo+Chemotherapy arm have been reported for death (2.0% vs. 1.0%), cholangitis (1.2% vs. 0.2%), gastric haemorrhage (1.2% vs. 0.2%), gastrointestinal haemorrhage (1.2% vs. 0.4%), sepsis (1.2% vs. 0.4%), immune-mediated hepatitis (1.0% vs. 0.2%) and pneumonitis (1.0% vs. 0%).

The **incidences of treatment-related SAEs** were higher in the Tislelizumab+Chemotherapy arm of Study 305 (23.1%) compared to the Placebo+Chemotherapy arm (14.6%) and the Tislelizumab monotherapy pool (11.8%). The incidence in the Tislelizumab combination therapy pool (25.3%) was more or less comparable with the Tislelizumab+Chemotherapy arm. These observations appear to reflect overall the add-on toxicity of Tislelizumab in combination with a chemotherapy. Most frequently reported related SAEs to any component of study treatment in study 305, which was numerically higher in the Tislelizumab+Chemotherapy arm compared to the Placebo+Chemotherapy arm were e.g. pneumonitis (T+PtF:1.0% vs. P+PtF: 0%), aspartate aminotransferase increased (T+PtF: 0.8% vs. P+PtF: 0.2%), death (T+PtF: 0.8% vs. P+PtF: 0%), alanine aminotransferase increased (T+PtF: 0.6% vs. P+PtF: 0%), hepatic function abnormal (T+PtF: 0.6% vs. P+PtF: 0%) and sepsis (T+PtF:0.6% vs. P+PtF: 0%).

The number of patients who died on treatment were slightly higher in the Tislelizumab+Chemotherapy arm (8.4%) compared to the Placebo+Chemotherapy arm (7.1%) and the Tislelizumab monotherapy pool (7.8%). The most cause of death on treatment in study 305 was reported as disease under study (4.6%). In 3.8% of the patients in the Tislelizumab+chemotherapy arm an adverse event was reported as cause of death. **PTs leading to death** in at least two patients in the Tislelizumab+chemotherapy arm were e.g. death, sepsis, pulmonary embolism, respiratory failure, general physical health deterioration, gastric haemorrhage and gastrointestinal haemorrhage.

However, no specific event leading to death was identified. No new safety signals for Tislelizumab were observed in study 305 and the reported events that led to death might be attributed to symptoms of the underlying disease and/or the medical conditions of the participants.

The incidences of **immune-mediated adverse events** in the Tislelizumab+Chemotherapy arm was 30.9% and overall comparable with the Tislelizumab monotherapy pool (33.0%). The incidence in the Tislelizumab combination therapy pool was higher (37.9%) compared to Tislelizumab+Chemotherapy arm. In contrast, the incidence in the Placebo+Chemotherapy arm in study 305 was much lower (11.7%) compared to the Tislelizumab groups. The most imTEAEs reported for the Tislelizumab groups appear to be grade 1 and grade 2. The highest incidence of grade 3, 4 and grade 5 imTEAEs were reported for the Tislelizumab combination therapy (6.9%, 1.0% and 0.5%), followed by the Tislelizumab+Chemotherapy arm of study 305 (6.8%, 0.6% and 0.2%) and the lowest incidence besides the Placebo+Chemotherapy arm in study 305 (1.8%, 0.2% and 0%) was reported in the Tislelizumab monotherapy pool (3.8%, 0.8% and 0.1%).

For the Tislelizumab+Chemotherapy arm of study 305 the following incidence were reported: 7.4% serious TEAEs, 4.4% imTEAEs leading to any study drug discontinuation, 4.2% imTEAEs leading to Tislelizumab/placebo discontinuation, 9.2% imTEAEs leading to any drug modification, 6.6% imTEAEs leading to Tislelizumab/placebo dose modification and 0.2% imTEAEs leading to death.

However, since imTEAEs are typical AEs for monoclonal antibodies and known from other checkpoint inhibitors, a higher number of imTEAEs was expected in the Tislelizumab groups compared to the Placebo+Chemotherapy arm in study 305. Moreover, the imTEAEs results for Tislelizumab in study 305 are similar to available information from other approved checkpoint inhibitors.

The **most common immune-mediated adverse events** reported for the Tislelizumab+Chemotherapy arm of study 305 were immune-mediated endocrinopathies (hypothyroidism) (12.7%), immune-mediated skin adverse reaction (10.6%), immune-mediated pneumonitis (3.8%) and immune-mediated endocrinopathies (hyperthyroidism) (3.2%). Most of the reported events were grade 1 and grade 2. The most common reported serious immune-mediated adverse events (≥1%) for Tislelizumab were reported in the category immune-mediated pneumonitis (n=7 [1.4%]), immune-mediated hepatitis (n=6 [1.2%]), Immune-mediated endocrinopathies (diabetes mellitus) (n=5 [1.0%]) and Immune-mediated colitis (n=5 [1.0%]). The grade 5 immune-mediated TEAE (n=1 [0.2%]) has been reported as immune-mediated colitis.

At the time of the cut-off date (28 February 2023), approximately 53.4% (125/234) of all immune-mediated TEAEs reported for Tislelizumab (T+PtF) were resolved. However, approximately 37.6% (88/234) of all immune-mediated TEAEs reported for Tislelizumab+Chemotherapy were still not recovered/resolved at the time of the cut-off date. The highest incidence (≥50%) of not recovered/resolved immune -mediated TEAEs were reported for Other immune-mediated reactions (blood dyscrasias) (n=1/1 [100.0%]), Immune-mediated endocrinopathies (hypothyroidism) (n=45/77 [58.4%]) and Immune-mediated endocrinopathies (hypophysitis) (n=1/2 [50%]). Although no major safety concern has been identified, it needs to be considered that approximately 37.6% (88/234) of all immune-mediated TEAEs reported for Tislelizumab+Chemotherapy were still not recovered/resolved at the time of the cut-off date and that in several imTEAE categories the incidence of not resolved/recovered imTEAEs were quite high (≥30%).

The number of subjects with at least one TEAE of infusion-related reactions reported in study 305 was 6.6% in the Tislelizumab+Chemotherapy arm and 3.0% in the Placebo+Chemotherapy arm. The most infusion-related reactions were reported as grade 1 and grade 2. In addition, 1.0% were reported as grade 3 in the Tislelizumab+Chemotherapy arm and 0.6% in the Placebo+Chemotherapy arm. No infusion-related reactions of grade 4 and 5 were reported for either study arms. The most common infusion related reactions reported for Tislelizumab were chills (T+PtF: 3.0% vs. P+PtF: 0.4%), drug hypersensitivity (T+PtF: 1.4% vs. P+PtF: 0.6%) and rash (T+PtF: 1.2% vs. P+PtF: 0.2%).

The **laboratory evaluations** overall reflected the known safety profile of Tislelizumab.

Regarding **safety analyses in subgroups**, listings have been provided for age, gender, hepatic and renal impairment, race/ethnicity and ECOG status. In addition, safety data set of PD-L1-positive patients (i.e. patients with a PD-L1 score ≥ 5%) has been provided as well.

Age

More serious TEAEs were reported for patients ≥75 years in the Tislelizumab+Chemotherapy arm (64.3%) compared to the age group of <65 years (40.1%) and the age group of ≥65 to <75 years (43.6%). Moreover, such a significant difference was not observed in the Placebo+Chemotherapy arm (< 65 years: 33.0%; ≥65 to <75 years: 41.2% and ≥75 years: 41.4%;) and in the Tislelizumab monotherapy pool (<65 years: 33.4%; ≥ 65 to <75 years: 37% and ≥75 years: 41.5%), but also in the Tislelizumab combination therapy pool (<65 years:39.4%; ≥65 to <75 years:48.1% and ≥75 years: 62.2%). However, the number of patients in the age group ≥ 75 years (T+PtF: n=28; P+PtF: n=29; mono: n=65; combi: n=45) is low and the results should be interpreted with caution. Overall, although the increase in serious TEAEs in the older patient population (≥ 75 years) treated with Tislelizumab+Chemotherapy needs to be considered and it is noted that a combination of

Tislelizumab+Chemotherapy, potentially attributed due to the add-on toxicity of Tislelizumab in combination with chemotherapy, appears to have higher impact on the health status/safety of the elderly population (≥ 75 years) compared to patients <75 years, the serious TEAEs were distributed across various SOCs and appear not to be driven by specific medical disease entities for the older patient population (≥ 75 years) treated with Tislelizumab+Chemotherapy. In addition, the serious TEAEs appear to generally reflect the underlying disease and no new safety signal has been identified. Moreover, differences by age were only identified for serious TEAEs and not for fatal or grade≥3 TEAEs in patients ≥ 75 years. In summary, the number of patients in the age group ≥ 75 years is quite small and it is reflected in the SmPC that the number of patients ≥ 75 years is currently too low to draw a final conclusion.

Gender

In general, less females were included in the safety data set of the study, which could limit the interpretation of subgroup analysis by gender. However, no clinical meaningful differences in the occurrence of TEAEs were observed between male and female in study 305, in the Tislelizumab monotherapy pool and in the Tislelizumab combination therapy pool in general.

Hepatic and renal function

No consistent, clinically meaningful differences were observed for hepatic and renal function.

Race/ethnicity

The majority of patients included in study 305 were Asian (~75%). Only approx. 22% of the patients included in the study were White and thus representatives of the European population. This could limit the interpretation of subgroup analysis by ethnicity. However it was demonstrated in previous marketing authorisations for Tislelizumab that mainly in Asian patients derived results are applicable to European patients and thus can be extrapolated. Therefore, it is considered that the totality of the reported safety data in this application is representative for the European patients. The number of TEAEs reported by ethnicity were in general similar between Asian and White in study 305 for both treatment arms and no clinical meaningful differences in the occurrence of TEAEs were observed.

The number of patients for other ethnicities are too limited to draw reliable conclusions and were therefore not discussed.

Overall, it appears that no clinical meaningful differences between the treatment arms were observed for the majority of special population categories and the results for the PD-L1-positive safety data set was consistent with those for the safety data set of Study 305.

The number of subjects with at least one **event leading to discontinuation** of any component of the study treatment by preferred term was higher in the Tislelizumab+Chemotherapy arm (14.7%) compared to the Placebo+Chemotherapy arm (7.5%). The most common TEAEs by PT in the Tislelizumab+Chemotherapy arm were death (1.2%), fatigue (0.8%), gastrointestinal haemorrhage (0.6%) and pneumonitis (0.6%). These TEAEs were not reported for the Placebo+Chemotherapy arm, except death (0.4%). Moreover, the occurrence of these TEAEs were also slightly higher in the Tislelizumab+Chemotherapy arm than in the Tislelizumab monotherapy pool and in the Tislelizumab chemotherapy pool. Similar results were observed for TEAEs grade≥3.

The most common TEAEs by PT in the Tislelizumab+Chemotherapy arm were death (1.2%), pneumonitis (1.0%) and fatigue (0.8%). The most common TEAEs by PT in the Placebo+Chemotherapy arm were death (0.4%), general physical health deterioration (0.6%), pneumonia (0.4%) and upper gastrointestinal haemorrhage (0.4%). Based on the currently data available Tislelizumab treatment with

or without chemotherapy results in a numerical higher TEAE incidence that lead to discontinuation of treatment compared to the Placebo+Chemotherapy treatment. However, no new safety signals have been observed. Moreover, less patients that received Tislelizumab+Chemotherapy discontinued treatment due to disease progression compared to the Placebo+Chemotherapy (T+PtF: 56.0% vs. P+PtF: 67.2%).

2.5.2. Conclusions on clinical safety

Overall, the safety data set of study 305 for Tislelizumab (200 mg administered IV Q3W) in combination with platinum- and fluoropyrimidine-based chemotherapy in patients with locally advanced unresectable or metastatic G/GEJ adenocarcinoma in first-line setting reflect in general the known toxicity profile of Tislelizumab and of other checkpoint inhibitors. No new safety signals for Tislelizumab have been identified.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted/was requested to submit an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 3.0 is acceptable.

Safety concerns

Table 91: Summary of Safety Concerns

Summary of Safety Concerns	
Important Identified Risks	Immune-mediated adverse reactions
Important Potential Risks	Reproductive and developmental toxicity
Missing Information	None

The list of safety concerns remains unchanged.

Pharmacovigilance plan

None.

Risk minimisation measures

Table 92: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risks		
Immune-Mediated Adverse Reactions	Routine Risk Minimisation Measures: SmPC Section 4.2 where guidelines for withholding or permanent discontinuation of treatment are provided. SmPC Section 4.4 where advice is provided regarding monitoring and management of immune-mediated adverse reactions. SmPC Section 4.8 where the adverse drug reactions of immune-mediated adverse reactions are listed. PL Section 2 and PL Section 4 where guidance on how to early identify signs and symptoms and seek medical attention is included. Additional Risk Minimisation Measures: Patient card Legal Status: Restricted medical prescription	Routine Pharmacovigilance Activities Beyond Adverse Reactions Reporting and Signal Detection: Targeted follow-up checklist Additional Pharmacovigilance Activities: None
Important Potential Risks		
Reproductive and Developmental Toxicity	Routine Risk Minimisation Measures: SmPC Section 4.6 where advice is provided regarding the need for women of childbearing potential to avoid getting pregnant for lactating women to avoid breastfeeding infants while taking tislelizumab, and that women of childbearing potential should use effective contraception during treatment with tislelizumab and for 4 months after the last dose. SmPC Section 5.3. PL Section 2 where guidance on how to early identify signs and symptoms and seek medical attention is included. Additional Risk Minimisation Measures: None Legal Status: Restricted medical prescription	Routine Pharmacovigilance Activities Beyond Adverse Reactions Reporting and Signal Detection: None Additional Pharmacovigilance Activities: None
Missing Information		
None		

Abbreviations: PL, Product Label; SmPC, Summary of Product Characteristics.

2.7. Update of the Product information

As a result of this variation, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet (PL) is updated accordingly. In addition, the MAH took the opportunity to introduce minor editorial changes to the Product Information.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

The changes in the package leaflet are related to the extension of the indication "a type of advanced gastric or gastroesophageal junction adenocarcinoma (stomach cancer) that has spread to other parts of the body, that has not been treated by anti-cancer therapy and cannot be removed by surgery" in section 1 "What Tevimbra is and what it is used for". In addition, section 4 'Possible side effects' includes new side effects and updated frequencies. There are no other proposed changes to the content of the package leaflet. In particular the key messages for the safe use of the medicinal product are not impacted. Furthermore, the design, layout and format of the package leaflet will not be affected by the proposed revisions.

2.7.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Tevimbra (tislelizumab) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU; Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The approved indication is:

Tevimbra, in combination with platinum and fluoropyrimidine-based chemotherapy, is indicated for the first-line treatment of adult patients with HER-2-negative locally advanced unresectable or metastatic gastric or gastroesophageal junction (G/GEJ) adenocarcinoma whose tumours express PD L1 with a tumour area positivity (TAP) score $\geq$ 5%.

Gastric cancer (GC) is the fifth most common cancer worldwide. Adenocarcinoma is the dominant histologic subtype of GC worldwide (approximately 90%). Approximately 80% are true GCs (non-cardia), and the remainder are GEJ cancers (cardia). Approximately 75% of the patients with G/GEJ are HER2 negative. The initial diagnosis generally occurs when the tumour is advanced. The 5-year survival rate is 32% if the cancer has extended into the gastric wall or metastasized to locoregional

lymph nodes, and further reduced to 6% if the tumour has metastasized to distant sites. The overall 5-year relative survival of GC is about 20%-30% in most areas worldwide, including North America and Europe. GC survival is higher in East Asia with the 5-year survival rate being 67% in Korea, 69% in Japan and 36% in China in recent years. *(Lordick et al 2022)*.

3.1.2. Available therapies and unmet medical need

Treatment of advanced stage G/GEJ cancer is based on systemic therapy. The preferred chemotherapy regimen for HER2 negative disease in the first-line setting is fluoropyrimidine (fluorouracil or capecitabine) combined with either oxaliplatin or cisplatin (ESMO guideline 2022, NCCN Guidelines v2. 2023).

Recently, nivolumab and pembrolizumab received EU approvals in combination with fluoropyrimidine- and platinum-containing chemotherapy for the 1L treatment of patients with HER2 negative advanced or metastatic G/GEJ (or esophageal) adenocarcinoma with tumors expressing PD-L1 CPS ≥ 5 or CPS ≥ 1, respectively (Keytruda II/133 EC Decision on 23 November 2023 and Opdivo II/96 EC Decision on 19 October 2021).

3.1.3. Main clinical studies

The pivotal double-blind Study 305 randomized 997 patients with locally advanced unresectable or metastatic G/GEJ adenocarcinoma in a 1:1 ratio to receive a 1L treatment of tislelizumab plus chemotherapy versus placebo plus chemotherapy. Randomization was stratified by region, PD-L1 expression (≥ 5% vs. < 5%), presence of peritoneal metastasis and ICC option (oxaliplatin plus capecitabine vs. cisplatin plus 5-FU). Primary endpoints were OS in the PD-L1-positive analysis set (patients with PD-L1 TAP score ≥ 5%) and OS in the ITT analysis set. Efficacy results were provided from the interim analysis (data cutoff date: 08-Oct-2021), and the final analysis (data cutoff date: 28-Feb-2023).

3.2. Favourable effects

Study 305 demonstrated a statistically significant OS and PFS benefit for the 1L treatment with tislelizumab plus chemotherapy (T+PtF) over placebo plus chemotherapy (P+PtF) in patients with G/GEJ cancer in the PD-L1-Positive Analysis Set (patients with PD-L1 TAP score ≥5%).

For patients with PD-L1 TAP score ≥5%, the primary **OS** endpoint was met at the interim analysis (IA) with a stratified HR of 0.74 (95% CI: 0.59, 0.94; 1-sided p value of 0.0056; median OS 14.6 vs 12.6 months for T+PtF vs P+PtF). The OS benefit was confirmed at the final analysis with a stratified OS HR of 0.71 (95% CI 0.58, 0.86) and an improvement in median OS of 3.6 months (16.4 months [95% CI 13.6, 19.1] for T+PtF vs. 12.8 [95% CI 12.0, 14.5] for P+PtF).
The secondary endpoint **PFS** showed also statistically significant results for patients with PD-L1 TAP score ≥5% at the IA with a stratified HR of 0.67 (95% CI: 0.55, 0.83; *P*-value <0.0001) and median PFS of 7.2 vs 5.9 months for Arm T+PtF compared with Arm P+PtF. The PFS results at the FA were consistent: stratified HR 0.68 (95% CI: 0.56, 0.83), median PFS 7.2 vs 5.9 months.

The ORR was numerically higher in Arm T+PtF than in Arm P+PtF (51.5% vs. 42.6% at the FA).

3.3. Uncertainties and limitations about favourable effects

A benefit was not apparent in the subgroup of patients ≥75 years old (OS HR=1.06; 95% CI: 0.58, 1.95). However, numbers are too limited (n=57) to draw firm conclusions.

3.4. Unfavourable effects

The incidence rates of TEAEs grade ≥ 3 were overall comparable between both treatment arms (69.5% in the Tislelizumab+Chemotherapy arm vs. 65.6% in the Placebo+Chemotherapy arm). The most commonly reported (≥ 10%) TEAEs grade ≥ 3 by Preferred Term in the Tislelizumab+Chemotherapy arm were neutrophil count decreased and platelet count decreased.

The incidence rate of serious TEAEs was higher in the Tislelizumab+Chemotherapy arm than in the Placebo+Chemotherapy arm (42.4% vs. 36.0%). The most common serious TEAEs (≥ 2%) by Preferred Term in the Tislelizumab+Chemotherapy arm were platelet count decreased and pneumonia.

The incidence rate of deaths due to adverse events was numerically higher in the Tislelizumab+Chemotherapy arm than in the Placebo+Chemotherapy arm (3.8 % vs. 2.8%).

The incidence rate of TEAEs leading to discontinuation of tislelizumab/placebo was higher in the Tislelizumab+Chemotherapy arm than in the Placebo+Chemotherapy arm (15.9% vs. 7.3%; discontinuation of any component of treatment: 23.1% vs. 13.6%). Death, pneumonitis, fatigue, ascites, colitis, and immune-mediated hepatitis were the most commonly reported TEAEs by Preferred Term (≥ 0.5%, all grades) in the Tislelizumab+Chemotherapy arm.

The incidence rate of imTEAEs was higher in the Tislelizumab+Chemotherapy arm than in the Placebo+Chemotherapy arm (30.9% vs. 11.7%). The most common imTEAEs by category (≥ 1%) in the Tislelizumab+Chemotherapy arm included immune-mediated endocrinopathies (hypothyroidism), immune-mediated skin adverse reaction, immune-mediated pneumonitis, immune-mediated endocrinopathies (hyperthyroidism), immune-mediated hepatitis, immune-mediated endocrinopathies (diabetes mellitus), immune-mediated colitis, and other immune-mediated reactions (musculoskeletal).

Infusion-related reactions (all grades) were reported for 6.6% of patients in the Tislelizumab+Chemotherapy arm and for 3.0% of patients in the Placebo+Chemotherapy arm.

3.5. Uncertainties and limitations about unfavourable effects

Data for patients aged ≥ 75 years in Study 305 is limited. This has been reflected in section 4.8 of the SmPC.

3.6. Effects Table

Table 93: Effects Table for Tevimbra in combination with platinum and fluoropyrimidine-based chemotherapy for 1L treatment of advanced HER2-negative gastric or gastro-oesophageal junction adenocarcinoma; data cut-off: 28 Feb 2023)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	
Favourable Effects (for patients whose tumours express PD L1 TAP score ≥ 5%)						
OS	time from randomization date to the date of death due to any cause	months (95% CI)	16.4 (13.6, 19.1)	12.8 (12.0, 14.5)		CSR
		HR (95% CI)	0.71 (0.58, 0.86)			
PFS	time from the randomization date to disease progression or death, whichever occurred first	months (95% CI)	7.2 (5.8, 8.4)	5.9 (5.6, 7.0)		
		HR (95% CI)	0.68 (0.56, 0.83)			
Unfavourable Effects (ITT population)						
TEAEs grade ≥ 3	All causality	%	69.5	65.6		SCS
	related	%	54.2	49.8		SCS
Serious TEAEs	All causality	%	**42.4**	**36.0**		SCS
	related	%	23.1	14.6		SCS
Deaths related to AEs	On treatment	%	3.8	2.8		SCS
TEAEs leading to DC	All causality	%	**23.1**	**13.6**		SCS
imTEAEs	related	%	**30.9**	**11.7**		SCS
IRR	related	%	6.6	3.0		SCS

Abbreviations: DC – discontinuation; im – immune-mediated; IRR – Infusion-related reaction; PT – Preferred Term; SCS – Summary of Clinical Safety; SOC – System Organ Class; TEAE- Treatment-emergent adverse event

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Study 305 demonstrated statistically significant and clinically meaningful improvements in overall survival and PFS for tislelizumab in addition to standard chemotherapy in the 1L treatment of patients with GEJ/gastric cancer whose tumours express PD-L1 with a tumour area positivity (TAP) score ≥5%.

Higher incidence rates of serious TEAEs, imTEAEs, and TEAEs leading to discontinuation have been observed for the Tislelizumab+Chemotherapy arm compared to the Placebo+Chemotherapy arm. However, the safety data set of study 305 for Tislelizumab (200 mg administered IV Q3W) in combination with platinum- and fluoropyrimidine-based chemotherapy in patients with locally advanced unresectable or metastatic G/GEJ adenocarcinoma in first-line setting reflect in general the established safety profile of tislelizumab and the administered chemotherapy regimens and is similar to other checkpoint inhibitors. No new safety concerns for tislelizumab have been identified at present.

3.7.2. Balance of benefits and risks

For patients whose tumours express PD-L1 with a tumour area positivity (TAP) score ≥5%, the benefit in overall survival outweighs the additional toxicity that is associated with the combination of tislelizumab plus chemotherapy.

3.7.3. Additional considerations on the benefit-risk balance

None.

3.8. Conclusions

The B/R balance of Tevimbra, in combination with platinum and fluoropyrimidine-based chemotherapy, is considered positive in the first-line treatment of adult patients with HER-2-negative locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma whose tumours express PD L1 with a tumour area positivity (TAP) score ⩾ 5%.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends, the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include in combination with platinum and fluoropyrimidine-based chemotherapy the first-line treatment of adult patients with human epidermal growth factor receptor-2 (HER-2)-negative locally advanced unresectable or metastatic gastric or gastroesophageal junction (G/GEJ) adenocarcinoma whose tumours express PD-L1 with a tumour area positivity (TAP) score ⩾ 5% for TEVIMBRA, based on results from the phase 3 study BGB-A317-305 (study 305); this is a global, randomized, double-blind, placebo-controlled study at the approved registrational dosing regimen for Tevimbra (200 mg administered IV Q3W), in combination with platinum and fluoropyrimidine-based chemotherapy, in adult patients with HER-2 negative locally advanced unresectable or metastatic gastric or gastroesophageal junction (G/GEJ) adenocarcinoma. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 3.0 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the Product Information.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.