17 October 2024
EMA/510875/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tevimbra

International non-proprietary name: Tislelizumab

Procedure No. EMEA/H/C/005919/II/0003

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

Abbreviation	Full text
10E9	10^9
1L / 2L	First line / Second line
5-FU	5-fluorouracil
5-HT3	5-hydroxytryptamine
ADA	Anti-drug antibodies
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse events of special interest
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
Antibi	Hepatitis B core antibody
AntiHBe	Hepatitis Be antibody
AST	Aspartate aminotransferase
AUCss	Area under the concentration-time curve steady state
BILI	Bilirubin
BIRC	Blinded independent central review
BLA	Biologics License Application
BOR	Best overall response
BSL	Baseline
C1q	Complement 1q
CC	Cholangiocarcinoma
CDE	Drug evaluation of China
cHL	Classical Hodgkin Lymphoma
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CIP	Cumulative incidence proportions
CKD-EPI	Chronic kidney disease epidemiology collaboration
CL	Clearance rate
Cmax,ss	Maximum concentration steady state
CMH	Cochran-Mantel-Haenszel
Cmin,ss	Minimum concentration steady state
CO	Clinical overview
COVID-19	Coronavirus disease 2019
CPI	Checkpoint inhibitor
CPS	Combined positive score
CR	Complete response
CRC	Colorectal cancer
CRF	Case report form
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P
D	Day
DC	Discontinuation
DCR	Disease control rate
DLP	Data lock point
DME	Designated Medical Event
dMMR	Mismatch repair deficient
DOR	Duration of response
EAIR	Exposure adjusted incidence rate
EC	Esophageal cancer
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EOP2	End of Phase II
EORTC QLQ-C30	European organisation for research and treatment of cancer quality of life questionnaire-core 30
EORTC QLQ-OES18	European organisation for research and treatment of cancer quality of life Questionnaire-oesophagus cancer module

Abbreviation	Full text
EQ 5D 5L	European quality of life 5-dimension 5-level
ER	Exposure-response
ESMO	European Society For Medical Oncology
FDA	Food And Drug Administration
FU	5'Fluorouracil
GC	Gastric cancer
GEJ	Gastroesophageal junction
GIST	Gastrointestinal stromal tumour
HBcAb	Hepatitis B core antibody
HbsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HER-2	Human epidermal growth factor receptor 2
HL	Hodgkin lymphoma
HLGT	High level group term
HLT	Higher level term
HNSCC	Head and neck squamous cell carcinoma
HR	Hazard ratio
HRQoL	Health-related quality of life
ICC	Investigator's choice of chemotherapy
ICF	Informed consent form
ICH	International council for harmonisation of technical requirements for Pharmaceuticals for human use
ICI	Immune checkpoint inhibitor
IDMC	Independent data monitoring committee
IEC	Independent Ethics Committee
IgG4	Immunoglobulin G4
imADR	Immune-mediated adverse drug reaction
imAE	Immune-mediated adverse event
IMP	Investigational medicinal product
imTEAE	Immune-mediated treatment-emergent adverse event
IR	Incidence rate
IRB	Institutional Review Board
IRR	Infusion-related reaction
IRT	Interactive response technology
ISI	Integrated summary of immunogenicity
ITT	Intend-to-treat
IV	Intravenous
KD	Dissociation constant
LDH	Lactate dehydrogenase
LLN	Lower limit of normal
m2	Square metre
MAA	Marketing authorisation application
MCC	Merkel-cell carcinoma
MedDRA	Medical Dictionary for Regulatory Activities
MM	Melanoma
MSH-h	Microsatellite Instability – High
MTD	Maximum tolerated dose
NA	Not available
NAb	Neutralising antibody
NCI	National Cancer Institute
NMPA	National medical products administration
NPC	Nasopharyngeal carcinoma
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
OS	Overall survival
OSCC	Oesophageal squamous cell carcinoma
P+C	Placebo plus chemotherapy
PBRER	Periodic Benefit Risk Evaluation Report
PC	Pancreatic cancer
PD	Pharmacodynamics

Abbreviation	Full text
PD-1	Programmed cell death protein-1
PD-L1	Programmed cell death protein ligand-1
PD-L1/PD-L2	Programmed cell death ligand 1/ ligand 2
PD-L2	Programmed cell death protein ligand-2
PFS	Progression-free survival
PFS2	PFS after next line of treatment
PK	Pharmacokinetics
PMDA	Pharmaceuticals and medical devices agency
PopPK	Population pharmacokinetics
PR	Partial response
PRO	Patient-reported outcomes
PS	Performance status
PT	Preferred Term
Q	Quartile
Q2W / Q3W	Once every 2 weeks / 3 weeks
QTcF	QT interval corrected per Fridericia
R/R	Relapsed/refractory
RCC	Renal cell carcinoma
RDI	Relative dose intensity
RECIST	Response evaluation criteria in solid tumours
RMST	Restricted mean survival time
RoW	Rest of the world
RP2D	Recommended Phase II dose
SAE	Serious adverse event
sBLA	Supplemental Biologics License Application
SCLC	Small cell lung cancer
SCNEC	Small cell neuroendocrine carcinoma
SCS	Summary of clinical safety
SD	Standard deviation
SMQ	Standardised MedDRA Queries
SOC	System organ class
SOP	Standard operating procedure
ST	Solid tumour
T+C	Tislelizumab + chemotherapy
T+nPC	Tislelizumab + nab-paclitaxel + carboplatin
T+PC	Tislelizumab + paclitaxel + carboplatin
$T_{1/2}$	Terminal elimination half-life
T4	Thyroxin
TBIL	Total bilirubin
TEAE	Treatment-emergent adverse event
TNBC	Triple negative breast cancer
TNM	Tumour node metastasis
TSH	Thyroid stimulating hormone
U	Unit
UBC	Urethral bladder cancer
UC	Urothelial carcinoma
ULN	Upper limit of normal
UM	Uveal melanoma
US	United States
W	Week

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 10 January 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-based chemotherapy the first-line treatment of adult patients with unresectable, locally advanced or metastatic oesophageal squamous cell carcinoma (OSCC) for TEVIMBRA, based on results from study BGB-A317-306; this is a multi-regional, randomized, placebo-controlled, double-blind phase 3 study evaluating the efficacy and safety of tislelizumab in combination with chemotherapy compared to placebo in combination with chemotherapy as first-line treatment in patients with unresectable or locally advanced recurrent or metastatic OSCC. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.6, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 1.1 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI.

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 31 May 2018 (EMEA/H/SA/3646/3/2018/II) and 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	10 January 2024
Start of procedure:	27 January 2024
CHMP Rapporteur Assessment Report	25 March 2024
PRAC Rapporteur Assessment Report	27 March 2024
PRAC Outcome	11 April 2024
CHMP members comments	15 April 2024
Updated CHMP Rapporteur(s) (Joint) Assessment Report	18 April 2024
Request for supplementary information (RSI)	25 April 2024
CHMP Rapporteur Assessment Report	20 August 2024
PRAC Rapporteur Assessment Report	22 August 2024
PRAC members comments	28 August 2024
Updated PRAC Rapporteur Assessment Report	n/a
PRAC Outcome	05 September 2024
CHMP members comments	09 September 2024
Updated CHMP Rapporteur Assessment Report	12 September 2024
Request for supplementary information (RSI)	19 September 2024
Re-start of procedure:	25 September 2024
CHMP Rapporteur Assessment Report	30 September 2024
CHMP members comments	07 October 2024
Updated CHMP Rapporteur(s) Assessment Report	10 October 2024
Opinion	17 October 2024

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Locally advanced, unresectable or metastatic oesophageal squamous cell carcinoma (OSCC).

State the claimed the therapeutic indication

Tevimbra, in combination with platinum-based chemotherapy, is indicated for the first-line treatment of adult patients with unresectable, locally advanced or metastatic oesophageal squamous cell carcinoma (OSCC).

Epidemiology and risk factors, screening tools/prevention

Oesophageal cancer (EC) is the eighth most common cancer and the sixth most common cause of cancer-related death worldwide, with an estimated 604,100 new cases and 544,076 deaths (5.5% of all cancer mortality) observed in 2020 (GLOBOCAN 2020). In 2018, the highest mortality rates of EC were found in Eastern Asia (with an age-standardized rate of 10.7), Eastern Africa (8.2), Southern Africa (7.2), and Northern Europe (4.3) (Huang et al 2021). Although EC is a rare disease in Europe (annual incidence approximately 1/13,300, according to Orphanet), it remains a highly fatal disease and a major cause of cancer mortality.

Oesophageal cancers are histologically classified as squamous cell carcinoma (OSCC) or adenocarcinoma (EAC), which differ in their pathology, tumour location, and prognosis. Although OSCC accounts for ~90% of cases of oesophageal cancer worldwide (Abnet et al. 2018), mortality rates associated with EAC are rising and have surpassed those of OSCC in several regions in the EU (Castro et al. Ann Oncol 2014). Oesophageal carcinoma is rare in young people and increases in incidence with age, peaking in the seventh and eighth decades of life. EAC is three to four times as common in men as it is in women, whereas the sex distribution is more equal for OSCC (Rustgi et al. N Engl J Med 2014). The main risk factors for OSCC in Western countries include tobacco and alcohol consumption.

Biologic features, Aetiology and pathogenesis

The molecular biology of OSCC is not yet fully understood. Of note, comprehensive molecular analyses of EC by The Cancer Genome Atlas Program (TCGA) have shown that OSCC is molecularly distinct from EAC. Based on these analyses, OSCC has stronger resemblance to other squamous tumours like SCCHN than to EAC, and consequently, EAC resembles gastric cancer more than OSCC.

The Cancer Genome Atlas research network identified three subtypes of oesophageal SCC (oesophageal SCC1, oesophageal SCC2 and oesophageal SCC3), which are each associated with defects in specific molecular pathways. So far, no distinct therapeutic options for these subtypes are available (ESMO Clinical Practice Guideline 2022).

Clinical presentation, diagnosis and stage/prognosis

OSCC is usually asymptomatic until an advanced disease stage with common presenting symptoms being dysphagia (at first with solids then progressing to fluids) and weight loss. Thus, diagnosis is often made late in the disease course in countries where screening programs for early detection of EC are not in use or are impractical because of low incidence rates. According to the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) Program (SEER 2021), one-third of US patients with OSCC had lymphatic spread to regional lymph nodes, and 39% had distant metastases at the time of diagnosis. The 5-year survival for localized disease is 32.0% but drops to 24.0% for regional disease and 6.1% for patients with distant metastases. Patients diagnosed or treated once OSCC has progressed face a very poor prognosis (Abraham et al 2020).

Management

Depending on the clinical situation, patients with advanced (metastatic, unresectable, or recurrent after curative therapy) OSCC have different palliative treatment options. Platinum-based doublet chemotherapy (cisplatin/oxaliplatin plus fluoropyrimidines) is usually offered as first-line palliative therapy aiming at an extension of survival (Lordick et al. 2016, NCCN 2020) of patients with good performance status. Unfit patients (ECOG PS > 1) are treated with best supportive care. Localized treatments such as radiotherapy (including external radiation or brachytherapy) and endoscopic therapies (stents) are applied for the symptomatic treatment of obstruction and dysphagia.

Recently, patients with OSCC have been shown to benefit from PD-1 blockade and the use of immune checkpoint inhibitors (ICI) in combination with chemotherapy has improved survival for patients with patients with advanced unresectable or metastatic OSCC in the first-line setting. Accordingly, ICI chemotherapy has become the standard first-line treatment for advanced EC.

Based on results of Study KEYNOTE-590 Variation Keytruda-H-C-3820-II-97
EC Decision 24/06/2021, pembrolizumab became approved in combination with platinum and fluoropyrimidine-based chemotherapy for the first-line treatment of locally advanced unresectable or metastatic carcinoma of the oesophagus in adults whose tumours express PD-L1 with a CPS $\geq$ 10 (Sun et al 2021). Similarly, nivolumab was approved OPDIVO-H-C/003985/II-0107
EC decision on 01/04/2022 in combination with fluoropyrimidine- and platinum-based combination chemotherapy for the first-line treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma with tumour cell PD-L1 expression $\geq$ 1% based on Study CheckMate 648 (Doki et al 2022).

2.1.2. About the product

Tislelizumab is a humanized IgG4 variant monoclonal antibody that binds to the T-cell surface receptor programmed cell death protein 1 (PD-1) with high specificity and affinity (K_D = 0.15 nM). It competitively blocks the binding of both PD-L1 and PD-L2, inhibiting PD-1-mediated negative signalling. As such, upregulation of PD-1 ligands occurs in some tumours and signalling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumours, which is counteracted by the administration of PD-1 inhibitors like tislelizumab. The antibody does not bind to Fc gamma receptors and C1q and therefore does not induce antibody-dependent cellular cytotoxicity or complement-dependent cytotoxicity.

Tislelizumab belongs to the therapeutic subgroup L01 (antineoplastic agents) of the Anatomical Therapeutic Chemical Classification System.

The applied indication is:

Tevimbra, in combination with platinum-based chemotherapy, is indicated for the first-line treatment of adult patients with unresectable, locally advanced or metastatic oesophageal squamous cell carcinoma (OSCC).

The final approved indication is:

Tevimbra, in combination with platinum-based chemotherapy, is indicated for the first-line treatment of adult patients with unresectable, locally advanced or metastatic OSCC whose tumours express PD-L1 with a tumour area positivity (TAP) score ≥ 5%.

Tislelizumab concentrate for solution for infusion is formulated in vials of 10 mL containing 100 mg tislelizumab. The recommended dose of tislelizumab is 200 mg administered by intravenous infusion once every 3 weeks. Tislelizumab treatment should be continued until disease progression or unacceptable toxicity.

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

The clinical development of tislelizumab has paralleled that of other CPIs targeting the PD-1/PD-L1 pathway.

Study 306, a global phase 3, randomized, double-blind, placebo-controlled study at the recommended dose of tislelizumab 200 mg administered IV Q3W in combination with standard platinum-based chemotherapy (platinum [cisplatin or oxaliplatin] + either fluoropyrimidine [5-fluorouracil or capecitabine] or paclitaxel) in patients with unresectable, locally advanced or metastatic OSCC, represents the pivotal study for the current application for extension of indication.

The MAH received Scientific Advice from the CHMP on 31 May 2018 (EMEA/H/SA/3646/3/2018/II). The Scientific Advice pertained to clinical aspects of the dossier, including the proposed study population, primary endpoint, interim and statistical analysis of Study BGB-A317-306 and acceptability of the data derived from Study BGB-A317-306 to support an extension of indication. The MAH overall followed the recommendations of the CHMP scientific advice, except for not considering PD-L1 expression status, disease status and type of prior treatments for recurrent disease as stratification factors (e.g. instead of the proposed stratification factor "prior definitive therapy (yes vs no)").

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

GCP

Study 306 is conducted in accordance with the current International Council for Harmonisation (ICH) and Good Clinical Practice (GCP) consolidated guidelines and the ethical principles of the Declaration of Helsinki as claimed by the applicant.

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: Summary of pivotal study 306

Phase, design	Patient population	Treatment regimen	Efficacy endpoints
Randomized placebo-controlled, double blind, global Phase III study	Unresectable, locally advanced or metastatic ESCC, Intent-to-treat population, N=649	Tislelizumab[a] (N=326) or matched placebo[a] (N=323) + ICC: platinum (cisplatin[b] or oxaliplatin[c]) + fluoropyrimidine (capecitabine[d] or 5-FU[e]) or paclitaxel[f]	Primary: OS Secondary: PFS, ORR, DOR by investigator; OS in PD-L1 score ≥10% subgroup; HRQoL Exploratory*: PFS, ORR, and DOR by BIRC; PFS2

*Includes endpoints presented in this SCE.
Study treatment was given in cycles. One treatment cycle is 21 days in length.
[a] Tislelizumab: 200 mg i.v. or matched placebo on Day 1 of each cycle.
[b] Cisplatin: 60-80 mg/m^2 i.v. on Day 1 of each cycle.
[c] Oxaliplatin: 130 mg/m^2 i.v. on Day 1 of each cycle.
[d] Capecitabine: 1000 mg/m^2 orally twice a day on Days 1 to 14 of each cycle.
[e] 5-Fluorouracil: 750-800 mg/m^2 i.v. on Days 1 to 5 of each cycle.
[f] Paclitaxel: 175 mg/m^2 i.v. on Day 1 of each cycle.

Source: Table 1 SCE

2.3.2. Pharmacokinetics

With this application for extension of indication, the Applicant is seeking approval of tislelizumab, a humanized IgG4 variant mAb against programmed cell death protein-1 (PD-1), for the first-line treatment of oesophageal squamous cell carcinoma (OSCC).

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 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. A 3-compartment model with first order elimination from the central compartment, and redistribution into the peripheral compartments best characterised tislelizumab PK following IV administration.

Previously, an original PopPK analysis was performed based on pooled data (PK, dosing information, demographics, and patient or disease characteristics) across 12 clinical studies (Studies 001, 102, 203, 204, 205, 206, 208, 209, 302, 303, 304, and 307).

In the pivotal Study 306, only sparse PK samples were collected at the following time-points: Predose on Day 1 of Cycles 1, 2, 5, 9 and 17; postdose on Day 1 of Cycles 1 and 5. An additional PK sample was collected at the Safety Follow-up Visit.

PK data from Study 306 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 306.

Bioanalytical methods

Biopharmaceutics information was submitted with the dossier EMEA/H/C/005919/0000 in the 2L treatment of OSCC in the summary of biopharmaceutics [SBP]. No new information is provided with the current dossier, as there is no change in bioanalytical methods and assays.

Population PK model

The initial PopPK model analysis, as submitted with the MAA for tislelizumab in 2nd line OSCC, was conducted in NONMEM using FOCE-I (first-order conditional estimation) algorithm. The NONMEM PopPK model was now translated into a Monolix PopPK model using SAEM (Stochastic Approximation Expectation-Maximization) algorithm ("Monolix model"). The translated final Monolix model was intended to be used for any further PopPK analysis, and was used in the external validation of the model for Study 306.

Model qualification

1. Model translation

The structural and covariate models in NONMEM were directly translated into Monolix. For the residual model, the combined2 residual model in Monolix was adopted.

2. Model estimation

Parameter estimation of the translated Monolix model were conducted with the final NONMEM model parameters set as the initial values. In addition, convergence assessment was carried out to evaluate the robustness of the parameter estimation.

The evaluation of the qualification of the Monolix model was based on:

- Comparison of estimated population and individual PK parameters from Monolix and NONMEM models
- Comparison of the predicted PK metrics from the Monolix model and the NONMEM model: scatter plots for comparing the predicted Cavg,dose1, Cmax,dose1, Cavg,ss and Cmax,ss using planned dose of 200 mg Q3W based on EBEs (empirical bayes estimates) from respective models.
- Residual diagnostics of the Monolix model: plots of weighted residuals vs. time and predicted concentrations.
- Observed vs. predicted diagnostics of the Monolix model: plots of population/individual predicted concentration vs. observed concentrations.
- Visual predictive check (VPC) were (i) employed for the visual evaluation of the Monolix model and (ii) compared between the NONMEM and the Monolix models. In the VPC, the final model parameters were fixed and used to simulate 500 virtual trials of the original dataset. The median, 5th and 95th percentiles of the observations, along with the 90% confidence interval of the median, 5th and 95th percentiles of the predictions were quantified.
- The consistency of the estimates for the model parameters from the convergence assessment were evaluated.

The analysis was performed using the Monolix software system, Monolix 2021R1 (Lixoft, Paris, France) utilizing the Novartis DaVinci high performance computing environment accessed from GPSII.

Results

The estimated PK parameters using Monolix were comparable to that of previously reported parameters with the NONMEM model, as shown in Table 2.

Table 2: Comparison of population PK parameters

Parameter	Monolix model estimates	Parameter
CL (L/day)	0.14904 [0.827]	0.153 [0.165]
Vc (L)	3.02 [0.464]	3.05 [0.611]
Q2 (L/day)	0.7704 [7.74]	0.739 [0.739]
V2 (L)	1.18 [4.62]	1.27 [11.48]
Q3 (L/day)	0.1032 [4.06]	0.092 [0.77]
V3 (L)	1.66 [5.07]	2.097 [5.44]
WT on CL	0.572 [5.74]	0.562 [5.473]
WT on V1	0.4 [5.15]	0.399 [5.171]
Sex on V1	-0.118 [7.56]	-0.116 [8.50]
ALB on CL	-0.46 [10.8]	-0.456 [11.18]
TUMSZ on CL	0.0752 [12.6]	0.073 [10.74]
AGE on V1	0.0952 [18.1]	0.096 [19.24]
ADA on CL	0.116 [13.7]	0.111 [13.8]
GC on CL	0.0742 [45.6]	0.068 [48.7]
cHL on CL	-0.228 [15.9]	-0.216 [16.08]
ω^2_{CL}	26.7 [2]	26.30 [1.87]
ω^2_{Vc}	16.7 [1.99]	16.74 [2.04]
ω^2_{V2}	78.7 [4.13]	74.77 [3.19]
ω^2_{V3}	109 [4.54]	99.98 [3.87]
Correlation Vc~ CL	0.423 [6.03]	0.455* [6.55]
Proportional residual error (%)	12.7 [1.02]	12.58 [1.04]
Additive residual error (µg/mL)	1.87 [4.44]	2.08 [4.07]

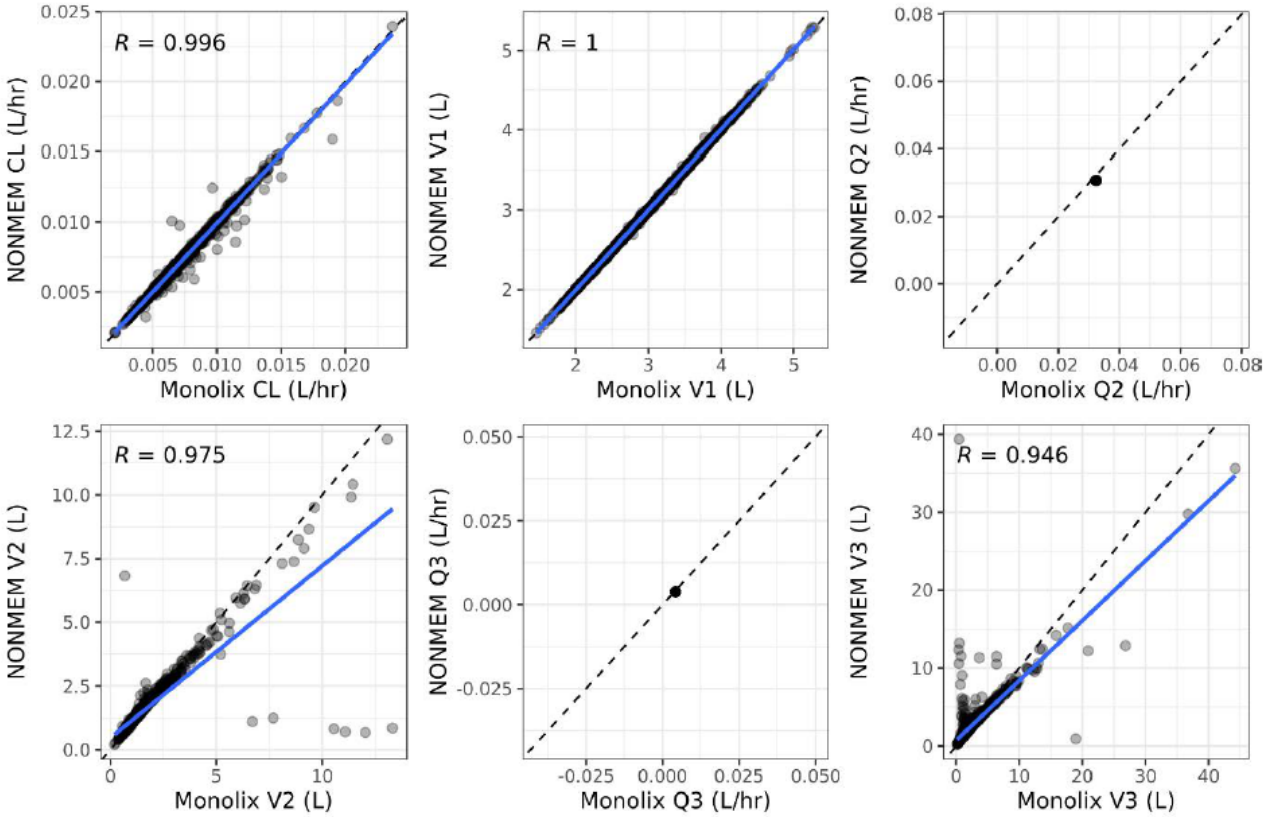
%RSE: %Relative standard error as defined by SE/estimate * 100%

$\omega_{parameter}$: standard deviation for the random effects (parameter)

* Covariance in NONMEM converted to correlation using $\frac{covar(\theta_i, \theta_j)}{(\sqrt{var(\theta_i)} * \sqrt{var(\theta_j)}}$

Source: Table 5-1 Model Qualification Report

Figure 1: Correlation of Individual PK parameters based on NONMEM vs Monolix



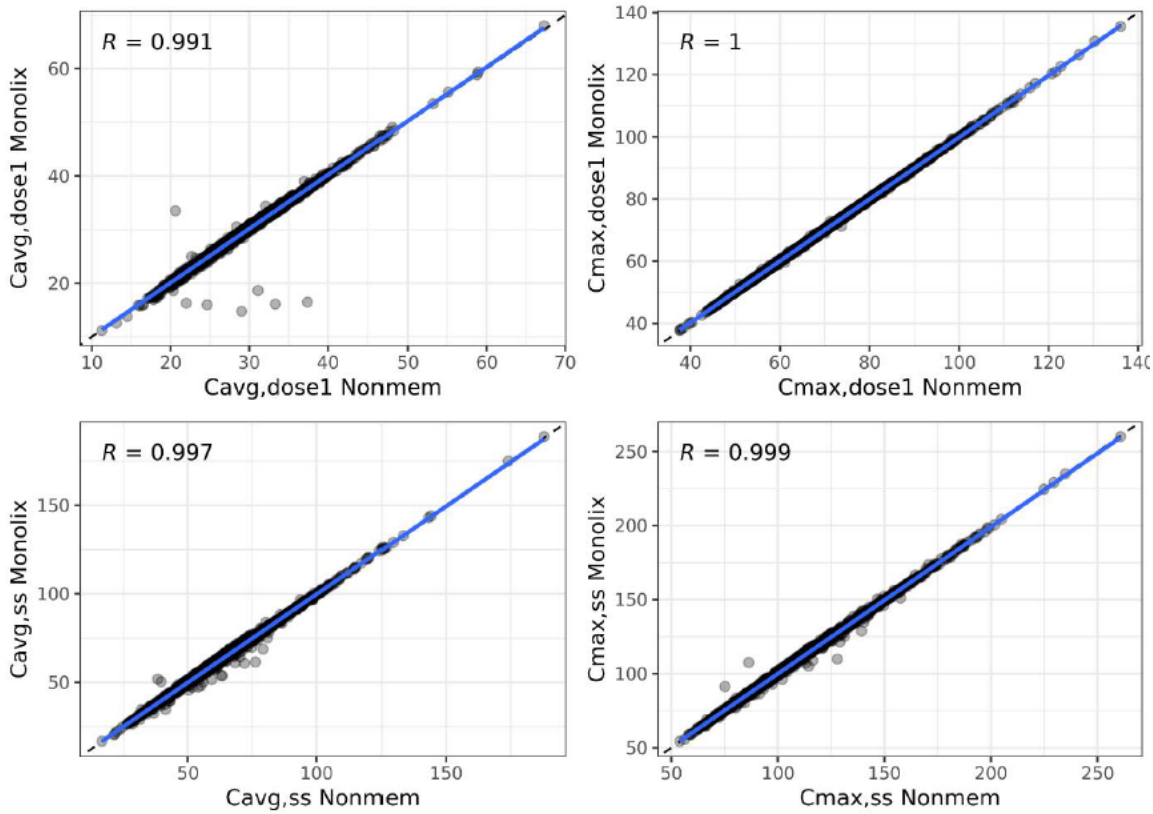
CVDT482G1/mas/mas_1/model/pgm_001/PopPK/Model_qualification//Task01_Monolix_NONMEM_correlation.R
CVDT482G1/mas/mas_1/model/pgm_001/PopPK/Model_qualification/PKparameters_Correlation.png

no inter-subject variability was set for Q2 and Q3 in the PopPK model.
Black dots represent individual PK parameters from Monolix and NONMEM models, dashed line represents line of identity and solid blue line represents regression line
Values are spearman's correlation coefficients between two variables.

Source: Figure 5-1 Model Qualification Report

Model predicted Cmax and Cavg after the first dose (Cmax,dose1 and Cavg,dose1) and at steady state (Cmax,steady state and Cavg,ss) at 200 mg Q3W were similar, as the identity line and the regression line largely overlap each other, with the correlation of (R > 0.99) between Monolix and NONMEM prediction. Standard goodness of fit plots of the Monolix model shows a good agreement between observed concentrations and predicted concentrations. Furthermore, the predictive performance of the Monolix model was evaluated using a pcVPC based on 500 replicates of the original dataset.The pcVPC plot showed that the observed percentiles (5th, 50th and 95th) of the tislelizumab PK concentration-time profiles were mostly within or closely associated with the 90% confidence intervals for the corresponding model predicted median and 5th and 95th percentiles.

Figure 2: PopPK predicted PK metrics from the Monolix and the NONMEM models

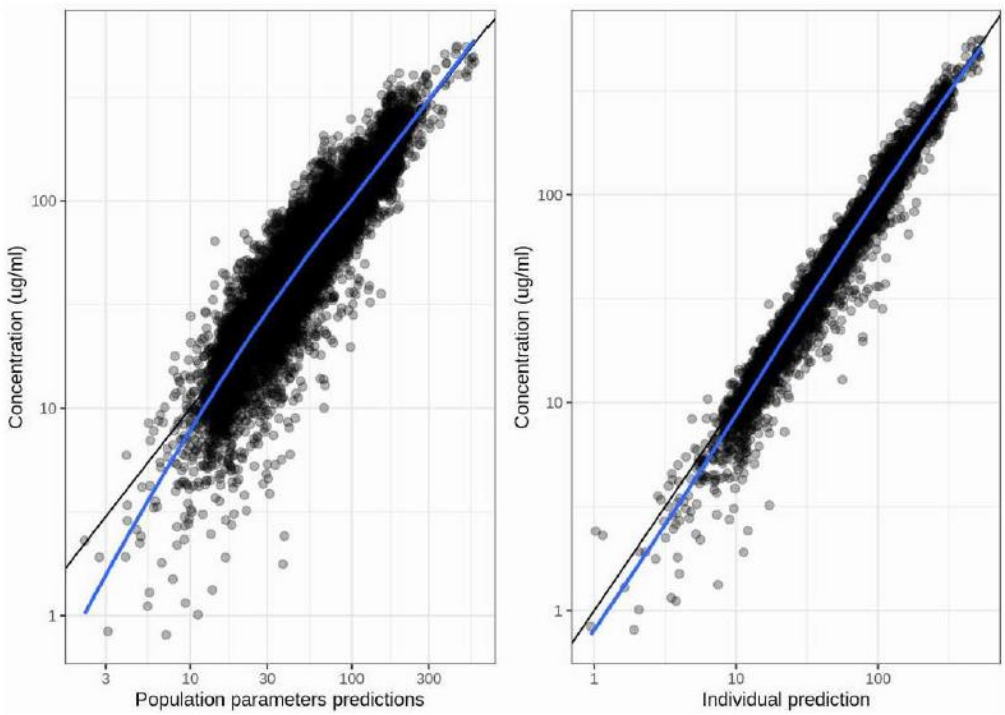


CVDT482G1/mas/mas_1/model/pgm_001/PopPK/Model_qualification//Task01_Monolix_Nonmem_correlation.R
CVDT482G1/mas/mas_1/model/pgm_001/PopPK/Model_qualification/PKmetrics_Correlation.png

Black dots represent individual PK parameters from Monolix and NONMEM models; dashed lines represent line of identity and solid blue line represent regression line.
Values are spearman's correlation coefficients between two variables.

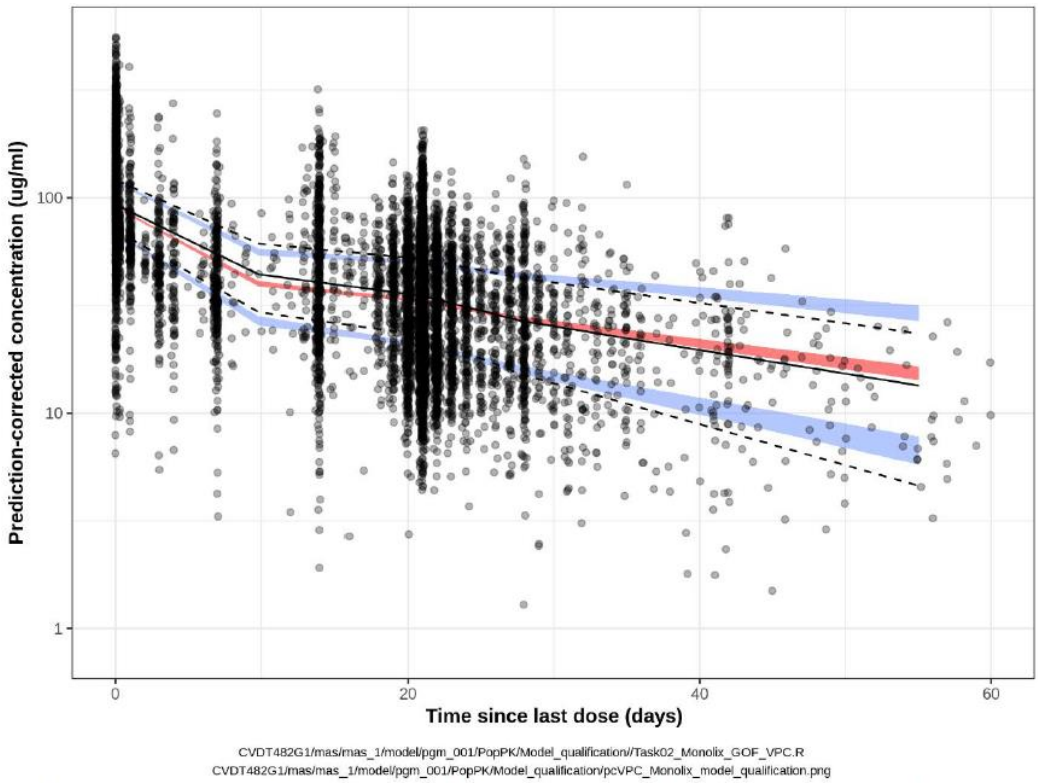
Source: Figure 5-2 Model Qualification Report

Figure 3: Predicted vs observed concentrations using the Monolix model



Source: Figure 5-3 Model Qualification Report

Figure 4: Prediction-corrected visual predictive check of tislelizumab serum concentration-time profiles across all studies



Black dots represent observed concentrations, dashed lines represent 5th and 95th percentiles of observed concentrations; solid black line represents 50th percentile of observed concentrations.
Blue and red shaded areas: 90% confidence interval around the 5th and 95th percentiles of simulations, while red shaded area represents 90% confidence interval around 50th percentile of simulations.

Source: Figure 5-5 Model Qualification Report

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

Population PK analysis:

The steady-state volume of distribution is 6.42 L. Vc, V2, and V3 were estimated to be 3.05 L, 1.27 L, and 2.10 L, respectively. According to the translated final Monolix PopPK model, volume of distribution is 5.86 L. Vc, V2, and V3 were estimated to be 3.02 L, 1.18 L, and 1.66 L, respectively.

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.

Population PK analysis:

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 and 0.149 L/day based on the translated final Monolix 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-A317-306 (Study 306)

A total of 649 patients were enrolled in this ongoing, global study, 324 of whom received 200 mg tislelizumab administered intravenously Q3W in combination with chemotherapy. Patients may continue study treatment (tislelizumab/placebo) until disease progression, intolerable toxicity, or other reasons. PK data were available for a total of 316 patients.

Pharmacokinetic results and conclusions:

The mean (± SD) predose and postdose serum concentrations after the intravenous doses of tislelizumab 200 mg Q3W, as of the PK data cut-off date (01-Nov-2021), are presented in Table 3

Table 3: Summary of tislelizumab serum concentrations in Study 306 (PK Analysis Set)

	Tislelizumab concentration: Geometric Means ± Standard Deviation (µg/mL)	
Visit	Predose	Postdose
Cycle 1 Day 1	NE	64.39 ± 16.988
Cycle 2 Day 1	15.91 ± 5.198	--
Cycle 5 Day 1	37.38 ± 14.243	100.92 ± 85.897
Cycle 9 Day 1	45.17 ± 18.963	--
Cycle 17 Day 1	48.14 ± 23.147	--

Source: Table 2-13, SCP

External validation of the final PopPK model for Study 306

The qualified final PopPK model in Monolix was used to simulate tislelizumab PK for the 316 patients included in the PK analysis dataset of Study 306. For each patient, the PK simulation was based on actual dosing records, PK sampling times, number of PK samples and the following baseline characteristics: WT, ALB, TUMSZ, AGE, SEX, TUMTP and ADA status (negative or positive). Individual random effects of the parameters were sampled from the normal distributions following the final PopPK model estimates for random effects, including both variance and covariance. Estimated residual

variability of the final PopPK model was included in the simulation as the goal of this step was to reproduce the random variability of the observed PK data.

Simulations were conducted for 500 replicates with 316 patients in each replicate. Simulated concentrations for the 316 patients from all the replicates were then binned and summarized at the 5th, 50th and 95th percentiles. For each of the calculated percentile, the 90% confidence interval (CI) was calculated as the 5th and 95th quantiles of the 500 replicates. In addition, the 5th, 50th and 95th percentiles of the observed concentrations in Study 306 were also summarized according to the same binning criteria. Finally, observed PK data, observed percentiles, simulated percentiles and associated prediction interval (PI) were plotted over time. To assess whether the final PopPK model adequately described the data from Study 306, the simulated PK concentrations based on the final PopPK model were required to fulfil the following criteria:

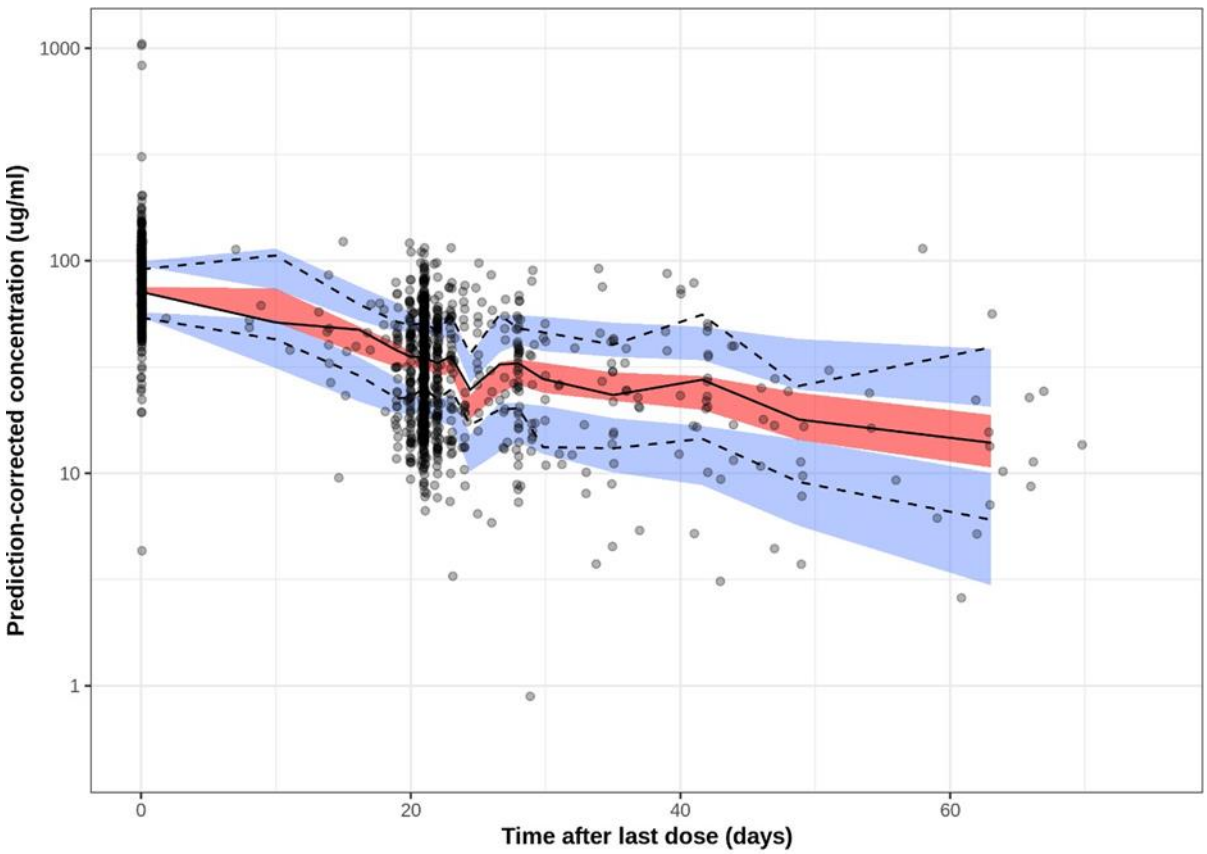
• The observed percentiles were adequately contained within the 90% CIs of the corresponding predicted percentiles.

The number of patients and observations for the PopPK data were 316 and 1412, respectively.

The ability of the final PopPK model to reproduce the distribution of tislelizumab concentration data over time was evaluated using pcVPC based on 500 simulated replicates of the Study 306 dataset. The pcVPC plot of tislelizumab serum concentration-time profiles is shown in Figure 5.

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.

Figure 5: Prediction-corrected concentration (µg/ml) vs. time after last dose (days)



Time after last dose = time elapsed since previous dose.
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 are model

predicted percentiles and represent 90% confidence interval for 5th and 95th percentile, while red shaded area represent 90% confidence interval for 50th percentile.

Source: Figure 3-8, SCP

PopPK-predicted exposure of tislelizumab is presented below.

Table 4: Summary of the PopPK-predicted exposure of tislelizumab in Study 306

Characteristics	Study 306
No. of subjects [N (%)]	316 (100)
Cmin,ss (µg/mL) Geomean (Geometric CV%)	46.52 (37.76)
Cmax,ss (µg/mL) Geomean (Geometric CV%)	115.66 (28.41)
AUCss (µg.day/mL) Geomean (Geometric CV%)	1388.42 (28.93)
CL (L/day) Geomean (Geometric CV%)	0.14 (32.65)
Body weight [min; median; max] (kg)	33.5; 59; 124
Albumin [min; median; max] (g/L)	29.4; 41; 52
Age [min; median; max] (years)	26; 64; 84
Tumor size [min; median; max] (mm)	10; 37.93; 184.68
Sex [M/F, N(%)]	273 (86.4)/ 43 (13.6)
ADA [Negative/Positive/Missing N(%)]	250 (79.1)/ 66 (20.9)/ 0 (0)

ADA = anti-drug antibody; AUCss = area under the curve at steady state; CL = clearance; Cmax,ss = maximum concentration at steady state; Cmin,ss = trough concentration at steady state.

Source: Table 8-1, PopPK addendum report

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.

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.

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.

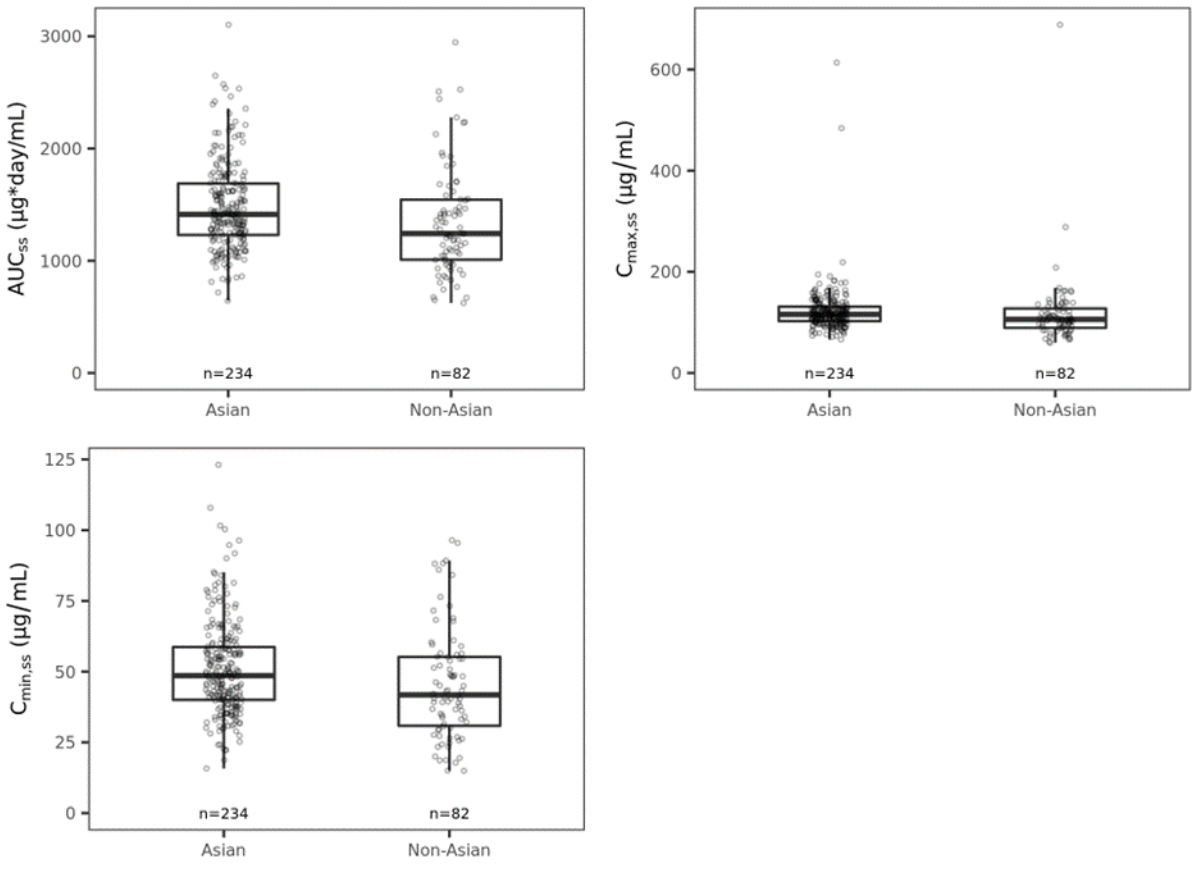
Race

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.

Further simulations were conducted for the evaluation of the impact of race and region on pharmacokinetics of tislelizumab with Study 306 in 1L OSCC 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 306. The difference in percentage of non-Asian patients as compared to Asian patients in clearance and steady state exposure metrics (Cmin,ss, Cmax,ss, AUCss) was 7.14%, - 14.37%, -7.59%, and -11.26%, respectively.

Figure 6: Steady state exposure of tislelizumab by Asian and non−Asian following 200 mg Q3W dosing



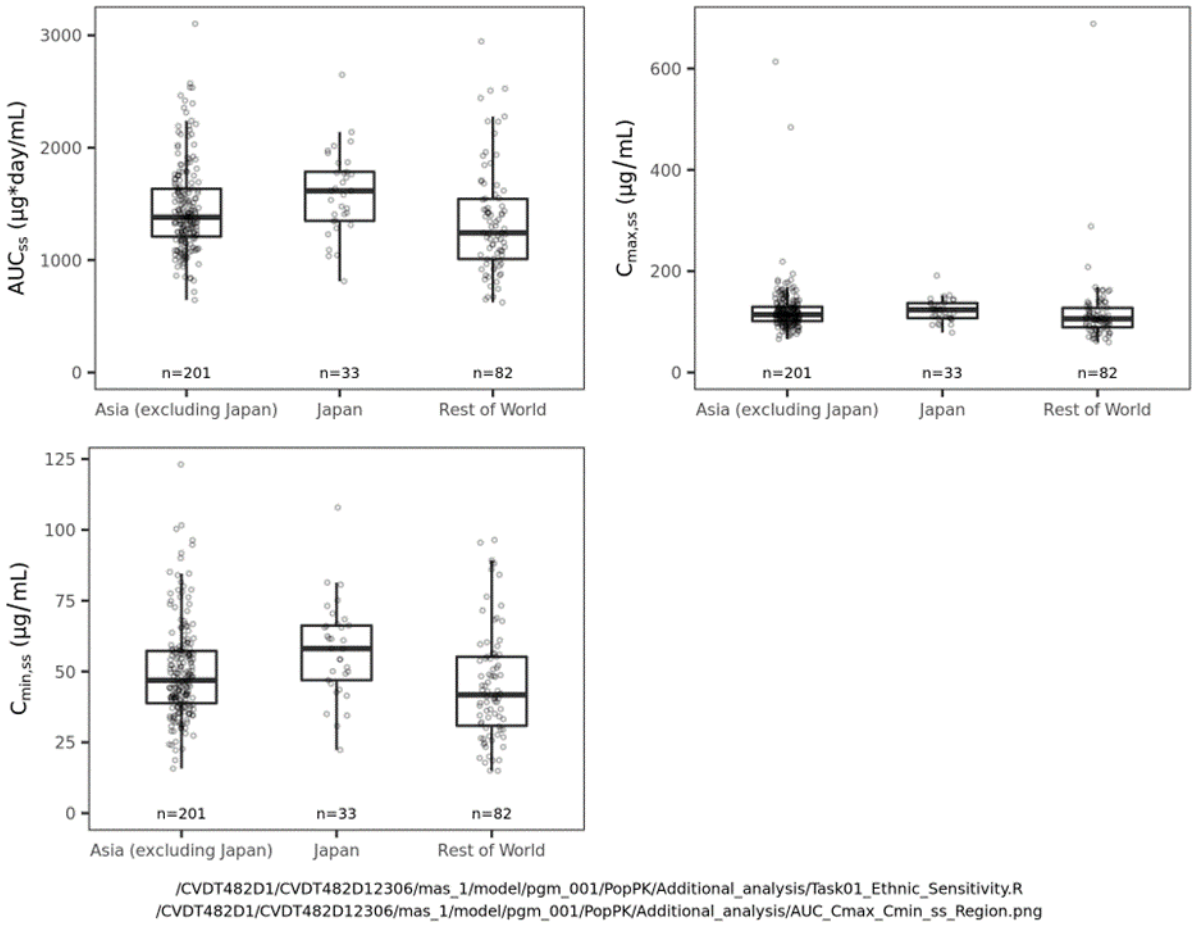
/CVDT482D1/CVDT482D12306/mas_1/model/pgm_001/PopPK/Additional_analysis/Task01_Ethnic_Sensitivity.R
/CVDT482D1/CVDT482D12306/mas_1/model/pgm_001/PopPK/Additional_analysis/AUC_Cmax_Cmin_ss_ASN_NonASN_boxplot.png

Source: Figure 3-9, SCP

To assess the impact of region on PK of tislelizumab, the model predicted steady-state exposures were assessed by region (i.e. Asia (excluding Japan) vs. Japan vs. RoW.

Clearance in Japanese and rest of world (RoW; non-Asian) patients was 14.29% lower and 7.14% higher compared to Asian (excluding Japanese) patients, respectively. Steady State exposure metrics (Cmin,ss, Cmax,ss, AUCss) in Japanese patients were 2.33 – 16.33% higher compared to Asian (excluding Japan) patients. Steady State exposure metrics (Cmin,ss, Cmax,ss, AUCss) in RoW patients were 7.29 – 12.53% lower compared to Asian (excluding Japanese) patients.

Figure 7: Simulated steady state exposure of tislelizumab by Asia (excluding Japan) vs. Japan vs. RoW following 200 mg Q3W dosing



Source: Figure 3-10, SCP

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 paediatric 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 in combination 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 306.

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-A317-306.

Immunogenicity of tislelizumab in combination with chemotherapy was assessed as exploratory objective in Study 306.

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 tumours and signalling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumours.

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 signalling, 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

The immunogenicity profile of tislelizumab has been characterized in clinical studies using validated assays. Serum samples from 2810 tislelizumab-treated patients in 11 Phase I to III clinical studies (monotherapy: studies 001, 102, 203, 204, 208, 302, and 303; in combination with chemotherapy:

studies 206, 304, 307 and 306) were assessed for treatment-emergent ADA and Nab. Analyses of ADA and its potential impact on PK, efficacy, and safety were performed for 2577 evaluable patients.

ADA incidence

Overall, across all tislelizumab doses and tumour types, the incidence of treatment-emergent ADA was 18.6% (479/2577 ADA evaluable patients). Patients treated with tislelizumab 200 mg Q3W as monotherapy had an incidence of 16.3% of treatment-emergent ADA (232/1424 evaluable patients), while a slightly higher incidence of 23.2% was seen in patients treated with tislelizumab 200 mg Q3W in combination with platinum-containing chemotherapy (184/792 evaluable patients). The higher incidence of ADA in combination therapy studies was driven primarily by an increase in transient ADA. Most patients developed ADA by the second dose and before the third dose the Q3W regimen. Nab were detected in 19 patients (0.7% of 2577 evaluable patients), distributed fairly evenly across the studies that tested the fixed dose of 200 mg Q3W. Nab were not detected among the small number of patients treated with weight-based dosing in the dose escalation part of Study 001.

Table 5: ADA incidence by dose regimen – Studies 001, 102, 203, 204, 206, 208, 302, 303, 304, 306, 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+chemo	306	300	66 (22.0)	0	66 (22.0)	29 (9.7)	37 (12.3)	1 (0.3)
200 mg Q3W combo[2]		**792**	**184 (23.2)**	**4 (0.5)**	**180 (22.7)**	**70 (8.8)**	**110 (13.9)**	**8 (1.0)**
200 mg Q3W total		**2216**	**416 (18.8)**	**12 (0.5)**	**404 (18.2)**	**207 (9.3)**	**197 (8.9)**	**19 (0.9)**
Total		**2577**	**479 (18.6)**	**13 (0.5)**	**466 (18.1)**	**238 (9.2)**	**228 (8.8)**	**19 (0.7)**

Source: Table 5-4 ISI v2.1

Immunogenicity in Study 306

The immunogenicity profile for OSCC patients treated with tislelizumab 200 mg Q3W in combination with chemotherapy in the first-line setting was generally consistent with that observed in other Phase III studies.

Table 6: Summary of immunogenicity results for Study 306 (ADA analysis set)

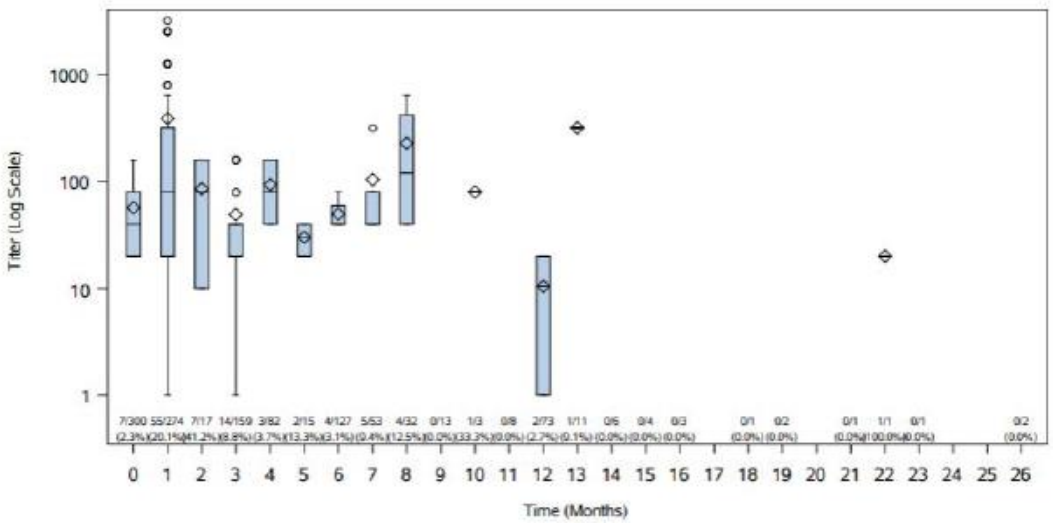
	Arm A N = 300) N (%)
Treatment-emergent ADA	66 (22.0)
Treatment-boosted ADA	0
Treatment-induced ADA	66 (22.0)
Persistent ADA response	29 (9.7)
Transient ADA response	37 (12.3)
Nab positive	1 (0.3)

Source: Table 4-1 SCE

No difference in immunogenicity by race or region was observed in Study 306. In the Asian subgroup, treatment-emergent ADA were detected in 22.1% of patients, while in the White subgroup treatment-emergent ADA were detected in 23.0% of patients. Similarly, treatment-emergent ADA were found at comparable rates in patients from region Asia (22.1%) vs. region US, Europe, RoW (21.8%).

In Study 306, the median titers mostly fluctuated between 10 and 100 over 12 months, with a few patients having titers ≥500 early after start of tislelizumab combination therapy.

Figure 8: Median and range of ADA titers over time for tislelizumab in combination with chemotherapy – Study 306 (ADA evaluable patients)

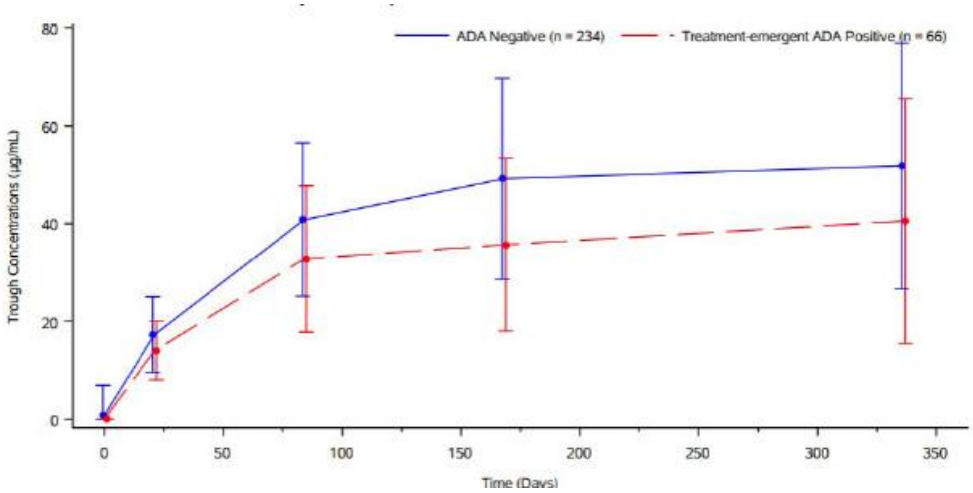


Source: Figure 5-1 ISI v2.1

Impact of ADA on PK (Study 306)

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

Figure 9: ADA impact on mean (± SD) trough tislelizumab serum concentrations for tislelizumab 200 mg Q3W + chemotherapy – Study 306 (ADA evaluable patients)



Source: Figure 5-2 ISI v2.1

Impact of ADA on efficacy (Study 306)

In Study 306, treatment-emergent ADA-positive patients had generally lower clinical response rates compared with ADA-negative patients.

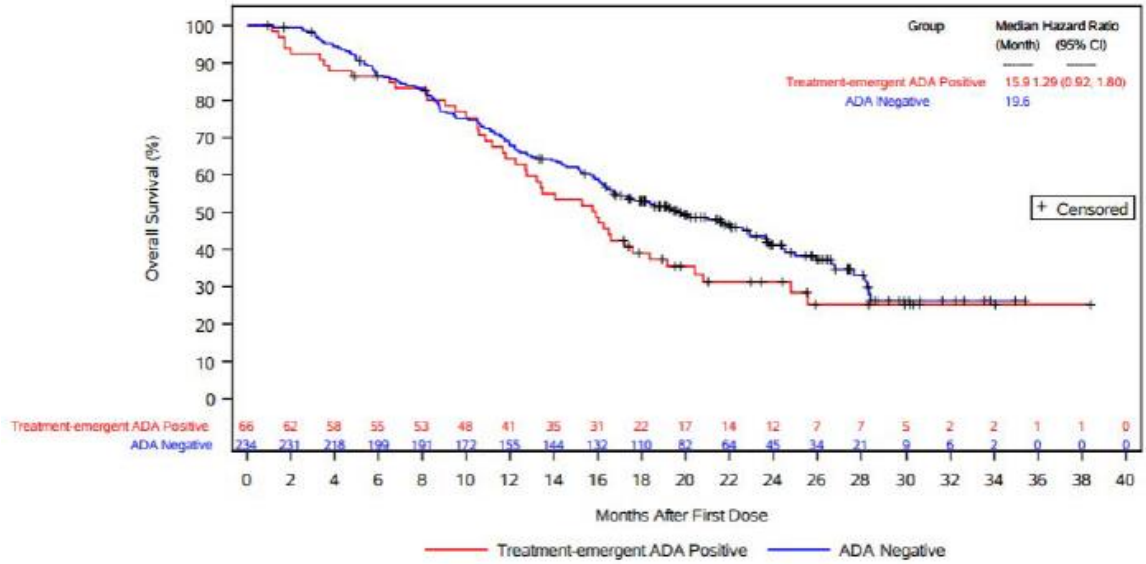
Table 7: Clinical response endpoints for tislelizumab-treated patients by ADA status (Study 306)

Clinical Endpoint	Treatment-emergent ADA positive	Treatment-emergent ADA negative
Study 306 – 1L ESCC: T+chemo		
Objective Response – n/N (%)	38/66 (57.6)	139/234 (59.4)
Disease Control – n/N (%)	57/66 (86.4)	219/234 (93.6)
Clinical Benefit – n/N (%)	43/66 (65.2)	174/234 (74.4)

Source: Table 5-11 ISI v2.1

Kaplan-Meier (KM) curves for OS by ADA status are presented below:

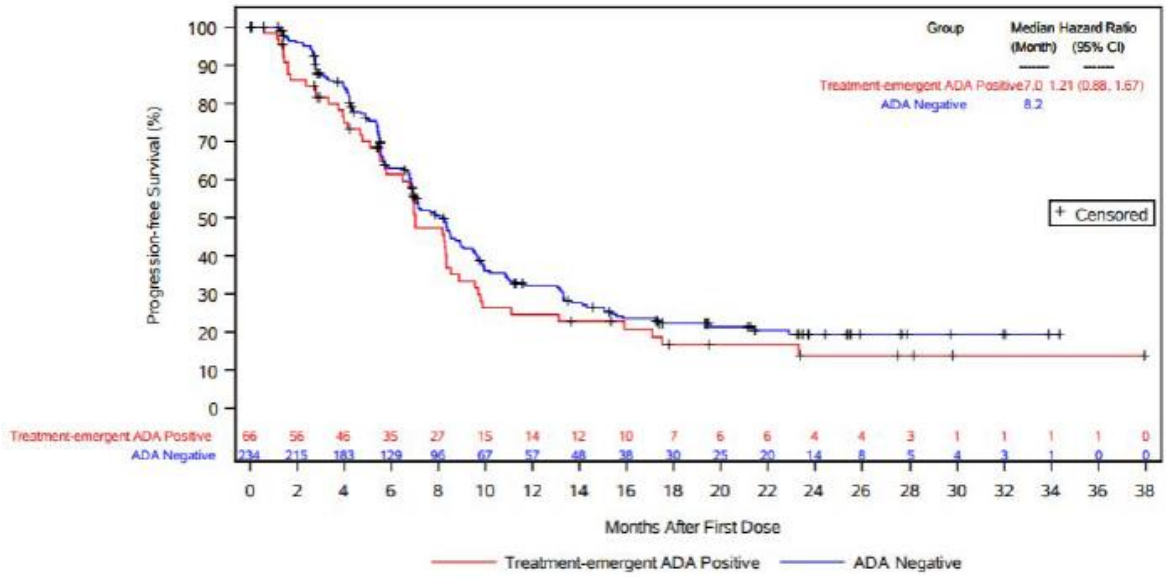
Figure 10: Overall survival by ADA status for tislelizumab in combination with chemotherapy – Study 306 (ADA evaluable patients)



Source: Figure 5-5 ISI v2.1

Kaplan-Meier (KM) curves for PFS by ADA status are presented below:

Figure 11: Progression-free survival by ADA status for tislelizumab in combination with chemotherapy – Study 306 (ADA evaluable patients)



Source: Figure 5-6 ISI v2.1

Impact of ADA on safety (Study 306)

In Study 306, the rates of Grade ≥ 3 AEs, imAEs, IRRs, AEs causing treatment discontinuation, and AEs causing dose modification were comparable between the ADA groups, while the rate of SAEs was higher in the ADA-positive group.

Table 8: Treatment-emergent adverse events by ADA status in Study 306

	Treatment-emergent ADA positive n (%)	Treatment-emergent ADA negative n (%)
Combination therapy study in 1L ESCC (306: T+chemo), N	66	234
Immune-mediated AEs, n (%)	21 (31.8)	83 (35.5)
Infusion-related reactions, n (%)	1 (1.5)	2 (0.9)
AEs Grade ≥ 3, n (%)	53 (80.3)	184 (78.6)
SAEs, n (%)	35 (53.0)	108 (46.2)
AEs causing treatment discontinuation, n (%)	8 (12.1)	32 (13.7)
AEs causing dose modification, n (%)	34 (51.5)	124 (53.0)

Source: Excerpt from Table 5-15 ISI v2.1

In response to the list of questions, the Applicant provided pooled data on TEAEs by ADA Status in monotherapy and combination therapy studies for tislelizumab at the claimed posology of 200 mg Q3W, see below.

Table 9: Treatment-Emergent Adverse Events by ADA Status in Monotherapy Studies and Combination Therapy Studies for Patients Treated With Tislelizumab 200 mg Q3W - ADA Evaluable Patients.

	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 (%)	75 (32.3)	408 (34.2)
Infusion-related reactions, n (%)	4 (1.7)	39 (3.3)
AEs Grade >= 3, n (%)	120 (51.7)	491 (41.2)
SAEs, n (%)	88 (37.9)	369 (31.0)
AEs causing treatment discontinuation, n (%)	28 (12.1)	128 (10.7)
AEs causing dose modification, n (%)	67 (28.9)	315 (26.4)
Combination therapy studies (304, 306, 307), N	177	564
Immune-mediated AEs, n (%)	78 (44.1)	241 (42.7)
Infusion-related reactions, n (%)	14 (7.9)	35 (6.2)
AEs Grade >= 3, n (%)	148 (83.6)	443 (78.5)
SAEs, n (%)	86 (48.6)	235 (41.7)
AEs causing treatment discontinuation, n (%)	23 (13.0)	77 (13.7)
AEs causing dose modification, n (%)	102 (57.6)	347 (61.5)

Source: ADIS, ADAE.

Abbreviations: ADA = anti-drug antibody; AE = adverse event; AEs Grade >=3 = treatment-emergent adverse events greater than or equal to grade 3; SAE = serious AE.

unblind/bgb_a317/pk/306_eu_rtq/dev/pgm/tlfs/t-ada-ae.sas 05MAY2024 23:33 t-1-ada-ae.rtf

Imbalances were not driven by specific SOC or PT but rather by small differences in diverse, unrelated AEs. These SAE PTs are not conditions typically associated with ADA.

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 306 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.

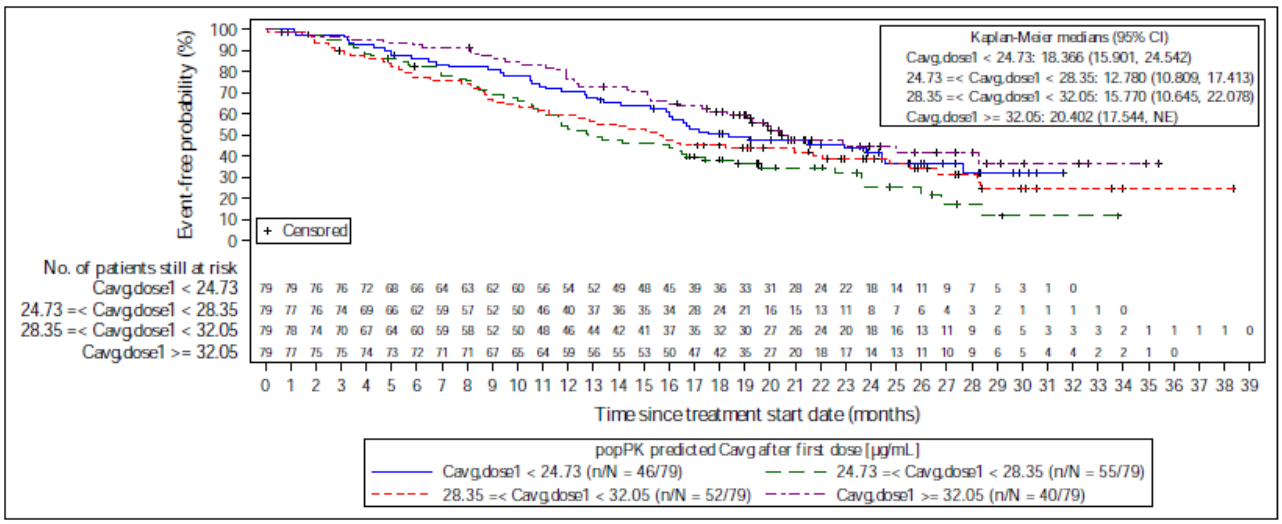
Exposure-efficacy analysis:

The exposure-efficacy relationship for tislelizumab was explored using efficacy datasets containing data from 316 patients who received at least one dose of tislelizumab and had PopPK model predicted Cavg,dose1 for exposure - efficacy. The efficacy endpoints analysed were OS (primary endpoint), PFS, and responders/non-responders status based on BOR (secondary endpoints).

Exposure versus OS and PFS

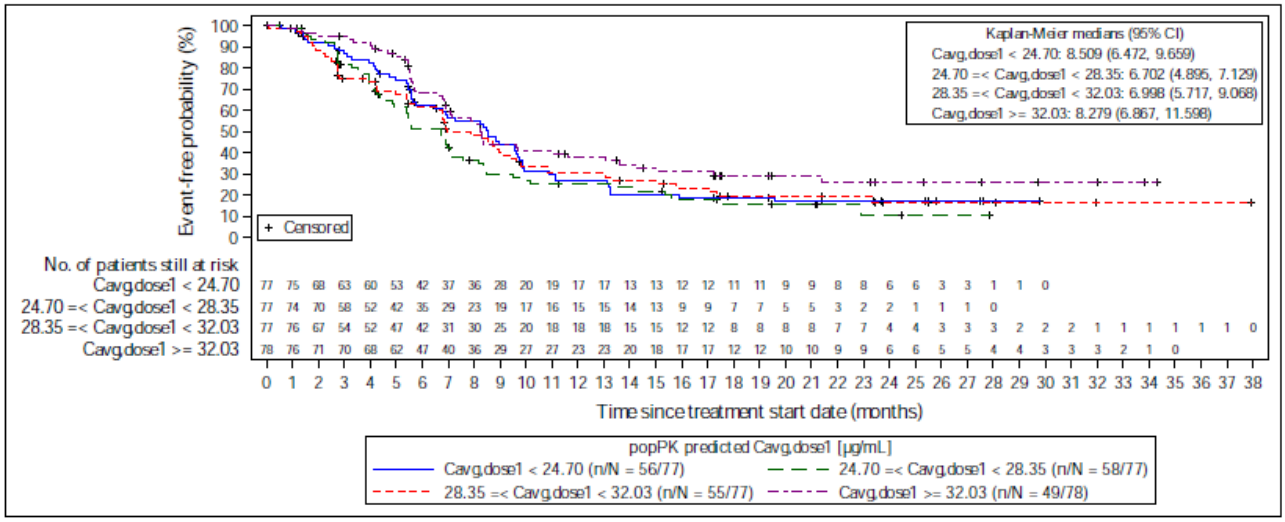
There is no monotonic relationship between Cavg,dose1 and OS or PFS. There is limited separation between the Kaplan-Meier curves when stratified by quartiles Cavg,dose1.

Figure 12: Kaplan-Meier curves of OS stratified by Cavg,dose1 quartiles - 1L OSCC (1L OSCC PK-Efficacy set)



Source: Figure 4-1 Exposure-Response Report

Figure 13: Kaplan-Meier curves of PFS stratified by quartiles of Cavg,dose1 - 1L OSCC (1L OSCC PK-Efficacy set)



Source: Figure 4-3 Exposure-Response Report

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 negative and the 95% CI includes zero, suggesting that there is no statistically significant relationship between Cavg,dose1 and OS or PFS across the exposures evaluated.

Table 10: Summary of Cox model parameters for OS – 1L OSCC (1L OSCC PK-Efficacy set)

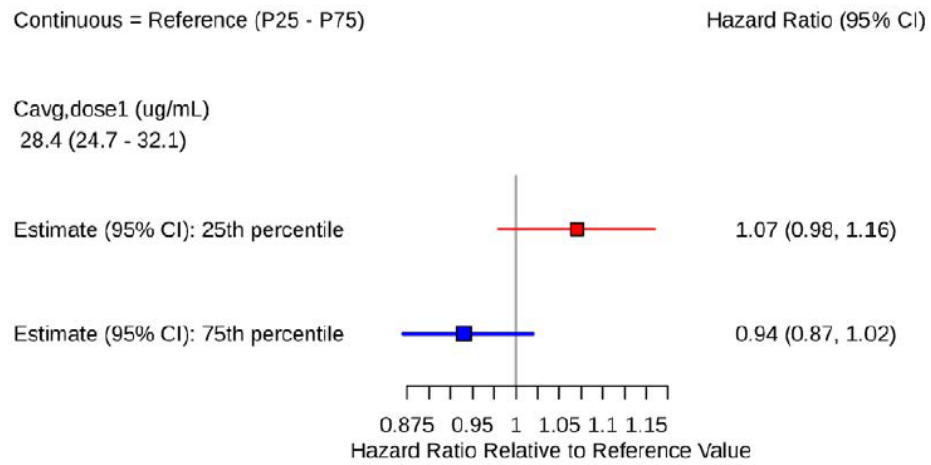
Run	Predictor Variables	coeff	Exp (coeff)	Wald p-value	95% CI of coeff
1	Log(Cavg,dose1)	−0.4728	0.6232	0.1391006	−1.0994, 0.1537
Source: Appendix-Table 8.2-7					

Table 11: Summary of the final Cox model parameters for PFS - (1L OSCC PK-Efficacy set)

Run	Predictor Variables	coeff	Exp (coeff)	Wald p-value	95% CI of coeff
1	Log(Cavg,dose1)	−0.4678	0.6264	0.09275979	−1.0132, 0.0776
Source: Appendix-Table 8.2-5					

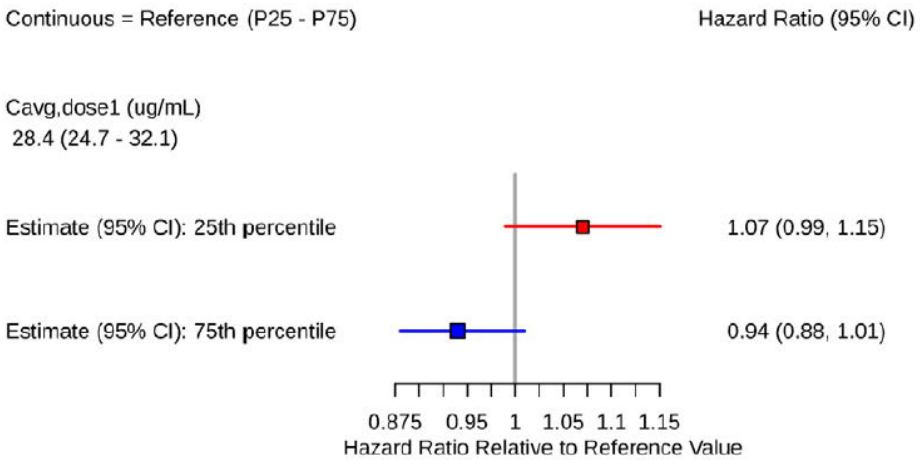
Forest plots illustrated that there is no statistically significant relationship between Cavg,dose1 and the risk of disease progression or death, since the 95% CI of HR of 25th and 75th percentiles versus median Cavg,dose1 crosses the line of null effect.

Figure 14: Estimated effects of significant covariates and Cavg,dose1 in the final Cox model for OS in tislelizumab treated patients - 1L OSCC (1L OSCC PK-Efficacy set)



Source: Figure 4-2 Exposure-Response Report

Figure 15: Estimated effects of significant covariates and Cavg,dose1 in the final Cox model for PFS in tislelizumab treated patients - 1L OSCC (1L OSCC PK-Efficacy set)



Source: Figure 4-4 Exposure-Response Report

Exposure versus BOR

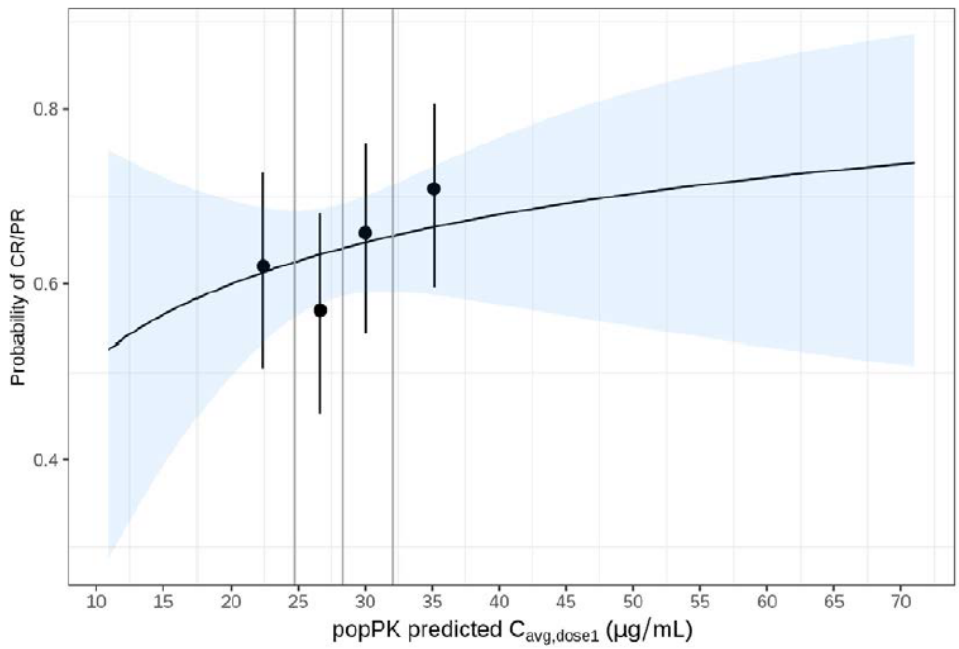
Table 12: PopPK predicted Cavg,dose1 by unconfirmed responder status – 1L OSCC (1L OSCC PK-Efficacy set)

	Responders	No-responders		All subjects
		All Non responders	BOR=SD	
Statistics	N=202	N=114	N=59	N=316
popPK predicted Cavg,dose1 [µg/mL]				
n	202	114	59	316
Mean (SD)	29.1 (7.01)	28.2 (5.97)	27.9 (6.73)	28.8 (6.66)
CV%	24.1	21.1	24.1	23.1
Geo-mean	28.4	27.7	27.3	28.1
CV% geomean	23.4	20.0	21.2	22.2
Median	28.7	27.7	27.0	28.4

Source: Table 4-7 Exposure-Response Report

Logistic regression was used to evaluate the relationship between exposure and response status. The probability estimates of unconfirmed response versus PopPK predicted Cavg,dose1 were evaluated across the four quartiles of Cavg,dose1 (below).

Figure 16: Predicted probability of unconfirmed BOR being CR/PR vs. PopPK predicted Cavg,dose1 - 1L OSCC (1L OSCC PK-efficacy set)



Source: Table 4-7 Exposure-Response Report

Exposure-safety analysis:

The AESI safety endpoints in Study 306 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

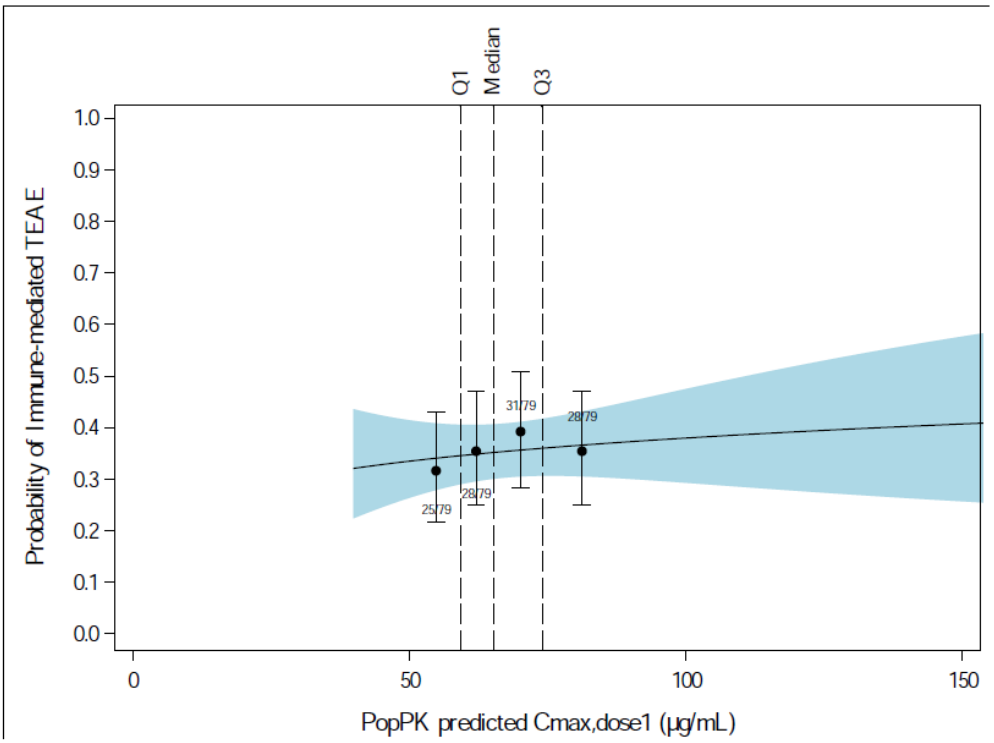
Table 13: PopPK predicted Cmax,dose1 by immune-mediated TEAEs (Yes/No) – 1L OSCC (1L OSCC PK-Safety set)

	Immune-mediated TEAE		
	Yes*	No	All subjects
Statistics	N=112	N=204	N=316
PopPK predicted Cmax,dose1 [µg/mL]			
n	112	204	316
Mean (SD)	72.2 (36.7)	71.7 (51.1)	71.9 (46.5)
CV%	50.9	71.3	64.7

Source: Table 4-10 Exposure-Response Report

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 below.

Figure 17: Logistic regression of probability of immune-mediated TEAE vs. popPK predicted Cmax,dose1 - 1L OSCC (1L OSCC PK-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 4-10 Exposure-Response Report

Infusion-related reactions

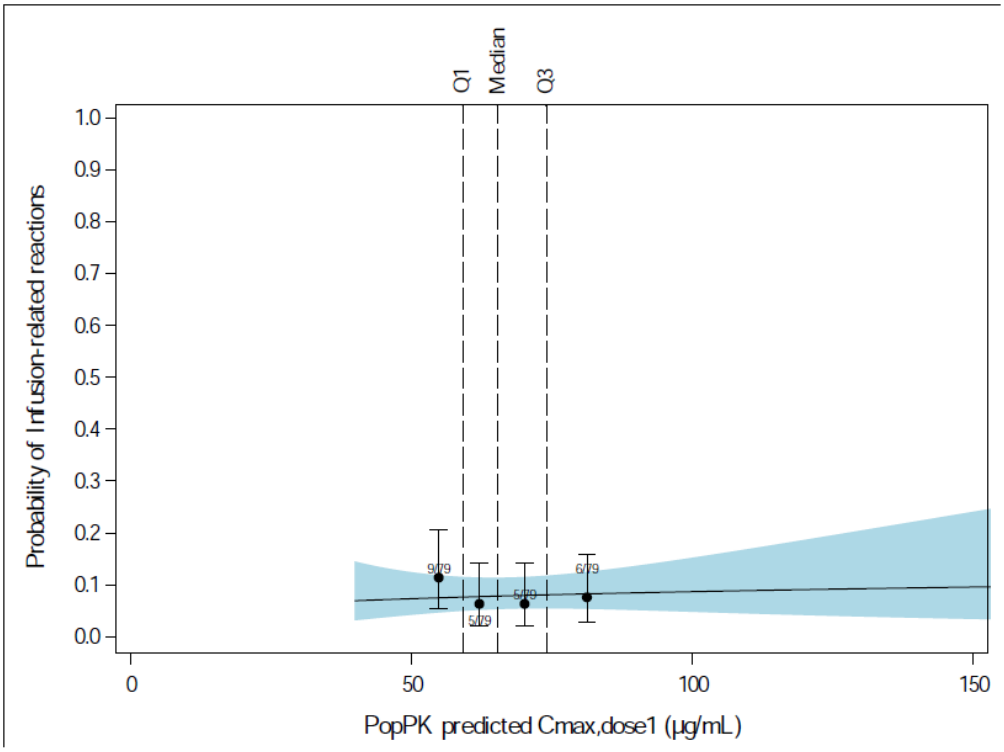
Table 14: PopPK predicted Cmax,dose1 by infusion-related reactions (Yes/No) – (1L OSCC PK-Safety set)

	Infusion-related reaction (IRR)		
	Yes*	No	All subjects
Statistics	N=25	N=291	N=316
PopPK predicted Cmax,dose1 [µg/mL]			
n	25	291	316
Mean (SD)	78.8 (68.9)	71.3 (44.1)	71.9 (46.5)
CV%	87.5	61.9	64.7

Source: Table 4-12 Exposure-Response Report

To quantify the relationship between exposure and infusion related reactions, logistic regression was conducted to estimate the probability of IRR by exposure, as shown:

Figure 18: Logistic regression of probability of infusion-related reactions (IRR) vs. popPK predicted Cmax,dose1 - 1L OSCC (1L OSCC PK-Safety set)



Model is log(p/(1-p)) = intercept + log popPK predicted Cmax,dose1, where p is the probability of experiencing at least one infusion-related reaction.

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 4-13 Exposure-Response Report

TEAE with CTCAE grade ≥ 3

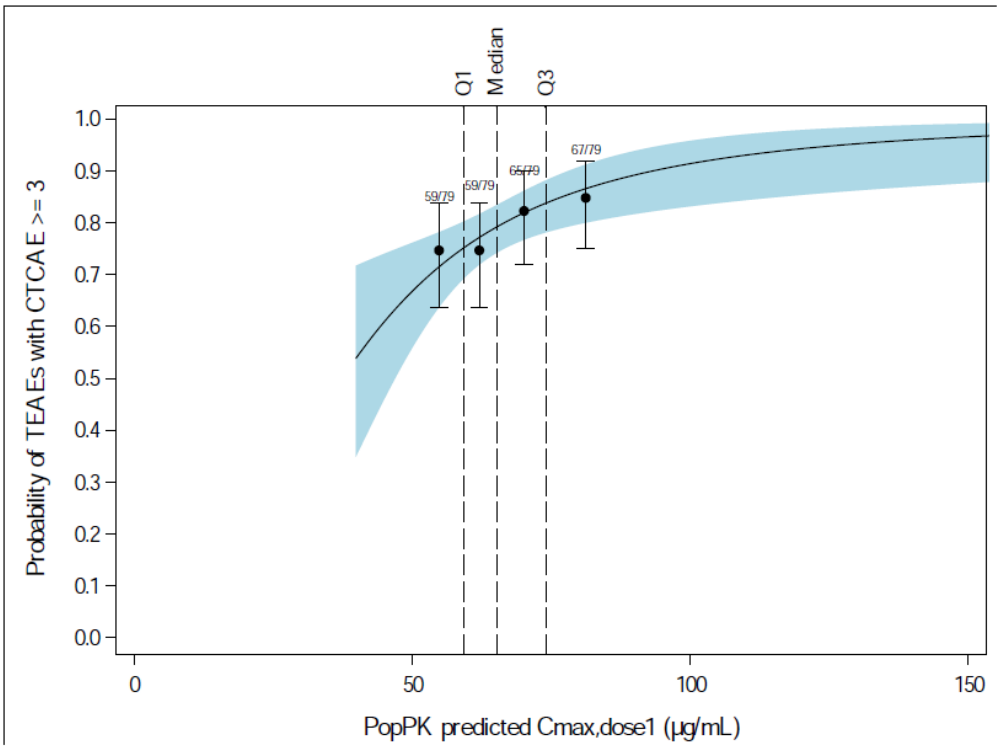
Table 15: PopPK predicted Cmax,dose1 by TEAEs with CTCAE grade ⩾ 3 (Yes/No) – 1L OSCC (1L OSCC PK-Safety set)

	TEAE with CTCAE grade ≥ 3		
	Yes*	No	All subjects
Statistics	N=250	N=66	N=316
PopPK predicted Cmax,dose1 [µg/mL]			
n	250	66	316
Mean (SD)	74.1 (51.7)	63.3 (11.2)	71.9 (46.5)
CV%	69.8	17.7	64.7

Source: Table 4-14 Exposure-Response Report

To 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 below. The results show that there was a positive relationship between exposure and TEAE with CTCAE grade ≥ 3 among subjects treated with tislelizumab.

Figure 19: Logistic regression of probability of TEAE with CTCAE >= 3 vs. popPK predicted Cmax,dose1 - 1L OSCC (1L OSCC PK-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: Figure 4-16 Exposure-Response Report

Table 16: Predicted probability of experiencing at least one TEAE with CTCAE grade ⩾ 3 by PopPK predicted Cmax,dose1 quartile groups - 1L OSCC (1L OSCC PK-Safety 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)
<59.2	54.8	59/79 (74.7) (63.6, 83.8)	71.5 (63.7, 78.2)
59.2-<65.2	62.0	59/79 (74.7) (63.6, 83.8)	77.2 (71.9, 81.7)
65.2-<74.0	70.1	65/79 (82.3) (72.1, 90.0)	81.9 (76.7, 86.2)
≥ 74.0	81.2	67/79 (84.8) (75.0, 91.9)	86.6 (80.0, 91.2)

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.
The 95% CIs for the observed proportions are based on the Clopper-Pearson method.

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

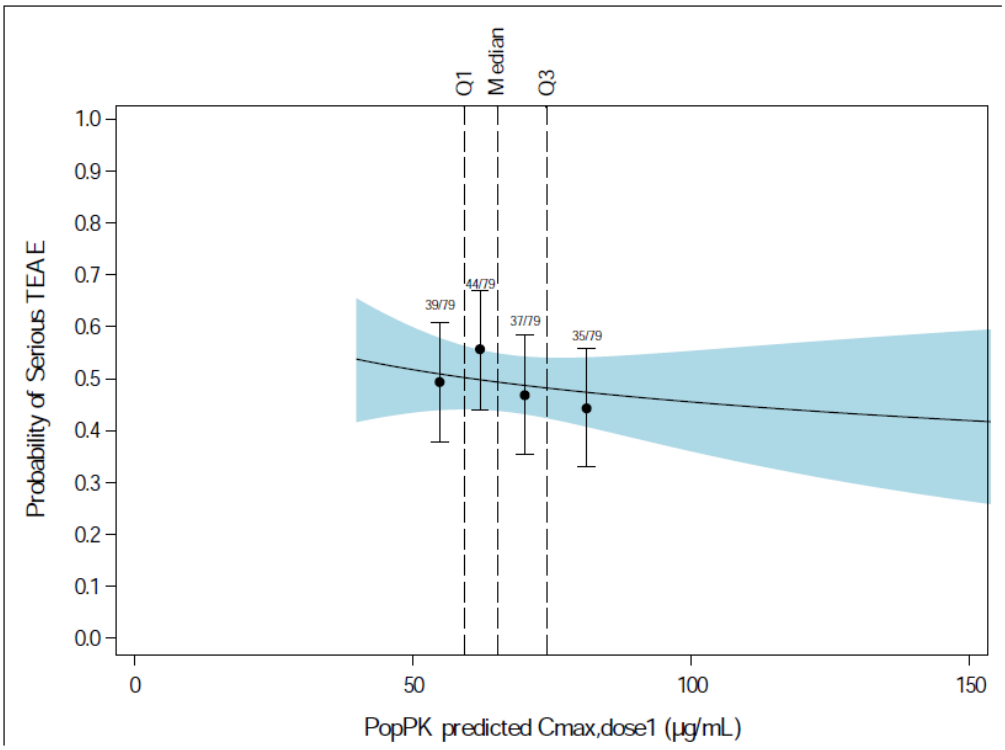
Table 17: PopPK predicted Cmax,dose1 by serious TEAE (Yes/No) – 1L OSCC (1L OSCC PK-Safety set)

	Serious TEAE		
Statistics	Yes* N=155	No N=161	All subjects N=316
PopPK predicted Cmax,dose1 [µg/mL]			
n	155	161	316
Mean (SD)	69.2 (30.0)	74.4 (58.1)	71.9 (46.5)
CV%	43.4	78.0	64.7

Source: Table 4-21 Exposure-Response Report

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

Figure 20: Logistic regression of probability of serious TEAE vs. popPK predicted Cmax,dose1 - 1L OSCC (1L OSCC PK-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: Figure 4-26 Exposure-Response Report

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 OSCC, 1L and 2L locally advanced or metastatic NSCLC).

In the pivotal study BGB-A317-306 supporting the current application in OSCC, only sparse PK samples were collected. 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. The PK data were used for external validation of the predictive performance and robustness of the previously developed population PK model for Study 306. Of note, the initially developed PopPK model (based on NONMEM) was now translated into a Monolix PopPK model using SAEM (Stochastic Approximation Expectation-Maximization) algorithm. A model qualification report was provided which included an evaluation of the translated Monolix model regarding 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 (Figure 1). In addition, the accuracy of the predictions for Q2 and Q3 seems to be considerably lower in the Monolix model. The observed differences in parameter estimates may

have resulted from the limited PK data available during the distribution phase in order to adequately inform estimation of peripheral volumes of distribution and intercompartmental clearances. This may have led to differences due to the change of the estimation method from FOCE-I (first-order conditional estimation with interaction) to SEAM (Stochastic Approximation Expectation Maximization).

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 model.

However, since estimates for clearance and central volume of distribution as well as overall tislelizumab exposure metrics were similar between the Monolix model and the NONMEM model, estimates for tislelizumab exposure derived from Monolix can be considered sufficiently fit for purpose (i.e. use in exposure-response modelling for Study 306).

Apart from the variations EMEA/H/C/005919/II/0003 and EMEA/H/C/005919/II/0006, any future tislelizumab submissions will use the original final PopPK model developed in NONMEM to conduct external validation or other PopPK modeling activities.

In general, pre- and post-dose concentrations of tislelizumab in Study 306 were similar to the concentrations reported in previous studies in which tislelizumab was either administered as monotherapy or in combination with chemotherapy.

The external validation using the data from Study 306 showed that final Monolix PopPK model was able to adequately describe the observed PK data from Study 306 (see Figure 5). The simulated steady state exposure of tislelizumab ($Cmax_{ss}$, $Cmin_{ss}$, AUC_{ss}) in Study 306 was comparable to the simulated steady state exposure of tislelizumab in previous studies included in the original PopPK model.

PK in special populations

Further simulations based on PK data from Study 306 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 RoW, respectively. However, the observed differences were rather small in comparison to the overall variability of tislelizumab exposure and individual exposure values in Asian patients largely overlap with those in non-Asian/RoW patients. Differences in PK estimates by race and region are not considered clinically significant.

Pharmacodynamics

Immunogenicity

In Study 306, the incidence of treatment-emergent ADA was 22.0%. Of those, nearly 10% presented with a persistent ADA response. Neutralizing ADA were solely detected in 1 patient (0.3%). ADA rates reported in Study 306 were within the range seen in other Phase III combination therapy studies 304 and 307 (17.7% to 37.4%).

The analysis of impact of ADA-positive status on PK revealed reduced exposure of tislelizumab in ADA-positive patients (see Figure 9). Similar, but less pronounced tendencies have been observed in other tislelizumab combination therapy studies (Study 304 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.

Referring to the analyses of the impact of ADA status on efficacy, also less benefit (response rates and OS) is indicated in ADA-positive patients (see Table 7 and Figure 10). Corresponding analyses in the

NSCLC studies (Study 304 and Study 307) also indicated a trend towards reduced benefit in patients that were found to be ADA positive. However, no firm conclusions may be drawn on a potential clinically relevant impact of ADA-positivity on PK and/or efficacy. In Study 306, a higher baseline tumour size in ADA-positive as compared to ADA-negative patients may have confounded results on tislelizumab exposure and no consistent trend of less benefit was observed at lower tislelizumab exposures (e.g. related to the probability of OS, exposure quartiles were not ranked in an ascending order, see Figure 12 and Figure 13).

In line with findings from previous tislelizumab studies, the rate of serious adverse events was higher in the ADA-positive population as compared to the ADA-negative population in Study 306 (53.0% vs. 46.2%, see above). No meaningful differences were seen in the frequency of imAEs, IRRs, TEAEs with CTCAE grade ≥ 3 and TEAEs leading to dose modification or treatment discontinuation.

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. As such, data from 316 patients who received at least one dose of tislelizumab and had PopPK model predicted Cavg,dose1 and Cmax,dose1 were utilized.

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. Likewise, logistic regression models of these safety endpoints did not suggest a statistically significant relationship between the probability of occurrence of safety events and predicted exposure. Moreover, exposure-safety analyses conducted in support of the MAA of tislelizumab for 2L OSCC did not reveal any meaningful relationship between tislelizumab exposure and safety (i.e. also TEAE with CTCAE grade ≥ 3) endpoints.

2.3.6. Conclusions on clinical pharmacology

Pharmacokinetics and pharmacodynamics of tislelizumab have been sufficiently characterized. Results from the pivotal study BGB-A317-306 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

No dose-response studies were submitted as part of this application.

The already approved dosing regimen of tislelizumab 200 mg Q3W was administered to participants enrolled in Study 306 and randomized to the tislelizumab plus chemotherapy treatment arm.

2.4.2. Main study

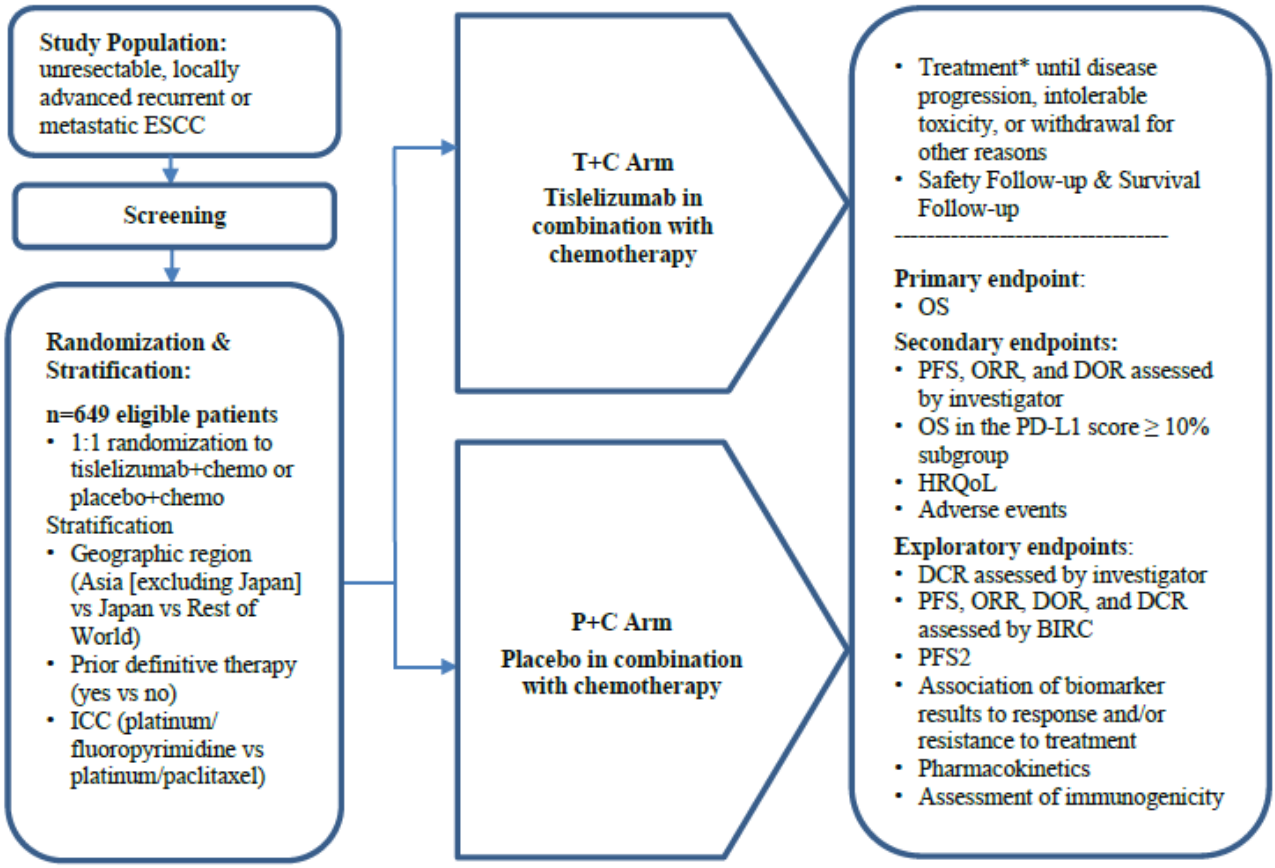
Title of Study

A Randomized, Placebo-Controlled, Double-Blind Phase 3 Study to Evaluate the Efficacy and Safety of Tislelizumab (BGB-A317) in Combination With Chemotherapy as First-Line Treatment in Patients With Unresectable, Locally Advanced Recurrent or Metastatic Oesophageal Squamous Cell Carcinoma.

Methods

The study is composed of an initial screening period (up to 28 days), a treatment period, a safety follow-up period (including an End of Treatment/Safety Follow-up Visit up to 30 days after the last dose), and a survival follow-up period.

Figure 21: Study scheme of Study 306



Abbreviations: BIRC, blinded independent review committee; chemo, chemotherapy; DCR, disease control rate; DOR, duration of response; ESCC, esophageal squamous cell carcinoma; HRQoL, health-related quality of life; ICC, investigator choice of chemotherapy; ORR, objective response rate; OS, overall survival; PD-L1, programmed cell death protein ligand-1; PFS, progression-free survival; PFS2, PFS after next line of treatment.
* When a patient reached a 24-month treatment, the patient might continue study therapy beyond 24-month treatment based on the investigator's evaluation and BeiGene's approval.

Source: Figure 1 CSR Study 306

A total of 649 patients were randomized worldwide; 326 patients were randomized to tislelizumab in combination with chemotherapy and 323 patients were randomized to placebo in combination with chemotherapy.

In order to reflect clinical practice in multiple regions/countries, the study was designed to allow a choice of chemotherapy regimen, including oxaliplatin or cisplatin plus fluoropyrimidine (capecitabine or 5 FU) or paclitaxel, based on local and/or country-specific guidelines and at the investigators' discretion. Randomization was stratified by geographic region (Asia [excluding Japan] vs. Japan vs. RoW, the latter including Europe, the US and Australia), prior definitive therapy (yes vs. no) and investigator choice of platinum-based chemotherapy regimen (ICC; platinum with fluoropyrimidine versus platinum with paclitaxel). The choice of chemotherapy regimen was determined prior to randomization and cross-over between treatment arms or between fluoropyrimidine and paclitaxel was not allowed.

A Blinded Independent Central Review (BIRC) was established to perform an independent review of all radiologic images for the efficacy analysis and to determine all instances of response and disease progression based on RECIST v1.1, in addition to the local investigator review of radiographs. BIRC-

assessed efficacy analyses were however moved from dual primary endpoint (PFS) and secondary endpoints (ORR, DOR) to exploratory endpoints in the late conduct of the study.

Regular safety monitoring and the planned interim analysis was performed by an IDMC. The IDMC could recommend modifications to the study, including termination due to safety concerns.

Study participants

Key inclusion criteria

- Pathologically (histologically) confirmed diagnosis of OSCC.
- Stage IV unresectable OSCC at first diagnosis OR unresectable, locally advanced recurrent or metastatic disease (per American Joint Committee on Cancer 7th Edition), if there was prior neoadjuvant/adjuvant therapy with platinum-based chemotherapy, a treatment-free interval of at least 6 months was required.
- Measurable or evaluable disease as defined per RECIST v1.1.
- ECOG PS score ≤ 1.
- Adequate organ function as indicated by the laboratory values (as defined in the protocol) ≤ 14 days prior to randomization.
- Had newly obtained or archival tissue sample available for biomarker assessment.

Key exclusion criteria:

1. Prior systemic therapy for unresectable, locally advanced recurrent or metastatic OSCC.

   Note: Patients with prior systemic concurrent chemotherapy in concurrent chemoradiotherapy (cCRT) were eligible.
2. Patients with evidence of fistula (either oesophageal/bronchial or oesophageal/aorta).
3. Uncontrollable pleural effusion, pericardial effusion, or ascites requiring frequent drainage or medical intervention (clinically significant recurrence requiring an additional intervention within 2 weeks of intervention).
4. Evidence of complete oesophageal obstruction not amenable to treatment.
5. Received prior therapies targeting PD-1, PD-L1, or PD-L2.
6. Active leptomeningeal disease or uncontrolled brain metastasis.
7. Active autoimmune diseases or history of autoimmune diseases that might have relapsed.
8. Any condition that required 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 lung diseases including pulmonary fibrosis, acute lung diseases, etc.
10. With infections (including tuberculosis infection, etc) requiring systemic antibacterial, antifungal or antiviral therapy within 14 days prior to randomization.
11. A known history of HIV infection.
12. Prior allogeneic stem cell transplantation or organ transplantation.

13. Unintentional weight loss ≥ 5% within 1 month prior to randomization or Nutritional Risk Index (NRI) < 83.5 per investigator's choice.
14. Locally advanced oesophageal carcinoma that was resectable or potentially curable with radiation therapy per local investigator.
15. Patients with untreated chronic hepatitis B or chronic hepatitis B virus (HBV) carriers whose HBV DNA was ≥ 500 IU/mL or patients with active hepatitis C virus (HCV).

Treatments

Eligible patients were randomized 1:1 to receive either tislelizumab 200 mg or placebo in combination with investigator's choice of chemotherapy (ICC, see Table 18) in a double-blind manner. Study treatment was administered every 3 weeks (q3w), based on treatment cycles of 21 days in length.

Study treatment was administered until disease progression, intolerable toxicity, or another reason that met the treatment discontinuation criteria. Platinum therapy could be stopped after 6 cycles, per site or investigator preference or standard practice. If platinum treatment was stopped, the non-platinum agent (fluoropyrimidine or paclitaxel) could continue at the regular schedule.

Patients may have continued study therapy beyond 2 years if the investigator considered this to be in the best interest of the patient based on an assessment of clinical benefit and potential risks. At the 3-year data cut-off, a total of 39 (12.0%) of patients in the T+C arm had received treatment for > 24 months (up to a maximum of 60 months).

In both arms, treatment beyond the initial investigator-assessed, RECIST v1.1-defined disease progression was permitted provided that the patient a) had investigator-assessed clinical benefit, b) was tolerating the study treatment.

Table 18: Selection and Timing of Dose for Each Patient

Intervention	Study Drug	Dose	Frequency of Administration	Route of Administration	Duration of Treatment
Investigational product	Tislelizumab	200 mg	Day 1 of each cycle, Q3W	Intravenous infusion	Section 9.1
Matched Placebo	None	N/A	Day 1 of each cycle, Q3W	Intravenous infusion	
Chemotherapy Doublet A	Cisplatin OR Oxaliplatin[a]	60-80 mg/m^2 (cisplatin) 130 mg/m^2 (oxaliplatin)	Day 1 of each cycle, Q3W	Intravenous infusion	
	5-Fluorouracil	750-800 mg/m^2	Days 1 to 5 of each cycle, Q3W	Intravenous infusion	
Chemotherapy Doublet B	Cisplatin OR Oxaliplatin[a]	60-80 mg/m^2 (cisplatin) 130 mg/m^2 (oxaliplatin)	Day 1 of each cycle, Q3W	Intravenous infusion	
	Capecitabine	1000 mg/m^2	Days 1 to 14[b] of each cycle, Twice a day	Oral	
Chemotherapy Doublet C	Cisplatin OR Oxaliplatin[a]	60-80 mg/m^2 (cisplatin) 130 mg/m^2 (oxaliplatin)	Day 1 or 2[c] of each cycle, Q3W	Intravenous infusion	
	Paclitaxel	175 mg/m^2	Day 1 of each cycle, Q3W	Intravenous infusion	

Abbreviations: N/A, not applicable; Q3W, once every 3 weeks.

Note: Platinum therapy could be stopped after 6 cycles, per site or investigator preference or standard practice. If platinum treatment was stopped, the non-platinum agent (fluoropyrimidine or paclitaxel) could continue at the regular schedule.

[a] The platinum agent could be cisplatin or oxaliplatin (except in China, Taiwan, Japan, and countries where oxaliplatin substitution was not permitted) according to site or investigator preference or standard practice as determined prior to randomization.

[b] Capecitabine was self-administered 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 cycle.

[c] For Chemotherapy Doublet C, cisplatin could be administered on Days 1 or 2, or in 3 divided doses on Days 1, 2, and 3 depending on local guidelines. The total dose given had to be between 60 to 80 mg/m^2 per cycle.

Source: Table 3 CSR Study 306

Objectives

Primary objective

- To evaluate and compare the OS following treatment with tislelizumab in combination with chemotherapy compared to placebo in combination with chemotherapy when given as first-line treatment in patients with unresectable, locally advanced recurrent or metastatic OSCC.

Secondary objectives

- To evaluate and compare the efficacy of tislelizumab in combination with chemotherapy compared to placebo in combination with chemotherapy as a first-line treatment in unresectable, locally advanced recurrent or metastatic OSCC as measured by progression-free survival (PFS), objective response rate (ORR), and duration of response (DOR) assessed by the investigator per Response Evaluation Criteria in Solid Tumours (RECIST) version (v) 1.1
- To evaluate and compare the efficacy of tislelizumab in combination with chemotherapy with the efficacy of placebo in combination with chemotherapy as a first-line treatment in

unresectable, locally advanced recurrent or metastatic OSCC as measured by OS in the PD-L1 score ≥ 10% subgroup.

- To evaluate and compare health-related quality of life (HRQoL) based on patient-reported outcomes (PRO) between tislelizumab in combination with chemotherapy and placebo in combination with chemotherapy
- To compare the safety between tislelizumab in combination with chemotherapy and placebo in combination with chemotherapy

Exploratory Objectives

- To characterize the disease control rate (DCR) with tislelizumab in combination with chemotherapy assessed by the investigator per RECIST v1.1
- To evaluate PFS, ORR, DOR, and DCR assessed by blinded independent review committee (BIRC) per RECIST v1.1
- To assess PFS after next line of treatment (PFS2)
- To evaluate the potential association of biomarkers with patient prognosis, response, or resistance to tislelizumab in combination with chemotherapy
- To assess the pharmacokinetics (PK) of tislelizumab in combination with chemotherapy
- To assess host immunogenicity to tislelizumab in combination with chemotherapy

Biomarker

PD-L1 expression was determined by PD-L1 score assessed by tumour area positive score (TAP) (previously referred to as visually-estimated combined positive score [vCPS] in protocol), which is defined as the total percentage of the tumour area (tumour and any desmoplastic stroma) covered by tumour cells with PD-L1 membrane staining at any intensity and tumour-associated immune cells with PD-L1 staining at any intensity, as visually estimated using VENTANA PD-L1 (SP263) assay.

Outcomes/endpoints

Primary efficacy endpoint

The primary efficacy endpoint for this study was **overall survival (OS) in the ITT Analysis Set**, defined as time from randomization date to the documented death date for patients who died prior to or on the clinical cut-off date. For patients who were alive by the cut-off date of clinical data, OS was censored at the last known alive date (LKADT). The last known alive date was defined as either the cut-off date of clinical data for patients who were still on treatment, or last available date showing patients alive or cut-off date, whichever came first for other alive patients.

Secondary efficacy endpoints

Progression-Free Survival by Investigator, defined as the time from the date of randomization to the date of first documentation of disease progression assessed by investigator per RECIST v1.1 or death, whichever occurred first

Objective Response Rate by Investigator, defined as the proportion of patients whose best overall response (BOR) was CR or PR assessed by investigator per RECIST v1.1 in the ITT Analysis Set

Overall Survival in ITT PD-L1 Score ≥ 10% Subgroup

Duration of Response by Investigator, defined as progression/death event free time counted from the first objective response date to the first documented radiological PD date/or death date, whichever occurred first

Health-Related Quality of Life (HRQoL): Questionnaires EORTC QLQ-C30, EORTC QLQ-OES18, and EQ-5D-5L

Exploratory efficacy endpoints

Disease control rate Assessed by the Investigator, defined as the proportion of patients whose BOR was CR, PR, non-CR/non-PD, or stable disease. DCR assessed by the investigators was analyzed similarly to ORR in the ITT Analysis Set

PFS, ORR and DOR Assessed by Blinded Independent Review Committee (BIRC)

Second Progression-Free Survival by the Investigator (PFS2), defined as the time from randomization to second/subsequent disease progression, or death from any cause, whichever occurred first

Sample size

The initial sample size calculation was based on the primary efficacy analysis of PFS and OS in the comparison between tislelizumab plus chemotherapy arm and placebo plus chemotherapy arm in the ITT Analysis Set. Hazard ratios in PFS and OS were assumed as 0.65 and 0.73, respectively, with median PFS of 5 months and OS of 9 months in the comparator arm. Approximately 319 PFS events were planned to have a power of 90% with an alpha of 0.005. A group sequential testing of OS would be performed. The interim analysis was planned after approximately 67% of the total planned death events had occurred (241). The final analysis would be performed when approximately 360 death events had been observed. This number of death events would provide 82% power to show a significant difference at an alpha level of 0.02. Assuming a 17-month enrollment period, a total of 480 patients would be enrolled in a 1:1 randomization.

The initial sample size calculation was amended in protocol amendment 3.0 on 25 May 2020. The study sample size was increased from 480 to 622. The targeted event numbers were increased, for both PFS (319 to 423) and death (360 to 467) to account for the delayed treatment effect and increased usage of subsequent immunotherapies that were observed in the newly published immuno-oncology trials in the second-line treatment of OSCC (Kojima et al 2019; Kato et al 2019; Huang et al 2019). In addition, a 5% annual dropout rate was added to the planning assumptions.

After the enrollment was completed with 649 randomized patients on 24 November 2020, the protocol was amended (Study 306 Protocol Amendment Version 4.0 [Appendix 16.1.1]) to remove BIRC-assessed PFS from the primary endpoints based on the results from immunooncology trials (Sun et al 2021). OS became the sole primary efficacy endpoint. The HR for OS was assumed to be 0.74 at the time of final analysis after an initial 1-month delayed treatment effect (eg, assuming HR = 1 in the first month), and the number of deaths required in the final analysis was increased from 467 to 488 to provide a power of 90% at one-sided alpha of 0.025 to detect superiority of tislelizumab plus chemotherapy over placebo plus chemotherapy in OS.

Randomisation

Randomization was stratified by the following 3 factors:

- Geographic region (Asia [excluding Japan] versus Japan versus Rest of World)
- Prior definitive therapy (yes versus no)
- Investigator choice of chemotherapy (ICC; platinum with fluoropyrimidine versus platinum with paclitaxel)

Blinding (masking)

Patients were randomized to receive tislelizumab or matched placebo in a double-blind fashion such that neither the investigator, nor the patient, nor medical or ancillary medical staff, nor the blinded sponsor's staff or its designees, knew which drug was being administered in addition to chemotherapy.

Statistical methods

Estimand

Estimand was defined in the SAP (Study 306 CSR Appendix 16.1.9).Analysis Sets

The Intent-to-Treat (ITT) analysis set was planned to include all randomized patients. Patients were planned to be analysed according to their randomized treatment arms. This was planned to be the primary analysis population for all efficacy analysis.

The Safety analysis set was planned to include all patients who received at least 1 dose of study drug; it was planned to be the primary population for the safety analyses.

The PK analysis set was planned to include all patients who receive at least 1 dose of tislelizumab per the protocol, for whom any post-dose PK data are available.

The ADA analysis set was planned to include all patients who have non-missing baseline ADA and at least 1 non-missing postbaseline ADA results.

Multiplicity

The primary endpoint of OS in the ITT analysis set was planned to be tested at a one-sided alpha of 0.025.

By using the graphic approach of Bretz et al (2009), if the null hypothesis for OS in the ITT analysis set is rejected, the corresponding alpha was planned to be shifted to the hypothesis tests of the secondary endpoints PFS by the investigator in the ITT analysis set, ORR by the investigator in the ITT analysis set, OS in the PD-L1 vCPS $\geq$ 10% subgroup, and HRQoL in the ITT analysis set, which will be tested sequentially. The inferential test was planned to be stopped at the first nonsignificant endpoint.

Primary Efficacy Analysis

The null hypothesis to be tested was:

H0: OS in Arm A $\leq$ OS in Arm B

against the alternative:

H1: OS in Arm A > OS in Arm B

The primary analysis of OS was planned to be carried out when approximately 488 OS events are reached (amendment 4.0, initially planned: 360, see sample size for changes).

In absence of confirmation of death, patients were planned to be censored either at the date that the patient was last known to be alive or the date of data cut-off, whichever comes earlier.

OS was planned to be compared between Arm A and Arm B in a one-sided, stratified log-rank test using the stratification factors of pooled geographic region (Asia [including Japan] vs Rest of World), prior definitive therapy (yes vs no), and the investigator choice of chemotherapy (ICC) option (platinum with fluoropyrimidine vs platinum with paclitaxel). A significance level of one-sided 0.025 was planned to be used in the OS testing.

The median OS and the cumulative probability of OS at every 3 months including 9-month OS and 18-month OS, if estimable, were planned to be calculated for each treatment arm and presented with 2-sided 95% CIs. Kaplan-Meier survival probabilities for each arm were planned to be plotted over time. OS rate at 9 and 18 months based on Kaplan-Meier estimate were planned to be compared between the 2 treatment arms for landmark analysis.

The treatment effect was planned to be estimated by fitting a Cox regression model to the OS times including treatment arm as a covariate and geographical region and prior definitive therapy as strata. From this model, the HR of OS was planned to be estimated and presented with a 2-sided 95% CI.

Interim analysis

1 interim analysis of OS was planned utilizing the O'Brien-Fleming boundary approximated by Hwang-Shih-DeCani spending function with the gamma parameter set at -4. The interim analysis was planned to be performed at the time when approximately 423 death events (87% of the target number of OS events) among the 2 treatment arms are observed. It was estimated that it would take approximately 33 months to observe 423 death events. An IDMC was planned to oversee the interim analysis of OS. The final analysis of OS was planned to take place after approximately 488 OS events have been observed. Stopping boundaries in p-value and Z score for primary analyses of OS are shown in Table 19. The boundaries were planned to be updated according to the actual numbers of events in the interim and final analyses, and the revised alpha level due to alpha shifting as described above, using the above pre-specified alpha spending function.

Table 19: Stopping boundaries of primary analysis of overall survival:

Endpoint	Analysis	Analysis Time (months)	# Events	p-value[1] (Z score) for Efficacy	Approximate HR Threshold
OS	Interim analysis	33	423	< 0.0145 (> 2.18)	0.809
	Final analysis	40	488	< 0.0216 (> 2.02)	0.833

Abbreviations: HR = hazard ratio; OS = overall survival
[1]one-sided

Secondary Efficacy Analysis

The following analyses were planned according to amendment 4.0 of the study protocol. Further details were added in the SAP.

Progression Free Survival (PFS)

One analysis of PFS in the ITT analysis set was planned to be carried out after superiority of OS in the ITT analysis set has been demonstrated (according to amendment 4.0, the plan was different previously). Similar statistical analysis methods used for the OS testing was planned to be applied to PFS analysis.

The p-value from one-sided, stratified log-rank test was to be presented using the stratification factors of pooled geographic region, prior definitive therapy, and ICC option.

PFS assessed by the investigator was planned to be estimated using the Kaplan-Meier method in the ITT analysis set. The PFS censoring rule was planned to follow United States (US) Food and Drug Administration (FDA) Guidance for Industry, Clinical Trial Endpoints for Approval of Cancer drugs and Biologics (FDA 2018). Data for patients without disease progression or death at the time of analysis were planned to be censored at the time of the last tumour assessment. Data for patients who are lost to follow-up prior to documented disease progression were planned to be censored at the last tumour assessment date when the patient is known to be progression-free. Data for patients who start to receive new anti-cancer therapy were planned to be censored at the last tumour assessment date prior to the introduction of a new therapy.

The median PFS and the cumulative probability of PFS at every 3 months, including 6-month PFS, if estimable, were planned to be calculated for each treatment arm and presented with 2-sided 95% CIs.

Kaplan-Meier estimates of PFS for each arm were planned to be plotted over time. The PFS rate at 6 months based on the Kaplan-Meier estimate were planned to be compared between the 2 treatment arms for landmark analysis.

HR estimated from a Cox regression model was planned to be presented with its 95% CI.

OS in the vCPS ≥ 10% subgroup

This analysis for the baseline vCPS ≥ 10% subgroup is similar to the OS analysis in the ITT analysis.

Other secondary efficacy endpoints

The null hypotheses of no difference in ORR per RECIST v1.1 by the investigator was planned to be tested using Cochran-Mantel-Haenszel (CMH) method, adjusting for stratification factors of pooled geographic region, prior definitive therapy, and ICC options in the ITT analysis set. Patients with no post-baseline response assessment (for any reason) were to be considered non-responders. The 2-sided 95% CIs for the odds ratio in ORR were to be calculated along with Clopper-Pearson 95% Cis of ORR for each treatment arm.

DOR assessed by the investigator was planned to be calculated similarly to PFS by the investigator in the responders. Median DOR per arm, if estimable, was planned to be presented.

HRQoL was planned to be analyzed and compared between the treatment arms via the post-baseline scores of QLQ-C30's Global Health Status/QoL (GHS), functional scales and symptom scores and symptoms single item scores, QLQ-OES18's index score and symptoms scales and single item scores, and EQ-5D-5L descriptive scale scores as well as the visual analogue scale (VAS) scores.

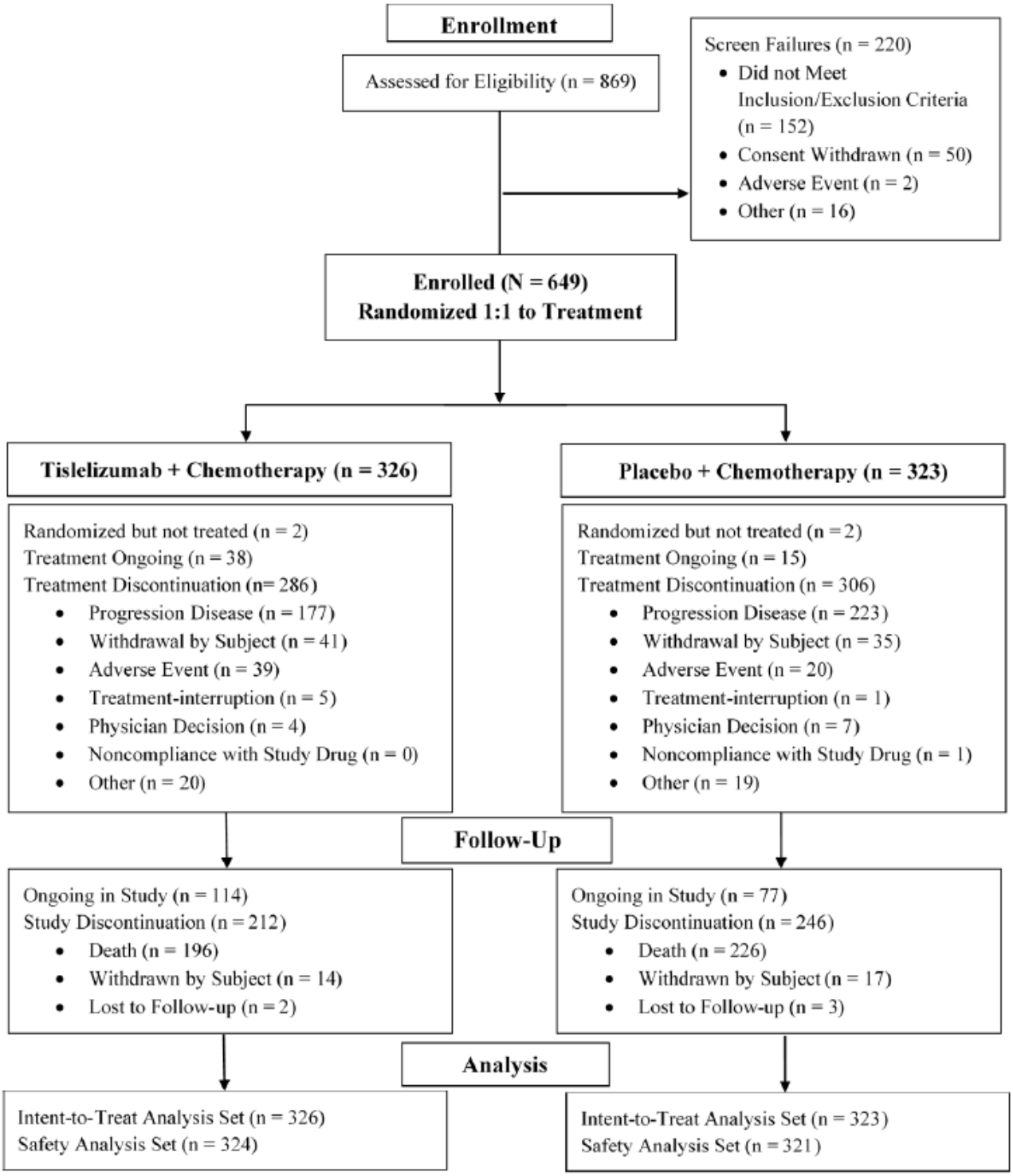
Observed values and changes from baseline were planned to be summarized using descriptive statistics. A mixed-effect model analysis for measuring clinically meaningful changes post-baseline was planned to be performed using the GHS, physical function and fatigue domains of QLQ-C30 and dysphagia, reflux, pain and eating of QLQ-OES18.

Time to clinically meaningful deterioration in the aforementioned scales was planned to be estimated using the Kaplan-Meier method and Cox regression model. Deterioration thresholds were planned to be defined based on the published 10-point EORTC threshold, and a secondary deterioration threshold based on data may be explored.

Results

Participant flow

Figure 22: Patient Disposition of BGB-A317-306 Study



Source: Figure 2 CSR Study 306

Between 11-Dec-2018 and 24-Nov-2020, a total of 649 patients were randomized 1:1 into the T+C Arm (326 patients) or the P+C Arm (323 patients).

Table 20: Patient Disposition and Reasons for Discontinuation - Study 306 (ITT Analysis Set)

	Tislelizumab + chemotherapy N = 326 n (%)	Placebo + chemotherapy N = 323 n (%)	Total N = 649 n (%)
Number of patients randomized	**326 (100.0)**	**323 (100.0)**	**649 (100.0)**
Patients randomized, but not treated	2 (0.6)	2 (0.6)	4 (0.6)
Primary reason for not treated [a]			
Adverse event	1 (0.3)	1 (0.3)	2 (0.3)
Withdrawal by patient	1 (0.3)	0	1 (0.2)
Other [b]	0	1 (0.3)	1 (0.2)
Number of patients treated	**324 (99.4)**	**321 (99.4)**	**645 (99.4)**
Number of patients discontinued from treatment	**286 (87.7)**	**306 (94.7)**	**592 (91.2)**
Primary reason for study drug discontinuation [c]			
Progressive disease	177 (54.3)	223 (69.0)	400 (61.6)
Radiographic progression	162 (49.7)	202 (62.5)	364 (56.1)
Clinical progression	15 (4.6)	21 (6.5)	36 (5.5)
Withdrawal by patient	41 (12.6)	35 (10.8)	76 (11.7)
Adverse event	39 (12.0)	20 (6.2)	59 (9.1)
Related to COVID-19	0 (0.0)	1 (0.3)	1 (0.2)
Treatment-interruption [d]	5 (1.5)	1 (0.3)	6 (0.9)
Physician decision	4 (1.2)	7 (2.2)	11 (1.7)
Non-compliance with study drug	0	1 (0.3)	1 (0.2)
Other	20 (6.1)	19 (5.9)	39 (6.0)
Death [e]	12 (3.7)	16.(5.0)	28 (4.3)
Number of patients remained on treatment	**38 (11.7)**	**15 (4.6)**	**53 (8.2)**
Number of patients discontinued from study	**212 (65.0)**	**246 (76.2)**	**458 (70.6)**
Primary reason for study discontinuation			
Death	196 (60.1)	226 (70.0)	422 (65.0)
Related to COVID-19	3 (0.9)	2 (0.6)	5 (0.8)
Withdrawal by subject	14 (4.3)	17 (5.3)	31 (4.8)
Lost to follow-up	2 (0.6)	3 (0.9)	5 (0.8)
Number of patients remained on study	**114 (35.0)**	**77 (23.8)**	**191 (29.4)**
Follow-up duration [f] (months)			
n	326	323	649
Mean (SD)	15.6 (8.63)	12.6 (8.68)	14.1 (8.78)
Median	16.3	9.8	12.8
Q1, Q3	8.6, 21.8	5.8, 19.0	6.8, 20.2
Min, max	0.1, 38.4	0.1, 37.3	0.1, 38.4
Minimum study follow-up time [g] (months)	15.2	15.4	15.2

Percentages were based on N.
[a] Patients randomized but not treated for any treatment component.
[b] Other: one patient was not treated due to IWRS TECHNICAL ISSUE.
[c] Reason for patients discontinued from treatment was the reason for treatment component whichever discontinued last. If tislelizumab and chemotherapy discontinued at the same date, the reason for discontinuation of tislelizumab is presented.
[d] Patients with confirmed CR, PR, or stable disease after 2 years of study treatment could stop the treatment.
[e] For patients who passively discontinued from study treatment due to death, the primary reason for study drug discontinuation is 'Other', and specified as 'death'.
[f] Follow-up duration was based on individual patient data and defined as the duration from the randomization date to the study discontinuation date (due to death, consent withdrawal, lost to follow-up etc.) or to the cutoff date if a patient is still ongoing.
[g] Minimum study follow-up time was defined as a difference between the date of cutoff and the date of last patient randomized.

Source: Table 3 SCE

Recruitment

This study was conducted at 162 study centers in 16 countries/regions globally. Patients were enrolled in Australia (5); Belgium (24); China (355); Czech Republic (2); France (36); Germany (6); Italy (11);

Japan (66); Korea (50); Poland (15); Romania (7); Russian Federation (27); Spain (23); Taiwan (15); the United Kingdom (5); and the United States (2).

The first patient enrolled in Study BGB-A317-306 was randomized on 11 December 2018; the last patient was randomized on 24 November 2020. Data cut-off is 28 February 2022. The study is ongoing.

As of the data cut-off date, the median patient's follow-up time was 16.3 months (range: 0.1 to 38.4 months) for the tislelizumab plus chemotherapy arm and 9.8 months (range: 0.1 to 37.3 months) for the placebo plus chemotherapy arm.

Conduct of the study

Protocol amendments

The original global protocol for this study was dated 13 February 2018. The global protocol was amended a total of 4 times before the data cut-off date for the clinical study report. All patients were enrolled after the implementation of Protocol Amendment Version 1.0. Key changes to the protocol are summarized below.

Amendment Version 1.0 (Global, Dated 19 September 2018)

- Added a third stratification factor of investigator choice of chemotherapy for randomization
- Revised inclusion criterion to only allow histologically confirmed diagnosis of OSCC but not either histologically or cytologically confirmed ones
- Revised inclusion criteria for patients with HBV and deleted HCV-associated criteria
- Added criteria to exclude patients who recurred after definitive surgery but still amenable to definitive radiation therapy and/or chemoradiotherapy
- Added enrollment guidelines and monitoring measures for Japanese patients prior to opening full enrollment in Japan
- Added treatment guidance that allowed platinum agent being cisplatin or oxaliplatin (except in China and Japan where oxaliplatin was not permitted) and being stopped after 6 cycles per site or investigator preference or per standard practice
- Added the dose delay or modification guidelines for oxaliplatin
- Added eye exam, visual acuity test, and optical coherence tomography (or equivalent diagnostic test) assessed by an appropriate specialist for increased risks of ophthalmologic AEs after receiving PD-1 inhibitors
- Changed imaging of pelvis to imaging of neck, ie made neck a mandatory site for tumour assessment
- Added potential imAEs of myositis/rhabdomyolysis and myocarditis, including laboratory monitoring for these imAEs and evaluation and management guidelines
- Added the follow-up tumour assessment for patients who continued treatment beyond initial disease progression should be performed no more than 6 to 8 weeks after the initial assessment of radiographic disease progression per Regulatory Authorities' requirement

Amendment Version 2.0 (Global, Dated 15 August 2019), 116 patients randomized

- Added additional guidance for patients to take a pulmonary function test at screening

- Added 24 months as the treatment duration and the options of whether to keep on treatment when patients complete the 24 months of treatment.
- Added new inclusion criterion "Have newly obtained or archival tissue sample available for biomarker assessment." to require mandatory collection of tumour tissue
- Clarified inclusion criteria to allow the enrollment of patients whose OSCC with adenocarcinoma differentiation < 5% of the viable tumour sample
- Revised exclusion criterion to exclude any patients who had chance to receive definitive surgery or was potentially curable with radiation therapy
- Updated the enrollment guidelines and monitoring measures for Japanese patients
- Revised the overdose definition for tislelizumab with detailed dose limit
- Added a table with the guidance on dose management including the recommended dose reduction level of each chemotherapy drug

Amendment Version 3.0 (Global, Dated 25 May 2020), 436 patients randomized

- Increased sample size from 480 to 622

  Rationale: *The study sample size was increased from 480 to 622 to: 1) allow the increase of targeted numbers of PFS events (319 to 423) and death events (360 to 467), which was to account for the delayed treatment effect and increased usage of subsequent immunotherapies that were observed in the newly published immuno-oncology trials in the second-line treatment of OSCC (Kojima et al 2019; Kato et al 2019; Huang et al 2019); and 2) take into consideration a 5% annual dropout rate.*
- Added cardiac enzyme monitoring per the latest protocol template update
- Specified that nonserious AEs that were considered unequivocally due to disease progression should not be recorded, however if there was any uncertainty, it should be recorded as an AE. All SAEs and deaths regardless of relatedness to disease progression should be recorded and reported per the latest protocol template update.

Amendment Version 4.0 (Global, Dated 30 April 2021), all patients (N=649) randomized

- Moved BIRC-assessed PFS from a dual primary objective/endpoint to an exploratory objective/endpoint

  Rationale:

  - The recently published results for anti-PD-1 therapies in the first-line treatment of oesophageal carcinomas indicate a significant and clinical meaningful improvement in OS as a gold standard for clinical benefit, and the magnitude of PFS improvement is 0.5 month, which is not considered sufficient to support PFS as a surrogate endpoint for OS.

  - The double-blinded nature of this study doesn't necessarily require a PFS assessed by BIRC, and PFS assessed by the investigator is already included as a secondary endpoint.
- Moved BIRC-assessed ORR and BIRC-assessed DOR from secondary endpoints to exploratory endpoints
- Added one secondary objective: OS in the PD-L1 score ≥ 10% subgroup
- Adjusted the timing for the interim analyses of OS

- Defined PFS assessed by the investigator, OS in the PD-L1 score ≥ 10% subgroup, ORR assessed by the investigator, and HRQoL for hierarchical sequential testing with alpha control

Protocol deviations

In the ITT Analysis Set, a total of 143 patients (22.0%), including 69 patients (21.2%) in the T+C Arm and 74 patients (22.9%) in the P+C Arm, had ≥ 1 important protocol deviation. The percentage of patients with ≥ 1 important protocol deviation was similar in the 2 treatment arms for most categories (below).

Table 21: Summary of Important Protocol Deviations (ITT Analysis Set)

Classification PD Term	Tislelizumab + Chemotherapy (N = 326) n (%)	Placebo + Chemotherapy (N = 323) n (%)	Total (N = 649) n (%)
Patients With at Least One Important Protocol Deviation	69 (21.2)	74 (22.9)	143 (22.0)
INFORMED CONSENT	40 (12.3)	46 (14.2)	86 (13.3)
Sites were not reconsenting patients at their next visit after the ICF was approved by IRB/EC and available for use (implemented at site).	36 (11.0)	36 (11.1)	72 (11.1)

Patient's signature and/or date was missing in the Informed Consent document, including initial, re-consent and optional consent.	6 (1.8)	8 (2.5)	14 (2.2)
Patient was consented with incorrect study ICF or not IRB approved ICF	1 (0.3)	6 (1.9)	7 (1.1)
ICF is signed after study procedure was done, except results or examinations considered standard of care.	0 (0.0)	3 (0.9)	3 (0.5)
AE SAE	18 (5.5)	13 (4.0)	31 (4.8)
Failed to report SAE or pregnancy to sponsor/study team within protocol defined timeline and/or per local requirement	15 (4.6)	12 (3.7)	27 (4.2)
Failed to report SAE/SUSAR/other safety reports to RA/LEC as major/important case per local requirement.	5 (1.5)	1 (0.3)	6 (0.9)
INC/EXCL CRITERIA	8 (2.5)	5 (1.5)	13 (2.0)
Not met Inclusion criteria 8. Have newly obtained or archival tissue sample available for biomarker assessment.	6 (1.8)	1 (0.3)	7 (1.1)
Met Exclusion Criteria 17. Any of the cardiovascular risk factors as defined in protocol.	1 (0.3)	0 (0.0)	1 (0.2)
Not met Inclusion criteria 3, Pathologically (histologically) confirmed diagnosis of ESCC	1 (0.3)	0 (0.0)	1 (0.2)
Met Exclusion Criteria 19. Has received any Chinese medicines used to control cancer and within 14 days of the first study drug administration	0 (0.0)	3 (0.9)	3 (0.5)
Met Exclusion Criteria 26. With uncontrolled diabetes or abnormal lab tests =< 14 days before randomization.	0 (0.0)	1 (0.3)	1 (0.2)

DISALLOWED MEDICATIONS	5 (1.5)	6 (1.9)	11 (1.7)
Use of the prohibited concomitant medications/procedures stated in protocol section 6.1.2.	5 (1.5)	6 (1.9)	11 (1.7)
PROCEDURES/TESTS	4 (1.2)	10 (3.1)	14 (2.2)
Tumor assessments not performed for two or more sequential planned assessments during specified visits as per protocol, for no specified reasons or reasons other than preserving patient safety.	4 (1.2)	10 (3.1)	14 (2.2)
IP ADMIN/STUDY TREAT	3 (0.9)	2 (0.6)	5 (0.8)
Patient received wrong IMP (Tislelizumab/Placebo) kit, not the drug assigned by IVRS.	2 (0.6)	2 (0.6)	4 (0.6)
Patient was dosed with study treatment rejected for use following temperature excursion.	1 (0.3)	0 (0.0)	1 (0.2)
WITHDRAWAL CRITERIA	3 (0.9)	2 (0.6)	5 (0.8)
Patient continued receiving treatment after withdrawal and/or discontinuation criteria were met.	3 (0.9)	2 (0.6)	5 (0.8)

Source: Table 9 CSR Study 306

Impact of COVID-19 pandemic on the conduct of the study

The study began in November 2018, which included the period during which the COVID-19 pandemic was occurring globally. During the study, the period impacted by the COVID-19 pandemic was from January 2020 in Asia, and from March 2020 in Australia, Europe, and North America through the data cut-off date. Since 01 January 2020, 189 patients were on treatment (148 patients in Asia and 41 patients in Europe/Australia/North America), and 94 patients discontinued study treatment and were in survival follow-up before the COVID-19 pandemic. From 01 January 2020 until enrollment was closed on 24 November 2020, additional 366 patients were enrolled and randomized at all clinical sites.

Due to travel and other restrictions, as well as disruptions in laboratory testing availability, some protocol-defined scheduled visits and assessments were not performed as originally planned or were not performed within the protocol-defined visit and time windows due to COVID-19. The change in study conduct which met the criteria of protocol deviation were reported to be protocol deviations related to COVID-19. Summaries of important protocol deviations related to COVID-19 in the ITT Analysis Set are provided below.

Table 22: Summary of Important Protocol Deviations Related to COVID-19 (ITT Analysis Set)

Classification PD Term	Tislelizumab + Chemotherapy (N = 326) n (%)	Placebo + Chemotherapy (N = 323) n (%)	Total (N = 649) n (%)
Patients With at Least One Important Protocol Deviation Related to COVID-19	2 (0.6)	4 (1.2)	6 (0.9)
INFORMED CONSENT	2 (0.6)	1 (0.3)	3 (0.5)
Patient's signature and/or date was missing in the Informed Consent document, including initial, re-consent and optional consent.	2 (0.6)	0 (0.0)	2 (0.3)
Sites were not reconsenting patients at their next visit after the ICF was approved by IRB/EC and available for use (implemented at site).	0 (0.0)	1 (0.3)	1 (0.2)
PROCEDURES/TESTS	0 (0.0)	3 (0.9)	3 (0.5)
Tumor assessments not performed for two or more sequential planned assessments during specified visits as per protocol, for no specified reasons or reasons other than preserving patient safety.	0 (0.0)	3 (0.9)	3 (0.5)

Source: Table 6 CSR Study 306

Baseline data

Table 23: Demographics and Baseline Disease Characteristics - Study 306 (ITT Analysis Set)

Parameter	Tislelizumab + chemotherapy N = 326	Placebo + chemotherapy N = 323	Total N = 649
Age (years)			
n	326	323	649
Median	64.0	65.0	64.0
Min, max	26, 84	40, 84	26, 84
Age group, n (%)			
<65 years	176 (54.0)	161 (49.8)	337 (51.9)
≥65 years	150 (46.0)	162 (50.2)	312 (48.1)
Sex, n (%)			
Female	44 (13.5)	42 (13.0)	86 (13.3)
Male	282 (86.5)	281 (87.0)	563 (86.7)
Region, n (%)			
Asia	243 (74.5)	243 (75.2)	486 (74.9)
RoW	83 (25.5)	80 (24.8)	163 (25.1)
Race, n (%)			
Asian	243 (74.5)	243 (75.2)	486 (74.9)
Chinese	182 (55.8)	188 (58.2)	370 (57.0)
Japanese	33 (10.1)	33 (10.2)	66 (10.2)
Korean	28 (8.6)	22 (6.8)	50 (7.7)
White	79 (24.2)	76 (23.5)	155 (23.9)
Not reported	3 (0.9)	2 (0.6)	5 (0.8)
American Indian or Alaska Native	0	1 (0.3)	1 (0.2)
Unknown	1 (0.3)	1 (0.3)	2 (0.3)

Parameter	Tislelizumab + chemotherapy N = 326	Placebo + chemotherapy N = 323	Total N = 649
ECOG PS, n (%)			
0	109 (33.4)	104 (32.2)	213 (32.8)
1	217 (66.6)	219 (67.8)	436 (67.2)
Tobacco consumption, n (%)			
Never	68 (20.9)	81 (25.1)	149 (23.0)
Former	200 (61.3)	181 (56.0)	381 (58.7)
Current	47 (14.4)	50 (15.5)	97 (14.9)
Missing	11 (3.4)	11 (3.4)	22 (3.4)
Alcohol consumption, n (%)			
Never	78 (23.9)	87 (26.9)	165 (25.4)
Former	188 (57.7)	177 (54.8)	365 (56.2)
Current	44 (13.5)	37 (11.5)	81 (12.5)
Missing	16 (4.9)	22 (6.8)	38 (5.9)
Time from initial diagnosis to study entry (months)			
n	326	323	649
Mean (SD)	13.50 (21.860)	13.68 (20.188)	13.59 (21.028)
Median	2.04	2.33	2.30
Min, max	0.1, 155.9	0.2, 124.2	0.1, 155.9
Primary site of esophageal cancer, n (%)			
Cervical	19 (5.8)	18 (5.6)	37 (5.7)
Upper thoracic	51 (15.6)	56 (17.3)	107 (16.5)
Middle thoracic	138 (42.3)	147 (45.5)	285 (43.9)
Lower thoracic	118 (36.2)	101 (31.3)	219 (33.7)
Missing	0	1 (0.3)	1 (0.2)
Histologic type, n (%)			
Squamous cell carcinoma	325 (99.7)	323 (100.0)	648 (99.8)
Other [a]	1 (0.3)	0	1 (0.2)
Disease status at study entry, n (%)			
Metastatic	279 (85.6)	282 (87.3)	561 (86.4)
Locally advanced	47 (14.4)	41 (12.7)	88 (13.6)
PD-L1 status, n (%)			
PD-L1 score ≥10%	116 (35.6)	107 (33.1)	223 (34.4)
PD-L1 score <10%	151 (46.3)	168 (52.0)	319 (49.2)
Unknown	59 (18.1)	48 (14.9)	107 (16.5)

[a] One patient was randomized based on a pathological report stating the tumour was squamous cell carcinoma. After randomization, the histologic type of the tumour was confirmed to be 'Neuroendocrine tumour' in a new pathological report according to the biopsy performed before randomization.

Source: Excerpt from Table 4 and Table 5 SCE

Reasons for unknown PD-L1 status included withdrawal of informed consent, unevaluable sample types, and testing failures. Thirteen patients were enrolled prior to PD-L1 testing became mandatory per protocol amendment 2.0.

The number of patients aged ≥75 years was limited (N=38, with 13 patients in the T+C arm and 25 patients in the P+C arm).

The majority of patients (86.4%) had metastatic disease at study entry, with 24.8% having 2 metastatic sites, and 17.4% having 3 or more metastatic sites. The most frequent location of metastases was the lymph nodes (52.7% of patients), followed by lung (38.8%), liver (22.3%), and bone (11.2%). Only 1 patient (0.3%) in the placebo + chemotherapy treatment group presented with brain metastases.

Demographics and baseline characteristics in relevant subgroups by PD-L1 expression status ≥5% and <5% are shown below.

Table 24: Summary of Demographics and Baseline Characteristics by Baseline PD-L1 Cut ⩾ 5% - ITT Analysis Set

	Baseline PD-L1 ≥ 5%			Baseline PD-L1 < 5%		
Parameter	**T+C (N = 172)**	**P+C (N = 186)**	**Total (N = 358)**	**T+C (N = 95)**	**P+C (N = 89)**	**Total (N = 184)**
Age (years)						
n	172	186	358	95	89	184
Median	62.0	64.0	63.0	64.0	66.0	65.0
Min, Max	41, 81	40, 84	40, 84	38, 84	41, 78	38, 84
Age Group, n (%)						
< 65 years	100 (58.1)	98 (52.7)	198 (55.3)	50 (52.6)	38 (42.7)	88 (47.8)
≥ 65 years	72 (41.9)	88 (47.3)	160 (44.7)	45 (47.4)	51 (57.3)	96 (52.2)
Sex, n (%)						
Female	31 (18.0)	23 (12.4)	54 (15.1)	6 (6.3)	10 (11.2)	16 (8.7)
Male	141 (82.0)	163 (87.6)	304 (84.9)	89 (93.7)	79 (88.8)	168 (91.3)
Region, n (%)						
Asia	133 (77.3)	147 (79.0)	280 (78.2)	70 (73.7)	66 (74.2)	136 (73.9)
Asia (excluding Japan)	116 (67.4)	131 (70.4)	247 (69.0)	58 (61.1)	54 (60.7)	112 (60.9)
Japan	17 (9.9)	16 (8.6)	33 (9.2)	12 (12.6)	12 (13.5)	24 (13.0)
Rest of World	39 (22.7)	39 (21.0)	78 (21.8)	25 (26.3)	23 (25.8)	48 (26.1)
Race, n (%)						
Asian	133 (77.3)	147 (79.0)	280 (78.2)	70 (73.7)	66 (74.2)	136 (73.9)
Chinese	100 (58.1)	120 (64.5)	220 (61.5)	52 (54.7)	50 (56.2)	102 (55.4)
Japanese	17 (9.9)	16 (8.6)	33 (9.2)	12 (12.6)	12 (13.5)	24 (13.0)
Korean	16 (9.3)	11 (5.9)	27 (7.5)	6 (6.3)	4 (4.5)	10 (5.4)
White	39 (22.7)	36 (19.4)	75 (20.9)	22 (23.2)	22 (24.7)	44 (23.9)
American Indian or Alaska Native	0 (0.0)	1 (0.5)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Not Reported	0 (0.0)	1 (0.5)	1 (0.3)	2 (2.1)	1 (1.1)	3 (1.6)
Unknown	0 (0.0)	1 (0.5)	1 (0.3)	1 (1.1)	0 (0.0)	1 (0.5)
ECOG Status, n (%)						
0	50 (29.1)	57 (30.6)	107 (29.9)	40 (42.1)	38 (42.7)	78 (42.4)
1	122 (70.9)	129 (69.4)	251 (70.1)	55 (57.9)	51 (57.3)	106 (57.6)
Tobacco Consumption, n (%)						
Never	35 (20.3)	45 (24.2)	80 (22.3)	18 (18.9)	21 (23.6)	39 (21.2)
Former	104 (60.5)	103 (55.4)	207 (57.8)	57 (60.0)	51 (57.3)	108 (58.7)
Current	27 (15.7)	29 (15.6)	56 (15.6)	15 (15.8)	16 (18.0)	31 (16.8)
Missing	6 (3.5)	9 (4.8)	15 (4.2)	5 (5.3)	1 (1.1)	6 (3.3)
Alcohol Consumption, n (%)						
Never	44 (25.6)	50 (26.9)	94 (26.3)	17 (17.9)	22 (24.7)	39 (21.2)
Former	99 (57.6)	104 (55.9)	203 (56.7)	59 (62.1)	47 (52.8)	106 (57.6)
Current	24 (14.0)	17 (9.1)	41 (11.5)	14 (14.7)	15 (16.9)	29 (15.8)
Missing	5 (2.9)	15 (8.1)	20 (5.6)	5 (5.3)	5 (5.6)	10 (5.4)
ICC option per IRT, n (%)						
Platinum with Fluoropyrimidine	69 (40.1)	78 (41.9)	147 (41.1)	47 (49.5)	46 (51.7)	93 (50.5)
Platinum with Paclitaxel	103 (59.9)	108 (58.1)	211 (58.9)	48 (50.5)	43 (48.3)	91 (49.5)
Time from initial diagnosis to study entry (months)						
n	172	186	358	95	89	184

Parameter	Baseline PD-L1 ≥ 5%			Baseline PD-L1 < 5%		
	T+C (N = 172)	P+C (N = 186)	Total (N = 358)	T+C (N = 95)	P+C (N = 89)	Total (N = 184)
Mean (SD)	13.98 (23.620)	10.96 (16.447)	12.41 (20.241)	11.91 (16.790)	17.95 (24.347)	14.83 (20.953)
Median	1.58	1.66	1.61	8.61	10.55	8.80
Min, max	0.3, 152.7	0.2, 83.1	0.2, 152.7	0.1, 100.8	0.2, 116.8	0.1, 116.8
Primary site of oesophageal cancer, n (%)						
Cervical	9 (5.2)	9 (4.8)	18 (5.0)	3 (3.2)	5 (5.6)	8 (4.3)
Upper thoracic	30 (17.4)	38 (20.4)	68 (19.0)	11 (11.6)	14 (15.7)	25 (13.6)
Middle thoracic	74 (43.0)	78 (41.9)	152 (42.5)	41 (43.2)	46 (51.7)	87 (47.3)
Lower thoracic	59 (34.3)	61 (32.8)	120 (33.5)	40 (42.1)	23 (25.8)	63 (34.2)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.5)
Histologic type, n (%)						
Squamous cell carcinoma	172 (100.0)	186 (100.0)	358 (100.0)	95 (100.0)	89 (100.0)	184 (100.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Disease status at study entry, n (%)						
Metastatic	148 (86.0)	166 (89.2)	314 (87.7)	86 (90.5)	74 (83.1)	160 (87.0)
Locally advanced	24 (14.0)	20 (10.8)	44 (12.3)	9 (9.5)	15 (16.9)	24 (13.0)

Source: Appendix A – Table 1.2.1, Responses to 1st RSI, and Table 2, Responses to 2nd RSI

Prior anticancer therapy

Table 25: Prior Anticancer Therapy – Study 306 (ITT Analysis Set)

Parameter	Tislelizumab + chemotherapy N = 326	Placebo + chemotherapy N = 323	Total N = 649
Patients with at least one prior definitive therapy, n (%)	**143 (43.9)**	**141 (43.7)**	**284 (43.8)**
Definitive radiotherapy with/without chemotherapy	40 (12.3)	40 (12.4)	80 (12.3)
Definitive surgery with/without adjuvant/neo-adjuvant treatment	107 (32.8)	107 (33.1)	214 (33.0)
Time from end of last prior anti-cancer therapy to study entry (months)			
n	149	147	296
Median	13.27	13.93	13.49
Min, Max	1.0, 104.2	0.6, 174.4	0.6, 174.4
Prior anti-cancer systemic therapy, n (%)	**98 (30.1)**	**111 (34.4)**	**209 (32.2)**
Platinum based prior anti-cancer systemic therapy			
Yes	97 (29.8)	107 (33.1)	204 (31.4)
No	1 (0.3)	4 (1.2)	5 (0.8)
Treatment setting of prior anti-cancer systemic therapies, n (%) [a]			
Neo-adjuvant setting	36 (11.0)	44 (13.6)	80 (12.3)
Adjuvant setting	32 (9.8)	47 (14.6)	79 (12.2)
In combination with definitive radiotherapy	39 (12.0)	35 (10.8)	74 (11.4)

Source: Excerpt from Table 6 SCE

Table 26: Prior Anticancer Therapy by Baseline PD-L1 score < 5% and ⩾ 5% (ITT Analysis Set)

	PD-L1 ≥ 5%			PD-L1 < 5%	
Parameter	**T + C N = 172**	**P + C N = 186**	**Total N = 358**	**T + C N = 95**	**P N**
Patients with at least one prior definitive therapy, n (%) [a]	**68 (39.5)**	**73 (39.2)**	**141 (39.4)**	**47 (49.5)**	**46**
Definitive radiotherapy with/without chemotherapy	18 (10.5)	19 (10.2)	37 (10.3)	13 (13.7)	16
Definitive surgery with/without adjuvant/neo-adjuvant treatment	53 (30.8)	57 (30.6)	110 (30.7)	34 (35.8)	32
Time from end of last prior anti-cancer therapy to study entry (months)					
n	70	77	147	50	47
Median	15.38	12.98	13.86	9.92	16
Min, Max	4.8, 91.7	0.6, 174.4	0.6, 174.4	1.0, 100.3	0.
Prior anti-cancer systemic therapy, n (%)	**46 (26.7)**	**59 (31.7)**	**105 (29.3)**	**33 (34.7)**	**34**
Platinum based prior anti-cancer systemic therapy					
Yes	45 (26.2)	56 (30.1)	101 (28.2)	33 (34.7)	34
No	1 (0.6)	3 (1.6)	4 (1.1)	0 (0.0)	0
Treatment setting of prior anti-cancer systemic therapies, n (%) [a]					
Neo-adjuvant setting	14 (8.1)	22 (11.8)	36 (10.1)	16 (16.8)	14
Adjuvant setting	17 (9.9)	28 (15.1)	45 (12.6)	9 (9.5)	13
In combination with definitive radiotherapy	19 (11.0)	19 (10.2)	38 (10.6)	12 (12.6)	11

Source: Table 3, Response to 2nd RSI

A total of 209 patients (32.2%; 98 patients [30.1%] in the T+C Arm and 111 patients [34.4%] in the P+C Arm) received prior anticancer systemic therapy in the setting of adjuvant, neoadjuvant, or in combination with radiotherapy. Among them, 97 patients (29.8%) in the T+C Arm and 107 patients (33.1%) in the P+C Arm received platinum-based prior systemic therapy. In addition to platinum, taxanes (18.4% versus 18.6%, respectively) and pyrimidine analogues (15.6% versus 18.0%, respectively) were the most commonly used prior anticancer systemic therapies.

Several imbalances between the Asian and the Rest of World (RoW) subpopulations and within treatment groups of the respective subpopulation were identified. An overview of relevant imbalances is presented in Table 27 below.

Table 27: Overview of imbalances in baseline characteristics and prior anticancer therapy by region and treatment (ITT analysis set)

	RoW			Asia		
	T+C (N = 83)	**P+C (N = 80)**	**Total (N = 108)**	**T+C (N = 243)**	**P+C (N = 243)**	**Total (N = 404)**
Gender, n (%)						
Male	70 (84.3)	59 (73.8)	129 (79.1)	212 (87.2)	222 (91.4)	434 (89.3)
ECOG PS, n (%)						
1	52 (62.7)	50 (62.5)	102 (62.6)	165 (67.9)	169 (69.5)	334 (68.7)
Disease status, n(%)						
Metastatic	67 (80.7)	60 (75.0)	127 (77.9)	212 (87.2)	222 (91.4)	434 (89.3)
PD-L1 Status, n (%)						
TAP ≥ 10%	34 (41.0)	18 (22.5)	52 (31.9)	89 (36.6)	95 (39.1)	184 (37.9)
TAP < 10%	38 (45.8)	49 (61.3)	87 (53.4)	127 (52.3)	127 (52.3)	254 (52.3)
Missing	11 (13.3)	13 (16.3)	24 (14.7)	27 (11.1)	21 (8.6)	48 (9.9)
Patients with at Least One Prior Definitive Therapy, n (%)	32 (38.6)	27 (33.8)	59 (36.2)	111 (45.7)	114 (46.9)	225 (46.3)

	RoW			Asia		
	T+C (N = 83)	P+C (N = 80)	Total (N = 108)	T+C (N = 243)	P+C (N = 243)	Total (N = 404)
Definitive Radiotherapy with/without Chemotherapy	18 (21.7)	15 (18.8)	33 (20.2)	22 (9.1)	25 (10.3)	47 (9.7)
Definitive Surgery with/without Adjuvant/Neo-adjuvant Treatment	15 (18.1)	14 (17.5)	29 (17.8)	92 (37.9)	93 (38.3)	185 (38.1)

Source: Excerpts from Tables 14.1.2.1a, 14.1.3.1a and 14.1.5.1a

Numbers analysed

All 649 patients who were randomized to the study were included in the ITT Analysis Set (see Table 28)

Table 28: Analysis Sets (ITT Analysis Set)

Analysis Set	Tislelizumab + Chemotherapy (N = 326) n (%)	Placebo + Chemotherapy (N = 323) n (%)	Total (N = 649) n (%)
Intent-to-Treat (ITT) Analysis Set [a]	326 (100.0)	323 (100.0)	649 (100.0)
Safety Analysis Set [b]	324 (99.4)	321 (99.4)	645 (99.4)
PK Analysis Set [c]	316 (96.9)	Not Collected	316 (48.7)
ADA Analysis Set [d]	300 (92.0)	Not Collected	300 (46.2)

a ITT Analysis Set includes all randomized patients. The ITT Analysis Set is grouped based on randomized treatment.
b Safety Analysis Set includes all patients who received at least 1 dose of study drug. The Safety Set is based on actual treatment received.
c PK Analysis Set includes all patients who received at least 1 dose of tislelizumab per the protocol, for whom any post-dose PK data are available.
d ADA Analysis Set includes all patients who received at least 1 dose of tislelizumab, have non-missing baseline ADA and at least one post-baseline ADA result.

Source: Table 10 CSR Study 306

Outcomes and estimation

The efficacy results are based on the planned interim analysis conducted with a cut-off date of 28 February 2022, at which time a total of 422 death events (196 events in the T+C Arm, and 226 events in the P+C Arm) had occurred.

Outcomes overall ITT population

- **Primary efficacy endpoint**

OS in the ITT Analysis Set

Table 29: OS - Study 306 (ITT Analysis Set)

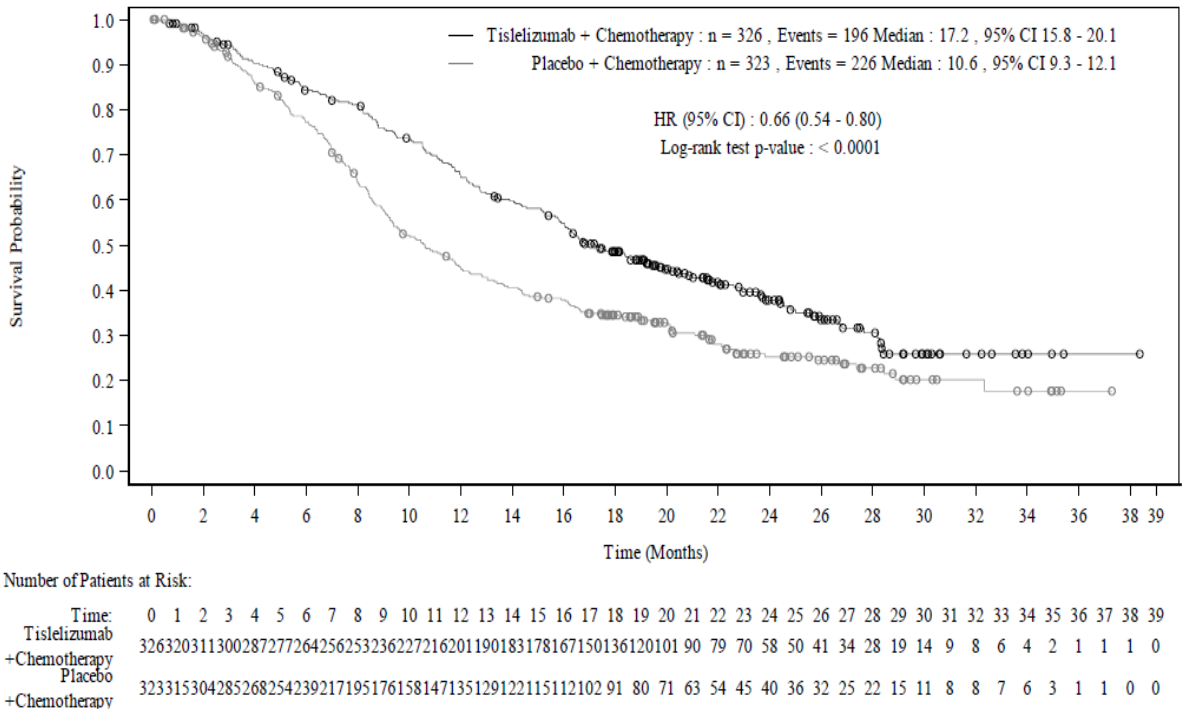
	Tislelizumab + chemotherapy N = 326	Placebo + chemotherapy N = 323
Number of patients		
Death, n (%)	196 (60.1)	226 (70.0)
Censored, n (%)	130 (39.9)	97 (30.0)
Ongoing without events	114 (35.0)	77 (23.8)
Lost to follow-up	2 (0.6)	3 (0.9)
Withdrawal by patient	14 (4.3)	17 (5.3)
One-sided stratified log-rank test p-value [a]	<0.0001	
Stratified HR (95% CI) [b]	0.66 (0.54, 0.80)	
Unstratified HR (95% CI) [c]	0.68 (0.56, 0.82)	

	Tislelizumab + chemotherapy N = 326	Placebo + chemotherapy N = 323
OS, months (95% CI)		
Median	17.2 (15.8, 20.1)	10.6 (9.3, 12.1)
OS rate, % (95% CI)		
6 months	84.3 (79.8, 87.9)	77.3 (72.2, 81.5)
12 months	65.0 (59.4, 70.0)	44.9 (39.2, 50.3)
24 months	37.8 (31.9, 43.6)	25.3 (20.1, 30.7)
Follow-up time, months (95% CI)		
Median	23.9 (22.0, 25.5)	23.5 (22.3, 26.1)

Percentages were based on N.
In absence of death on or before data cutoff, patients were censored either at the date that the patient was last known to be alive or the date of data cutoff, whichever came earlier.
Medians and other quartiles were estimated by K-M method with 95% CIs estimated using the method of Brookmeyer and Crowley. Overall survival rates (cumulative probability of OS) were estimated by K-M method with 95% Cis estimated using Greenwood's formula. Median follow-up time was estimated by the reverse K-M method.
[a] Primary OS analysis: One-sided p-value was estimated from log rank test stratified by pooled geographic region (Asia vs. RoW) per IRT, prior definitive therapy (yes vs. no) per IRT and ICC option (platinum + fluoropyrimidine vs. platinum + paclitaxel) per IRT.
[b] Primary OS estimand summary measure: Hazard ratio (T+C vs. P+C) was based on Cox regression model including treatment as covariate, and pooled geographic region (Asia vs. RoW) per IRT, prior definitive therapy (yes vs. no) per IRT and ICC option (platinum + fluoropyrimidine vs. platinum + paclitaxel) per IRT as strata.
[c] Unstratified OS sensitivity analysis: HR (T+C vs. P+C) was based on unstratified Cox regression model only including treatment arm as a covariate
Data cutoff: 28-Feb-2022. Data extraction: 06-Apr-2022.

Source: Excerpt from Table 7 SCE

Figure 23: K-M Plot of OS - Study 306 (ITT Analysis Set)



Number of Patients at Risk:

Time:	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39
Tislelizumab +Chemotherapy	326	320	311	300	287	277	264	256	253	236	227	216	201	190	183	178	167	150	136	120	101	90	79	70	58	50	41	34	28	19	14	9	8	6	4	2	1	1	1	0
Placebo +Chemotherapy	323	315	304	285	268	254	239	217	195	176	158	147	135	129	122	115	112	102	91	80	71	63	54	45	40	36	32	25	22	15	11	8	8	7	6	3	1	1	0	0

One sided p value was estimated from log rank test stratified by pooled geographic region (Asia [including Japan] vs. RoW) per IRT, prior definitive therapy (yes vs. no) per IRT, and ICC option (platinum + fluoropyrimidine vs. platinum + paclitaxel) per IRT.
HR (T+C vs. P+C) was based on Cox regression model including treatment as covariate, and pooled geographic region (Asia [including Japan] vs. RoW) per IRT, prior definitive therapy (yes vs. no) per IRT, and ICC option (platinum + fluoropyrimidine vs. platinum + paclitaxel) per IRT as strata.
Source: Figure 1 SCE

Early censoring of survival data (i.e. within 3 months after randomization) occurred for 8 patients (2.5%) in the T+C Arm and 11 patients (3.4%) in the P+C Arm. The reason for censoring in all these patients was "Withdrawal by Subject".

Supportive analyses for OS

The robustness of the OS results from the primary analysis was assessed using pre-specified sensitivity, supportive, and supplementary analyses, as well as post-hoc analyses as shown in Table 30. These analyses consistently showed superiority of the T+C Arm vs. the P+C Arm in terms of OS, with treatment effect estimates similar to the results of the primary analysis. In particular, the post-hoc analyses conducted to assess the effect of the random imbalance in baseline PD-L1 status by adding PD-L1 (3 subgroups: PD-L1 score ≥10%, <10%, and unknown) as an additional stratification factor or as an additional covariate to the stratified Cox regression model, indicate that the imbalance in baseline PD-L1 expression status had little impact on the treatment effect estimate in the primary analysis of OS.

Furthermore, the supportive and supplementary analyses assessing the proportional hazard assumption did not provide evidence of violation of the proportional hazard assumption.

Table 30: Overview of Prespecified (Sensitivity, Supportive, Supplementary) and Post-hoc Analyses of OS – Study 306 (ITT Analysis Set)

Analysis	HR (95% CI) or result
Primary analysis of OS	0.66 (0.54, 0.80)[b]
Prespecified analyses	
Supportive analyses	
Proportional hazard assumption assessment, with a time-dependent interaction of treatment by log(time)	2-sided stratified p-value of 0.1668 for treatment by log(time) interaction[c]
Supplementary analyses	
Proportional hazard assumption	
Max-combo test	0.63 (0.50, 0.79) [d]
RMST analysis	avg 4.08 mo improvement (2.01, 6.15)[e]
Multivariate adjusted analysis	0.67 (0.55, 0.81)[b]
Post-hoc analyses	
Sensitivity analysis with unpooled region as stratification factor	0.66 (0.54, 0.80)[b]
Sensitivity analysis with baseline PD-L1 as additional stratification factor	0.68 (0.56, 0.83)[b]
Analysis excluding patients with unknown baseline PD-L1 status	0.70 (0.57, 0.86)[b]
Analysis with treatment and baseline PD-L1 as covariates	0.67 (0.55, 0.81)[b]

[a] Unstratified HR (T+C vs. P+C) was based on unstratified Cox regression model
[b] Stratified HR (T+C vs. P+C) was based on stratified Cox regression model
[c] Analysis was based on Cox regression model including treatment and an interaction term between treatment and log-transformed follow-up time as covariates, and pooled geographic region (Asia vs. ROW) per IRT, prior definitive therapy (Yes vs. No) per IRT and ICC option (platinum with fluoropyrimidine vs. platinum with paclitaxel) per IRT as strata. A two-sided p-value of less than 0.1 for the interaction term may indicate potential violation of proportional hazard assumption.
[d] 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 with weight of FH (1,0) was selected while multiplicity was considered using joint asymptotic distribution.
[e] Restricted mean survival time test with the minimum of the largest observed time in each of the two treatment arms.

Source: Excerpt from Table 8 SCE

Updated OS results in the ITT population

Supportive, updated OS data were provided based on a cut-off of 28 April 2023, providing 14 more months of follow-up compared to the primary analysis.

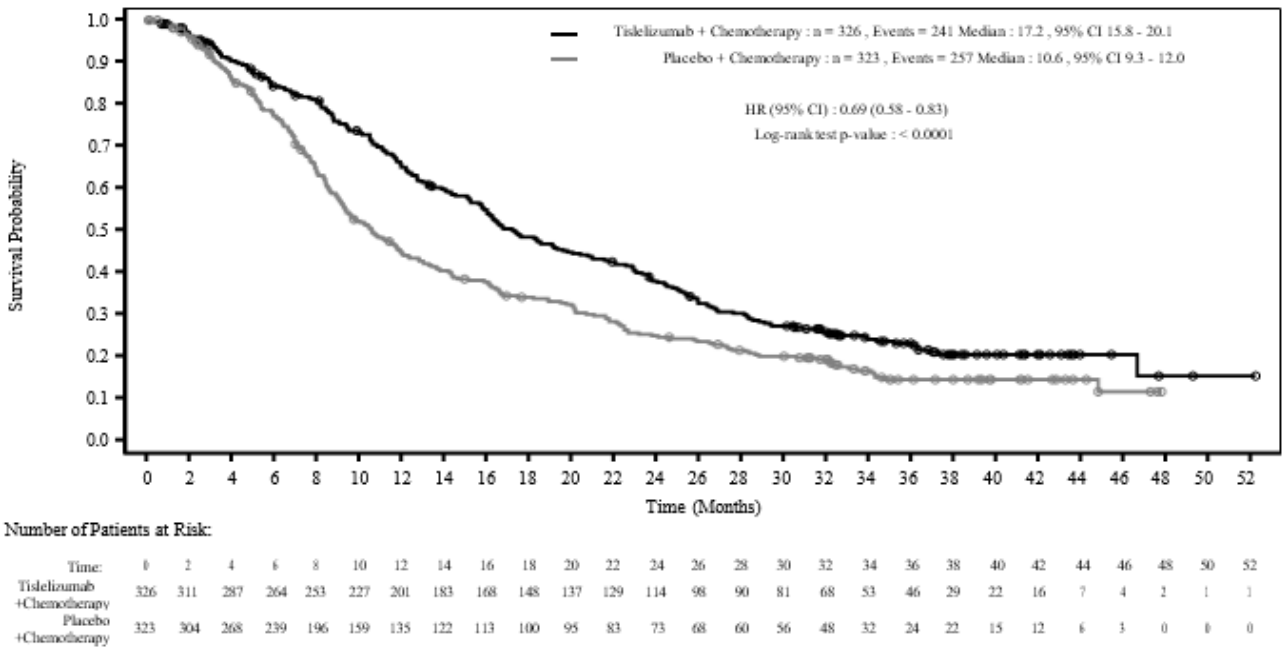
Table 31: Updated OS (DCO: 28 April 2023) - Study 306 (ITT Analysis Set)

	Tislelizumab + chemotherapy N = 326	Placebo + chemotherapy N = 323
Number of patients		
Death, n (%)	241 (73.9)	257 (79.6)
Censored, n (%)	85 (26.1)	66 (20.4)
Ongoing without events	63 (19.3)	40 (12.4)
Lost to follow-up	5 (1.5)	5 (1.5)
Withdrawal by patient	17 (5.2)	21 (6.5)
One-sided stratified log-rank test p-value [a]	<0.0001	
Stratified HR (95% CI) [b]	0.69 (0.58, 0.83)	
Unstratified HR (95% CI) [c]	0.71 (0.59, 0.84)	
OS, months (95% CI)		
Median	17.2 (15.8, 20.1)	10.6 (9.3, 12.0)
OS rate, % (95% CI)		
6 months	84.3 (79.8, 87.9)	77.3 (72.2, 81.5)
12 months	65.0 (59.4, 70.0)	44.7 (39.0, 50.1)
24 months	37.9 (32.5, 43.2)	24.8 (20.1, 29.8)
Follow-up time, months (95% CI)		
Median	37.8 (36.0, 38.4)	36.2 (33.9, 39.8)

Percentages were based on N.
In absence of death on or before data cutoff, patients were censored either at the date that the patient was last known to be alive or the date of data cutoff, whichever came earlier.
Medians and other quartiles were estimated by K-M method with 95% CIs estimated using the method of Brookmeyer and Crowley. Overall survival rates (cumulative probability of OS) were estimated by K-M method with 95% Cis estimated using Greenwood's formula. Median follow-up time was estimated by the reverse K-M method.
[a] Primary OS analysis: One-sided p-value was estimated from log rank test stratified by pooled geographic region (Asia vs. RoW) per IRT, prior definitive therapy (yes vs. no) per IRT and ICC option (platinum + fluoropyrimidine vs. platinum + paclitaxel) per IRT.
[b] Primary OS estimand summary measure: Hazard ratio (T+C vs. P+C) was based on Cox regression model including treatment as covariate, and pooled geographic region (Asia vs. RoW) per IRT, prior definitive therapy (yes vs. no) per IRT and ICC option (platinum + fluoropyrimidine vs. platinum + paclitaxel) per IRT as strata.
[c] Unstratified OS sensitivity analysis: HR (T+C vs. P+C) was based on unstratified Cox regression model only including treatment arm as a covariate
Data cutoff: 28APR2023. Data extraction: 09JUN2023.

Source: Table 3-1 SCE Addendum

Figure 24: K-M Plot of updated OS (DCO: 28 April 2023) - Study 306 (ITT Analysis Set)



Data cutoff: 28APR2023. Data extraction: 09JUN2023.

Source: Figure 3-1 SCE Addendum

- **Secondary Efficacy Analysis**

According to the predefined hierarchy testing order of secondary endpoints after rejecting the null hypothesis for primary endpoint, treatment with tislelizumab plus chemotherapy also resulted in a statistically significant improvement over placebo plus chemotherapy in the secondary endpoints of investigator-assessed PFS, investigator-assessed ORR, and OS in the PD-L1 score ≥10% subgroup. The difference was not statistically significant for HRQoL (the 3 most prevalent OSCC symptoms of dysphagia, eating, and reflux) which were tested last. The results for the secondary endpoint DOR, which was not part of the hierarchical testing strategy, are also presented below.

PFS assessed by investigator

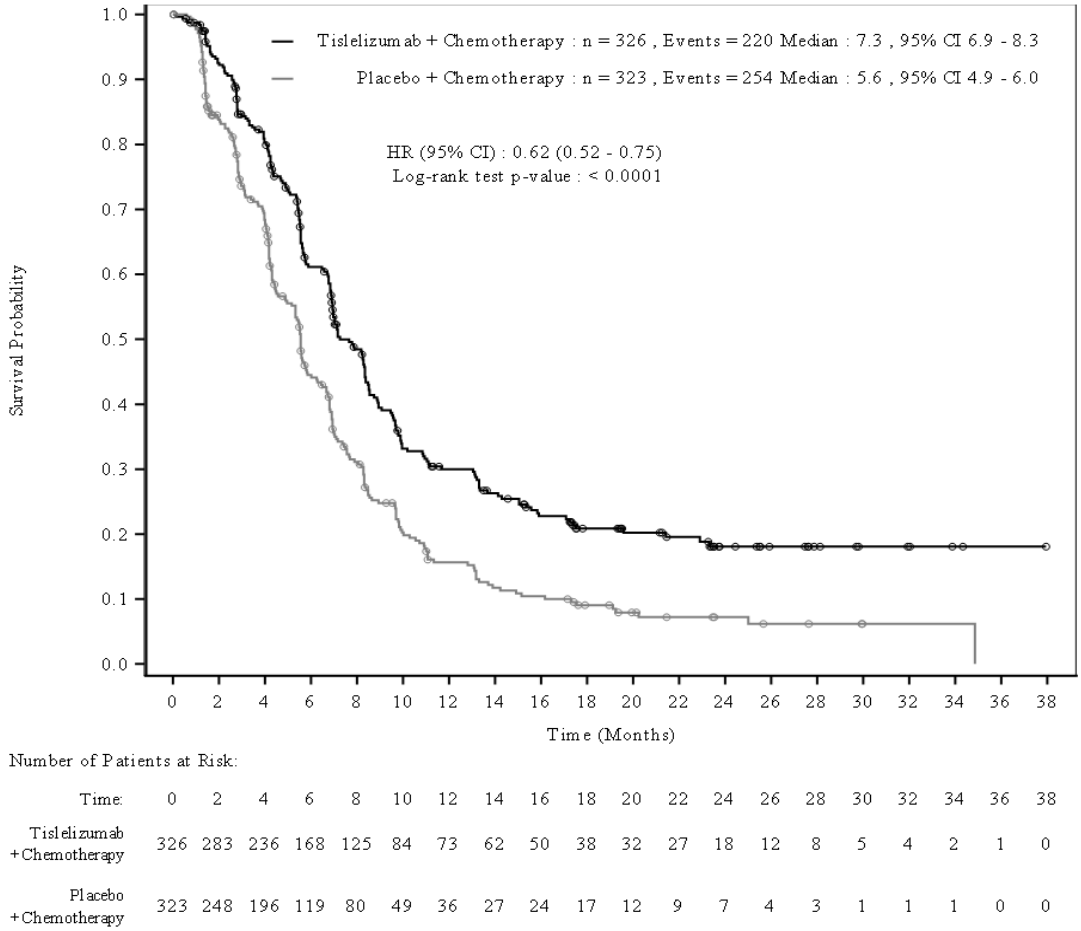
Table 32: PFS by Investigator - Study 306 (ITT Analysis Set)

	Tislelizumab + chemotherapy N = 326	**Placebo + chemotherapy N = 323**
Progression free survival		
Events, n (%)	220 (67.5)	254 (78.6)
PD	185 (56.7)	217 (67.2)
Death	35 (10.7)	37 (11.5)
Censored, n (%)	106 (32.5)	69 (21.4)
No post-Baseline and discontinued from study	8 (2.5)	9 (2.8)
New anticancer therapy	21 (6.4)	24 (7.4)
PD/death after >1 missed assessment	12 (3.7)	11 (3.4)
No PD/death [a]	65 (19.9)	25 (7.7)
Ongoing without events	52 (16.0)	19 (5.9)
Withdrawal by patient	11 (3.4)	6 (1.9)
Lost to follow-up	2 (0.6)	0 (0.0)
One-sided stratified log-rank test p-value [b]	<0.0001	
Stratified HR (95% CI)[c]	0.62 (0.52, 0.75)	
Unstratified HR (95% CI)[d]	0.61 (0.51, 0.74)	
Progression free survival, months (95% CI)		
Median	7.3 (6.9, 8.3)	5.6 (4.9, 6.0)
Progression free survival rate, % (95% CI)		
6 months	61.1 (55.3, 66.5)	44.5 (38.6, 50.2)
12 months	30.0 (24.6, 35.6)	15.7 (11.5, 20.4)

Percentages were based on N.
Medians and other quartiles were estimated by K-M method with 95% CIs estimated using the method of Brookmeyer and Crowley. Progression free rates (cumulative probabilities of PFS) were estimated by K-M method with 95% CIs estimated using the Greenwood's formula.
[a] Patients ongoing without PD and with no Post-baseline assessments are counted in 'No PD/Death Ongoing Without Events' category.
[b] One-sided p-value was estimated from log rank test stratified by pooled geographic region (Asia vs. RoW) per IRT, prior definitive therapy (yes vs. no) per IRT and ICC option (platinum + fluoropyrimidine vs. platinum + paclitaxel) per IRT.
[c] Stratified HR (T+C vs. P+C) was based on Cox-regression model including treatment arm as a covariate and stratified by pooled geographic region (Asia vs. RoW) per IRT, prior definitive therapy (yes vs. no) per IRT and ICC option (platinum + fluoropyrimidine vs. platinum + paclitaxel) per IRT.
[d] Unstratified HR (T+C vs. P+C) was based on unstratified Cox-regression model including treatment arm as a covariate.
Data cutoff: 28-Feb-2022. Data extraction: 06-Apr-2022.

Source: Excerpt from Table 9 SCE

Figure 25: K-M Plot of PFS by Investigator - Study 306 (ITT Analysis Set)



One-sided p-value was estimated from log rank test stratified by pooled geographic region (Asia vs. RoW) per IRT, prior definitive therapy (yes vs. no) per IRT and ICC option (platinum + fluoropyrimidine vs. platinum + paclitaxel) per IRT.
HR (T+C vs. P+C) was based on Cox regression model including treatment as covariate, and pooled geographic region (Asia [including Japan] vs. RoW) per IRT, prior definitive therapy (yes vs. no) per IRT and ICC option (platinum + fluoropyrimidine vs. platinum + paclitaxel) per IRT as strata.
Source: Figure 2 SCE

Supportive analyses for PFS

Two pre-specified supportive analyses employing different censoring rules

- Use actual date of progression or death, irrespective of use of new anticancer therapy
- Use actual date of progression or death, irrespective of missing tumour assessment

were conducted for PFS. The results were consistent with the main analysis (a) HR = 0.63 [95% CI: 0.53, 0.75] and b) HR = 0.62 [95% CI: 0.52, 0.74].

ORR Based on Investigator Assessment

Table 33: ORR by Investigator - Study 306 (ITT Analysis Set)

	Tislelizumab + chemotherapy N = 326	**Placebo + chemotherapy N = 323**
ORR unconfirmed, n	**207**	**137**
ORR, % (95% CI) [a]	63.5 (58.0, 68.7)	42.4 (37.0, 48.0)
Odds ratio for ORR (95% CI) [b]	2.38 (1.73, 3.27)	

	Tislelizumab + chemotherapy N = 326	Placebo + chemotherapy N = 323
CMH test p-value [c]	<0.0001	
ORR difference, % (95% CI) [b]	21.2 (13.7, 28.6)	
BOR unconfirmed, n (%)		
CR	15 (4.6)	8 (2.5)
PR	192 (58.9)	129 (39.9)
Stable disease [d]	83 (25.5)	122 (37.8)
PD	13 (4.0)	42 (13.0)
Could not be determined [e]	23 (7.1)	22 (6.8)
ORR confirmed, n	**184**	**117**
ORR, % (95% CI) [a]	56.4 (50.9, 61.9)	36.2 (31.0, 41.7)
Odds ratio for ORR (95% CI) [b]	2.31 (1.68, 3.17)	
CMH test p-value [c]	<0.0001	
ORR difference, % (95% CI) [b]	20.3 (12.8, 27.8)	
BOR confirmed, n (%)		
CR	13 (4.0)	8 (2.5)
PR	171 (52.5)	109 (33.7)
Stable disease [d]	104 (31.9)	142 (44.0)
PD	13 (4.0)	42 (13.0)
Could not be determined [e]	25 (7.6)	22 (6.8)

Percentages were based on N. ORR is unconfirmed and defined as proportion of number of patients with a PR or CR per RECIST v1.1 (i.e., ORR = CR+PR).
[a] Two-sided 95% CI was calculated using Clopper-Pearson method.
[b] Objective response rate, ORR differences and odds ratios between arms were calculated using the Cochran-Mantel-Haenszel method, stratified by pooled geographic region (Asia vs. RoW) per IRT, prior definitive therapy (yes vs. no) per IRT and ICC option (platinum + fluoropyrimidine vs. platinum + paclitaxel) per IRT.
[c] Two-sided CMH test based on pre-defined strata.
[d] Stable disease includes stable disease and non-CR/non-PD.
[e] Best overall response of could not be determined included patients with no post-baseline response assessment (NA) or assessment as NE per RECIST v1.1.
Data cutoff: 28-Feb-2022. Data extraction: 06-Apr-2022.

Source: Table 11 SCE + Table 14.2.4.5 CSR Study 306

DOR by Investigator Assessment

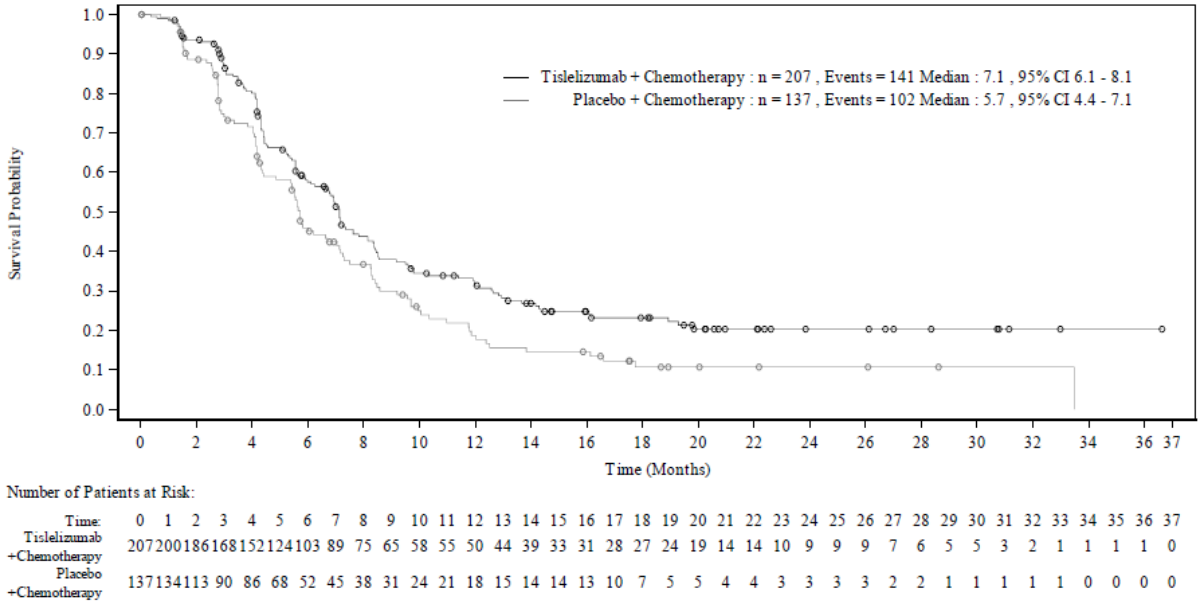
Table 34: DOR by Investigator - Study 306 (ITT Analysis Set)

	Tislelizumab + chemotherapy N = 326	Placebo + chemotherapy N = 323
Unconfirmed DOR		
Number of responders	207	137
DOR, n (%)		
Events	141 (68.1)	102 (74.5)
PD	128 (61.8)	97 (70.8)
Death	13 (6.3)	5 (3.6)
Censored	66 (31.9)	35 (25.5)
DOR, months (95% CI)		
Median	7.1 (6.1, 8.1)	5.7 (4.4, 7.1)
Confirmed DOR		
Number of Responders	184	117
DOR, n (%)		
Events	123 (66.8)	86 (73.5)
PD	114 (62.0)	81 (69.2)
Death	9 (4.9)	5 (4.3)
Censored	61 (33.2)	31 (26.5)
DOR, months (95% CI)		
Median	7.4 (6.9, 8.5)	6.6 (5.6, 8.3)

Percentages were based on the number of responders (patients with CR/PR) in relevant treatment arm.
Duration of response analysis included patients with unconfirmed objective response.
Medians and other quartiles were estimated by K-M method with 95% CIs estimated using the method of Brookmeyer and Crowley. Duration of response rates (cumulative probabilities of DOR) were estimated by K-M method with 95% CIs estimated using the Greenwood's formula.
Data cutoff: 28-Feb-2022. Data extraction: 06-Apr-2022.

Source: Excerpts from Table 12 SCE + Table 14.2.5.6 CSR Study 306

Figure 26: K-M Plot of DOR (unconfirmed) by Investigator - Study 306 (ITT Analysis Set)



Source: Figure 3 SCE

Health-Related Quality of Life

Outcomes of HRQoL were assessed using the European Organization for Research on Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30), the EORTC Quality of Life Questionnaire-Oesophageal Cancer Module (EORTC QLQ-OES18), and the European Quality of Life 5-Dimension 5-Level Questionnaire (EQ-5D-5L) to further characterize treatment benefits of tislelizumab beyond radiographic measures.

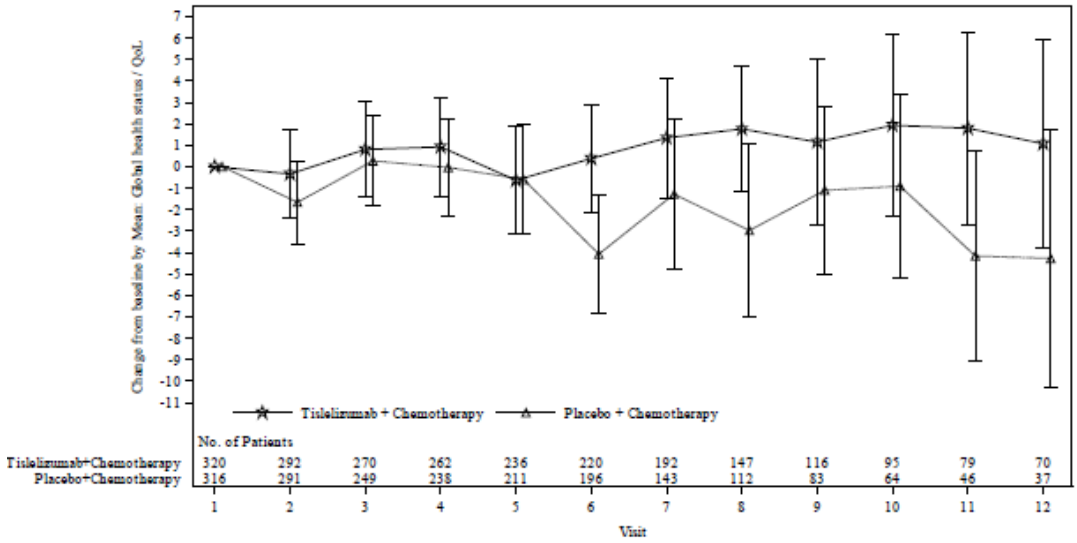
The adjusted completion rates (ie, the number of patients who completed all questionnaires divided by the total number of patients in relevant treatment arm at the predefined visits) from baseline through Cycle 6 and Cycle 8 were > 90% for each questionnaire and were similar in both treatment arms.

Overall, there were no significant differences between treatment arms in the quality of life (HRQoL) reported by the patients.

Least square mean change from baseline to Cycle 6 and Cycle 8

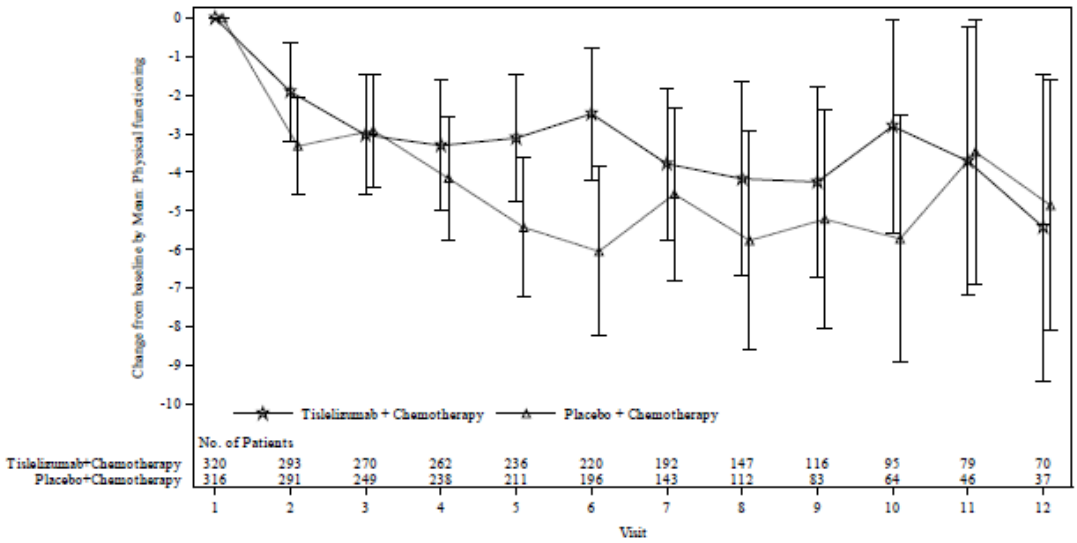
Changes of scores from baseline to Cycle 6 indicated a decrease in global health status (GHS) at Cycle 6 in the P+C arm, which was less apparent in the T+C arm. Physical function decreased for both arms in both cycles, with patients in the T+C Arm having less decrease than those in the P+C Arm at Cycle 6 but returning to a similar level of decrease between arms at Cycle 8. The VAS score indicated lower decrease in health status in the T+C Arm compared with the P+C Arm at Cycles 6 and 8 (Figure 29).

Figure 27: EORTC QLQ-C30 Scores by Visit: Global Health Status/QoL



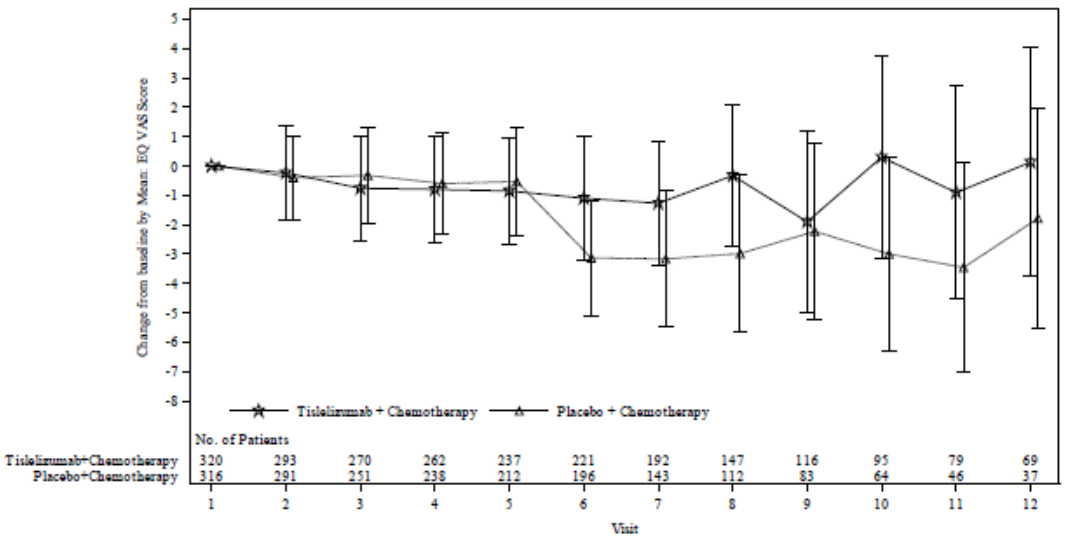
Source: Figure 14.2.7.1 CSR Study 306

Figure 28: EORTC QLQ-C30 Scores by Visit: Physical Functioning



Source: Figure 14.2.7.1 CSR Study 306

Figure 29: EQ-5D-5L Scores by Visit: VAS Score

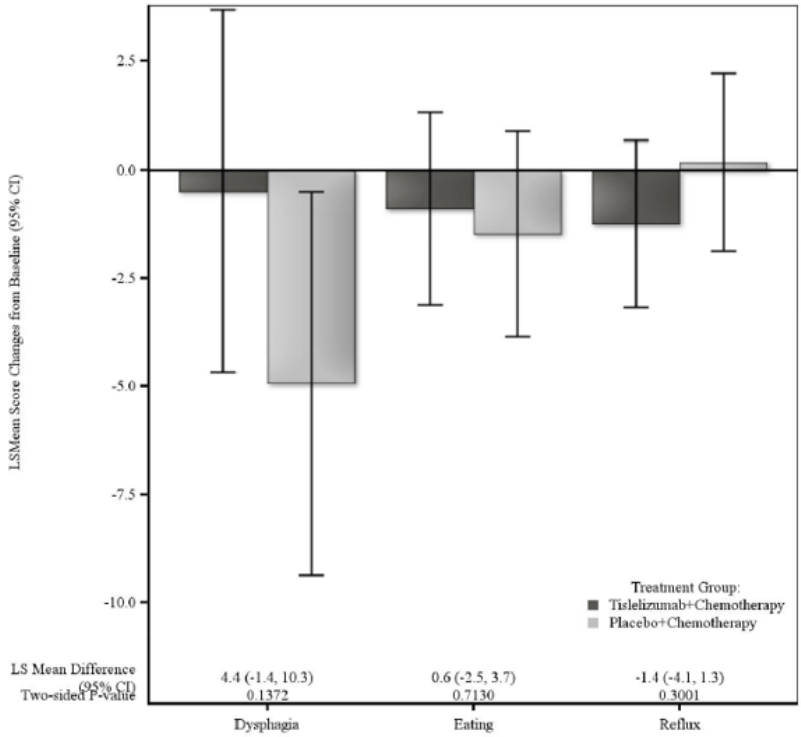


Source: Figure 14.2.7.3 CSR Study 306

A mixed effect model analysis for measuring changes postbaseline adjusted for baseline was performed using the global health status (GHS/QoL), physical function, and fatigue domains of QLQ-C30; and index score, dysphagia, reflux, pain, and eating of QLQ-OES18. Treatment effects on the above PRO endpoints from baseline were evaluated at Cycle 6 (to compare short-term effects after study treatment) and at Cycle 8 (to compare longer-term effects). To adjust for multiplicity, Bonferroni alpha-splitting method was applied to the test of QLQ-OES18 symptoms of dysphagia, eating, and reflux using two-sided alpha of 0.0167 at Cycle 6.

No meaningful differences in the PRO endpoints of disease-specific symptoms between treatment arms were observed from baseline to Cycle 6 and Cycle 8. For PRO endpoints within predefined hierarchy testing (dysphagia, eating, and reflux) with an alpha of 0.0167 (2-sided) at Cycle 6, no significant difference between the 2 treatment arms was observed.

Figure 30: Bar Plot of Least Square Mean Changes from Baseline in EORTC QLQ-OES18 scores - Cycle 6 - Study 306 (ITT Analysis Set)



Based on a mixed effect model analysis for measuring relevant changes, post baseline with QLQ OES18 scores until cycle 18 as the response variable, and treatment by study visit interaction, baseline mean score, and randomization stratification factors as covariates.

Source: Figure 4 SCE

Time to Clinically Meaningful Worsening

Clinically meaningful worsening was defined as ≥10 reduction in mean from baseline for GHS and physical functioning and an increase for symptom scales. A deterioration was not counted as an event if a subsequent improvement returned the overall worsening from baseline to <10 points.

The results based on stratified HR showed that both treatment arms were at similar risk of experiencing a deterioration event for all PRO endpoints.

- **Exploratory efficacy analyses**

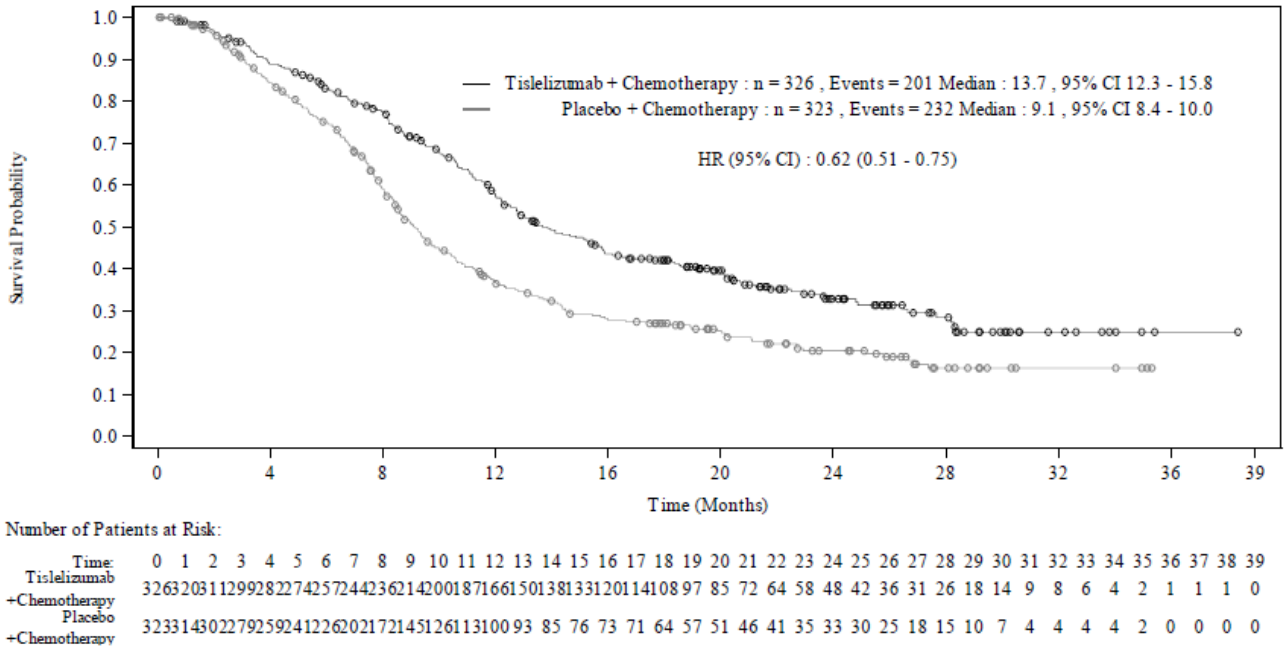
Assessments by Blinded Independent Review Committee (PFS, ORR, DOR by BIRC)

- **BIRC-assessed PFS**:
  Stratified HR = 0.60 (95% CI: 0.49 to 0.74), median BIRC-assessed PFS of 8.4 months in the T+C arm vs. 5.7 months in the P+C arm
- **BIRC-assessed ORR:**
  ORR was 67.8% in the T+C arm vs. 48.9% in the P+C arm
- **BIRC-assessed DOR:**
  Median DOR of 9.0 months in the T+C arm vs. 5.6 months in the P+C Arm

Second Progression-Free Survival by the Investigator (PFS2)

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 cut-off date, 201 patients (61.7%) in the T+C arm and 232 patients (71.8%) in the P+C arm experienced a PFS2 event. The stratified HR was 0.62 (95% CI: 0.51 to 0.75).

Figure 31: K-M Plot of PFS2 (ITT Analysis Set)



Number of Patients at Risk:

Time:	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39
Tislelizumab +Chemotherapy	326	320	311	299	282	274	257	244	236	214	200	187	166	150	138	133	120	114	108	97	85	72	64	58	48	42	36	31	26	18	14	9	8	6	4	2	1	1	1	0
Placebo +Chemotherapy	323	314	302	279	259	241	226	202	172	145	126	113	100	93	85	76	73	71	64	57	51	46	41	35	33	30	25	18	15	10	7	4	4	4	4	2	0	0	0	0

Source: Figure 14.2.4.4 CSR Appendix

Additional PD-L1 Score Subgroup Analyses:

Outcomes in subgroups by PD-L1 expression

Demographic and baseline characteristics were generally similar across the 3 PD-L1 subgroups (PD-L1 score ≥10%, PD-L1 score <10% and unknown). The characteristics were generally balanced between the 2 treatment arms in each of the 3 PD-L1 subgroups, except for sex and race in the PD-L1 score ≥10% subgroup: the proportion of males in the T+C Arm was slightly lower than in the P+C Arm (81.0% vs. 89.7%, respectively) and the proportion of Asian patients was lower in the T+C Arm than in the P+C Arm (74.1% vs. 84.1%, respectively).

In the 3 PD-L1 subgroups, the disease history and characteristics were generally similar among all 3 subgroups, and between the 2 treatment arms within each PD-L1 subgroup.

- **OS by PD-L1 Score expression status ≥ 10% (secondary endpoint)**

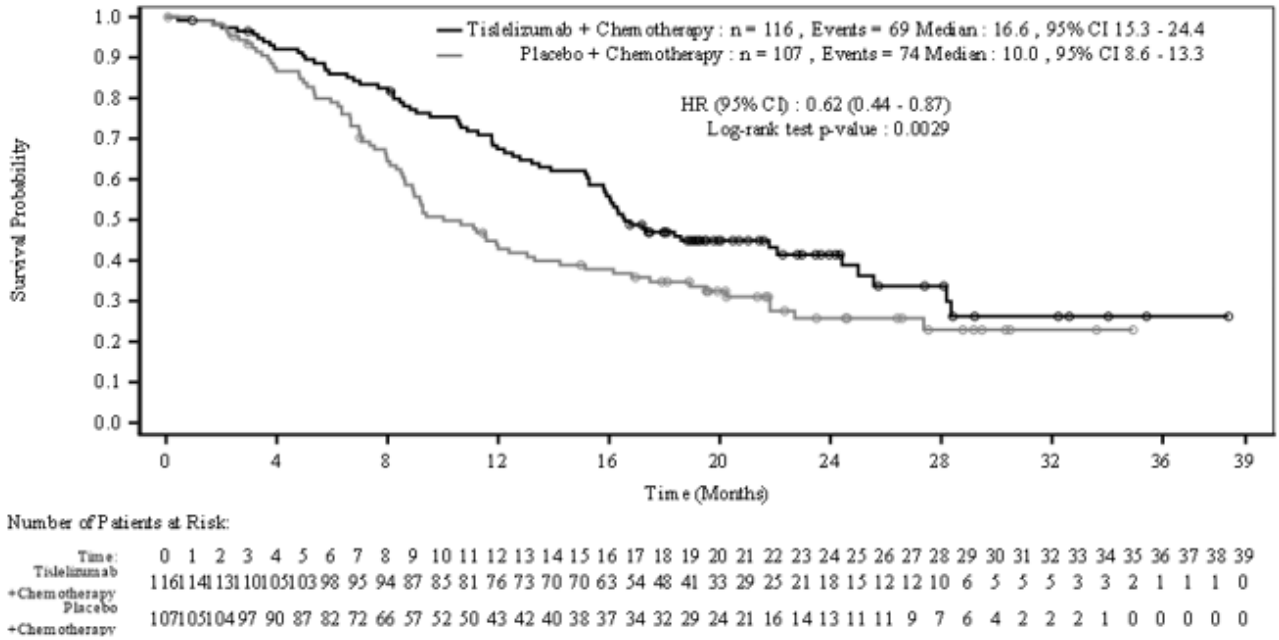
Table 35: OS by Baseline PD-L1 Expression Status - Study 306 (ITT Analysis Set)

	PD-L1 score ≥10%		PD-L1 score <10%		Unknown	
	Tislelizumab + Chemotherapy N = 116	Placebo + Chemotherapy N = 107	Tislelizumab + Chemotherapy N = 151	Placebo + Chemotherapy N = 168	Tislelizumab + Chemotherapy N = 59	Placebo + Chemotherapy N = 48
Patients, n (%)						
Death	69 (59.5)	74 (69.2)	98 (64.9)	120 (71.4)	29 (49.2)	32 (66.7)
Censored	47 (40.5)	33 (30.8)	53 (35.1)	48 (28.6)	30 (50.8)	16 (33.3)
Ongoing	44 (37.9)	26 (24.3)	49 (32.5)	42 (25.0)	21 (35.6)	9 (18.8)
Lost to follow-up	1 (0.9)	0 (0.0)	0 (0.0)	3 (1.8)	1 (1.7)	0 (0.0)
Withdrawal by patient	2 (1.7)	7 (6.5)	4 (2.6)	3 (1.8)	8 (13.6)	7 (14.6)
One-sided stratified log-rank test p-value [a]	0.0029					
Stratified HR (95% CI) [b]	0.62 (0.44, 0.87)		0.77 (0.59, 1.01)		0.54 (0.32, 0.91)	
Unstratified HR (95% CI)c	0.66 (0.48, 0.92)		0.76 (0.58, 0.99)		0.53 (0.32, 0.88)	
OS, months (95% CI)						
Median	16.6 (15.3, 24.4)	10.0 (8.6, 13.3)	15.8 (12.3, 19.6)	10.4 (9.0, 13.6)	23.7 (16.6, 28.4)	11.7 (7.4, 21.7)
OS rate at, % (95% CI)						
6 months	86.0 (78.2, 91.2)	78.9 (69.8, 85.6)	80.5 (73.2, 86.0)	77.7 (70.6, 83.3)	91.1 (80.0, 96.2)	71.6 (55.3, 82.8)
12 months	67.4 (58.0, 75.2)	42.9 (33.2, 52.2)	59.5 (51.2, 66.9)	45.7 (37.9, 53.1)	75.1 (60.9, 84.7)	46.9 (31.2, 61.1)
24 months	41.5 (31.7, 50.9)	25.7 (16.9, 35.4)	31.9 (23.7, 40.4)	24.2 (17.3, 31.8)	48.3 (33.4, 61.8)	27.8 (14.7, 42.5)
Follow-up, months (95% CI)						
Median	21.6 (19.9, 24.2)	23.5 (20.2, 26.6)	24.0 (21.7, 25.8)	23.3 (19.7, 26.1)	26.3 (21.7, 27.4)	28.1 (20.2, 28.8)

Percentages were based on N.
In absence of death on or before data cutoff, patients were censored either at the date that the patient was last known to be alive or the date of data cutoff, whichever came earlier.
Medians and other quartiles were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley. Overall Survival rates (cumulative probability of OS) were estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula. Median follow-up time was estimated by the reverse Kaplan-Meier method.
PD-L1 status is determined using VENTANA PD-L1 (SP263) Assay. Unknown refers to the patients without sample collection, not evaluable at baseline or scored with unqualified sample.
a One sided p value was estimated from a log rank test stratified by pooled geographic region (Asia vs. RoW) per IRT, prior definitive therapy (yes vs. no) per IRT, and ICC option (platinum + fluoropyrimidine vs. platinum + paclitaxel) per IRT.
b HR (T+C vs. P+C) was based on a Cox regression model including treatment as a covariate, and pooled geographic region (Asia vs. RoW) per IRT, prior definitive therapy (yes vs. no) per IRT, and ICC option (platinum + fluoropyrimidine vs. platinum + paclitaxel) per IRT as strata.
c HR (T+C vs. P+C) was based on unstratified Cox regression model only including treatment as covariate.
Data cutoff: 28 Feb 2022. Data extraction: 06 Apr 2022

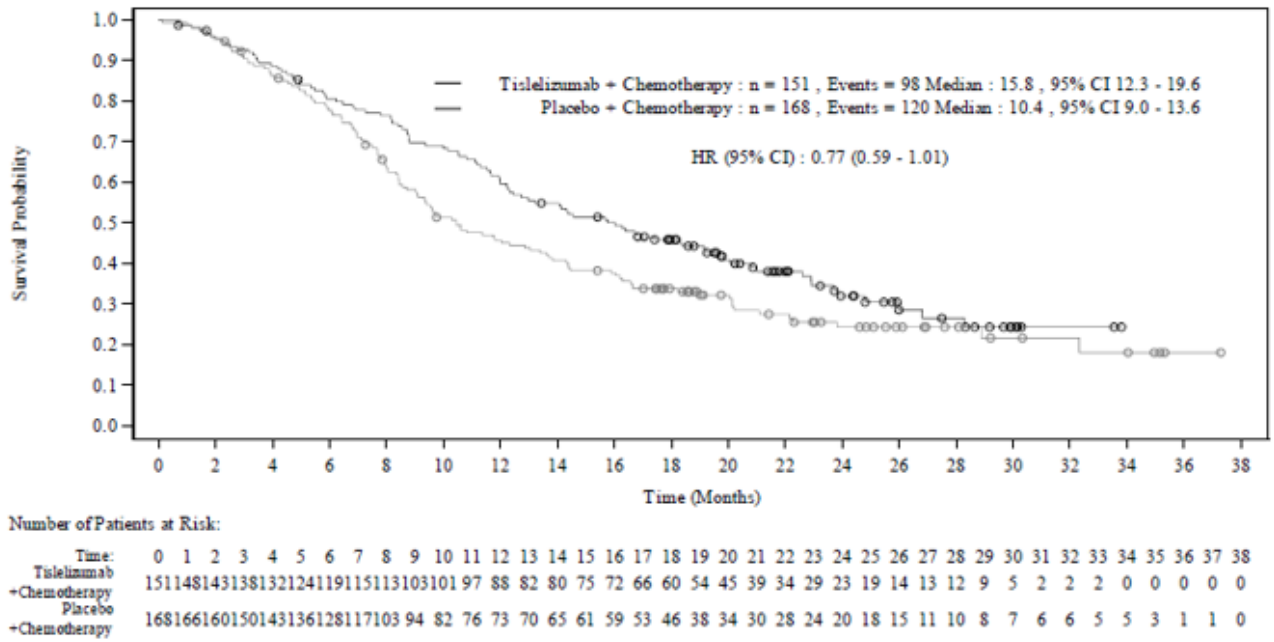
Source: Table 13 SCE

Figure 32: Kaplan-Meier Plot of Overall Survival (OS) by Baseline PD-L1 Status - PDL1 Score ⩾ 10% (ITT Analysis Set)



Source: Figure 8 SCE

Figure 33: Kaplan-Meier Plot of Overall Survival (OS) by Baseline PD-L1 Status - PDL1 Score < 10% (ITT Analysis Set)



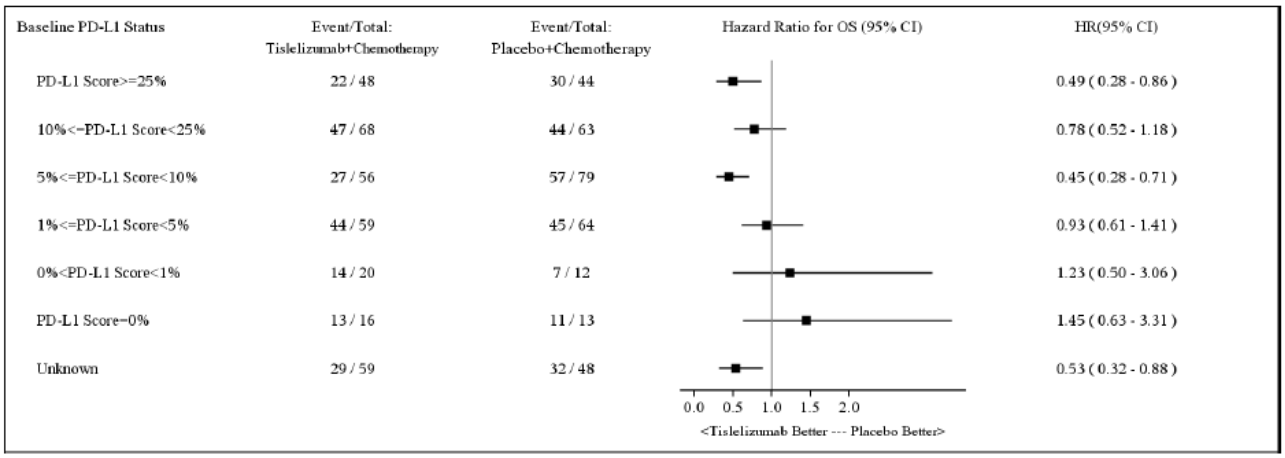
Source: Figure 9 SCE

- **Additional PD-L1 Score Subgroup Analyses**

To further inform on the efficacy of tislelizumab by baseline PD-L1 status, additional subgroup analyses by baseline PD-L1 expression status (corresponding to PD-L1 scores of 25%, 5%, 1% and 0%) were conducted.

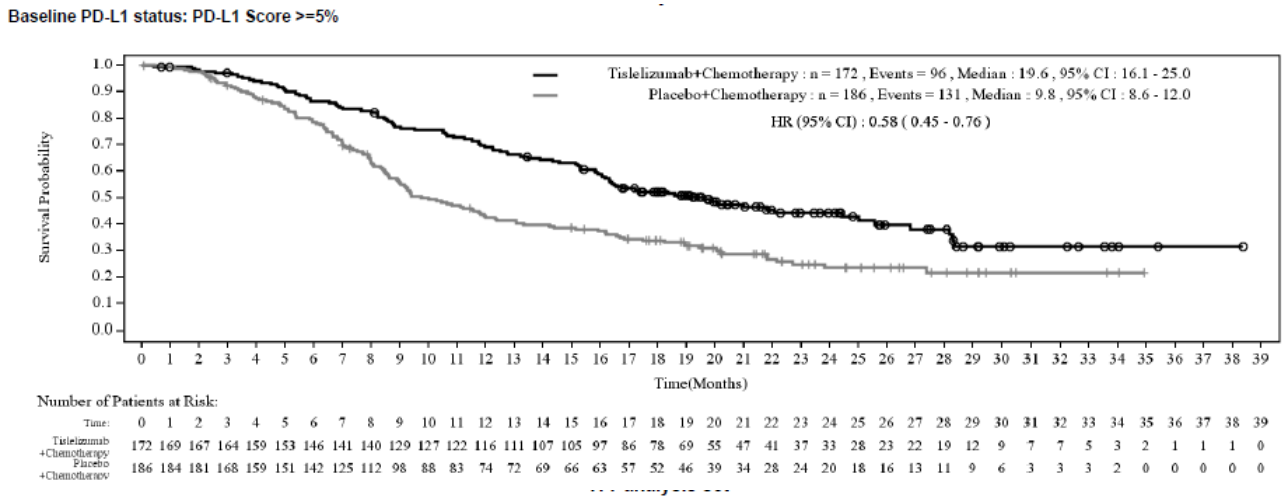
Overall Survival

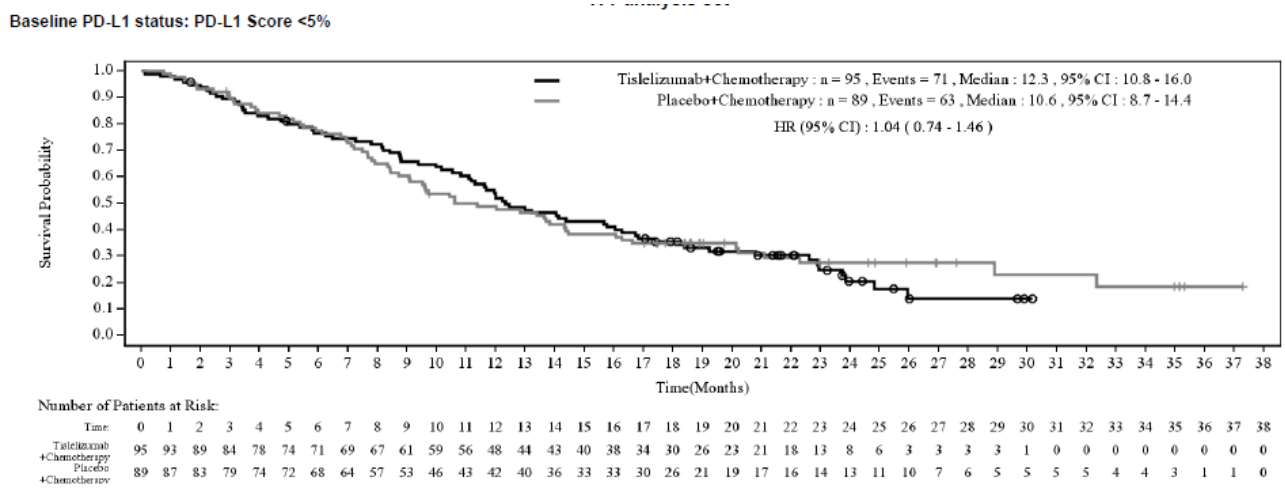
Figure 34: Forest Plot of OS Using PD-L1 Cut-offs 25%, 10%, 5%, 1%, and 0% (ITT Analysis Set)



Source: Figure 11 SCE-data cut off: 28 Feb2022

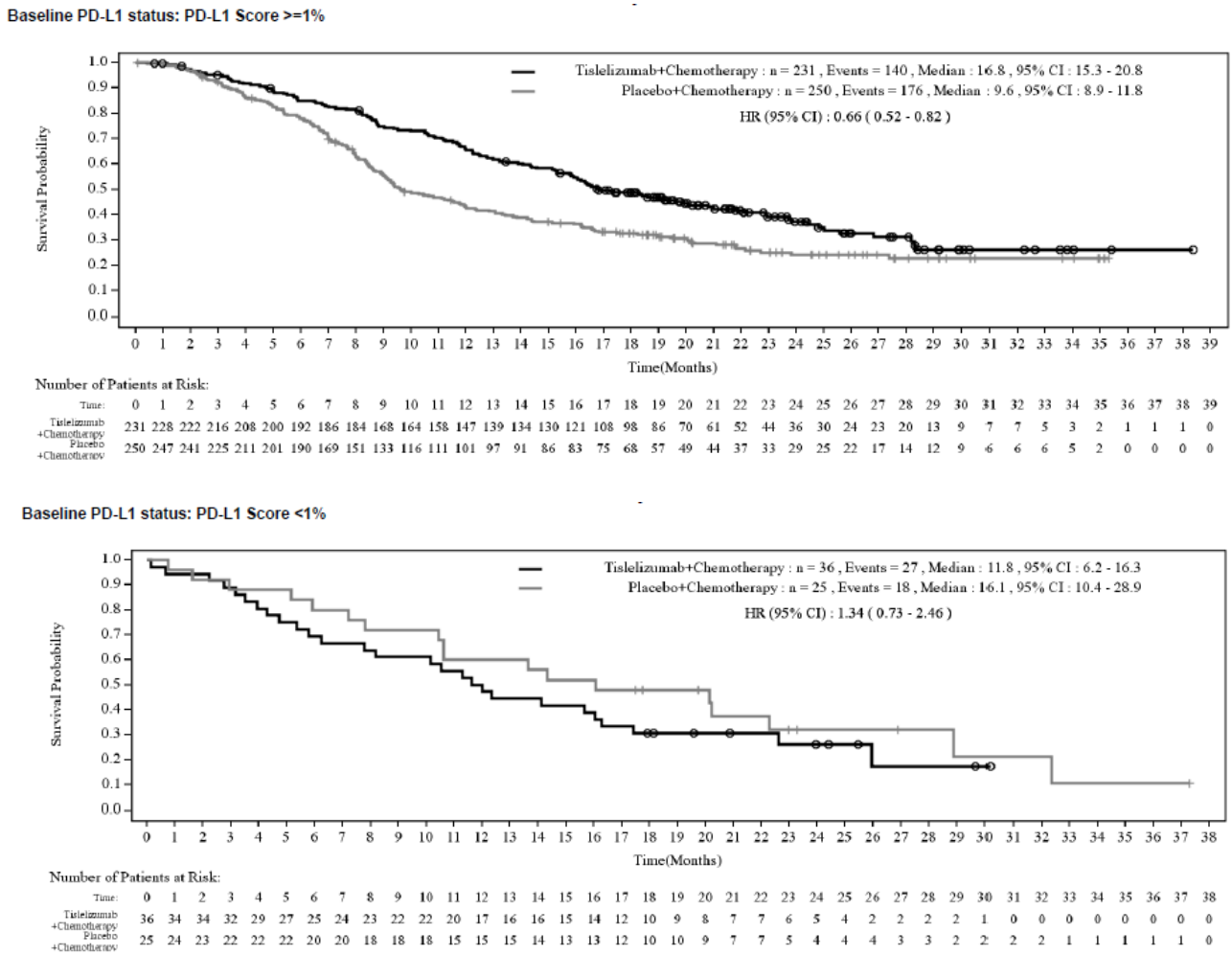
Figure 35: Kaplan-Meier Plots of Overall Survival by Baseline PD-L1 Status 5% Cut-off (ITT analysis set)





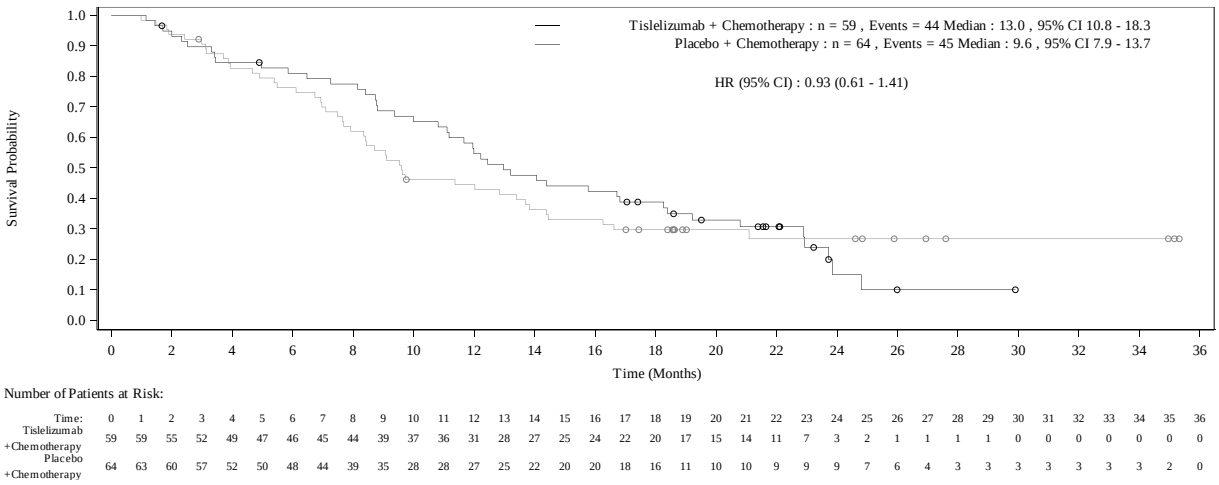
Source: Figure 3-18 SCE Appendix 2-Data cutoff: 28FEB2022.

Figure 36: Kaplan-Meier Plots of Overall Survival by Baseline PD-L1 Status 1% Cut-off (ITT analysis set)



Source: Figure 3-18 SCE Appendix 2

Figure 37: Kaplan-Meier Plot of Overall Survival by Baseline PD-L1 Status 1% to <5% (ITT analysis set)



Source: Appendix A Figure 2.1.1.1, Responses 1st RFI

Updated OS results in relevant PD-L1 subgroups

Along the procedure, the Applicant provided additional follow-up data (Day 120 and 3-year Follow-up) for PD-L1 expression scores ≥5%, 1 to <5%, and ≥1%. The table summarizing unstratified OS results and Kaplan-Meier plots for the 3-year Follow-up are presented below.

In addition, to account for numerical imbalances in baseline characteristics between the subgroups of patients with different PD-L1 cut-offs, sensitivity analyses of multivariate Cox regression model adjusting for these factors were conducted to determine the effect of the imbalances on the degree of OS benefit in the PD-L1 1% to < 5% subgroup. In the PD-L1 1% to < 5% subgroup, the adjusted unstratified HR was 0.78 (95% CI: 0.51 to 1.22) at interim analysis (see **Table 36**).

Table 36: Overall Survival (OS) by Baseline PD-L1 Category 1% to < 5% and ≥1% (ITT Analysis Set) - Interim Analysis, Day 120 and 3-year Follow-up Interim Analysis

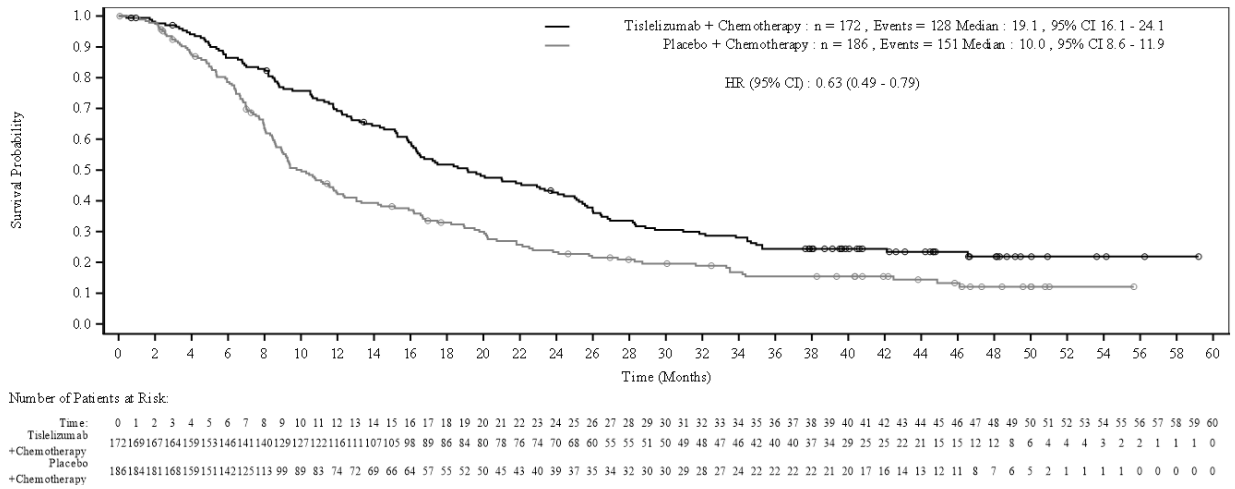
Baseline PD-L1	≥ 5%		1% to < 5%		≥ 1%	
	T+C (N = 172)	P+C (N =186)	T+C (N = 59)	P+C (N = 64)	T+C (N = 231)	P+C (N = 250)
Interim Analysis (DCO 28 February 2022)						
Death, n (%)	97 (56.4)	132 (71.0)	44 (74.6)	45 (70.3)	141 (61.0)	177 (70.8)
Unstratified Hazard Ratio (95% CI) [a]	0.58 (0.45, 0.76)		0.93 (0.61, 1.41)		0.66 (0.53, 0.82)	
Adjusted Unstratified Hazard Ratio (95% CI) [b]	0.58 (0.44, 0.76)		0.78 (0.51, 1.22)		0.64 (0.51, 0.80)	
Median OS (months), (95% CI)	19.6 (16.1, 25.0)	10.0 (8.6, 11.9)	13.0 (10.8, 18.3)	9.6 (7.9, 13.7)	16.8 (15.3, 20.8)	9.6 (8.9, 11.8)
OS rate at, % (95% CI)						
6 Months	86.4 (80.3, 90.8)	78.6 (71.9, 83.9)	81.0 (68.3, 89.0)	76.3 (63.8, 85.0)	85.0 (79.7, 89.1)	78.0 (72.3, 82.7)
12 Months	69.2 (61.6, 75.5)	42.1 (34.8, 49.3)	54.6 (40.9, 66.4)	44.4 (32.0, 56.2)	65.5 (58.9, 71.3)	42.7 (36.4, 48.9)
18 Months	52.2 (44.4, 59.5)	33.5 (26.6, 40.4)	38.7 (26.2, 51.1)	29.6 (18.9, 41.2)	48.8 (42.1, 55.1)	32.5 (26.6, 38.4)
120 Day (DCO 28 April 2023)						
Death, n (%)	121 (70.3)	146 (78.5)	50 (84.7)	55 (85.9)	171 (74.0)	201 (80.4)
Unstratified Hazard Ratio (95% CI) [a]	0.62 (0.49, 0.79)		0.87 (0.59, 1.28)		0.68 (0.55, 0.83)	
Adjusted Unstratified Hazard Ratio (95% CI) [b]	0.62 (0.48, 0.79)		0.77 (0.52, 1.16)		0.66 (0.54, 0.81)	
Median OS (months), (95% CI)	19.1 (16.1, 24.1)	10.0 (8.6, 11.9)	13.0 (10.8, 18.3)	9.6 (7.9, 13.7)	16.8 (15.3, 20.8)	9.6 (8.9, 11.8)
OS rate at, % (95% CI)						
18 Months	51.7 (43.9, 59.0)	32.9 (26.1, 39.9)	38.7 (26.2, 51.1)	29.6 (18.9, 41.2)	48.4 (41.8, 54.8)	32.1 (26.3, 38.0)
24 Months	42.7 (35.1, 50.1)	23.4 (17.4, 29.9)	22.9 (13.0, 34.4)	23.0 (13.5, 34.1)	37.7 (31.3, 44.0)	23.3 (18.1, 28.9)
36 Months	30.5 (23.7, 37.6)	20.2 (14.6, 26.5)	19.4 (10.4, 30.5)	19.8 (10.9, 30.5)	27.7 (22.0, 33.7)	20.1 (15.2, 25.5)

Baseline PD-L1	≥ 5%		1% to < 5%		≥ 1%	
	T+C (N = 172)	P+C (N =186)	T+C (N = 59)	P+C (N = 64)	T+C (N = 231)	P+C (N = 250)
3-Year Follow-up (DCO 24 November 2023)						
Death, n (%)	128 (74.4)	151 (81.2)	50 (84.7)	56 (87.5)	178 (77.1)	207 (82.8)
Unstratified Hazard Ratio (95% CI) [a]	0.63 (0.49, 0.79)		0.86 (0.59, 1.26)		0.68 (0.55, 0.83)	
Adjusted Unstratified Hazard Ratio (95% CI) [b]	0.63 (0.50, 0.81)		0.76 (0.50, 1.13)		0.66 (0.54, 0.81)	
Median OS (months), (95% CI)	19.1 (16.1, 24.1)	10.0 (8.6, 11.9)	13.0 (10.8, 18.3)	9.6 (7.9, 13.7)	16.8 (15.3, 20.8)	9.6 (8.9, 11.8)
OS rate at, % (95% CI)						
18 Months	51.7 (43.9, 59.0)	32.9 (26.1, 39.9)	38.7 (26.2, 51.1)	29.6 (18.9, 41.2)	48.4 (41.8, 54.8)	32.1 (26.3, 38.0)
24 Months	42.7 (35.1, 50.1)	23.4 (17.4, 29.9)	22.9 (13.0, 34.4)	23.0 (13.5, 34.1)	37.7 (31.3, 44.0)	23.3 (18.1, 28.9)
36 Months	24.4 (18.2, 31.2)	15.4 (10.4, 21.4)	12.3 (5.4, 22.2)	11.5 (5.1, 20.9)	21.3 (16.2, 26.9)	14.3 (10.1, 19.2)

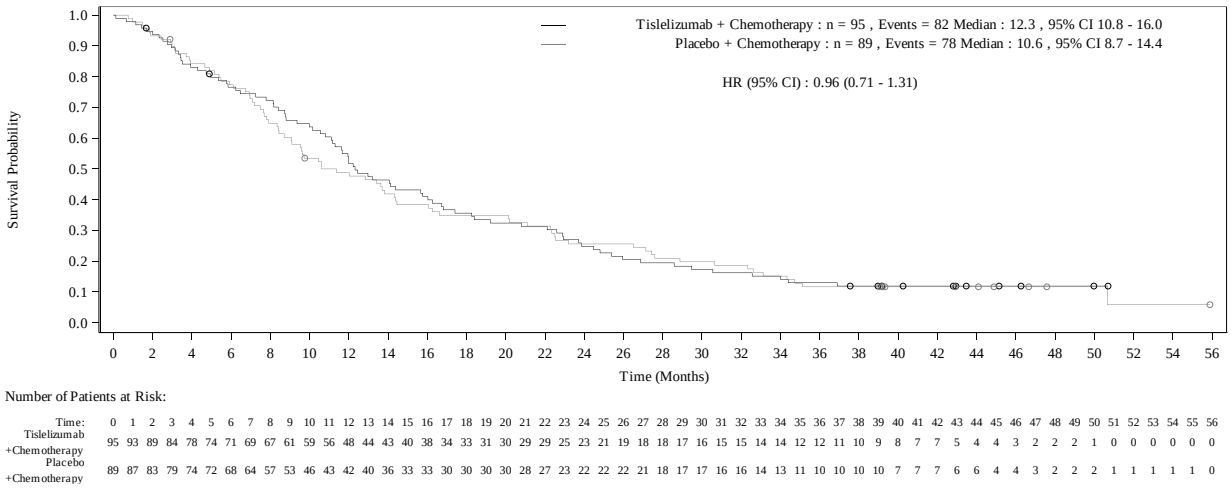
For Interim Analysis: Data cutoff: 28FEB2022. Data extraction: 06APR2022
For Day 120: Data cutoff: 28APR2023. Data extraction: 09JUN2023.
For 3-year Follow-up: Data cutoff: 24NOV2023. Data extraction: 28DEC2023
[a] Hazard ratio (Tislelizumab+Chemotherapy vs. Placebo+Chemotherapy) was based on unstratified Cox regression model only including treatment as covariate.
[b] Hazard ratio (Tislelizumab + Chemotherapy vs Placebo + Chemotherapy) was based on unstratified Cox regression model including treatment arm, age, sex, smoking status, ECOG status, metastatic disease, pooled geographic region per IRT, prior definitive therapy per IRT and ICC option per IRT as covariates.
Source: Appendix A Table 2.1.1.1, Table 2.1.1.2, Table 2.1.3.1, Table 2.1.3.2 , Table 2.1.1.5, Table 2.1.1.6, Table 2.1.1.9, Table 2.1.1.10, Table 2.1.3.5, Table 2.1.3.6, Table 2.1.3.9, Table 2.1.3.10, Responses to 1st RSI

Figure 38: Kaplan-Meier Plot of OS by Baseline PD-L1 Cut < 5% and ⩾ 5% (ITT Analysis Set) – 3 Year Follow-up Data-DCO 24 November 2023

Baseline PD-L1 Status, PD-L1 Score ≥ 5%

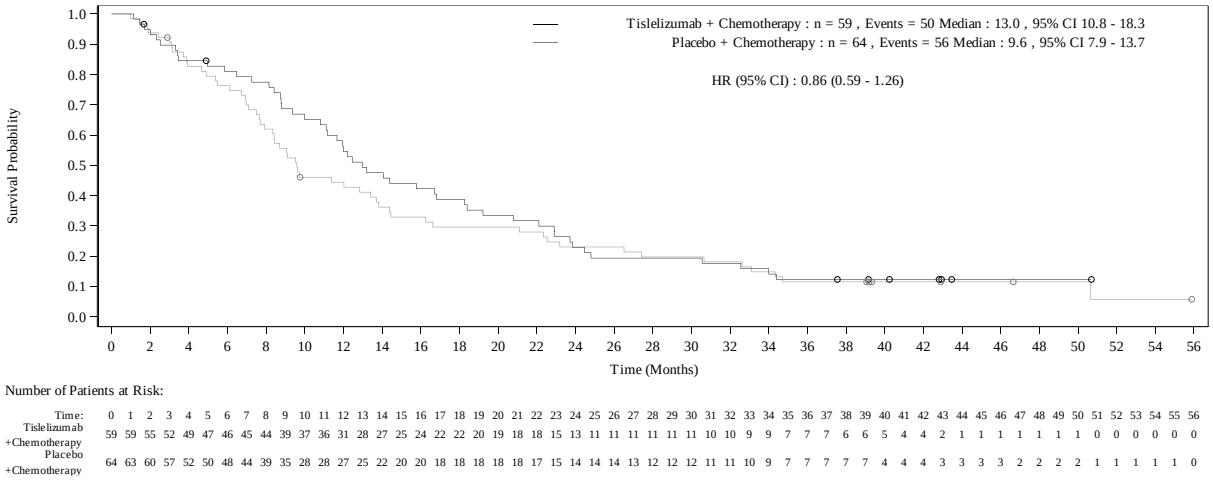


Baseline PD-L1 Status, PD-L1 Score < 5%



Source: Appendix A Figure 2.1.1.5, Responses 1st RFI

Figure 39: Kaplan-Meier Plot of OS by Baseline PD-L1 Category 1% to < 5% (ITT Analysis Set) – 3 Year Follow-up Data-DCO= 24NOV2023



Source: Appendix A Figure 2.1.1.5, Responses 1st RFI

The stratified OS HR comparing baseline PD-L1 score < 5% and ≥ 5% as of DCO 24 November 2023 (3 Year Follow-Up) is presented below.

Table 37: Overall Survival (OS) by Baseline PD-L1 Cut < 5% and ≥ 5% with 3 Year Follow-up Data (ITT Analysis Set)

	PD-L1 < 5%		PD-L1 ≥ 5%	
	T+C N = 95	P+C N = 89	T+C N = 172	P+C N = 186
Number of Patients				
Death, n (%)	82 (86.3)	78 (87.6)	128 (74.4)	151 (81.2)
Censored, n (%)	13 (13.7)	11 (12.4)	44 (25.6)	35 (18.8)
Ongoing Without Events	11 (11.6)	7 (7.9)	34 (19.8)	19 (10.2)
Lost to Follow-up	0 (0.0)	1 (1.1)	4 (2.3)	4 (2.2)
Withdrawal by Subject	2 (2.1)	3 (3.4)	6 (3.5)	11 (5.9)
Study Discontinuation Due to Other Reasons	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)

	PD-L1 < 5%		PD-L1 ≥ 5%	
	T+C N = 95	P+C N = 89	T+C N = 172	P+C N = 186
One-sided Stratified Log-rank Test p-value [a]	0.3533		< 0.0001	
Stratified Hazard Ratio (95% CI) [b]	0.94 (0.68, 1.29)		0.62 (0.49, 0.79)	
Overall Survival (months)				
Median (95% CI)	12.3 (10.8, 16.0)	10.6 (8.7, 14.4)	19.1 (16.1, 24.1)	10.0 (8.6, 11.9)
Follow-up Time (months)				
Median (95% CI)	42.9 (39.0, 46.3)	44.1 (39.2, 47.6)	44.2 (40.5, 46.6)	43.8 (40.3, 47.3)

Source: Appendix A Table 2.1.1.5, Responses 1st RFI

a One-sided p-value was estimated from log rank test stratified by pooled geographic region (Asia vs. Rest of World) per IRT, prior definitive therapy (Yes vs. No) per IRT and ICC option (Investigator choice of chemotherapy (platinum with fluoropyrimidine vs platinum with paclitaxel)) per IRT and displayed for descriptive purpose only.

b Hazard ratio (Tislelizumab+Chemotherapy vs. Placebo+Chemotherapy) was based on Cox regression model including treatment as covariate, and pooled geographic region (Asia vs. Rest of World) per IRT, prior definitive therapy (Yes vs. No) per IRT and ICC option (Investigator choice of chemotherapy (platinum with fluoropyrimidine vs platinum with paclitaxel)) per IRT as strata.

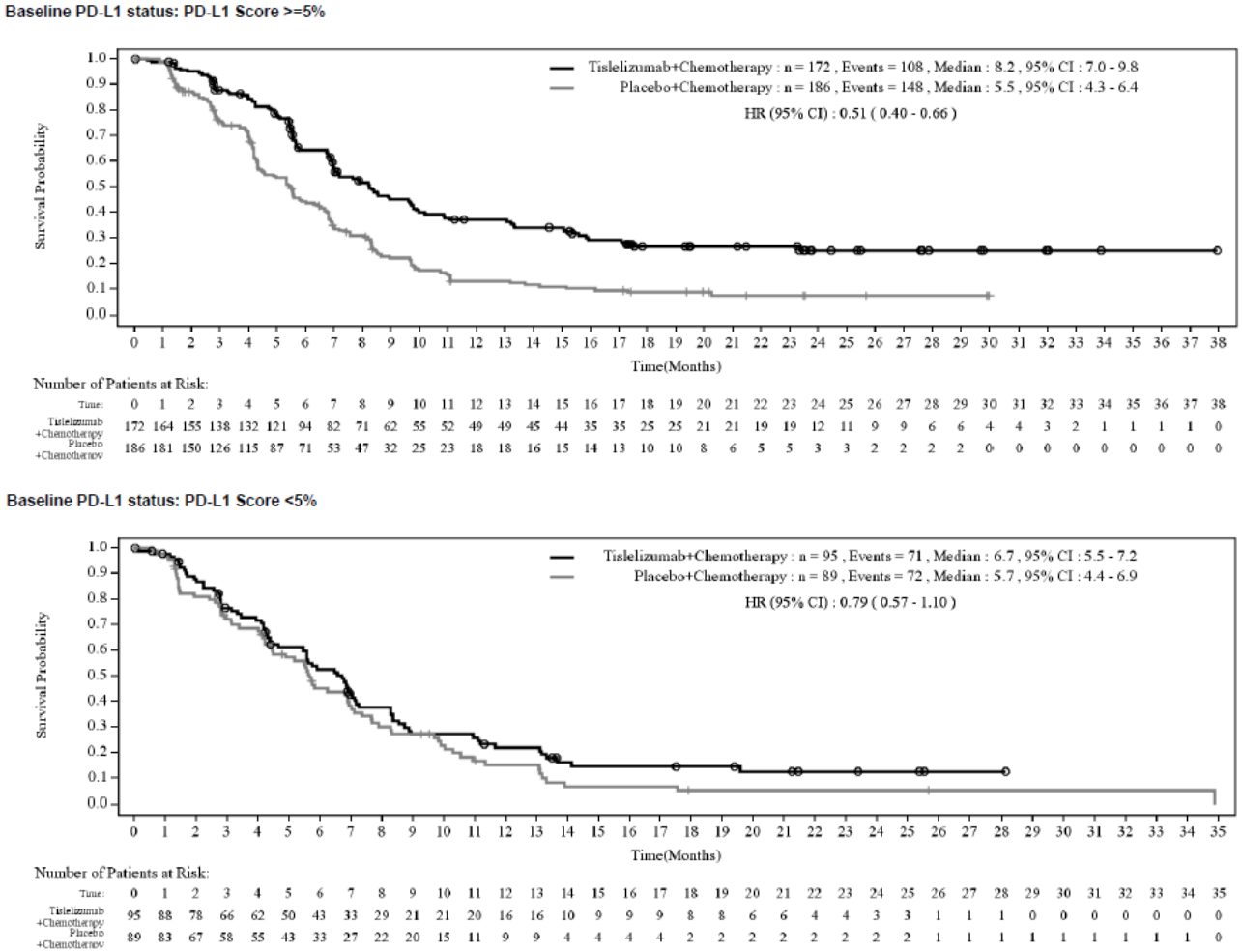
Progression-free survival

Table 38: Subgroup Analysis of PFS by PD-L1 Subgroups Assessed by Investigator - Study 306 (ITT Analysis Set)

	Median, months (95% CI) and events/no. of patients		
	Tislelizumab + chemotherapy	Placebo + chemotherapy	Unstratified HR (95% CI)
Overall	7.3 (6.9, 8.3), 220/326	5.6 (4.9, 6.0), 254/323	0.61 (0.51, 0.74)
PD-L1 score			
≥10%	8.3 (7.0, 10.2), 76/116	5.6 (4.3, 6.7), 90/107	0.50 (0.37, 0.69)
≥5%	8.2 (7.0, 9.8), 108/172	5.5 (4.3, 6.4), 148/186	0.51 (0.40, 0.66)
≥1%	7.2 (6.8, 8.5), 152/231	5.5 (4.5, 5.8), 199/250	0.56 (0.45, 0.70)
>0%	7.1 (6.8, 8.3), 169/251	5.5 (4.5, 6.0), 208/262	0.59 (0.48, 0.73)
<10%	6.9 (5.6, 7.9), 103/151	5.5 (4.3, 6.2), 130/168	0.68 (0.52, 0.88)
<5%	6.7 (5.5, 7.2), 71/95	5.7 (4.4, 6.9), 72/89	0.79 (0.57, 1.10)
<1%	6.9 (3.2, 8.9), 27/36	6.2 (4.1, 10.5), 21/25	0.89 (0.50, 1.58)
0%	8.9 (2.8, 14.1), 10/16	6.9 (3.4, 10.5), 12/13	0.65 (0.28, 1.53)
Unknown	8.4 (6.8, 9.5), 41/59	5.6 (3.5, 7.5), 34/48	0.76 (0.48, 1.20)

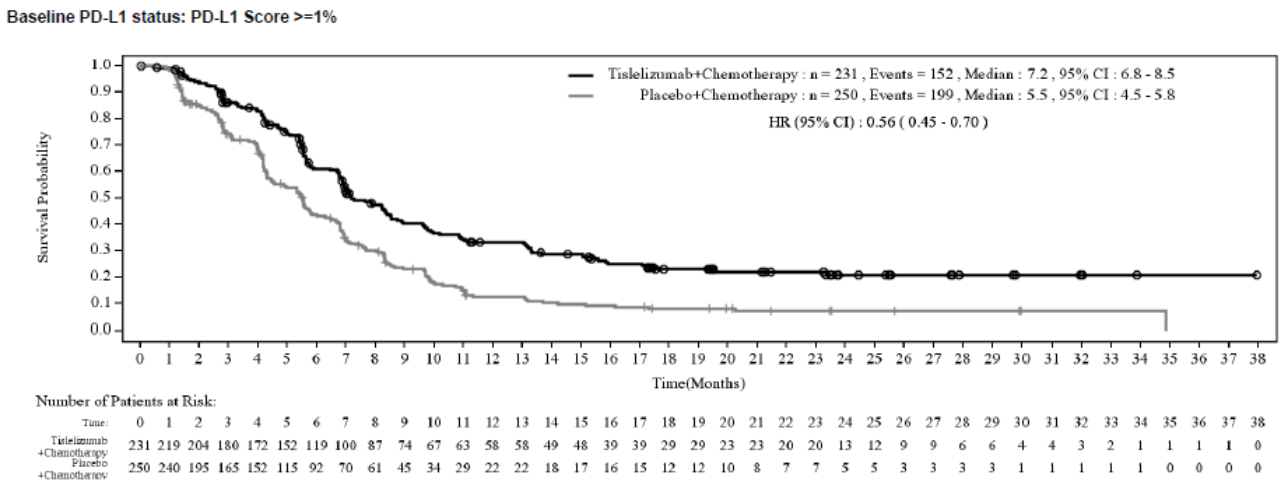
Source: Excerpt from Table 14 SCE

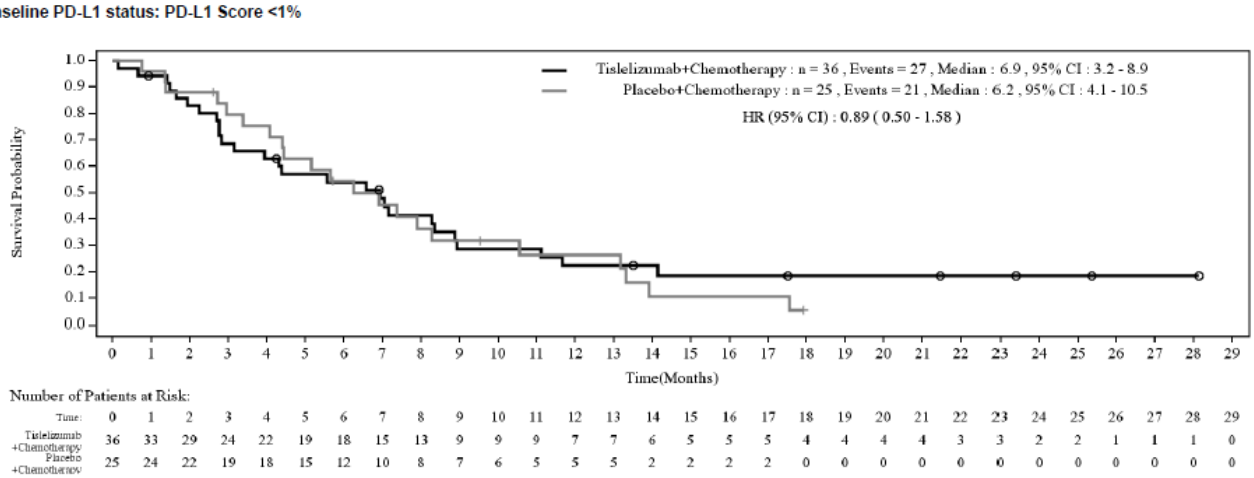
Figure 40: Kaplan-Meier Plot of Investigator Assessed Progression-Free Survival (PFS) by Baseline PD-L1 Status 5% Cut-off (ITT analysis set)



Source: Figure 3-22 SCE Appendix 2

Figure 41: Kaplan-Meier Plot of Investigator Assessed Progression-Free Survival (PFS) by Baseline PD-L1 Status 1% Cut-off (ITT analysis set)- Data cutoff: 28FEB2022.





Source: Figure 3-22 SCE Appendix 2

ORR

Table 39: Subgroup Analysis of ORR (Unconfirmed) by PD-L1 Subgroups Assessed by Investigator – Study 306 (ITT Analysis Set)

	ORR, % (95% CI), (no. of patients)		
	Tislelizumab + chemotherapy	Placebo + chemotherapy	Odds Ratio for ORR (95% CI)
Overall	63.5 (58.0, 68.7), (n=326)	42.4 (37.0, 48.0), (n=323)	2.38 (1.73, 3.27)
PD-L1 status			
≥10%	73.3 (64.3, 81.1), (n=116)	40.2 (30.8, 50.1), (n=107)	4.08 (2.32, 7.18)
≥5%	71.5 (64.1, 78.1), (n=172)	41.4 (34.2, 48.8), (n=186)	3.55 (2.29, 5.52)
≥1%	65.8 (59.3, 71.9), (n=231)	42.0 (35.8, 48.4), (n=250)	2.66 (1.84, 3.85)
>0%	63.7 (57.5, 69.7), (n=251)	42.7 (36.7, 49.0), (n=262)	2.35 (1.65, 3.36)
<10%	57.6 (49.3, 65.6), (n=151)	45.8 (38.1, 53.7), (n=168)	1.61 (1.03, 2.50)
<5%	51.6 (41.1, 62.0), (n=95)	48.3 (37.6, 59.2), (n=89)	1.14 (0.64, 2.03)
<1%	55.6 (38.1, 72.1), (n=36)	60.0 (38.7, 78.9), (n= 25)	0.83 (0.30, 2.35)
0%	75.0 (47.6, 92.7), (n=16)	61.5 (31.6, 86.1), (n=13)	1.88 (0.38, 9.20)
Unknown	59.3 (45.7, 71.9), (n=59)	35.4 (22.2, 50.5), (n=48)	2.66 (1.21, 5.84)

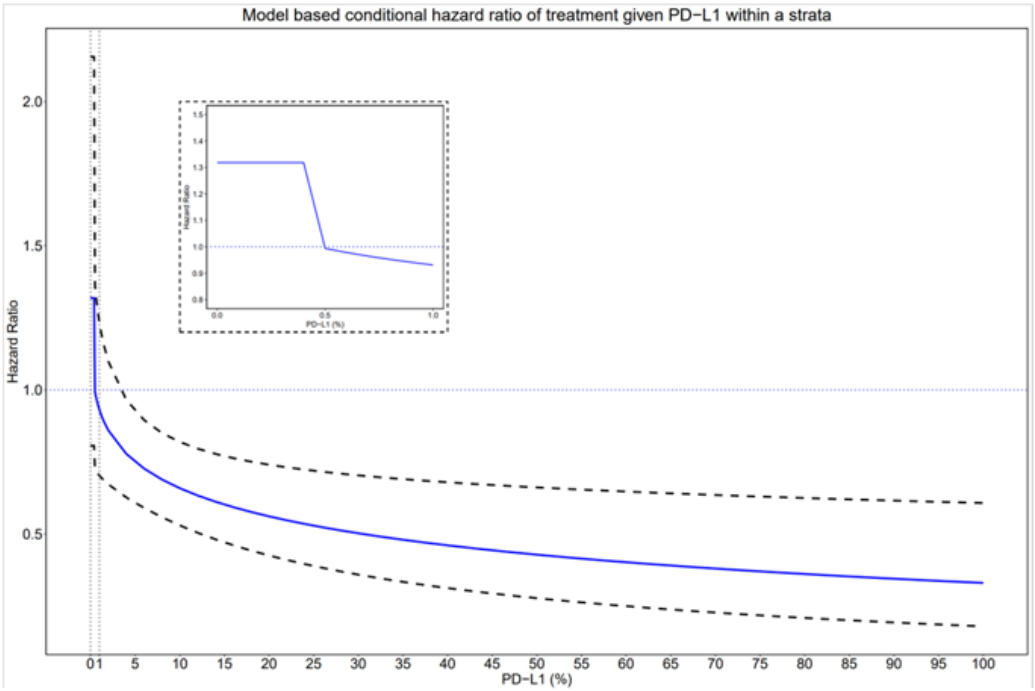
Source: Table 15 SCE

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

An exploratory modeling approach was used to further investigate the impact of baseline PD-L1 levels on the treatment effect in terms of the primary OS endpoint and to identify a potential 'switch point', i.e., a PD-L1 value below which there is no OS benefit based on the HR point estimate.

The primary modelling approach based on proportional hazard assumption suggests there is a sharp drop in the hazard ratio from no expression (at PD-L1 0%) to any positive expression of PD-L1 (above 0%), and there is a numerical OS treatment benefit based on HR point estimate in patients with baseline PD-L1 levels above 0%. Overall, the proportional hazards assumption appears to hold in the final model.

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

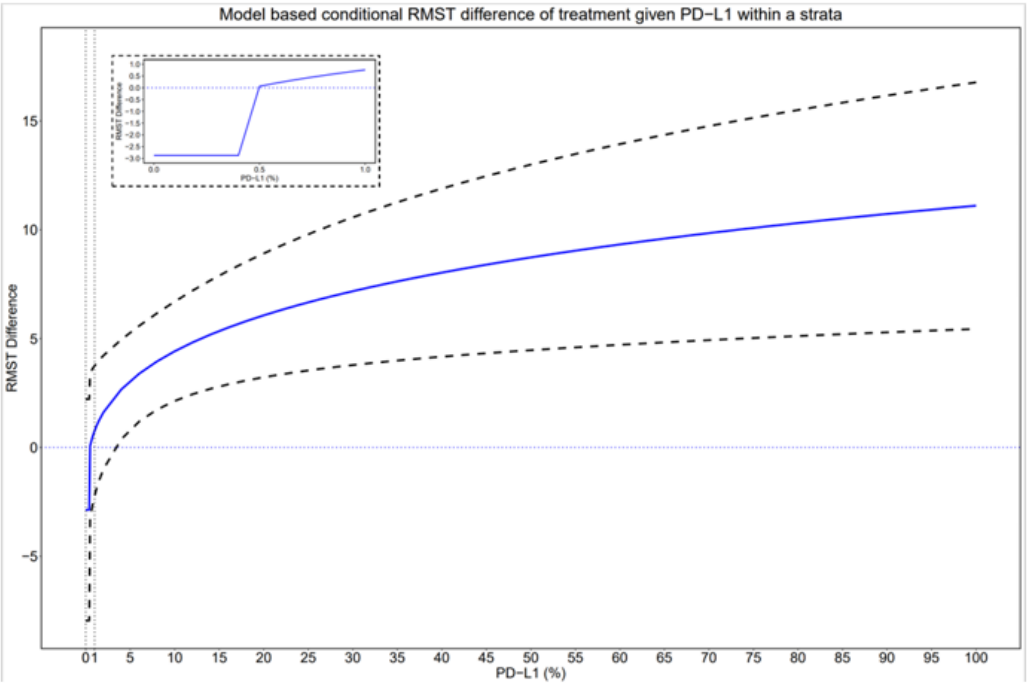


Conditional hazard ratio of PD-L1 level from 0% to 1% is enhanced in the figure for clarity.

Source: Figure 18 SCE

However, to overcome potential limitations of the proportional hazard assumption, restricted mean survival time (RMST) difference was provided as a supportive analysis.

Figure 43: Exploratory Overall Survival Modeling Approach Using Baseline PD-L1 Levels as a Continuous Variable: RMST difference



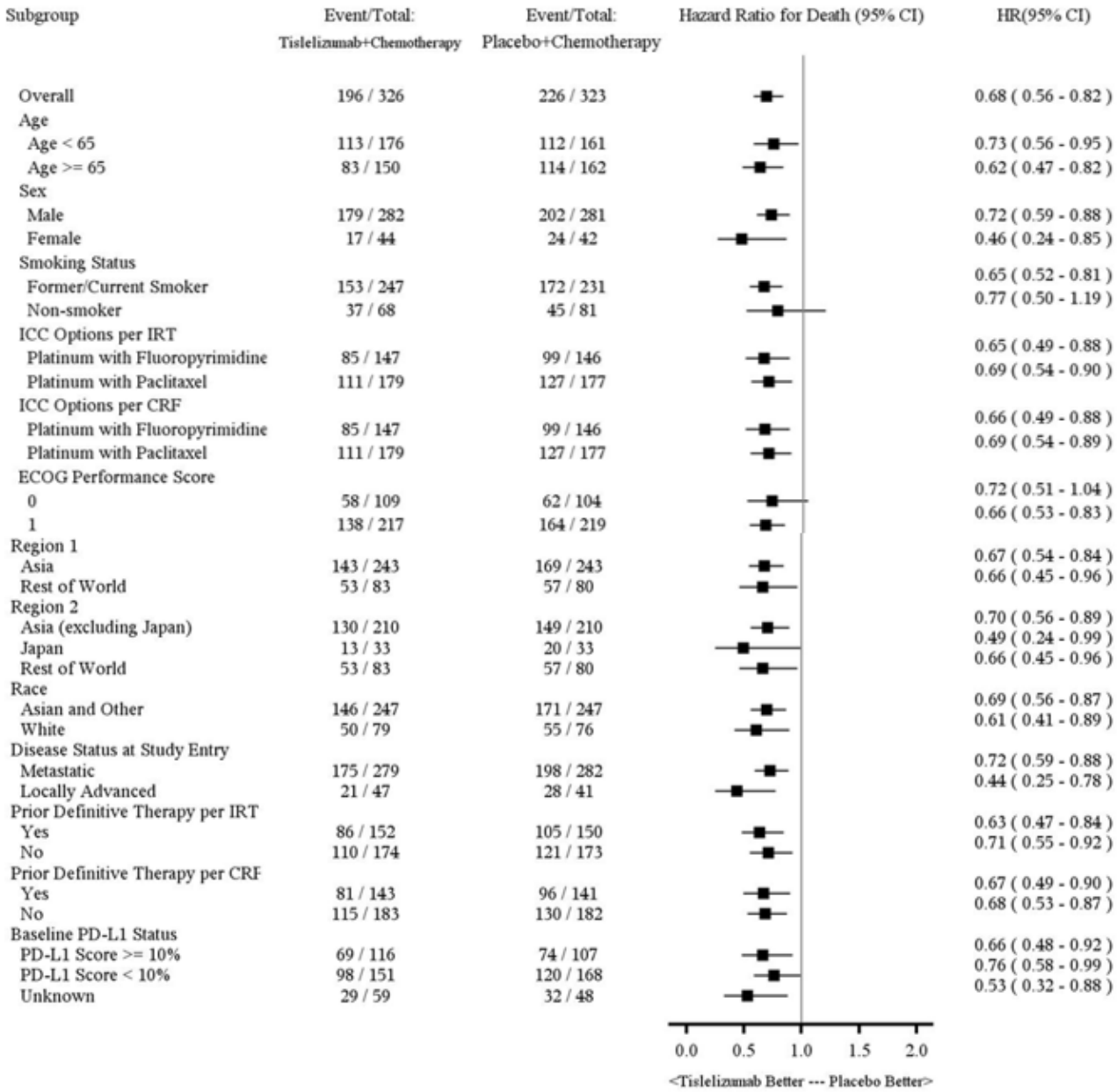
RMST difference of PD-L1 level from 0% to 1% is enhanced in the figure for clarity.

Source: Figure 19 SCE

Ancillary analyses

Efficacy outcomes by further relevant subgroups

Figure 44: Forest Plot of OS by Subgroups - Study 306 (ITT Analysis Set)



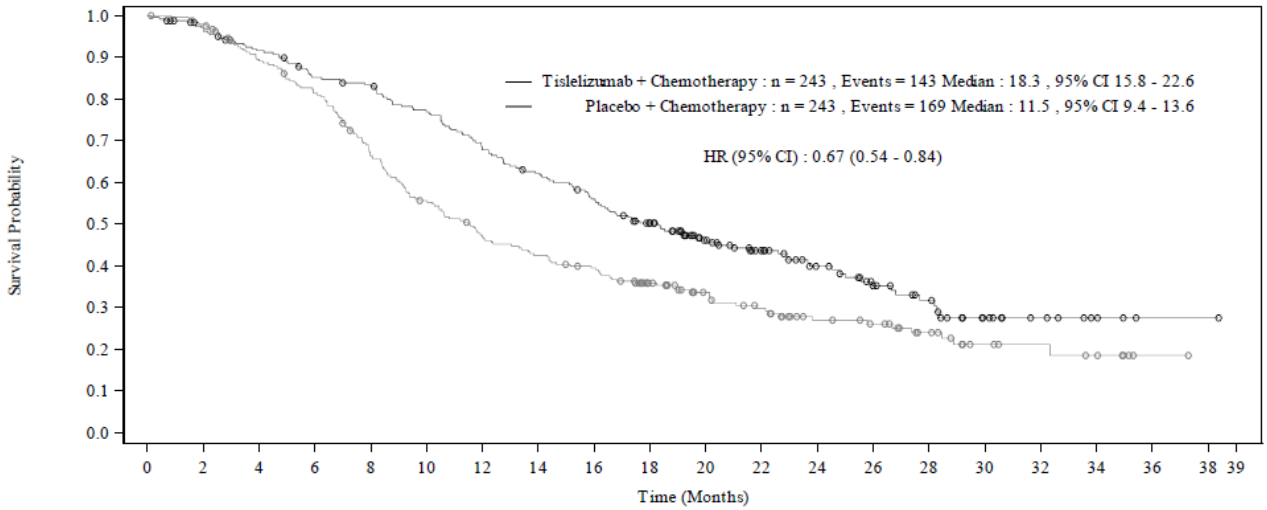
Source: Figure 5 SCE

In the subgroup of patients with prior definitive surgery with/without adjuvant/neo-adjuvant treatment (N=107), the unstratified HR is 0.65 (95% CI: 0.46-0.92). In the subgroup of patients with prior definitive radiotherapy with/without chemotherapy (N=40), the unstratified HR is 0.73 (95% CI: 0.42-1.25).

Outcomes in subgroups by region (Asia and RoW)

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

Figure 45: Kaplan-Meier Plot of OS in Region Asia – Study 306 (ITT Analysis Set)

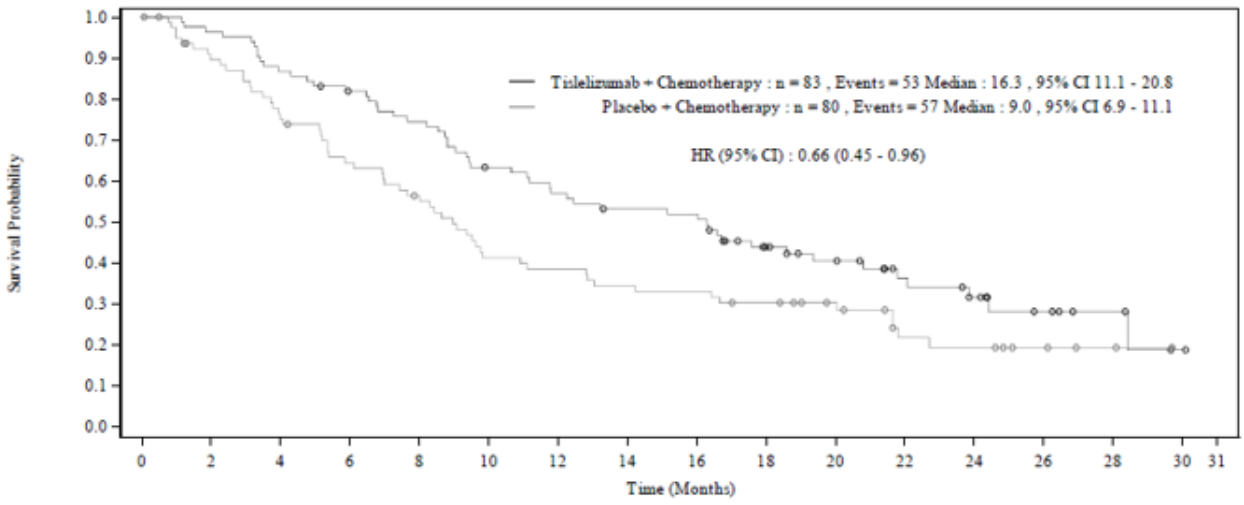


Number of Patients at Risk:

Time:	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39
Tislelizumab +Chemotherapy	243	237	231	221	215	208	198	194	193	181	177	167	156	147	142	137	127	118	108	96	78	70	63	55	46	42	34	30	24	17	13	9	8	6	4	2	1	1	1	0
Placebo +Chemotherapy	243	241	236	221	211	199	191	173	154	140	128	118	107	103	97	91	88	80	70	61	54	49	45	37	32	31	28	23	20	14	11	8	8	7	6	3	1	1	0	0

Source: Figure 6 SCE

Figure 46: Kaplan-Meier Plot of OS in Region RoW – Study 306 (ITT Analysis Set)



Number of Patients at Risk:

Time:	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
Tislelizumab +Chemotherapy	83	83	80	79	72	69	66	62	60	55	50	49	45	43	41	41	40	32	28	24	23	20	16	15	12	8	7	4	4	2	1	0
Placebo +Chemotherapy	80	74	68	64	57	55	48	44	41	36	30	29	28	26	25	24	24	22	21	19	17	14	9	8	8	5	4	2	2	1	0	0

Source: Figure 7 SCE

Additional subgroup analyses of OS by predefined PD-L1 status subgroups (≥10%, <10%, and unknown) and age (<65 years, ≥65 years) were conducted within each of the regions Asia and RoW.

Within the region Asia, subgroup analyses of OS by PD-L1 status showed consistent OS benefit for the T+C Arm compared to the P+C arm for patients with PD-L1 score ≥10% (HR=0.68, 95% CI: 0.47 to

0.99, n=176), PD-L1 score <10% (HR= 0.69, 95% CI: 0.51 to 0.95, n=240), and PD-L1 score unknown (HR=0.63, 95% CI: 0.34 to 1.18, n=70).

Within the region RoW, subgroup analyses of OS by PD-L1 status showed OS benefit for the T+C Arm compared to the P+C arm for patients with PD-L1 score ≥10% (HR=0.50, 95% CI: 0.25 to 1.02, n=47) and PD-L1 score unknown (HR= 0.39, 95% CI: 0.16 to 0.95, n=37), but not for PD-L1 score <10% (HR= 1.00, 95% CI: 0.59 to 1.68, n=79).

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

Table 40: Subgroup Analysis of PFS by Region Assessed by Investigator - Study 306 (ITT Analysis Set)

	Median, months (95% CI) and events/no. of patients		
	Tislelizumab + chemotherapy	Placebo + chemotherapy	Unstratified HR (95% CI)
Overall	7.3 (6.9, 8.3), 220/326	5.6 (4.9, 6.0), 254/323	0.61 (0.51, 0.74)
Region			
Asia (incl. Japan)	7.2 (6.9, 8.5), 157/243	5.6 (4.9, 6.4), 190/243	0.62 (0.50, 0.76)
RoW	7.7 (5.6, 9.5), 63/83	5.5 (3.1, 6.9), 64/80	0.59 (0.41, 0.83)

Source: Table 14 SCE

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

Table 40: Subgroup Analysis of ORR (Unconfirmed) by Region Assessed by Investigator – Study 306 (ITT Analysis Set)

	ORR, % (95% CI), (no. of patients)		
	Tislelizumab + chemotherapy	Placebo + chemotherapy	Odds Ratio for ORR (95% CI)
Overall	63.5 (58.0, 68.7), (n=326)	42.4 (37.0, 48.0), (n=323)	2.38 (1.73, 3.27)
Region			
Asia	64.2 (57.8, 70.2), (n=243)	42.8 (36.5, 49.3), (n=243)	2.40 (1.66, 3.45)
RoW	61.4 (50.1, 71.9) (n=83)	41.3 (30.4, 52.8) (n=80)	2.27 (1.21, 4.25)

Source: Table 15 SCE

Outcomes in subgroups by ICC option (platinum + fluoropyrimidine or platinum + paclitaxel)

- **OS by ICC option**

See Forest Plot in Figure 44. No Kaplan-Meier Plots for these subgroups were provided.

- **PFS by ICC option**

Table 41: Subgroup Analysis of PFS by ICC Option Assessed by Investigator - Study 306 (ITT Analysis Set)

	Median, months (95% CI) and events/no. of patients		
	Tislelizumab + chemotherapy	Placebo + chemotherapy	Unstratified HR (95% CI)
Overall	7.3 (6.9, 8.3), 220/326	5.6 (4.9, 6.0), 254/323	0.61 (0.51, 0.74)
ICC options per CRF			
Platinum + fluoropyrimidine	7.0 (6.7, 8.3), 107/147	5.5 (4.3, 5.8), 115/146	0.66 (0.51, 0.86)
Platinum + paclitaxel	8.2 (6.9, 8.9), 113/179	5.6 (4.9, 6.8), 139/177	0.57 (0.45, 0.74)

Source: Table 15 SCE

- **ORR by ICC option**

Table 42: Subgroup Analysis of ORR (Unconfirmed) by ICC Option Assessed by Investigator – Study 306 (ITT Analysis Set)

	ORR, % (95% CI), (no. of patients)		
	Tislelizumab + chemotherapy	Placebo + chemotherapy	Odds Ratio for ORR (95% CI)
Overall	63.5 (58.0, 68.7), (n=326)	42.4 (37.0, 48.0), (n=323)	2.38 (1.73, 3.27)
ICC options per CRF			
Platinum + fluoropyrimidine	64.6 (56.3, 72.3), (n=147)	43.2 (35.0, 51.6), (n=146)	2.41 (1.50, 3.85)
Platinum + paclitaxel	62.6 (55.0, 69.7), (n=179)	41.8 (34.5, 49.4), (n=177)	2.33 (1.52, 3.56)

Source: Table 15 SCE

Outcomes in subgroup of patients aged ≥ 75 years

Table 43: Efficacy in Patients Aged ⩾ 75 years (ITT Analysis Set) – Interim Analysis

	T+C (N = 13)	P+C (N = 25)
OS		
Unstratified Hazard Ratio (95% CI) [a]	0.91 (0.37, 2.26)	
Median OS (months), (95% CI)	18.5 (3.1, NE)	18.9 (8.0, NE)
PFS		
Unstratified Hazard Ratio (95% CI) [a]	0.69 (0.28, 1.67)	
Median PFS (months), (95% CI)	8.3 (2.8, NE)	6.8 (5.5, 7.2)
ORR		
ORR, % (95% CI)	46.2 (19.2, 74.9)	48.0 (27.8, 68.7)
Odds Ratio for ORR (95% CI)	0.93 (0.24, 3.56)	

[a] Hazard ratio (Tislelizumab + Chemotherapy vs Placebo + Chemotherapy) was based on an unstratified Cox regression model only including treatment as covariate.

Source: Appendix A Table 4.12.1, Table 4.12.2, Responses 1st RSI and SCE

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 44: Summary of Efficacy for Trial 306

Title: A randomized, Placebo-Controlled, Double-Blind Phase 3 Study to Evaluate the Efficacy and Safety of Tislelizumab (BGB-A317) in Combination with Chemotherapy as First-Line Treatment in Patient with Unresectable, Locally Advanced Recurrent or Metastatic Esophageal Squamous Cell Carcinoma	
Study identifier	BGB-A317-306
Design	A randomized, placebo-controlled, double-blind, global Phase 3 study to compare the efficacy and safety of treatment with tislelizumab in combination with standard chemotherapy to placebo in combination with chemotherapy when given as the first-line treatment in patients with locally advanced or metastatic OSCC.

	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 was administered on Day 1 of each 21-day cycle, once every 3 weeks. Chemotherapy: (1) platinum (cisplatin or oxaliplatin) and a fluoropyrimidine (capecitabine or 5-FU) or (2) platinum (cisplatin or oxaliplatin) and paclitaxel. <u>Duration:</u> Study treatment was administered until disease progression, intolerable toxicity, or another reason for treatment discontinuation criterion is met. <u>Number of patients</u>: 326 patients
	Placebo in combination with chemotherapy		Administration of the matched placebo followed the guidance given for tislelizumab. Chemotherapy: (1) platinum (cisplatin or oxaliplatin) and a fluoropyrimidine (capecitabine or 5-FU) or (2) platinum (cisplatin or oxaliplatin) and paclitaxel. <u>Duration</u>: Study treatment was administered until disease progression, intolerable toxicity, or another reason for treatment discontinuation criterion is met. <u>Number of patients</u>: 323 patients
Endpoints and definitions	Primary endpoint	OS – ITT Analysis Set	Overall survival (OS) in the ITT Analysis Set, defined as the time from the date of randomization until the date of death due to any cause.

	Secondary endpoints	- PFS by Investigator - ORR by Investigator - OS – PD-L1 score ≥ 10% - DOR by Investigator	- PFS - defined as the time from the date of randomization to the date of first documentation of disease progression assessed by the investigator per RECIST v1.1 or death, whichever occurs first - 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 - OS in the PD-L1 score ≥ 10% subgroup – defined as the time from the date of randomization until the date of death due to any cause in patients with PD-L1 score ≥ 10% - 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	Data Cut-off Date: 28 February 2022		

Results and Analysis

Analysis description	**Primary Analysis - OS**		
Analysis population and time point description	**Intent-to-treat analysis set** Interim analysis DCO: 28-Feb-2022		
Descriptive statistics and estimate variability	Treatment group	Tislelizumab + chemotherapy	Placebo + chemotherapy
	Number of patients	N=326	N=323
	Median OS (months)	17.2	10.6
	95% CI	15.8, 20.1	9.3, 12.1
Effect estimate per comparison	OS	Comparison groups	Tislelizumab + chemo vs chemo
		Stratified Hazard ratio (HR)	0.66
		95% CI	0.54, 0.80
		One-sided stratified log-rank test p-value	<0.0001
Analysis description	**Secondary endpoints analysis**		
Analysis population and time point description	**Intent-to-treat analysis set**		
Descriptive statistics and estimate variability	Treatment group	Tislelizumab + chemotherapy	Placebo + chemotherapy
	Number of patients	N=326	N=323
Progression free survival by investigator	Median PFS (months)	7.3	5.6
	95% CI	6.9, 8.3	4.9, 6.0
Unconfirmed Objective Response Rate by investigator	ORR, n	207	137
	ORR (%)	63.5	42.4

	95% CI	58.0, 68.7	37.0, 48.0
Overall Survival in PD-L1 Score ≥ 10% Subgroup	Number of patients	N = 116	N = 107
	Median OS (months)	16.6	10.0
	95% CI	15.3, 24.4	8.6, 13.3
Unconfirmed Duration of Response by Investigator	Number of responders	207	137
	Median DOR (months)	7.1	5.7
	95% CI	6.1, 8.1	4.4, 7.1
Effect estimate per comparison	PFS	Comparison groups	Tislelizumab + chemo vs chemo
		Stratified Hazard ratio (HR)	0.62
		95% CI	0.52, 0.75
		One-sided stratified log-rank test p-value	<0.0001
	ORR	Comparison groups	Tislelizumab + chemo vs chemo
		Odds ratio for ORR	2.38
		95% CI	1.73, 3.27
		Two-sided stratified CMH test p-value	<0.0001
	OS in PD-L1 Score ≥ 10% Subgroup	Comparison groups	Tislelizumab + chemo vs chemo
		Stratified Hazard ratio (HR)	0.62
		95% CI	0.44, 0.87
		One-sided stratified log-rank test p-value	0.0029

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

N/A

Clinical studies in special populations

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
Controlled Trials	Tisle+Chemo: 137/326 Placebo+Chemo: 137/323	Tisle+Chemo: 13/326 Placebo+Chemo: 25/323	Tisle+Chemo: Placebo+Chemo:

N/A; subgroup analyses of efficacy by age are presented above.

In vitro biomarker test for patient selection for efficacy

Baseline PD-L1 status was assessed from archival tumor tissue by a central laboratory using an immunohistochemistry assay. If no archival samples were available, a fresh tumor biopsy at baseline (within 28 days before randomization) was required (this requirement was added with protocol amendment 2).

After completion of the CSR for the interim analysis, the baseline PD-L1 score for 35 patients (21 in the T+C arm and 14 in the P+C arm) were identified to have been assessed using unsuitable samples. The baseline PD-L1 scores for those patients were re-classified as "unknown".

Supportive study(ies)

N/A

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The scope of this variation is to support the approval for Tevimbra (tislelizumab) in combination with platinum-based chemotherapy for the first-line treatment of adult patients with unresectable, locally advanced or metastatic oesophageal squamous cell carcinoma (OSCC).

The pivotal study BGB-A317-306 supporting this application is an ongoing randomized, placebo-controlled, double-blind, global Phase 3 study comparing the efficacy and safety of treatment with tislelizumab in combination with investigator's choice chemotherapy (ICC) to placebo in combination with ICC when given as first-line treatment in patients with locally advanced or metastatic OSCC. Overall, the study design is considered adequate. Stratification factors for this study were region (Asia [excluding Japan] vs. Japan vs. RoW), prior definitive therapy (yes vs. no), and ICC option (platinum + fluoropyrimidine vs. platinum + paclitaxel).

Patient population

The applied inclusion and exclusion criteria are considered adequate for selection of a population that is representative of a patient population eligible for 1st line palliative treatment with chemotherapy. Study 306 enrolled patients with a histologically confirmed diagnosis of OSCC with metastatic or locally advanced disease that was not amenable to definitive surgery or chemoradiation. All patients were enrolled regardless of their tumour PD-L1 expression level and were required to have at least one evaluable lesion per RECIST v1.1, ECOG PS score of ≤ 1, adequate organ function, and adequate nutritional status.

Patients with uncontrolled brain metastases or leptomeningeal disease, evidence of fistula (oesophageal/bronchial or oesophageal/aorta), evidence of complete oesophageal obstruction, and prior receipt of anti-PD-1/PD-L1 therapy were excluded from the study. Except for prior receipt of anti-PD-1/PD-L1 therapy, these exclusion criteria are reflected in the SmPC.

Treatments

Tislelizumab was administered at a dose of 200 mg Q3W, which corresponds to the dose that is currently approved for tislelizumab monotherapy in 2nd line OSCC. In study BGB-A317-306, tislelizumab was administered in combination with investigator's choice chemotherapy, which was either platinum (cisplatin or oxaliplatin) with fluoropyrimidine (5-FU or capecitabine) or platinum

(cisplatin or oxaliplatin) with paclitaxel. In line with the recommendations of a CHMP scientific advice, the type of chemotherapy backbone was selected prior to randomization and ICC option was included as stratification factor.

At the time of study initiation, the combination of platinum + fluoropyrimidine was standard of care in 1L treatment of unresectable, advanced or metastatic OSCC in the EU (Lordick et al 2016, NCCN 2017). Due to the global nature of the study, chemotherapy doublet comprising platinum + paclitaxel was allowed as further treatment option at the investigators' discretion to accommodate regional specific clinical practice. As a result, approximately 55% of patients enrolled in Study 306 received platinum + paclitaxel as chemotherapy backbone, which is not considered an adequate comparator in the EU. However, subgroup analyses of efficacy by ICC option revealed that the treatment effect is consistent: Comparable OS benefit favouring the T+C over the P+C arm was shown in analyses of subgroups by ICC option, either per IRT (OS HR = 0.65 [95% CI: 0.49, 0.88] for subgroup of patients treated with platinum + fluoropyrimidine and OS HR = 0.69 [95% CI: 0.54, 0.90] for subgroup of patients treated with platinum + paclitaxel) or per CRF (OS HR = 0.66 [95% CI: 0.49, 0.88] for subgroup of patients treated with platinum + fluoropyrimidine and OS HR = 0.69 [95% CI: 0.54, 0.89] for subgroup of patients treated with platinum + paclitaxel). Results in subgroups by ICC option are therefore reassuring and indicative of the applicability of the overall treatment effect to the EU population.

Endpoints

The study was initially designed with OS and BIRC-assessed PFS as dual primary endpoints. Following protocol amendment version 4.0, which was introduced approx. 5 months after the last patient was randomized, OS in the ITT Analysis Set was defined as single primary endpoint for this study. In general, the selection of OS as primary endpoint is endorsed, as OS represents the most persuasive outcome both from a clinical and methodological point of view. Moving BIRC-assessed PFS from dual primary endpoint to an exploratory endpoint was justified by the fact that recently published results for anti-PD-1 therapies in the 1st line treatment of oesophageal carcinomas indicated a significant and clinically meaningful improvement in OS as a gold standard for clinical benefit, while the magnitude of PFS improvement was 0.5 month and therefore not considered sufficient to support PFS as a surrogate endpoint for OS. In addition, the Applicant argued that the double-blinded nature of Study 306 did not necessarily require a PFS assessed by BIRC, and PFS assessed by the investigator was already included as a secondary endpoint. The argumentation can be followed.

OS in the ITT PD-L1 score ≥ 10% subgroup, PFS, ORR, and DOR assessed by investigator, as well as HRQoL were analysed as secondary endpoints in Study 306. These are standard endpoints applied in oncology trials and are in principle deemed acceptable. DCR, PFS, ORR and DOR assessed by BIRC, and PFS2 were exploratory endpoints and are considered appropriate.

Sample size

The study enrolled 649 patients, providing 90% power to demonstrate an effect on OS. The sample size is in principle reasonable, but some uncertainty was raised by the fact that it was amended twice during the ongoing study.

First, in protocol amendment 3.0 on 25 May 2020, the study sample size was increased from 480 to 622. The targeted event numbers were increased, for both PFS (319 to 423) and death (360 to 467) to account for the delayed treatment effect and increased usage of subsequent immunotherapies that were observed in the newly published immuno-oncology trials in the second-line treatment of OSCC (Kojima et al 2019; Kato et al 2019; Huang et al 2019).

Second, after the enrolment was completed with 649 randomized patients on 24 November 2020, the protocol was again amended to remove BIRC-assessed PFS from the primary endpoints, making OS

the sole primary efficacy endpoint, and the number of deaths required in the final analysis was again increased from 467 to 488. Each of the changes was considered reasonable, the applicant provided reassurance through supportive analyses that the changes were not influenced by emerging data from the study and that the overall interpretation of results was not substantially affected by these changes.

Statistical analysis

No estimand was prespecified, but it seems rather clear that the effect of treatment on OS was estimated irrespective of intercurrent events (unless they lead to unknown survival status in which case the patient is censored).

Overall the analysis methods, using a stratified logrank test for testing and a stratified Cox PH model for estimation are appropriate. Stratification of the analysis was planned to be consistent with stratified randomization, but eventually the geographic strata "Japan" and "Asia without Japan" were pooled in the analysis although they were independent strata for stratified randomization. This is not ideal, however, sensitivity analyses were conducted and do not raise concern.

Substantial changes have been made to the ongoing study, including change of primary endpoints (removal of PFS) and increase in sample size (both number of patients as well as number of events).It was reassured through additional OS analyses that the interpretation of primary results was not substantially altered by these late changes to the protocol.

Regarding secondary endpoints, a potential confirmatory interpretation should be done with caution for several reasons: OS in PD-L1 ≥10% was only added to the confirmatory strategy in amendment 4, several months after enrolment was completed. The multiplicity strategy for secondary endpoints was not fully understood due to some inconsistencies between text and figures in amendment 4. No alpha spending was planned for secondary time-to-event endpoints (such as OS in PD-L1≥10%), which might potentially inflate type I error for these endpoints. Some details for the analysis of confirmatory secondary endpoints were only specified in the SAP (such as a Bonferroni-split for dysphagia, eating and reflux). Thus, these endpoints should be interpreted with some caution. Nonetheless, in light of an overall positive study an ad-hoc interpretation may be possible and does not preclude that results are seen as clinically meaningful.

Censoring for PFS includes censoring for missed tumour visits and new anticancer treatment. Both may lead to informative censoring. In particular, new anticancer treatment likely indicates that the patient's condition indicated the need for further treatment. This could be seen as an indicator of progression. It is acknowledged that the applicant provided sensitivity analyses with different censoring.

Recruitment and conduct of the study

Study 306 is a global study which recruited patients from 16 countries/regions, including Asia, Australia, Europe and North America. The majority of patients was enrolled in China.

At the data cut-off date of 28 February 2022, the majority of patients had discontinued study treatment (91.2%), while 70.6% of patients had discontinued from the study as a whole. Treatment discontinuations and discontinuations from the study were more frequent in the P+C arm as compared to the T+C arm (94.7% vs. 87.7% and 76.2% vs. 65.0%, respectively), which could be mainly attributed to higher rates of progressive disease or death events in the P+C arm. The median study follow-up duration was longer in the T+C arm as compared to the P+C arm (16.3 months vs. 9.8 months, respectively), which can be explained by patients in the P+C arm having more frequently discontinued the study early (e.g. due to death).

The original global protocol for Study 306 was dated 13 February 2018. There were 4 global amendments of the clinical study protocol. Amongst others, changes affected the inclusion and

exclusion criteria, study assessments and dose modification/toxicity management guidance. Changes related to the study design and pre-planned analyses are discussed in above sections on sample size and statistical analysis.

A total of 22.0% of patients had important protocol deviations. In general, the number of patients with protocol deviations was low and no relevant differences were observed in the frequency of important protocol deviations between the treatment arms. A significant impact on the overall interpretation of efficacy outcomes is therefore not considered likely.

Baseline characteristics

The study population included in Study 306 was predominantly male (86.7%) and had a median age of 64.0 years. The sample size in the subgroup of patients aged ≥75 years was low and distribution of patients was imbalanced (N=13 in T+C and N=25 in P+C arm). Still, in line with observations made in patients aged ≥75 years in clinical trials with other PD-(L)1 inhibitors and with tislelizumab studied in other indications, clinical benefit in this subgroup of patients is uncertain (OS HR = 0.91 [95% CI: 0.37, 2.26]). The majority of patients was recruited at sites in Asia and thus, 74.9% of patients were from Asia, while only 25.1% of patients enrolled were from RoW. However, there were overall no apparent differences in OS by region (Asia: HR = 0.67 [95% CI: 0.54, 0.84] and RoW: HR = 0.66 [95% CI: 0.45, 0.96]). These results are considered reassuring in support of the EU extension of indication.

In part, imbalances in baseline characteristics of the ITT population and between the Asia and RoW subgroup were observed.

However, referring to the OS results presented by subgroups (Figure 44), these imbalances are not considered to have meaningfully impacted the overall efficacy outcome, since comparable benefit was demonstrated in subgroups by age, smoking status, gender, ECOG PS, disease status and prior definitive therapy.

Efficacy data and additional analyses

Efficacy data provided are based on the planned interim analysis with data cut-off date 28 February 2022 and database lock date 6 April 2022. During the procedure, the Applicant additionally provided 3-year follow-up data for PD-L1 subgroups with data cut-off 24 November 2023.

The study met its primary objective. The primary analysis of OS in the ITT population demonstrated a statistically significant benefit of tislelizumab + ICC over placebo + ICC control with an event rate of 60.1% and 70.0%, respectively (stratified HR = 0.66 [95% CI: 0.54 – 0.80], $p < 0.0001$, median OS 17.2 months for T+C vs. 10.6 months for P+C). The increase in median OS of 6.6 months is deemed clinically meaningful, particularly considering the poor prognosis of patients with advanced or metastatic OSCC. Sensitivity analyses of the primary endpoint OS were consistent with the primary analysis (see Table 29).

Given that the data cut-off date for the primary analysis was 28 February 2022, updated OS data based on data cut-off date 28 April 2023 with a longer OS follow-up (37 months vs. 23.7 months) and a total of 498 OS events were provided. The efficacy outcome remained consistent with the primary analysis results, showing a sustained and clinically meaningful OS benefit for the T+C over the P+C arm (stratified HR = 0.69 [95% CI: 0.58 – 0.83], $p < 0.0001$, median OS 17.2 months for T+C vs. 10.6 months for P+C).

Significant benefit of T+C over P+C was further demonstrated in the analyses of secondary endpoints:

Treatment with T+C resulted in a statistically significant improvement over P+C in investigator-assessed PFS (stratified HR = 0.62 [95% CI: 0.52 - 0.75]), p <0.0001, median PFS 7.3 months in the T+C arm vs. 5.6 in the P+C Arm). The result of PFS assessed by BIRC (Stratified HR = 0.60 [95% CI: 0.49 to 0.74]), which was moved from dual primary objective to exploratory objective with global protocol amendment 4.0, was consistent with the result reported for investigator-assessed PFS.

Analysis of both unconfirmed and confirmed ORR assessed by investigator demonstrated higher tumour response rates in the T+C Arm than in the P+C Arm (unconfirmed ORR: 63.5% vs. 42.4%, stratified ORR difference = 21.2%; confirmed ORR: 56.4% vs. 36.2%, stratified ORR difference = 20.3%). Since Study 306 was conducted as double-blind study, results on ORR assessed by investigator can be considered sufficiently substantive. Moreover, the analysis of ORR by BIRC, which was assessed as exploratory objective, consistently showed higher response rates in patients in the T+C arm as compared to the P+C arm (ORR by BIRC: 67.8% vs. 48.9%).

Analysis of both unconfirmed and confirmed DOR assessed by investigator revealed a trend towards more durable tumour response in the T+C Arm than in the P+C Arm (median unconfirmed DOR 7.1 months vs. 5.7 months, median confirmed DOR 7.4 months vs. 6.6 months).

No significant differences in PRO endpoints (as analysed by EORTC QLQ-C30, EORTC QLQ-OES18, and EQ-5D-5L questionnaires) were observed between patients in the T+C arm vs. patients in the P+C arm. As a result, inferential testing was stopped at the level of HRQoL endpoints. Given that a statistically significant improvement of HRQoL could not be demonstrated, the information on HRQoL endpoints with conclusion that HRQoL was "maintained" is deleted from the SmPC.

Of note, treatment with T+C also prolonged the time to disease progression or death after the next line of treatment (PFS2). HR was 0.62 (95% CI: 0.51 to 0.75) and median PFS2 was 13.7 months in the T+C arm vs. 9.1 months in the P+C arm.

Efficacy by PD-L1 expression status

The pivotal study BGB-A317-306 exhibited several uncertainties and deficiencies with regard to PD-L1 expression (analyses):

- Patients were enrolled regardless of their tumour PD-L1 expression level. With global protocol amendment 2.0, tumour tissue sample collection for biomarker assessment was implemented as inclusion criterion and thus became mandatory 10 months after the first patient was randomized. Still, approx. 15 – 20% of patients had PD-L1 status "unknown". In general, analysis of PD-L1 expression in all patients enrolled and stratification by PD-L1 expression status, as already outlined in preceding CHMP scientific advice and presubmission meetings, would have been beneficial. PD-L1 status was assessed by tumour area positive score (TAP) as determined using the VENTANA PD-L1 (SP263) assay.
- Patients were not stratified by PD-L1 expression status and thus, slight imbalances were observed between treatment groups with regard to PD-L1 expression score. The proportion of patients with PD-L1 score <10% was lower in the T+C Arm (46.3%) than the P+C Arm (52.0%), whereas the proportion of patients with PD-L1 score unknown was slightly higher in the T+C Arm (18.1%) than the P+C Arm (14.9%). Patients in the Asia versus RoW subgroup had a slightly higher proportion of PD-L1 score ≥ 10% (37.9% vs. 31.9%), and a lower proportion of PD-L1 status unknown (9.9% vs. 14.7%). Within the RoW subgroup, a higher proportion of patient presented with PD-L1 score ≥ 10% in the T+C arm as compared to the P+C arm (41.0% vs. 22.5%). However, imbalances with regard to PD-L1 expression status dichotomized at the 10% threshold are not deemed worrisome, since benefit was observed for patients with both PD-L1 score ≥10% and PD-L1 score <10%, as discussed below.

Conclusively, the selected threshold for PD-L1 is not considered most useful in the population studied and the issue is not further pursued.

- The analysis of OS in the subgroup of patients with PD-L1 TAP Score ≥ 10% was introduced approx. 5 months after the last patient was randomized. No valid justification for the choice of the 10% cut-off was provided and the 10% threshold for PD-L1 expression does not seem to be adequate to discriminate patients benefiting or not from the addition of tislelizumab to chemotherapy.

OS in patients with PD-L1 score ≥ 10% showed a statistically significant treatment effect of T+C as compared to P+C (stratified HR = 0.62 [95% CI: 0.44, 0.87]. The median OS was 16.6 months for the T+C arm and 10.0 months for the P+C arm. In line with what has been demonstrated as regards to the predictive value of PD-L1 expression level, a trend to a lower benefit of T+C is indicated in patients with PD-L1 score < 10% (stratified HR for OS = 0.77 [95% CI: 0.59, 1.01], median OS of 15.8 months in the T+C arm vs. 10.4 months in the P+C arm). It is noted that the subgroup of patients with PD-L1 expression status < 10% is largest (about 50% of the study population, comprising 319 patients, vs. 34.4% of patients with PD-L1 score ≥ 10% and 16.5% of patients with unknown PD-L1 status). Further subgroup analyses by lower cut-offs for PD-L1 expression were required to examine the potential presence of a subgroup of patients with lower PD-L1 expression status within the subgroup of patients with PD-L1 score < 10% which may not benefit from study treatment. As a consequence, additional subgroup analyses of OS, PFS and ORR by baseline PD-L1 expression status (corresponding to cut-offs 25%, 5%, 1%, and 0%) were provided.

In the PD-L1 expression score subgroups ≥25% (N=92), 10% to <25% (N=131), and 5% to <10% (N=135), HRs were in favour of the T+C arm as compared to the P+C arm (see Figure 34). However, analysis of the subgroups with lower PD-L1 expression ([1% to <5%] and [< 5%]) revealed no meaningful difference in OS: HR 1.04 [95% CI: 0.74, 1.46] in patients with PD-L1 score <5% (N=184) and HR was 0.93 [95% CI: 0.61, 1.41] in patients with PD-L1 score 1% to <5% (N=123). These data illustrate that already in the subgroup of patients with PD-L1 expression score between 1 to <5%, no clinically meaningful OS benefit of T+C over P+C is apparent. In the subgroup of patients with PD-L1 expression status >0 to <1%, and 0%, even detrimental OS effects were shown for the T+C as compared to the P+C arm (HR in patients with PD-L1 score >0 to <1% (N=32) was 1.23 [95% CI: 0.50, 3.06], and HR in patients with PD-L1 score 0% (N=29) was 1.45 [95% CI: 0.63, 3.31]), although of course the low number of patients included in the lowest PD-L1 expression subgroups (<1%) has to be taken into account and results should be interpreted with caution.

Similarly, analyses of PFS assessed by investigator revealed lower PFS benefit of T+C in the subgroup of patients with PD-L1 expression <5% (HR = 0.79, with the upper bound of the 95% CI crossing 1: [95% CI: 0.57, 1.10]). Furthermore, no clinically meaningful difference in unconfirmed ORR is apparent comparing the T+C arm vs. the P+C arm in patients with PD-L1 expression <5% (51.6% vs. 48.3%, odds ratio for ORR = 1.14).

In further support of the subgroup analyses by PD-L1 expression status, an exploratory modelling approach was used to investigate the association of baseline PD-L1 levels on the treatment effect on the primary OS endpoint. Results from the modelling exercise suggest a clear predictive effect of PD-L1, with a potential detriment with no expression and an increasing benefit with higher expression. Acknowledging the exploratory nature of these analyses, the characterization biomarker-dependent benefit supported the choice of cutoff for the restricted indication.

Accounting for the totality of data presented for subgroups of patients by PD-L1 expression status, the unrestricted indication as claimed by the Applicant was not agreed. Considering the toxicity profile and the fact that tislelizumab will be an add-on treatment for 1L advanced or metastatic OSCC, the

outcome in patients with PD-L1 TAP score <5% (OS HR = 1.04; PFS HR = 0.79; ORR 51.6% for T+C vs. 48.3% for P+C) is not deemed sufficient to conclude on a positive benefit-risk for this patient population. Despite the methodological uncertainties due to study design (lack of stratification, imbalances, and missing data regarding PD-L1 expression), the analyses in subgroups by PD-L1 expression are considered credible. This is based on the fact that external validity of the study is overall not questioned and that data confirmed the predictive value of PD-L1 expression as already demonstrated with other checkpoint inhibitors in 1L OSCC studies. Conclusively, the indication of tislelizumab in combination with platinum-based chemotherapy for 1L treatment of advanced or metastatic OSCC was restricted to patients with PD-L1 expression score TAP ≥ 5%.

OSCC Efficacy data by PD-L1 expression ≥5%, 1% to < 5%, and ≥1% were provided with data cut-off (28 April 2023) and a 3-year follow-up data cut-off (24 November 2023). OS results remain consistent with the primary efficacy outcome. At data cut-off date 28 April 2023, the stratified OS HR in the subgroup of patients with PD-L1 expression score <5% was 0.95, while in the subgroup of patients with PD-L1 expression score ≥5% the stratified OS HR was 0.62. At data cut-off date 24 November 2023, the stratified OS HR in the subgroup of patients with PD-L1 expression score <5% was 0.94 (95% CI: 0.68, 1.29), while in the subgroup of patients with PD-L1 expression score ≥5% the stratified OS HR was 0.62 (95% CI: 0.49, 0.79). Overall, the results provide reassurance in applying the ≥5% cut-off for PD-L1 expression, since a clear discrimination is evident between the subgroup of patients with more pronounced benefit (PD-L1 score ≥5%) and the subgroup of patients showing questionable benefit from treatment with T+C (PD-L1 score <5%) when compared to P+C.

The presumed marginal benefit in the subgroup of patients with PD-L1 expression 1% to <5% does not outweigh the additional toxicity of tislelizumab treatment in combination with chemotherapy. Thus, the B/R balance is not considered favourable in patients with PD-L1 expression <5%.

Efficacy in further relevant subgroups

The OS benefit in favour of the T+C arm was generally evident across all pre-defined subgroups (ICC options, region, ECOG PS, age, sex, smoking status, race, locally advanced vs metastatic disease, prior definitive therapy). HR point estimates ranged from 0.44 to 0.77 (see Figure 44).

Wording of the indication

The efficacy is considered established in the finally agreed indication, and this has been included in the section 4.1 of the SmPC:

Tevimbra, in combination with platinum-based chemotherapy, is indicated for the first-line treatment of adult patients with unresectable, locally advanced or metastatic OSCC whose tumours express PD-L1 with a tumour area positivity (TAP) score ≥ 5%.

2.4.4. Conclusions on the clinical efficacy

In the intended target population of patients with locally advanced or metastatic OSCC eligible for 1L systemic treatment, a clinically meaningful and statistically significant benefit favouring tislelizumab in combination with chemotherapy was demonstrated for the primary endpoint OS and secondary endpoints PFS and ORR in the ITT population.

Considering the subgroup results presented by PD-L1 score and the additional toxicity of tislelizumab in combination with chemotherapy, the B/R balance was not considered favourable in patients with PD-L1 expression <5%. Conclusively, the indication of tislelizumab in combination with platinum-based chemotherapy for 1L treatment of advanced or metastatic OSCC is restricted to patients with PD-L1 expression score (TAP) ≥5%.

2.5. Clinical safety

Introduction

Data from all tislelizumab-treated patients in Study BGB-A317-306 (hereafter referred to as Study 306) as of the interim data cut-off date of 28 February 2022 are the primary source of data supporting the safety of tislelizumab in combination with platinum-based chemotherapy in adult patients as a first-line treatment of unresectable, locally advanced or metastatic OSCC. For abbreviations, please see List of Abbreviations.

The safety profile of tislelizumab is complemented by the pooled safety data from 7 monotherapy studies (Table 43) and by the pooled safety data from 4 studies (Table 44) in which tislelizumab was administered in combination with various chemotherapies.

The safety data in the following sections are presented side-by-side in tables for the following populations:

- Study 306 tislelizumab + chemotherapy (N = 324)
  including all patients from Study 306 who received at least one dose of tislelizumab 200 mg in combination with platinum-based chemotherapy (**T+C Arm**)
- Study 306 placebo + chemotherapy (N = 321)
  including all patients from Study 306 who received at least one dose of placebo in combination with platinum-based chemotherapy (**P+C Arm**)
- **Tislelizumab Monotherapy Pool** (N = 1534)
  including all patients who received the approved registrational dosing regimen of tislelizumab 200 mg Q3W across various indications in Study 302, Study 001, Study 102, Study 203, Study 204, Study 208, and Study 303 (Table 45).

Table 45: Studies providing safety data for tislelizumab monotherapy (abridged)

	001	**102**	**208**	**204**	**203**	**302**	**303**
Phase	I†	I/II*	II	II	II	III	III
Disease type	Solid tumours	Solid tumours	Previously treated, unresectable HCC	UC	R/R cHL	Advanced unresectable/ metastatic OSCC	Locally advanced or metastatic NSCLC (squamous or nonsquamous)
Patients in Safety Set (N)	13 in 200 mg dose	300 (300 in 200 mg dose arm including 57 PK substudy who received 200 mg W1D1, W5D1 Q3W)	249	113	70	255	534
Data cut-off date	26-Aug-2020 (Final CSR data cut-off)	31-May-2020 (Final CSR data cut-off)	30-Jun-2021 (Final CSR data cut-off)	16-Sep-2019 (Interim CSR data cut-off)	02-Nov-2020 (Final CSR data cut-off)	01-Dec-2020 (Final CSR data cut-off)	15-Jul-2021 (Interim CSR data cut-off)

	001	102	208	204	203	302	303

† 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.
*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. Source: [Study 001], [Study 102], [Study 208], [Study 204], [Study 203], [Study 302], and [Study 303]
Source: Summary of Clinical Safety, excerpt from Table 2

In individual instances, the safety data of the **Tislelizumab Combination Therapy Pool** (N = 838) are presented as well. The Tislelizumab Combination Therapy Pool includes all patients who received the approved registrational dosing regimen of tislelizumab in combination with various chemotherapies and across various indications in Study 206, Study 304, **pivotal Study 306**, and Study 307 (Table 46).

Applications for marketing authorisation have been overlapping for tislelizumab in combination with chemotherapy for the first-line treatment of patients with unresectable, locally advanced or metastatic OSCC (based on Study 306) and for the first-line treatment of patients with unresectable, locally advanced or metastatic G/GEJ adenocarcinoma (based on Study 305)[1]. Therefore, 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 gastro-oesophageal junction (G/GEJ) adenocarcinoma and oesophageal squamous cell carcinoma (OSCC) who have been treated with tislelizumab + chemotherapy in Studies 206, 304, 305, 306, and 307. Of note not all 54 patients from Study 206 were included in the Tislelizumab Combination Therapy Pool presented in section 4.8 of the SmPC, but only the 37 NSCLC patients from this study are included (i.e., the 17 patients from the SCLC cohort are excluded).

Table 46: Studies providing safety data for tislelizumab in combination with chemotherapy including pivotal Study 306 (abridged)

	206	**304**	**Pivotal Study 306**	**307**
Phase	Phase II	Phase III	**Phase III**	Phase III
Disease type	Locally advanced or metastatic NSCLC (squamous or nonsquamous), SCLC	Non-squamous NSCLC	**Unresectable, locally advanced recurrent or metastatic OSCC**	Squamous NSCLC
Chemotherapy	Platinum-containing doublet chemotherapy as per histology	Platinum (cisplatin or carboplatin) plus pemetrexed[a]	**Platinum (cisplatin or oxaliplatin) with fluoropyrimidine (capecitabine or 5-FU) or platinum with paclitaxel[c]**	T+PC[b]: Paclitaxel and carboplatin; T+nPC[b]: Nab-paclitaxel and carboplatin
Safety Set (N) in tislelizumab arm	54	222	**324**	238

[1] Procedures EMEA/H/C/005919/II/0003 and EMEA/H/C/005919/II/0006, respectively

	206	304	Pivotal Study 306	307
Data cut-off date	31-Dec-2019 (Final CSR data cut-off)	26-Oct-2020 (Final CSR data cut-off)	**28-Feb-2022** **(Interim Analysis CSR data cut-off)**	30-Sep-2020 (Final CSR data cut-off)

[a]Cisplatin 75 mg/m^2 iv or Carboplatin AUC 5 iv, pemetrexed 500 mg/m^2 (4-6 cycles) iv. Maintenance treatment of pemetrexed 500 mg/m^2 Q3W
[b] T+PC: Paclitaxel 175 mg/m2 iv D1 Q3W, Carboplatin AUC 5 D1 Q3W iv (4-6 cycles); T+nPC: Nab-paclitaxel 100 mg/m2 iv D1, 8, 15 Q3W, Carboplatin AUC 5 D1 Q3W iv (4-6 cycles)
[c]Cisplatin: 60-80 mg/m2 iv or Oxaliplatin: 130 mg/m2 iv D1 every 3 weeks, 5-FU: 750-800 mg/m2 D1-5 every 3 weeks iv, Capecitabine: 1000 mg/m2 on D1-14 of each cycle oral bid (2x/day), Paclitaxel: 175 mg/m2 on Day 1 every 3 weeks iv.
Source: [Study 206], [Study 304], [Study 306], and [Study 307]
Source: Summary of Clinical Safety, excerpt from Table 3

Data from the Tislelizumab Monotherapy Pool and those from the Tislelizumab Combination Therapy Pool are considered as supportive and are only mentioned in individual instances. This is due to the fact that differences in the included studies' design, patient populations, tumour types, and previous therapy (first- or second-line) are substantial, precluding a direct comparison of data from Study 306 and those of the Tislelizumab Monotherapy Pool and Tislelizumab Combination Therapy Pool, respectively.

The data cut-off date for the ongoing pivotal Study 306 was 28 February 2022, and the data cut-off dates for the supportive studies range from 2019 to 2021. More recent data may be available for Study 306. However, as only a small number of patients in Study 306 remained on treatment at the cut-off date (11.7% in the T+C Arm vs. in the 4.7% P+C Arm), there is no need for data from a more recent cut-off date.

Patient exposure

Exposure in Study 306 and in the Tislelizumab Monotherapy Pool

Exposure to T+C, P+C (Study 306), and to tislelizumab monotherapy (Safety Set) is summarised in Table 47.

Table 47: Study medication administration - tislelizumab/placebo/tislelizumab monotherapy pool (Safety Set)

	Study 306		Tislelizumab Monotherapy Pool 200 mg Q3W N=1534
	T+C Arm N=324	P+C Arm N=321	
Total number of subjects receiving study drug, n (%)	324 (100.0)	321 (100.0)	1534 (100.0)
Duration of exposure (months)			
Mean (SD)	8.80 (7.759)	6.56 (6.055)	8.58 (9.650)
Median	6.41	4.90	4.17
Q1-Q3	3.33-11.12	2.53-8.34	2.07-11.04
Min-Max	0.1-38.3	0.6-34.9	0.2-43.3
Duration of exposure (categories), n (%)			
<1 month	22 (6.8)	21 (6.5)	117 (7.6)
1 - <3 months	55 (17.0)	84 (26.2)	515 (33.6)
3 - <6 months	76 (23.5)	92 (28.7)	276 (18.0)
6 - <12 months	95 (29.3)	83 (25.9)	258 (16.8)
12 - <18 months	30 (9.3)	21 (6.5)	117 (7.6)
18 - <24 months	21 (6.5)	10 (3.1)	83 (5.4)
≥ 24 months	25 (7.7)	10 (3.1)	168 (11.0)
Number of cycles received			
Mean (SD)	11.7 (10.50)	8.9 (8.09)	12.0 (13.30)
Median	8.0	7.0	6.0
Q1-Q3	4.0-15.0	3.0-11.0	3.0-16.0
Min-Max	1-55	1-50	1-62
Number of cycles received (categories), n (%)			
1 - <4 cycles	65 (20.1)	84 (26.2)	514 (33.5)
4 - <8 cycles	69 (21.3)	88 (27.4)	354 (23.1)
8 - <12 cycles	82 (25.3)	72 (22.4)	175 (11.4)
12 - <18 cycles	42 (13.0)	44 (13.7)	133 (8.7)
18 - <36 cycles	52 (16.0)	26 (8.1)	212 (13.8)
≥ 36 cycles	14 (4.3)	7 (2.2)	146 (9.5)

	Study 306		Tislelizumab Monotherapy Pool
	T+C Arm N=324	P+C Arm N=321	200 mg Q3W N=1534
- Data cut-off for 306: 28FEB2022. - Data cut-off for Tisle monotherapy: 001-26AUG2020, 102-31MAY2020, 203-02NOV2020, 204-16SEP2019, 208-30JUN2021, 302-01DEC2020, 303-15JUL2021.			
Source: [Summary of Clinical Safety Appendix 1-Table 1.2-1]			
Source: Summary of Clinical Safety, Table 5			

The median RDI for tislelizumab or placebo was comparable between the two treatment arms; it was 96.19% (range: 34.7% to 105.0%) in the T+C Arm and 97.67% (range: 56.2% to 105.0%) in the P+C Arm)[2].

Exposure to Investigator's Choice of Chemotherapy

As of the data cut-off date, 324 patients in the T+C Arm and 321 patients in the P+C Arm received chemotherapy. Of these, 146 patients in the T+C Arm and 144 patients in the P+C Arm received the chemotherapy regimen of platinum (cisplatin/oxaliplatin) with fluoropyrimidine (5-FU/capecitabine) while 178 patients in the T+C Arm and 177 patients in the P+C Arm received the chemotherapy regimen of platinum (cisplatin/oxaliplatin) with paclitaxel. Exposure to chemotherapy components for the Safety Set is summarised in Table 48.

[2] Data not shown in Table 5.3; source: Summary of Clinical Safety referencing Clinical Study Report Appendix 1 Table 14.3.1.1.1.

Table 48: **Study medication administration - chemotherapy (Safety Set)**

	Study 306 T+C Arm N = 324				Study 306 P+C Arm N = 321			
	Platinum + Fluoropyrimidine N1 = 146		Platinum + Paclitaxel N2 = 178		Platinum + Fluoropyrimidine N1 = 144		Platinum + Paclitaxel N2 = 177	
	Platinum (Cis./Oxa.) (n = 146)	Fluoropyr. (5-FU/Cap.) (n = 146)	Platinum (Cis./Oxa.) (n = 177)	Paclitaxel (n = 178)	Platinum (Cis./Oxa.) (n = 144)	Fluoropyr. (5-FU/Cap.) (n = 143)	Platinum (Cis./Oxa.) (n = 175)	Paclitaxel (n = 176)
Duration of Treatment (month) [a]								
Mean (SD)	4.59 (2.881)	6.91 (6.056)	3.95 (1.735)	5.13 (3.682)	3.93 (2.926)	5.47 (4.868)	3.75 (2.767)	4.72 (4.138)
Median	4.27	5.04	4.14	4.27	4.11	4.24	4.14	4.14
Q1, Q3	2.79, 5.49	2.86, 8.28	2.92, 4.47	2.99, 5.82	2.22, 4.63	2.56, 6.24	2.40, 4.30	2.40, 5.63
Min, Max	0.7, 18.1	0.3, 30.1	0.1, 13.6	0.1, 23.0	0.6, 26.0	0.6, 28.8	0.7, 30.3	0.7, 34.0
Duration of Treatment, n (%)								
< 1 month	9 (6.2)	9 (6.2)	10 (5.6)	13 (7.3)	7 (4.9)	7 (4.9)	13 (7.4)	14 (8.0)
≥1 to < 3 months	30 (20.5)	29 (19.9)	35 (19.8)	32 (18.0)	47 (32.6)	38 (26.6)	46 (26.3)	44 (25.0)
≥3 to < 6 months	77 (52.7)	47 (32.2)	121 (68.4)	93 (52.2)	79 (54.9)	60 (42.0)	110 (62.9)	81 (46.0)
≥6 to < 12 months	27 (18.5)	39 (26.7)	10 (5.6)	30 (16.9)	8 (5.6)	25 (17.5)	4 (2.3)	30 (17.0)
≥12 to ≤18 months	2 (1.4)	12 (8.2)	1 (0.6)	8 (4.5)	2 (1.4)	8 (5.6)	1 (0.6)	4 (2.3)
> 18 months	1 (0.7)	10 (6.8)	0 (0.0)	2 (1.1)	1 (0.7)	5 (3.5)	1 (0.6)	3 (1.7)
Number of Cycles Received								
Mean (SD)	5.7 (2.91)	8.9 (7.77)	5.2 (2.13)	6.8 (4.76)	5.1 (3.24)	7.1 (6.06)	4.9 (2.04)	6.3 (4.92)
Median	6.0	6.0	6.0	6.0	5.0	6.0	6.0	6.0
Q1, Q3	4.0, 7.0	4.0, 10.0	4.0, 6.0	4.0, 8.0	3.0, 6.0	3.0, 8.0	3.0, 6.0	3.0, 8.0
Min, Max	1, 19	1, 36	1, 17	1, 33	1, 29	1, 40	1, 13	1, 47
Number of Cycles Received, n (%)								
1-3	32 (21.9)	31 (21.2)	33 (18.6)	33 (18.5)	46 (31.9)	41 (28.7)	45 (25.7)	46 (26.1)
4-6	76 (52.1)	46 (31.5)	132 (74.6)	84 (47.2)	75 (52.1)	46 (32.2)	121 (69.1)	73 (41.5)
7-9	25 (17.1)	27 (18.5)	6 (3.4)	33 (18.5)	18 (12.5)	27 (18.9)	6 (3.4)	30 (17.0)
10-12	10 (6.8)	12 (8.2)	4 (2.3)	13 (7.3)	1 (0.7)	11 (7.7)	2 (1.1)	18 (10.2)
13-18	2 (1.4)	11 (7.5)	2 (1.1)	9 (5.1)	3 (2.1)	10 (7.0)	1 (0.6)	7 (4.0)
>18	1 (0.7)	19 (13.0)	0 (0.0)	6 (3.4)	1 (0.7)	8 (5.6)	0 (0.0)	2 (1.1)

	Study 306 T+C Arm N = 324				Study 306 P+C Arm N = 321			
	Platinum + Fluoropyrimidine N1 = 146		Platinum + Paclitaxel N2 = 178		Platinum + Fluoropyrimidine N1 = 144		Platinum + Paclitaxel N2 = 177	
	Platinum (Cis./Oxa.) (n = 146)	Fluoropyr. (5-FU/Cap.) (n = 146)	Platinum (Cis./Oxa.) (n = 177)	Paclitaxel (n = 178)	Platinum (Cis./Oxa.) (n = 144)	Fluoropyr. (5-FU/Cap.) (n = 143)	Platinum (Cis./Oxa.) (n = 175)	Paclitaxel (n = 176)
RDI (%) per Patient [b]								
Mean (SD)	85.64 (14.871)	80.56 (17.365)	89.54 (12.907)	84.06 (15.996)	86.30 (13.479)	79.94 (16.781)	93.62 (9.278)	86.83 (15.729)
Median	90.78	83.60	95.77	85.96	89.57	81.98	97.93	92.93
Q1, Q3	77.73, 98.67	72.25, 94.85	80.49, 99.72	76.04, 98.37	77.39, 98.05	68.71, 95.33	91.39, 99.75	77.93, 99.04
Min, Max	36.4, 104.6	3.3, 100.9	47.6, 104.1	1.3, 106.2	43.2, 103.3	36.7, 101.4	60.3, 102.9	1.8, 102.7

Source: Post-Text Table 14.3.1.1.5. Data cut-off: 28FEB2022. Data extraction: 06APR2022.
Abbreviations: 5-FU, 5-Fluorouracil; Cap, Capecitabine; Cis, Cisplatin; Fluoropyr., Fluoropyrimidine; Oxa, Oxaliplatin. Percentages were based on m.
Chemotherapy Doublet A: Cisplatin (60-80 mg/m2 Q3W IV) or Oxaliplatin (130 mg/m2 Q3W IV) and 5-Fluorouracil (750-800 mg/m2 Q3W IV); Chemotherapy Doublet B: Cisplatin (60-80 mg/m2 Q3W IV) or Oxaliplatin (130 mg/m2 Q3W IV) and Capecitabine (1000mg/m2 twice a day); Chemotherapy Doublet C: Cisplatin (60-80 mg/m2 Q3W IV) or Oxaliplatin (130 mg/m2 Q3W IV) and Paclitaxel (175mg/m2 Q3W IV).
a Duration of treatment (TD) for patients discontinued from treatment: For cisplatin or oxaliplatin or paclitaxel on a Q3W schedule, TD = (min(last dose date + 20, death date, cut-off date) - first dose date + 1)/30.4375; If patient received Chemotherapy Doublet C, cisplatin may be administered on Days 1 or 2, or in 3 divided doses on Days 1, 2, and 3 depending on local guidelines. Then TD = (min(last dose date + 20 (or 19 or 18), death date, cut-off date)- date of first dose + 1)/30.4375, respectively; For 5-FU, TD = (min(last dose date + 16, death date, cut-off date) - first dose date + 1)/30.4375; For capecitabine, TD = (min(last dose date + 7, death date, cut-off date) - first dose date + 1)/30.4375.
Duration of treatment (TD) for patients with ongoing treatment: TD = (cut-off date - first dose date + 1)/30.4375.
b RDI is actual dose intensity/planned dose intensity. The planned dose intensity is the total planned dose in a cycle.
unblind/bgb_a317/bgb_a317_306/interim/dev/pgm/intext/t-ex-chemo-comb.sas 07JUN2022 01:05 t-16-ex-chemo-comb-i.rtf
Source: Clinical Study Report Table 22

Exposure to chemotherapy was comparable in the two treatment arms of Study 306 with respect to the median duration of treatment and the median number of treatment cycles. The proportion of patients treated with the chemotherapy regimen of platinum (cisplatin/oxaliplatin) with paclitaxel was higher than the proportion of patients treated with the chemotherapy regimen of platinum (cisplatin/ oxaliplatin) with a fluoropyrimidine (5-FU/capecitabine), which is the European Standard of Care for the first-line treatment of patients with advanced OSCC. For a discussion on the consequences of the non-conformity with the European Standard of Care, please see Section 2.5.1 Discussion on clinical safety.

Exposure in the Tislelizumab Combination Therapy Pool

In the Tislelizumab Combination Therapy Pool, the median duration of exposure for combination therapy was 7.59 months (range: 0.1 to 38.3 months), and the median number of treatment cycles was 10 (range: 1 to 55 cycles) (data not shown)[3].

Adverse events

All TEAEs discussed in the following sections are treatment-emergent unless otherwise specified.

Adverse events summary

A summary of TEAEs (including related TEAEs) for T+C, P+C (Study 306), and for tislelizumab monotherapy is presented in Table 47. The respective EAIRs for the AE categories are presented in Table 48.

A harmonised TEAE definition was used for the analysis of safety parameters for the Tislelizumab Monotherapy Pool as well as for pivotal Study 306, as studies included in the Tislelizumab Monotherapy Pool had different TEAE definitions. A TEAE is now 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 include all imTEAEs identified as per a pre-defined fully automated process (see Section Other significant events), recorded up to 90 days after the last dose of the study treatment regardless of whether the patient started a new anticancer therapy. It should be noted that this differs from the analyses carried out for Study 306 in the Clinical Study Report. In the latter, imTEAEs starting beyond the 30-day time window after the last dose of study treatment or initiation of new anticancer therapy were not considered as a TEAE. As long as an AE met the criteria of the TEAE definition above, this same AE, defined as any consecutive records with the same Preferred Term, was considered as a TEAE until its last record, even if it worsened outside of the treatment-emergent period (but before crossover started for studies allowing the crossover).

Owing to the harmonisation of the TEAE definition and the recalculation of TEAE incidence rates, the safety data presented in this Assessment Report were extracted from the Summary of Clinical Safety and not from the Clinical Study Report.

[3] Source: Summary of Clinical Safety referencing Appendix 1-Table 6.3-1.

Table 49: Overview of treatment-emergent adverse events (Safety Set)

Category	Study 306 T+C Arm N=324 n (%)	Study 306 P+C Arm N=321 n (%)	Tislelizumab Monotherapy Pool 200 mg Q3W N=1534 n (%)
TEAEs	323 (99.7)	319 (99.4)	1479 (96.4)
Treatment-related	313 (96.6)	309 (96.3)	1137 (74.1)
Tislelizumab/placebo-related	226 (69.8)	195 (60.7)	1137 (74.1)
Chemotherapy-related	313 (96.6)	308 (96.0)	NA
TEAEs with grade ≥ 3	255 (78.7)	249 (77.6)	693 (45.2)
Treatment-related	217 (67.0)	207 (64.5)	259 (16.9)
Tislelizumab/placebo-related	104 (32.1)	65 (20.2)	259 (16.9)
Chemotherapy-related	203 (62.7)	202 (62.9)	NA
Serious TEAEs	158 (48.8)	127 (39.6)	533 (34.7)
Treatment-related	95 (29.3)	62 (19.3)	181 (11.8)
Tislelizumab/placebo-related	63 (19.4)	27 (8.4)	181 (11.8)
Chemotherapy-related	71 (21.9)	57 (17.8)	NA
Fatal serious TEAEs	26 (8.0)	30 (9.3)	128 (8.3)
Treatment-related	7 (2.2)	6 (1.9)	17 (1.1)
Tislelizumab/placebo-related	6 (1.9)	3 (0.9)	17 (1.1)
Chemotherapy-related	4 (1.2)	6 (1.9)	NA
TEAEs leading to any treatment discontinuation	104 (32.1)	72 (22.4)	199 (13.0)
Leading to Tislelizumab/placebo discontinuation	43 (13.3)	21 (6.5)	199 (13.0)
Tislelizumab/placebo-related	31 (9.6)	5 (1.6)	87 (5.7)
Chemotherapy-related	15 (4.6)	8 (2.5)	NA
Leading to Chemotherapy discontinuation	96 (29.6)	70 (21.8)	NA
Tislelizumab/placebo-related	25 (7.7)	12 (3.7)	NA
Chemotherapy-related	80 (24.7)	58 (18.1)	NA
TEAEs leading to any treatment modification	247 (76.2)	229 (71.3)	417 (27.2)
Leading to tislelizumab/placebo modification	170 (52.5)	128 (39.9)	417 (27.2)
Tislelizumab/placebo-related	89 (27.5)	33 (10.3)	252 (16.4)
Chemotherapy-related	107 (33.0)	89 (27.7)	NA
Leading to Chemotherapy modification	239 (73.8)	220 (68.5)	NA
Tislelizumab/placebo-related	78 (24.1)	43 (13.4)	NA
Chemotherapy-related	213 (65.7)	195 (60.7)	NA
Immune-mediated TEAEs	114 (35.2)	60 (18.7)	506 (33.0)
Infusion-Related Reaction	25 (7.7)	17 (5.3)	44 (2.9)

Category	Study 306 T+C Arm N=324 n (%)	Study 306 P+C Arm N=321 n (%)	Tislelizumab Monotherapy Pool 200 mg Q3W N=1534 n (%)

- Data cut-off for 306: 28FEB2022.
- Data cut-off for Tisle monotherapy: 001-26AUG2020, 102-31MAY2020, 203-02NOV2020, 204-16SEP2019, 208-30JUN2021,
302-01DEC2020, 303-15JUL2021.
NA: Not applicable. Numbers (n) represent counts of subjects.
A subject with multiple severity grades for an AE is only counted under the maximum grade.
The types of dose modification include dose delay, dose/infusion 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 25.1, CTCAE version v4.03.
Source: [Summary of Clinical Safety Appendix 1-Table 1.3-11]
Source: Summary of Clinical Safety Table 8

To account for differences in exposure, exposure-adjusted analyses were performed for the Summary of Clinical Safety, based on exposure-adjusted incidence rates (EAIRs). The latter were calculated as the number of patients with an event divided by the corresponding sum of the exposure duration for all patients, where duration of exposure in patients-months of exposure is counted up to the first qualifying event (or end of time at risk for patients without event).

Table 50: Treatment-emergent adverse event categories and Exposure-Adjusted Incidence Rates (Safety Set)

Category	Study 306 T+C Arm N=324	Study 306 P+C Arm N=321	Tislelizumab Monotherapy Pool N=1534
Subjects with at least one TEAE, n (%)	323 (99.7)	319 (99.4)	1479 (96.4)
EAIR, IR per 100 patient-months exposure (95% CI)	419.2 (374.8, 467.6)	398.9 (356.3, 445.2)	84.5 (80.3, 89.0)
Grade ≥ 3 TEAEs, n (%)	255 (78.7)	249 (77.6)	693 (45.2)
EAIR, IR per 100 patient-months exposure (95% CI)	26.1 (23.0, 29.5)	29.9 (26.3, 33.8)	5.9 (5.5, 6.4)
Serious TEAE	158 (48.8)	127 (39.6)	533 (34.7)
EAIR, IR per 100 patient-months exposure (95% CI)	6.5 (5.5, 7.6)	6.0 (5.0, 7.2)	4.0 (3.7, 4.4)
TEAE leading to any treatment discontinuation	104 (32.1)	72 (22.4)	199 (13.0)
EAIR, IR per 100 patient-months exposure (95% CI)	4.2 (3.5, 5.1)	3.3 (2.6, 4.1)	1.3 (1.1, 1.5)
Fatal serious TEAE	26 (8.0)	30 (9.3)	128 (8.3)
EAIR, IR per 100 patient-months exposure (95% CI)	0.8 (0.5, 1.1)	1.1 (0.7, 1.6)	0.8 (0.7, 1.0)
Immune-mediated TEAE	114 (35.2)	60 (18.7)	506 (33.0)
EAIR, IR per 100 patient-months exposure (95% CI)	4.7 (3.9, 5.7)	2.6 (2.0, 3.4)	4.7 (4.3, 5.2)
Grade ≥ 3 immune-mediated TEAE	29 (9.0)	4 (1.2)	72 (4.7)
EAIR, IR per 100 patient-months exposure (95% CI)	0.9 (0.6, 1.3)	0.1 (0.0, 0.4)	0.5 (0.4, 0.6)
Infusion-related TEAE	25 (7.7)	17 (5.3)	44 (2.9)

Category	Study 306 T+C Arm N=324	Study 306 P+C Arm N=321	Tislelizumab Monotherapy Pool N=1534
Subjects with at least one TEAE, n (%)	323 (99.7)	319 (99.4)	1479 (96.4)
EAIR, IR per 100 patient-months exposure (95% CI)	419.2 (374.8, 467.6)	398.9 (356.3, 445.2)	84.5 (80.3, 89.0)
EAIR, IR per 100 patients-months exposure (95% CI)	0.8 (0.5, 1.2)	0.6 (0.4, 1.0)	0.3 (0.2, 0.4)

Exposure-adjusted incidence rate (EAIR) is the number of patients with an event divided by the corresponding sum of the exposure duration for all subjects, where duration of exposure in subjects-months of exposure is counted up to the first qualifying event (or end of time at risk for patients without event). Two-sided 95% CI for EAIR rate refers to Sahai, 1993 and Ulm, 1990
Source: [Summary of Clinical Safety Appendix 1-Table 3.1-2a]
Source: Clinical Overview Table 11

As EAIRs are associated with a number of methodological limitations, this Assessment Report is based on the "naïve" rates of TEAEs which are deemed to provide a more realistic notion of the impact of prolonged treatment with an investigational medicinal product on patients.

Most common adverse events

The most common TEAEs by **System Organ Class** for T+C, P+C (Study 306), and for tislelizumab monotherapy are presented in Table 51 (related TEAEs: **Table 54**).

Table 51: Treatment-emergent adverse events by System Organ Class (Safety Set)

Primary System Organ Class	Study 306 T+C Arm N=324 n (%)	Study 306 P+C Arm N=321 n (%)	Tislelizumab Monotherapy Pool 200 mg Q3W N=1534 n (%)
Number of subjects with at least one event	323 (99.7)	319 (99.4)	1479 (96.4)
Gastrointestinal disorders	264 (81.5)	249 (77.6)	702 (45.8)
Investigations	261 (80.6)	247 (76.9)	916 (59.7)
Metabolism and nutrition disorders	234 (72.2)	212 (66.0)	680 (44.3)
Blood and lymphatic system disorders	231 (71.3)	199 (62.0)	519 (33.8)
General disorders and administration site conditions	198 (61.1)	201 (62.6)	665 (43.4)
Nervous system disorders	163 (50.3)	155 (48.3)	214 (14.0)
Skin and subcutaneous tissue disorders	149 (46.0)	114 (35.5)	377 (24.6)
Respiratory, thoracic and mediastinal disorders	143 (44.1)	119 (37.1)	584 (38.1)
Infections and infestations	122 (37.7)	91 (28.3)	492 (32.1)
Musculoskeletal and connective tissue disorders	108 (33.3)	105 (32.7)	422 (27.5)
Vascular disorders	63 (19.4)	48 (15.0)	122 (8.0)
Endocrine disorders	58 (17.9)	16 (5.0)	265 (17.3)
Psychiatric disorders	41 (12.7)	37 (11.5)	128 (8.3)
Cardiac disorders	37 (11.4)	31 (9.7)	147 (9.6)
Eye disorders	36 (11.1)	41 (12.8)	131 (8.5)
Renal and urinary disorders	35 (10.8)	36 (11.2)	166 (10.8)
Injury, poisoning and procedural complications	26 (8.0)	16 (5.0)	83 (5.4)
Reproductive system and breast disorders	14 (4.3)	3 (0.9)	30 (2.0)
Ear and labyrinth disorders	13 (4.0)	15 (4.7)	25 (1.6)

Primary System Organ Class	Study 306 T+C Arm N=324 n (%)	Study 306 P+C Arm N=321 n (%)	Tislelizumab Monotherapy Pool 200 mg Q3W N=1534 n (%)
Hepatobiliary disorders	13 (4.0)	10 (3.1)	107 (7.0)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	11 (3.4)	17 (5.3)	96 (6.3)
Immune system disorders	8 (2.5)	5 (1.6)	14 (0.9)
Product issues	0	0	2 (0.1)

- Data cut-off for 306: 28FEB2022.
- Data cut-off for Tisle monotherapy: 001-26AUG2020, 102-31MAY2020, 203-02NOV2020, 204-16SEP2019, 208-30JUN2021, 302-01DEC2020, 303-15JUL2021.
Numbers (n) represent counts of subjects.
MedDRA version 25.1.
Source: [Summary of Clinical Safety Appendix 1-Table 1.3-1]
Source: Summary of Clinical Safety Table 9

The most common TEAEs by **Preferred Term** for T+C, P+C (Study 306), and for tislelizumab monotherapy are presented in the next table.

Table 52: Treatment-emergent adverse events (≥ 20% in any group) all grades and grade ≥ 3 by Preferred Term (Safety Set)

	Study 306 T+C Arm N=324		Study 306 P+C Arm N=321		Tislelizumab Monotherapy Pool 200 mg Q3W N=1534	
Preferred Term	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	323 (99.7)	255 (78.7)	319 (99.4)	249 (77.6)	1479 (96.4)	693 (45.2)
Anaemia	197 (60.8)	56 (17.3)	180 (56.1)	50 (15.6)	429 (28.0)	76 (5.0)
Neutrophil count decreased	154 (47.5)	100 (30.9)	156 (48.6)	107 (33.3)	68 (4.4)	12 (0.8)
Decreased appetite	144 (44.4)	18 (5.6)	125 (38.9)	7 (2.2)	230 (15.0)	17 (1.1)
White blood cell count decreased	143 (44.1)	35 (10.8)	157 (48.9)	50 (15.6)	104 (6.8)	8 (0.5)
Nausea	123 (38.0)	9 (2.8)	136 (42.4)	5 (1.6)	155 (10.1)	3 (0.2)
Constipation	98 (30.2)	0	100 (31.2)	1 (0.3)	193 (12.6)	1 (0.1)
Weight decreased	94 (29.0)	6 (1.9)	89 (27.7)	2 (0.6)	228 (14.9)	10 (0.7)
Diarrhoea	91 (28.1)	14 (4.3)	78 (24.3)	6 (1.9)	145 (9.5)	12 (0.8)
Peripheral sensory neuropathy	75 (23.1)	10 (3.1)	62 (19.3)	7 (2.2)	6 (0.4)	0
Hypoalbuminaemia	74 (22.8)	0	60 (18.7)	0	181 (11.8)	4 (0.3)
Hyponatraemia	72 (22.2)	36 (11.1)	60 (18.7)	18 (5.6)	136 (8.9)	41 (2.7)
Vomiting	72 (22.2)	5 (1.5)	88 (27.4)	8 (2.5)	123 (8.0)	9 (0.6)
Hypokalaemia	65 (20.1)	28 (8.6)	55 (17.1)	22 (6.9)	116 (7.6)	25 (1.6)

	Study 306 T+C Arm N=324		Study 306 P+C Arm N=321		Tislelizumab Monotherapy Pool 200 mg Q3W N=1534	
	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3
Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**

- Data cut-off for 306: 28FEB2022.
- Data cut-off for Tisle monotherapy: 001-26AUG2020, 102-31MAY2020, 203-02NOV2020, 204-16SEP2019, 208-30JUN2021, 302-01DEC2020, 303-15JUL2021.
Numbers (n) represent counts of subjects.
A subject with multiple grades for an AE is only counted under the maximum grade.
MedDRA version 25.1, CTCAE version v4.03.
Source: [Summary of Clinical Safety Appendix 1-Table 1.3-2]
Source: Summary of Clinical Safety Table 10

The most common TEAEs of all grades and of grade ≥ 3 by **System Organ Class and Preferred Term** for T+C, P+C (Study 306), and for tislelizumab monotherapy are presented in Table 53. The thresholds for the incidence rates of Preferred Terms per System Organ Class have been selected on a case-by-case basis to present a succinct, but meaningful selection of TEAEs.

Table 53: Treatment-emergent adverse events all grades and grade ≥ 3 by System Organ Class and Preferred Term (Safety Set)

Table 3.1-4 (Page 1 of 79)
Treatment-emergent adverse events all grades and grade >=3 by system organ class, preferred term
Safety set

Primary system organ class Preferred term	306 Tisle+Chemo N=324 All grades n (%)	 Grade >=3 n (%)	306 Placebo+Chemo N=321 All grades n (%)	 Grade >=3 n (%)	Tisle Monotherapy 200 mg Q3W N=1534 All grades n (%)	 Grade >=3 n (%)
Number of subjects with at least one event	323 (99.7)	255 (78.7)	319 (99.4)	249 (77.6)	1479 (96.4)	693 (45.2)
Blood and lymphatic system disorders	231 (71.3)	85 (26.2)	199 (62.0)	76 (23.7)	519 (33.8)	99 (6.5)
Anaemia	197 (60.8)	56 (17.3)	180 (56.1)	50 (15.6)	429 (28.0)	76 (5.0)
Neutropenia	53 (16.4)	24 (7.4)	47 (14.6)	32 (10.0)	28 (1.8)	10 (0.7)
Leukopenia	34 (10.5)	9 (2.8)	30 (9.3)	10 (3.1)	48 (3.1)	4 (0.3)
Cardiac disorders	37 (11.4)	3 (0.9)	31 (9.7)	4 (1.2)	147 (9.6)	30 (2.0)
Atrial fibrillation	8 (2.5)	1 (0.3)	2 (0.6)	1 (0.3)	10 (0.7)	2 (0.1)
Ear and labyrinth disorders	13 (4.0)	0	15 (4.7)	0	25 (1.6)	2 (0.1)
Tinnitus	7 (2.2)	0	7 (2.2)	0	8 (0.5)	0
Endocrine disorders	58 (17.9)	6 (1.9)	16 (5.0)	0	265 (17.3)	5 (0.3)
Hypothyroidism	36 (11.1)	0	14 (4.4)	0	199 (13.0)	1 (0.1)
Hyperthyroidism	10 (3.1)	0	2 (0.6)	0	61 (4.0)	0
Adrenal insufficiency	6 (1.9)	4 (1.2)	0	0	4 (0.3)	1 (0.1)
Eye disorders	36 (11.1)	4 (1.2)	41 (12.8)	2 (0.6)	131 (8.5)	6 (0.4)
Cataract	6 (1.9)	2 (0.6)	4 (1.2)	1 (0.3)	28 (1.8)	3 (0.2)
Gastrointestinal disorders	264 (81.5)	73 (22.5)	249 (77.6)	53 (16.5)	702 (45.8)	121 (7.9)
Nausea	123 (38.0)	9 (2.8)	136 (42.4)	5 (1.6)	155 (10.1)	3 (0.2)
Constipation	98 (30.2)	0	100 (31.2)	1 (0.3)	193 (12.6)	1 (0.1)
Diarrhoea	91 (28.1)	14 (4.3)	78 (24.3)	6 (1.9)	145 (9.5)	12 (0.8)
Vomiting	72 (22.2)	5 (1.5)	88 (27.4)	8 (2.5)	123 (8.0)	9 (0.6)
Stomatitis	63 (19.4)	13 (4.0)	48 (15.0)	7 (2.2)	26 (1.7)	4 (0.3)
Dysphagia	44 (13.6)	20 (6.2)	35 (10.9)	13 (4.0)	49 (3.2)	21 (1.4)
Abdominal pain	25 (7.7)	0	13 (4.0)	1 (0.3)	79 (5.1)	8 (0.5)
Gastrooesophageal reflux disease	22 (6.8)	0	15 (4.7)	0	27 (1.8)	1 (0.1)
Abdominal distension	17 (5.2)	0	14 (4.4)	0	57 (3.7)	2 (0.1)

Table 3.1-4 (Page 1 of 79)
Treatment-emergent adverse events all grades and grade >=3 by system organ class, preferred term
Safety set

Primary system organ class Preferred term	306 Tisle+Chemo N=324 All grades n (%)	 Grade >=3 n (%)	306 Placebo+Chemo N=321 All grades n (%)	 Grade >=3 n (%)	Tisle Monotherapy 200 mg Q3W N=1534 All grades n (%)	 Grade >=3 n (%)
General disorders and administration site conditions	198 (61.1)	39 (12.0)	201 (62.6)	31 (9.7)	665 (43.4)	79 (5.1)
Fatigue	64 (19.8)	17 (5.2)	57 (17.8)	9 (2.8)	134 (8.7)	10 (0.7)
Pyrexia	52 (16.0)	1 (0.3)	39 (12.1)	2 (0.6)	242 (15.8)	5 (0.3)
Asthenia	43 (13.3)	7 (2.2)	45 (14.0)	3 (0.9)	162 (10.6)	14 (0.9)
Malaise	43 (13.3)	6 (1.9)	52 (16.2)	3 (0.9)	88 (5.7)	8 (0.5)
Hepatobiliary disorders	13 (4.0)	6 (1.9)	10 (3.1)	2 (0.6)	107 (7.0)	47 (3.1)
Hepatic function abnormal	4 (1.2)	1 (0.3)	4 (1.2)	0	20 (1.3)	7 (0.5)
Immune system disorders	8 (2.5)	4 (1.2)	5 (1.6)	2 (0.6)	14 (0.9)	2 (0.1)
Drug hypersensitivity	4 (1.2)	2 (0.6)	4 (1.2)	1 (0.3)	2 (0.1)	0
Infections and infestations	122 (37.7)	33 (10.2)	91 (28.3)	37 (11.5)	492 (32.1)	133 (8.7)
Pneumonia	42 (13.0)	19 (5.9)	35 (10.9)	20 (6.2)	152 (9.9)	74 (4.8)
Upper respiratory tract infection	28 (8.6)	2 (0.6)	16 (5.0)	0	140 (9.1)	12 (0.8)
Conjunctivitis	10 (3.1)	0	3 (0.9)	0	19 (1.2)	0
Pneumonia aspiration	10 (3.1)	3 (0.9)	8 (2.5)	4 (1.2)	3 (0.2)	3 (0.2)
Nasopharyngitis	9 (2.8)	0	6 (1.9)	0	40 (2.6)	0
Injury, poisoning and procedural complications	26 (8.0)	4 (1.2)	16 (5.0)	2 (0.6)	83 (5.4)	16 (1.0)
Fall	3 (0.9)	0	2 (0.6)	0	5 (0.3)	2 (0.1)
Procedural pain	3 (0.9)	0	3 (0.9)	1 (0.3)	7 (0.5)	0
Investigations	261 (80.6)	127 (39.2)	247 (76.9)	130 (40.5)	916 (59.7)	180 (11.7)
Neutrophil count decreased	154 (47.5)	100 (30.9)	156 (48.6)	107 (33.3)	68 (4.4)	12 (0.8)
White blood cell count decreased	143 (44.1)	35 (10.8)	157 (48.9)	50 (15.6)	104 (6.8)	8 (0.5)
Weight decreased	94 (29.0)	6 (1.9)	89 (27.7)	2 (0.6)	228 (14.9)	10 (0.7)
Platelet count decreased	62 (19.1)	9 (2.8)	55 (17.1)	3 (0.9)	93 (6.1)	13 (0.8)
Aspartate aminotransferase increased	52 (16.0)	7 (2.2)	37 (11.5)	4 (1.2)	327 (21.3)	40 (2.6)
Alanine aminotransferase increased	50 (15.4)	5 (1.5)	42 (13.1)	5 (1.6)	303 (19.8)	24 (1.6)
Blood creatinine increased	45 (13.9)	1 (0.3)	30 (9.3)	1 (0.3)	86 (5.6)	2 (0.1)
Metabolism and nutrition disorders	234 (72.2)	82 (25.3)	212 (66.0)	62 (19.3)	680 (44.3)	138 (9.0)
Decreased appetite	144 (44.4)	18 (5.6)	125 (38.9)	7 (2.2)	230 (15.0)	17 (1.1)
Hypoalbuminaemia	74 (22.8)	0	60 (18.7)	0	181 (11.8)	4 (0.3)
Hyponatraemia	72 (22.2)	36 (11.1)	60 (18.7)	18 (5.6)	136 (8.9)	41 (2.7)
Hypokalaemia	65 (20.1)	28 (8.6)	55 (17.1)	22 (6.9)	116 (7.6)	25 (1.6)
Hypochloraemia	36 (11.1)	4 (1.2)	31 (9.7)	1 (0.3)	41 (2.7)	3 (0.2)
Musculoskeletal and connective tissue disorders	108 (33.3)	6 (1.9)	105 (32.7)	6 (1.9)	422 (27.5)	33 (2.2)
Arthralgia	28 (8.6)	1 (0.3)	31 (9.7)	0	138 (9.0)	4 (0.3)
Myalgia	28 (8.6)	3 (0.9)	22 (6.9)	0	26 (1.7)	0
Pain in extremity	25 (7.7)	0	31 (9.7)	3 (0.9)	60 (3.9)	3 (0.2)
Back pain	21 (6.5)	1 (0.3)	20 (6.2)	2 (0.6)	114 (7.4)	7 (0.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	11 (3.4)	4 (1.2)	17 (5.3)	2 (0.6)	96 (6.3)	27 (1.8)
Cancer pain	3 (0.9)	1 (0.3)	8 (2.5)	1 (0.3)	46 (3.0)	6 (0.4)
Tumour pain	3 (0.9)	0	1 (0.3)	0	22 (1.4)	7 (0.5)
Nervous system disorders	163 (50.3)	20 (6.2)	155 (48.3)	16 (5.0)	214 (14.0)	40 (2.6)
Peripheral sensory neuropathy	75 (23.1)	10 (3.1)	62 (19.3)	7 (2.2)	6 (0.4)	0
Hypoaesthesia	34 (10.5)	1 (0.3)	40 (12.5)	1 (0.3)	21 (1.4)	0
Neurotoxicity	16 (4.9)	1 (0.3)	11 (3.4)	1 (0.3)	0	0
Headache	15 (4.6)	0	15 (4.7)	0	52 (3.4)	4 (0.3)
Paraesthesia	15 (4.6)	2 (0.6)	8 (2.5)	1 (0.3)	23 (1.5)	0
Dizziness	14 (4.3)	0	17 (5.3)	1 (0.3)	60 (3.9)	2 (0.1)
Product issues	0	0	0	0	2 (0.1)	1 (0.1)
Device occlusion	0	0	0	0	1 (0.1)	1 (0.1)
Thrombosis in device	0	0	0	0	1 (0.1)	0
Psychiatric disorders	41 (12.7)	2 (0.6)	37 (11.5)	2 (0.6)	128 (8.3)	3 (0.2)
Insomnia	29 (9.0)	0	25 (7.8)	0	95 (6.2)	1 (0.1)
Renal and urinary disorders	35 (10.8)	5 (1.5)	36 (11.2)	3 (0.9)	166 (10.8)	19 (1.2)
Acute kidney injury	9 (2.8)	3 (0.9)	8 (2.5)	2 (0.6)	3 (0.2)	2 (0.1)
Renal impairment	6 (1.9)	2 (0.6)	8 (2.5)	0	8 (0.5)	2 (0.1)

Primary system organ class Preferred term	306 Tisle+Chemo N=324 All grades n (%)	 Grade >=3 n (%)	306 Placebo+Chemo N=321 All grades n (%)	 Grade >=3 n (%)	Tisle Monotherapy 200 mg Q3W N=1534 All grades n (%)	 Grade >=3 n (%)
Reproductive system and breast disorders	14 (4.3)	1 (0.3)	3 (0.9)	0	30 (2.0)	1 (0.1)
Benign prostatic hyperplasia	4 (1.2)	0	1 (0.3)	0	7 (0.5)	0
Pelvic fluid collection	2 (0.6)	0	0	0	2 (0.1)	1 (0.1)
Respiratory, thoracic and mediastinal disorders	143 (44.1)	20 (6.2)	119 (37.1)	17 (5.3)	584 (38.1)	102 (6.6)
Cough	51 (15.7)	2 (0.6)	38 (11.8)	0	249 (16.2)	5 (0.3)
Productive cough	25 (7.7)	1 (0.3)	18 (5.6)	0	77 (5.0)	3 (0.2)
Dyspnoea	22 (6.8)	2 (0.6)	16 (5.0)	1 (0.3)	119 (7.8)	21 (1.4)
Hiccups	22 (6.8)	0	28 (8.7)	0	7 (0.5)	0
Pneumonitis	20 (6.2)	4 (1.2)	10 (3.1)	2 (0.6)	51 (3.3)	16 (1.0)
Oropharyngeal pain	19 (5.9)	1 (0.3)	4 (1.2)	0	23 (1.5)	0
Skin and subcutaneous tissue disorders	149 (46.0)	17 (5.2)	114 (35.5)	4 (1.2)	377 (24.6)	16 (1.0)
Skin and subcutaneous tissue disorders						
Alopecia	60 (18.5)	0	63 (19.6)	0	8 (0.5)	0
Pruritus	43 (13.3)	1 (0.3)	21 (6.5)	0	157 (10.2)	0
Rash	37 (11.4)	7 (2.2)	23 (7.2)	0	138 (9.0)	6 (0.4)
Palmar-plantar erythrodysaesthesia	13 (4.0)	3 (0.9)	13 (4.0)	3 (0.9)	4 (0.3)	0
Vascular disorders	63 (19.4)	17 (5.2)	48 (15.0)	10 (3.1)	122 (8.0)	44 (2.9)
Hypertension	20 (6.2)	9 (2.8)	17 (5.3)	6 (1.9)	70 (4.6)	32 (2.1)
Hypotension	14 (4.3)	5 (1.5)	6 (1.9)	1 (0.3)	22 (1.4)	4 (0.3)
Phlebitis	7 (2.2)	0	10 (3.1)	0	3 (0.2)	0
Vasculitis	6 (1.9)	0	1 (0.3)	0	0	0

Source: Summary of Clinical Safety Appendix 1, excerpt from Table 3.1-4

The most common TEAEs of all grades and grade ≥ 3 suspected by the Investigator to be causally related to any component of study treatment and to tislelizumab/placebo, respectively, by Preferred Term for T+C, P+C (Study 306), and for tislelizumab monotherapy are presented below. In view of the high degree of uncertainty associated with the assessment of relatedness in clinical trials, tables presenting related TEAEs are included in this Assessment Report, but the data will not be discussed further.

Table 54: Treatment-emergent adverse events (incidence ≥ 10%) all grades and grade ≥ 3 related to any component of study treatment by Preferred Term (Safety Set)

	306 Tisle+Chemo N=324		306 Placebo+Chemo N=321		Tisle monotherapy 200 mg Q3W N=1534	
Preferred Term	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	313 (96.6)	217 (67.0)	309 (96.3)	207 (64.5)	1137 (74.1)	259 (16.9)
Anaemia	173 (53.4)	47 (14.5)	155 (48.3)	41 (12.8)	158 (10.3)	21 (1.4)
Neutrophil count decreased	153 (47.2)	99 (30.6)	152 (47.4)	105 (32.7)	45 (2.9)	6 (0.4)
White blood cell count decreased	143 (44.1)	35 (10.8)	157 (48.9)	50 (15.6)	75 (4.9)	4 (0.3)
Decreased appetite	116 (35.8)	9 (2.8)	115 (35.8)	7 (2.2)	91 (5.9)	3 (0.2)
Nausea	112 (34.6)	8 (2.5)	130 (40.5)	5 (1.6)	65 (4.2)	1 (0.1)
Peripheral sensory neuropathy	73 (22.5)	10 (3.1)	61 (19.0)	7 (2.2)	2 (0.1)	0
Diarrhoea	63 (19.4)	9 (2.8)	59 (18.4)	5 (1.6)	71 (4.6)	6 (0.4)
Platelet count decreased	60 (18.5)	9 (2.8)	54 (16.8)	3 (0.9)	49 (3.2)	4 (0.3)
Alopecia	58 (17.9)	0	63 (19.6)	0	5 (0.3)	0
Stomatitis	58 (17.9)	13 (4.0)	47 (14.6)	7 (2.2)	13 (0.8)	4 (0.3)
Vomiting	57 (17.6)	4 (1.2)	74 (23.1)	7 (2.2)	35 (2.3)	1 (0.1)
Neutropenia	52 (16.0)	23 (7.1)	46 (14.3)	31 (9.7)	22 (1.4)	7 (0.5)
Fatigue	48 (14.8)	13 (4.0)	53 (16.5)	8 (2.5)	77 (5.0)	3 (0.2)
Weight decreased	46 (14.2)	1 (0.3)	45 (14.0)	0	33 (2.2)	2 (0.1)
Blood creatinine increased	43 (13.3)	1 (0.3)	28 (8.7)	1 (0.3)	49 (3.2)	1 (0.1)
Aspartate aminotransferase increased	42 (13.0)	5 (1.5)	29 (9.0)	2 (0.6)	234 (15.3)	22 (1.4)
Constipation	42 (13.0)	0	41 (12.8)	1 (0.3)	29 (1.9)	0
Alanine aminotransferase increased	41 (12.7)	5 (1.5)	33 (10.3)	5 (1.6)	228 (14.9)	16 (1.0)
Hyponatraemia	41 (12.7)	22 (6.8)	33 (10.3)	10 (3.1)	28 (1.8)	8 (0.5)
Malaise	41 (12.7)	6 (1.9)	50 (15.6)	3 (0.9)	55 (3.6)	5 (0.3)
Hypokalaemia	40 (12.3)	18 (5.6)	24 (7.5)	9 (2.8)	16 (1.0)	3 (0.2)
Asthenia	37 (11.4)	4 (1.2)	39 (12.1)	1 (0.3)	85 (5.5)	1 (0.1)
Hypoalbuminaemia	36 (11.1)	0	25 (7.8)	0	26 (1.7)	1 (0.1)
Hypoaesthesia	34 (10.5)	1 (0.3)	40 (12.5)	1 (0.3)	7 (0.5)	0
Hypothyroidism	34 (10.5)	0	14 (4.4)	0	184 (12.0)	1 (0.1)
Pruritus	34 (10.5)	0	19 (5.9)	0	114 (7.4)	0

Source: Summary of Clinical Safety Appendix 1, excerpt from Table 3.1-3

Table 55: Treatment-emergent adverse events (incidence ≥ 2% in the T+C Arm) all grades and grade ≥ 3 related to tislelizumab/placebo by Preferred Term (Safety Set)

able 1.3-4 Treatment-emergent adverse events all grades and grade >=3 related to Tislelizumab/ placebo by preferred term afety Set)

	306 Tisle+Chemo N=324		306 Placebo+Chemo N=321		Tisle monotherapy 200 mg Q3W N=1534	
Preferred Term	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	226 (69.8)	104 (32.1)	195 (60.7)	65 (20.2)	1137 (74.1)	259 (16.9)
Anaemia	35 (10.8)	6 (1.9)	46 (14.3)	10 (3.1)	158 (10.3)	21 (1.4)
Hypothyroidism	33 (10.2)	0	14 (4.4)	0	184 (12.0)	1 (0.1)
Neutrophil count decreased	31 (9.6)	18 (5.6)	31 (9.7)	18 (5.6)	45 (2.9)	6 (0.4)
White blood cell count decreased	28 (8.6)	9 (2.8)	32 (10.0)	12 (3.7)	75 (4.9)	4 (0.3)
Rash	27 (8.3)	7 (2.2)	16 (5.0)	0	110 (7.2)	4 (0.3)
Pruritus	26 (8.0)	0	17 (5.3)	0	114 (7.4)	0
Diarrhoea	25 (7.7)	5 (1.5)	23 (7.2)	1 (0.3)	71 (4.6)	6 (0.4)
Aspartate aminotransferase increased	24 (7.4)	5 (1.5)	15 (4.7)	1 (0.3)	234 (15.3)	22 (1.4)
Decreased appetite	23 (7.1)	3 (0.9)	20 (6.2)	1 (0.3)	91 (5.9)	3 (0.2)
Nausea	22 (6.8)	3 (0.9)	16 (5.0)	0	65 (4.2)	1 (0.1)
Alanine aminotransferase increased	21 (6.5)	4 (1.2)	17 (5.3)	2 (0.6)	228 (14.9)	16 (1.0)
Malaise	20 (6.2)	4 (1.2)	24 (7.5)	2 (0.6)	55 (3.6)	5 (0.3)
Pneumonitis	20 (6.2)	4 (1.2)	7 (2.2)	1 (0.3)	45 (2.9)	16 (1.0)
Fatigue	19 (5.9)	7 (2.2)	19 (5.9)	4 (1.2)	77 (5.0)	3 (0.2)
Stomatitis	18 (5.6)	1 (0.3)	6 (1.9)	2 (0.6)	13 (0.8)	4 (0.3)
Asthenia	17 (5.2)	1 (0.3)	20 (6.2)	0	85 (5.5)	1 (0.1)
Blood creatinine increased	17 (5.2)	0	9 (2.8)	0	49 (3.2)	1 (0.1)
Hyponatraemia	17 (5.2)	9 (2.8)	8 (2.5)	2 (0.6)	28 (1.8)	8 (0.5)
Amylase increased	16 (4.9)	6 (1.9)	15 (4.7)	3 (0.9)	14 (0.9)	5 (0.3)
Blood bilirubin increased	16 (4.9)	1 (0.3)	10 (3.1)	3 (0.9)	102 (6.6)	6 (0.4)
Hypoalbuminaemia	14 (4.3)	0	6 (1.9)	0	26 (1.7)	1 (0.1)
Hypokalaemia	14 (4.3)	6 (1.9)	5 (1.6)	2 (0.6)	16 (1.0)	3 (0.2)
Vomiting	14 (4.3)	1 (0.3)	20 (6.2)	3 (0.9)	35 (2.3)	1 (0.1)
Pyrexia	13 (4.0)	0	4 (1.2)	2 (0.6)	111 (7.2)	0
Lipase increased	12 (3.7)	4 (1.2)	11 (3.4)	6 (1.9)	5 (0.3)	3 (0.2)
Blood alkaline phosphatase increased	11 (3.4)	0	6 (1.9)	1 (0.3)	49 (3.2)	9 (0.6)
Blood urea increased	11 (3.4)	0	7 (2.2)	0	32 (2.1)	0
Platelet count decreased	11 (3.4)	2 (0.6)	13 (4.0)	0	49 (3.2)	4 (0.3)
Gamma-glutamyltransferase increased	10 (3.1)	4 (1.2)	8 (2.5)	1 (0.3)	62 (4.0)	13 (0.8)
Hyperglycaemia	10 (3.1)	1 (0.3)	3 (0.9)	1 (0.3)	40 (2.6)	4 (0.3)
Leukopenia	10 (3.1)	2 (0.6)	13 (4.0)	3 (0.9)	38 (2.5)	3 (0.2)
Neutropenia	10 (3.1)	4 (1.2)	15 (4.7)	9 (2.8)	22 (1.4)	7 (0.5)
Pneumonia	10 (3.1)	6 (1.9)	4 (1.2)	3 (0.9)	29 (1.9)	14 (0.9)
Weight decreased	10 (3.1)	0	9 (2.8)	0	33 (2.2)	2 (0.1)
Blood creatine phosphokinase increased	9 (2.8)	0	6 (1.9)	1 (0.3)	74 (4.8)	9 (0.6)
Constipation	9 (2.8)	0	8 (2.5)	1 (0.3)	29 (1.9)	0
Hyperthyroidism	9 (2.8)	0	2 (0.6)	0	56 (3.7)	0
Hyperuricaemia	8 (2.5)	0	6 (1.9)	0	25 (1.6)	1 (0.1)
Blood lactate dehydrogenase increased	7 (2.2)	1 (0.3)	4 (1.2)	0	35 (2.3)	1 (0.1)
Lymphocyte count decreased	7 (2.2)	2 (0.6)	9 (2.8)	3 (0.9)	31 (2.0)	8 (0.5)
Hypochloraemia	6 (1.9)	0	3 (0.9)	0	11 (0.7)	0

Source: Summary of Clinical Safety Appendix 1, excerpt from Table 3.1-4

Severe adverse events (grade ≥ 3)

An overview of TEAEs of all grades and grade ≥ 3 for T+C, P+C (Study 306), and for tislelizumab monotherapy by **System Organ Class** (and Preferred Term) is presented in Table 53 above.

Severe TEAEs (grade ≥ 3) for T+C, P+C (Study 306), and for tislelizumab monotherapy by **Preferred Term** (≥ 20% in any group) are presented in Table 52 (related severe TEAEs: Table 54 and Table 55) above.

TEAEs by **maximum CTCAE grade** for T+C, P+C (Study 306), and for tislelizumab monotherapy are presented in Table 56.

Table 56: Treatment-emergent adverse events by maximum grade (Safety Set)

Maximum grade	Study 306 T+C N=324 n (%)	Study 306 P+C N=321 n (%)	Tislelizumab Monotherapy Pool 200 mg Q3W N=1534 n (%)
Number of subjects with at least one event	323 (99.7)	319 (99.4)	1479 (96.4)
Grade 1	10 (3.1)	9 (2.8)	206 (13.4)
Grade 2	58 (17.9)	61 (19.0)	580 (37.8)
Grade 3	161 (49.7)	165 (51.4)	472 (30.8)
Grade 4	68 (21.0)	54 (16.8)	93 (6.1)
Grade 5	26 (8.0)	30 (9.3)	128 (8.3)
Missing	0 (0.0)	0 (0.0)	0 (0.0)

- Data cut-off for 306: 28FEB2022.
- Data cut-off for Tisle monotherapy: 001-26AUG2020, 102-31MAY2020, 203-02NOV2020, 204-16SEP2019, 208-30JUN2021,
302-01DEC2020, 303-15JUL2021.
Numbers (n) represent counts of subjects.
A subject with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version 25.1, CTCAE version v4.03.
Source: Summary of Clinical Safety Appendix 1 Table 3.1-5

Serious adverse events/deaths/other significant events

Serious treatment-emergent adverse events by System Organ Class are presented in Table 57 and serious TEAEs by Preferred Term are presented in Table 58 (incidence rate ≥ 1% for T+C, P+C (Study 306) and for tislelizumab monotherapy; related serious TEAEs by Preferred Term: Table 59, Table 60, Table 61).

Table 57: Serious treatment-emergent adverse events by System Organ Class - (Safety Set)

System Organ Class	Study 306 T+C N = 324 n (%)	Study 306 P+C N = 321 n (%)	Tislelizumab Monotherapy Pool 200 mg Q3W N = 1534 n (%)	Tislelizumab Combination Therapy Pool N = 838 n (%)
Patients with At Least One Serious TEAE	158 (48.8)	127 (39.6)	533 (34.7)	363 (43.3)
Gastrointestinal disorders	57 (17.6)	40 (12.5)	100 (6.5)	77 (9.2)
Infections and infestations	32 (9.9)	40 (12.5)	123 (8.0)	74 (8.8)
Metabolism and nutrition disorders	27 (8.3)	10 (3.1)	44 (2.9)	40 (4.8)
Respiratory, thoracic and mediastinal disorders	21 (6.5)	21 (6.5)	127 (8.3)	85 (10.1)
General disorders and administration site conditions	20 (6.2)	21 (6.5)	66 (4.3)	40 (4.8)
Blood and lymphatic system disorders	11 (3.4)	21 (6.5)	11 (0.7)	47 (5.6)
Investigations	11 (3.4)	7 (2.2)	18 (1.2)	40 (4.8)
Renal and urinary disorders	9 (2.8)	1 (0.3)	14 (0.9)	14 (1.7)
Nervous system disorders	7 (2.2)	7 (2.2)	39 (2.5)	22 (2.6)
Endocrine disorders	6 (1.9)	0 (0.0)	5 (0.3)	8 (1.0)
Hepatobiliary disorders	6 (1.9)	2 (0.6)	40 (2.6)	15 (1.8)
Musculoskeletal and connective tissue disorders	4 (1.2)	2 (0.6)	28 (1.8)	7 (0.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4 (1.2)	2 (0.6)	25 (1.6)	5 (0.6)
Skin and subcutaneous tissue disorders	4 (1.2)	0 (0.0)	8 (0.5)	9 (1.1)
Vascular disorders	4 (1.2)	6 (1.9)	11 (0.7)	6 (0.7)
Injury, poisoning and procedural complications	3 (0.9)	3 (0.9)	17 (1.1)	9 (1.1)
Cardiac disorders	2 (0.6)	3 (0.9)	31 (2.0)	13 (1.6)
Immune system disorders	2 (0.6)	0 (0.0)	2 (0.1)	2 (0.2)
Psychiatric disorders	2 (0.6)	0 (0.0)	2 (0.1)	4 (0.5)
Ear and labyrinth disorders	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)
Eye disorders	1 (0.3)	0 (0.0)	4 (0.3)	3 (0.4)
Product issues	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Reproductive system and breast disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)

Data cutoff: 001-26AUG2020, 102-31MAY2020, 203-02NOV2020, 204-16SEP2019, 208-30JUN2021, 302-01DEC2020, 303-15JUL2021, 206-31DEC2019, 304-26OCT2020, 306-28FEB2022, 307-30SEP2020.
Abbreviations: TEAE, treatment emergent adverse event.
Patients with multiple events for a given System Organ Class were counted once at the System Organ Class level.
Events were sorted by decreasing frequency of System Organ Class in the 'Study 306 Tisle+Chemo' group.
Adverse events were classified based on MedDRA v25.1.
unblind/bgb_a317/filing_escc306/escc306_2023_scs_eu_rtq/dev/pgm/tlfs/t-sae-soc.sas 07APR2024 08:41 t-3-21-3-sae-soc.rtf

Table 58: Serious treatment-emergent adverse events with an incidence ≥ 1% in any group by Preferred Term (Safety Set)

Preferred Term	Study 306 T+C N=324 n (%)	Study 306 P+C N=321 n (%)	Tislelizumab Monotherapy Pool 200 mg Q3W N=1534 n (%)
Any Preferred Term	158 (48.8)	127 (39.6)	533 (34.7)
Dysphagia	17 (5.2)	8 (2.5)	16 (1.0)
Pneumonia	17 (5.2)	22 (6.9)	79 (5.1)
Diarrhoea	7 (2.2)	3 (0.9)	5 (0.3)
Oesophageal stenosis	7 (2.2)	2 (0.6)	3 (0.2)
Pneumonitis	7 (2.2)	4 (1.2)	24 (1.6)
Acute kidney injury	6 (1.9)	0	2 (0.1)
Anaemia	6 (1.9)	6 (1.9)	4 (0.3)
Decreased appetite	6 (1.9)	2 (0.6)	11 (0.7)
Hyponatraemia	6 (1.9)	2 (0.6)	5 (0.3)
Vomiting	6 (1.9)	6 (1.9)	8 (0.5)
Febrile neutropenia	5 (1.5)	5 (1.6)	0
General physical health deterioration	5 (1.5)	4 (1.2)	10 (0.7)
Malaise	5 (1.5)	3 (0.9)	2 (0.1)
Nausea	5 (1.5)	2 (0.6)	4 (0.3)
Stomatitis	5 (1.5)	0	0
Adrenal insufficiency	4 (1.2)	0	1 (0.1)
Colitis	4 (1.2)	0	2 (0.1)
Neutrophil count decreased	4 (1.2)	3 (0.9)	0
Pneumonia aspiration	4 (1.2)	4 (1.2)	3 (0.2)
Pyrexia	4 (1.2)	1 (0.3)	15 (1.0)
Sepsis	4 (1.2)	2 (0.6)	5 (0.3)
Upper gastrointestinal haemorrhage	4 (1.2)	2 (0.6)	14 (0.9)
Death	3 (0.9)	4 (1.2)	16 (1.0)
Hypokalaemia	3 (0.9)	4 (1.2)	2 (0.1)
Respiratory failure	3 (0.9)	4 (1.2)	9 (0.6)
Leukopenia	1 (0.3)	4 (1.2)	0
Neutropenia	1 (0.3)	7 (2.2)	1 (0.1)
Dyspnoea	0	2 (0.6)	16 (1.0)

- Data cut-off for 306: 28FEB2022.
- Data cut-off for Tisle monotherapy: 001-26AUG2020, 102-31MAY2020, 203-02NOV2020, 204-16SEP2019, 208-30JUN2021, 302-01DEC2020, 303-15JUL2021.
Numbers (n) represent counts of subjects.
MedDRA version 25.1.
Source: [SCS Appendix 1-Table 1.3-5]
Source: Summary of Clinical Safety Table 12

The following paragraphs present an overview of serious TEAEs by Preferred Term considered by the Investigator to be **causally related to study treatment**.

Serious TEAEs related to any component of study treatment. Serious TEAEs suspected by the Investigator to be causally related to any component of study treatment for T+C, P+C (Study 306), and for tislelizumab monotherapy are presented in Table 59.

Table 59: **Serious treatment-emergent adverse events with an incidence ≥ 1% in any group related to any component of study treatment by Preferred Term (Safety Set)**

Table 3.1-10 (Page 1 of 7)
Serious treatment-emergent adverse events, related to any component of study treatment by preferred term
Safety set

Preferred Term	306 Tisle+Chemo N=324 n (%)	306 Placebo+Chemo N=321 n (%)	Tisle monotherapy 200 mg Q3W N=1534 n (%)
Any preferred term	95 (29.3)	62 (19.3)	181 (11.8)
Pneumonia	7 (2.2)	8 (2.5)	17 (1.1)
Pneumonitis	7 (2.2)	3 (0.9)	23 (1.5)
Anaemia	6 (1.9)	4 (1.2)	2 (0.1)
Diarrhoea	6 (1.9)	2 (0.6)	5 (0.3)
Febrile neutropenia	5 (1.5)	5 (1.6)	0
Nausea	5 (1.5)	2 (0.6)	3 (0.2)
Stomatitis	5 (1.5)	0	0
Acute kidney injury	4 (1.2)	0	0
Adrenal insufficiency	4 (1.2)	0	1 (0.1)
Colitis	4 (1.2)	0	1 (0.1)
Decreased appetite	4 (1.2)	2 (0.6)	2 (0.1)
Malaise	4 (1.2)	3 (0.9)	2 (0.1)
Neutrophil count decreased	4 (1.2)	3 (0.9)	0
Vomiting	4 (1.2)	5 (1.6)	4 (0.3)
Hypokalaemia	3 (0.9)	3 (0.9)	0
Hyponatraemia	3 (0.9)	2 (0.6)	3 (0.2)
Alanine aminotransferase increased	2 (0.6)	1 (0.3)	5 (0.3)
Aspartate aminotransferase increased	2 (0.6)	0	6 (0.4)
Electrolyte imbalance	2 (0.6)	0	1 (0.1)
Hyperglycaemia	2 (0.6)	1 (0.3)	2 (0.1)
Immune-mediated hepatitis	2 (0.6)	0	4 (0.3)
Malnutrition	2 (0.6)	0	0
Pyrexia	2 (0.6)	1 (0.3)	3 (0.2)

Source: Summary of Clinical Safety Appendix 1, excerpt from Table 3.1-10

Serious TEAEs related to tislelizumab/placebo. Serious TEAEs related to tislelizumab/placebo for T+C, P+C (Study 306), and for tislelizumab monotherapy are presented in Table 60.

Table 60: **Serious treatment-emergent adverse events with an incidence ≥ 1% in any group related to tislelizumab/placebo by Preferred Term (Safety Set)**

Table 3.1-11 (Page 1 of 6)
Serious treatment-emergent adverse events, related to Tislelizumab/placebo by preferred term
Safety set

Preferred Term	306 Tisle+Chemo N=324 n (%)	306 Placebo+Chemo N=321 n (%)	Tisle monotherapy 200 mg Q3W N=1534 n (%)
Any preferred term	63 (19.4)	27 (8.4)	181 (11.8)
Pneumonitis	7 (2.2)	2 (0.6)	23 (1.5)
Pneumonia	6 (1.9)	4 (1.2)	17 (1.1)
Diarrhoea	5 (1.5)	1 (0.3)	5 (0.3)
Adrenal insufficiency	4 (1.2)	0	1 (0.1)
Colitis	3 (0.9)	0	1 (0.1)
Malaise	3 (0.9)	3 (0.9)	2 (0.1)
Acute kidney injury	2 (0.6)	0	0
Alanine aminotransferase increased	2 (0.6)	0	5 (0.3)
Aspartate aminotransferase increased	2 (0.6)	0	6 (0.4)
Electrolyte imbalance	2 (0.6)	0	1 (0.1)
Hyperglycaemia	2 (0.6)	1 (0.3)	2 (0.1)
Immune-mediated hepatitis	2 (0.6)	0	4 (0.3)
Nausea	2 (0.6)	0	3 (0.2)
Acquired tracheo-oesophageal fistula	1 (0.3)	0	0
Adrenocorticotropic hormone deficiency	1 (0.3)	0	0
Agitation	1 (0.3)	0	0
Anaemia	1 (0.3)	1 (0.3)	2 (0.1)
Asthenia	1 (0.3)	0	0
Blood creatine phosphokinase increased	1 (0.3)	0	1 (0.1)
Carbuncle	1 (0.3)	0	0
Decreased appetite	1 (0.3)	1 (0.3)	2 (0.1)
Diabetic ketoacidosis	1 (0.3)	0	0
Diverticulitis	1 (0.3)	0	0

Source: Summary of Clinical Safety Appendix 1, excerpt from Table 3.1-11, see also Table 1.3.6

Serious TEAEs related to any chemotherapy component. Serious TEAEs suspected by the Investigator to be causally related to any chemotherapy component for T+C, P+C (Study 306) are presented in Table 61.

Table 61: **Serious treatment-emergent adverse events with an incidence ≥ 1% in any group related to any chemotherapy component by Preferred Term (Safety Set)**

Table 3.1-11.1 (Page 1 of 3)
Serious treatment-emergent adverse events, related to any chemotherapy component by preferred term
Safety set

Preferred Term	306 Tisle+Chemo N=324 n (%)	306 Placebo+Chemo N=321 n (%)
Any preferred term	71 (21.9)	57 (17.8)
Anaemia	6 (1.9)	4 (1.2)
Pneumonia	6 (1.9)	7 (2.2)
Diarrhoea	5 (1.5)	2 (0.6)
Febrile neutropenia	5 (1.5)	5 (1.6)
Stomatitis	5 (1.5)	0
Decreased appetite	4 (1.2)	2 (0.6)
Malaise	4 (1.2)	3 (0.9)
Nausea	4 (1.2)	2 (0.6)
Neutrophil count decreased	4 (1.2)	3 (0.9)
Acute kidney injury	3 (0.9)	0
Colitis	3 (0.9)	0
Hypokalaemia	3 (0.9)	3 (0.9)
Hyponatraemia	3 (0.9)	1 (0.3)
Pneumonitis	3 (0.9)	1 (0.3)
Vomiting	3 (0.9)	5 (1.6)
Electrolyte imbalance	2 (0.6)	0
Malnutrition	2 (0.6)	0
Pyrexia	2 (0.6)	1 (0.3)
Renal impairment	2 (0.6)	0
White blood cell count decreased	2 (0.6)	1 (0.3)
Abscess limb	1 (0.3)	0
Acquired tracheo-oesophageal fistula	1 (0.3)	1 (0.3)
Adrenal insufficiency	1 (0.3)	0
Alanine aminotransferase increased	1 (0.3)	1 (0.3)
Aspartate aminotransferase increased	1 (0.3)	0
Asthenia	1 (0.3)	1 (0.3)

Source: Summary of Clinical Safety Appendix 1, excerpt from Table 3.1-11.1

Deaths

On-treatment deaths (defined as deaths that occurred during the study treatment and up to 30 days after the last dose of study treatment) by Preferred Term for T+C, P+C (Study 306), and for tislelizumab monotherapy are presented in Table 62.

Table 62: On-treatment deaths by Preferred Term including ≥ 1 patient in either the T+C Arm or the P+C Arm (Safety Set)

Category Preferred term	Study 306 T+C N=324 n (%)	Study 306 P+C N=321 n (%)	Tislelizumab Monotherapy Pool 200 mg Q3W N=1534 n (%)
Number of subjects who died	21 (6.5)	27 (8.4)	120 (7.8)
Adverse event	14 (4.3)	16 (5.0)	48 (3.1)
Death	2 (0.6)	4 (1.2)	9 (0.6)
Brain injury	1 (0.3)	0	0
Gastrointestinal haemorrhage	1 (0.3)	0	0
Multiple organ dysfunction syndrome	1 (0.3)	0	2 (0.1)
Myocarditis	1 (0.3)	0	0
Pneumonia	1 (0.3)	3 (0.9)	8 (0.5)
Pneumonia aspiration	1 (0.3)	0	0
Pulmonary embolism	1 (0.3)	2 (0.6)	2 (0.1)

Category Preferred term	Study 306 T+C N=324 n (%)	Study 306 P+C N=321 n (%)	Tislelizumab Monotherapy Pool 200 mg Q3W N=1534 n (%)
Pulmonary tuberculosis	1 (0.3)	0	0
Respiratory failure	1 (0.3)	1 (0.3)	4 (0.3)
Sepsis	1 (0.3)	0	0
Sudden death	1 (0.3)	1 (0.3)	1 (0.1)
Upper gastrointestinal haemorrhage	1 (0.3)	0	2 (0.1)
Accidental death	0	1 (0.3)	0
Asphyxia	0	1 (0.3)	0
COVID-19 pneumonia	0	2 (0.6)	0
Septic shock	0	1 (0.3)	0
Disease under study	7 (2.2)	11 (3.4)	69 (4.5)
General physical health deterioration	2 (0.6)	4 (1.2)	7 (0.5)
Pneumonia	2 (0.6)	0	1 (0.1)
Cachexia	1 (0.3)	0	1 (0.1)
Death	1 (0.3)	0	5 (0.3)
Respiratory failure	1 (0.3)	2 (0.6)	4 (0.3)
Cardiac failure	0	1 (0.3)	1 (0.1)
Hepatic failure	0	1 (0.3)	4 (0.3)
Lung abscess	0	1 (0.3)	0
Pneumonia aspiration	0	1 (0.3)	0
Upper gastrointestinal haemorrhage	0	1 (0.3)	4 (0.3)

- Data cut-off for 306: 28FEB2022.
- Data cut-off for Tisle monotherapy: 001-26AUG2020, 102-31MAY2020, 203-02NOV2020, 204-16SEP2019, 208-30JUN2021,
302-01DEC2020, 303-15JUL2021.
Deaths occurring during the study treatment and up to 30 days after the last dose are summarized in this table.
MedDRA version 25.1.
Source: [SCS Appendix 1-Table 3.1-12]
Source: Summary of Clinical Safety, excerpt from Table 11

Other significant events

AESIs include immune-mediated TEAEs and infusion-related reactions; both types of adverse reaction are presented in the following paragraphs.

Immune-mediated TEAEs

As agreed with the CHMP as part of a scientific advice and with the US FDA as part of a Type C Meeting's written responses (both dated February 2023), a new programmatic algorithmic method for retrieval of imTEAEs was utilised for the Summary of Clinical Safety, and the data obtained by this method are presented in this Assessment Report.

The method is based on a list of terms with two components:

- A narrow list of terms for which the immune-mediated aetiology is specified in the Preferred Term and that are always considered imTEAEs (e.g., immune-mediated hypothyroidism)
- A broad list of terms that are known or possible imTEAEs, and that are considered imTEAEs when any of the following additional criteria are met:

- Treatment of the adverse event with steroids, other immunosuppressants or hormonal replacement therapy
- Investigator assessment as imTEAE in the CRF
- Investigator causality assessment as related to the study treatment
- Action taken with any study treatment as drug interruption/discontinuation

A TEAE was defined as an imTEAE as long as it satisfied one of the two components above.

All TEAEs for which the Preferred Term fell either into the narrow list or the broad list combined with at least one of the additional criteria were defined as an imTEAE, if the latter occurred on or after the first dose of the study treatment and up to 90 days after the last dose of the study treatment (tislelizumab/placebo) or the start of the crossover period (for studies allowing crossover), whichever occurred first.

This programmatic algorithmic approach identifies conditions with potential involvement of the immune system and potential causal association with tislelizumab treatment.

A summary of imTEAEs for T+C, P+C (Study 306), and for tislelizumab monotherapy is presented in Table 63.

Table 63: Overview of immune-mediated treatment-emergent adverse events (Safety Set)

imAE category: Overall	**Study 306 T+C N=324 n (%)**	**Study 306 P+C N=321 n (%)**	**Tislelizumab Monotherapy Pool 200 mg Q3W N=1534 n (%)**
Number of subjects with at least one imTEAEs	114 (35.2)	60 (18.7)	506 (33.0)
Cumulative incidence proportions (95% CI) (%) at:			
3 months	21.3 (17.0,25.9)	12.8 (9.4,16.7)	21.6 (19.6,23.7)
6 months	26.9 (22.1,31.8)	15.3 (11.6,19.4)	27.2 (25.0,29.4)
12 months	33.6 (28.5,38.8)	18.4 (14.3,22.8)	30.8 (28.5,33.1)
Maximum grade			
Grade 3	24 (7.4)	3 (0.9)	59 (3.8)
Grade 4	4 (1.2)	1 (0.3)	12 (0.8)
Grade 5	1 (0.3)	0	1 (0.1)
Serious imTEAEs	27 (8.3)	6 (1.9)	89 (5.8)
imTEAE leading to any study drug discontinuation	16 (4.9)	2 (0.6)	51 (3.3)
imTEAE leading to tislelizumab/placebo discontinuation	16 (4.9)	2 (0.6)	51 (3.3)
imTEAE leading to any study drug modification	45 (13.9)	7 (2.2)	95 (6.2)
imTEAE leading to tislelizumab/placebo dose modification	41 (12.7)	5 (1.6)	95 (6.2)
imTEAE leading to death	1 (0.3)	0	1 (0.1)

imAE category: Overall	Study 306 T+C N=324 n (%)	Study 306 P+C N=321 n (%)	Tislelizumab Monotherapy Pool 200 mg Q3W N=1534 n (%)

- Data cut-off for 306: 28FEB2022.
- Data cut-off for Tisle monotherapy: 001-26AUG2020, 102-31MAY2020, 203-02NOV2020, 204-16SEP2019, 208-30JUN2021,
302-01DEC2020, 303-15JUL2021.
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 25.1, CTCAE version v4.03, Case Retrieval Strategy version released 20230405.
Source: [SCS Appendix 1-Table 3-10]
Source: Summary of Clinical Safety Table 13

A summary of **imTEAE categories** for T+C, P+C (Study 306), and for tislelizumab monotherapy is presented in Table 64. Outcomes in the respective imTEAE categories are presented in Table 65.

Table 64: Overview of immune-mediated treatment-emergent adverse events by category (Assessor's Table)

	Study 306 T+C (N = 324) n (%)						
Category	**Any Grade**	**Grade 3**	**Grade 4**	**Grade 5**	**Serious**	**Leading to any study drug dis-continu-ation**	**Resulting in death**
Patients with at least one immune-mediated TEAE	114 (35.2)	24 (7.4)	4 (1.2)	1 (0.3)	27 (8.3)	16 (4.9)	1 (0.3)
Immune-mediated skin adverse reaction	41 (12.7)	8 (2.5)	1 (0.3)	0	2 (0.6)	2 (0.6)	0
Immune-mediated hypothyroidism	38 (11.7)	0	0	0	0	1 (0.3)	0
Immune-mediated pneumonitis	26 (8.0)	4 (1.2)	1 (0.3)	0	9 (2.8)	8 (2.5)	0
Immune-mediated hyperthyroidism	9 (2.8)	0	0	0	0	0	0
Other immune-mediated reactions (other[4])	6 (1.9)	0	0	0	0	0	0
Immune-mediated colitis	5 (1.5)	4 (1.2)	0	0	5 (1.5)	0	0
Immune-mediated endocrinopathies (adrenal insufficiency)	5 (1.5)	4 (1.2)	0	0	4 (1.2)	0	0
Other immune-mediated reactions (pancreatitis)	5 (1.5)	0	0	0	0	0	0
Immune-mediated hepatitis	4 (1.2)	3 (0.9)	1 (0.3)	0	4 (1.2)	1 (0.3)	0
Other immune-mediated reactions (musculoskeletal)	3 (0.9)	2 (0.6)	0	0	1 (0.3)	1 (0.3)	0
Immune-mediated endocrinopathies (hypophysitis)	3 (0.9)	1 (0.3)	0	0	1 (0.3)	0	0
Other immune-mediated reactions (ocular)	3 (0.9)	1 (0.3)	0	0	0	1 (0.3)	0
Immune-mediated endocrinopathies (diabetes mellitus)	2 (0.6)	0	1 (0.3)	0	1 (0.3)	0	0
Immune-mediated myocarditis/pericarditis	2 (0.6)	0	0	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)

[4] Vasculitis, Raynaud's phenomenon, Systemic scleroderma

Category	Study 306 T+C (N = 324) n (%)						
	Any Grade	Grade 3	Grade 4	Grade 5	Serious	Leading to any study drug discontinuation	Resulting in death
Immune-mediated myositis/rhabdomyolysis	1 (0.3)	0	0	0	1 (0.3)	1 (0.3)	0
Immune-mediated endocrinopathies (thyroiditis)	1 (0.3)	0	0	0	0	0	0
Immune-mediated nephritis and renal dysfunction	0	0	0	0	0	0	0

Source: Summary of Clinical Safety Appendix 1, excerpt from Table 3.1-22

Table 65: Outcomes of immune-mediated treatment-emergent adverse events by category (Assessor's Table)

Category	Study 306 T+C (N = 324) n (%)					
	Total number of events in the category	Resolved n (%)	Recovering/ resolving n (%)	Not recovered/ resolved n (%)	Fatal n (%)	Unknown n (%)
Immune-mediated skin adverse reaction	61	45 (73.8)	5 (8.2)	9 (14.8)	0	2 (3.3)
Immune-mediated hypothyroidism	42	13 (31.0)	9 (21.4)	16 (38.1)	0	4 (9.5)
Immune-mediated pneumonitis	27	15 (55.6)	1 (3.7)	9 (33.3)	0	2 (7.4)
Immune-mediated hyperthyroidism	10	7 (70.0)	0	3 (30.0)	0	0
Other immune-mediated reactions (other)[5]	6	4 (66.7)	0	2 (33.3)	0	0
Immune-mediated colitis	5	5 (100.0)	0	0	0	0
Immune-mediated endocrinopathies (adrenal insufficiency)	5	1 (20.0)	2 (40.0)	2 (40.0)	0	0
Other immune-mediated reactions (pancreatitis)	6	4 (66.7)	0	1 (16.7)	0	1 (16.7)
Immune-mediated hepatitis	4	4 (100.0)	0	0	0	0
Other immune-mediated reactions (musculoskeletal)	5	3 (60.0)	1 (20.0)	1 (20.0)	0	0
Immune-mediated endocrinopathies (hypophysitis)	3	1 (33.3)	0	2 (66.7)	0	0
Other immune-mediated reactions (ocular)	3	1 (33.3)	1 (33.3)	1 (33.3)	0	0

[5] Vasculitis, Raynaud's phenomenon, Systemic scleroderma

Category			Study 306 T+C (N = 324) n (%)			
Immune-mediated endocrinopathies (diabetes mellitus)	2	1 (50.0)	1 (50.0)	0	0	0
Immune-mediated myocarditis/pericarditis	2	0	0	1 (50.0)	0	1 (50.0)
Immune-mediated myositis/rhabdomyolysis	1	1 (100.0)	0	0	0	0
Immune-mediated endocrinopathies (thyroiditis)	1	0	0	0	0	1 (100.0)
Immune-mediated nephritis and renal dysfunction	0	0	0	0	0	0

Source: Summary of Clinical Safety Appendix 1, excerpt from Table 3.1-27

In the T+C Arm of Study 306, approximately one third of patients experienced imTEAEs (Table 64). The majority of cases (≥ 50%) recovered/resolved as far as immune-mediated colitis, hepatitis, myositis/rhabdomyolysis, skin adverse reactions, hyperthyroidism, other reactions, pancreatitis, musculoskeletal reactions, pneumonitis, and diabetes mellitus were concerned. However, a substantial proportion of cases (≥ 30%) did not recover/resolve for immune-mediated hypophysitis, myocarditis/pericarditis, adrenal insufficiency, hypothyroidism, pneumonitis, other reactions, ocular reactions, and hyperthyroidism (Table 65).

In patients treated with tislelizumab as monotherapy, hypophysitis (Grade 2) occurred in 0.2% of patients. The median time from first dose to onset of the event was 8.3 months (range: 22.0 days to 9.0 months). The median duration from onset to resolution was not evaluable based on currently available data (range: 13.0+ months to 23.3+ months; + denotes a censored observation, with ongoing events at the time of the analysis). Tislelizumab was not permanently discontinued in any patient and tislelizumab treatment was not interrupted in any patient. Hypophysitis was not resolved in any patient.

Infusion-related reactions

An IRR was defined as any event occurring the day of administration of study treatment (i.v.) and for which the Preferred Term belonged to a list of terms from a customised MedDRA query. Of note, the IRR definition in the Clinical Study Report of each study in the Tislelizumab Monotherapy Pool and Combination Therapy Pool, respectively, may differ from this harmonised definition for the Safety Set.

(Treatment-emergent) IRRs by Preferred Term and maximum grade for T+C, P+C (Study 306), and for tislelizumab monotherapy are presented in Table 66.

Table 66: Infusion-related reactions (treatment-emergent) by Preferred Term and maximum grade (Safety Set)

Table 3.1-31 (Page 1 of 2)
Infusion-related reactions treatment-emergent adverse events by preferred term and maximum grade
Safety set

Preferred term	306 Tisle+Chemo N=324 All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	306 Placebo+Chemo N=321 All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Tisle monotherapy 200 mg Q3W N=1534 All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Number of subjects with at least one TEAE	25 (7.7)	4 (1.2)	0	0	17 (5.3)	2 (0.6)	0	0	44 (2.9)	2 (0.1)	0	0
Rash	12 (3.7)	1 (0.3)	0	0	9 (2.8)	0	0	0	25 (1.6)	1 (0.1)	0	0
Chills	4 (1.2)	0	0	0	2 (0.6)	0	0	0	8 (0.5)	0	0	0
Drug hypersensitivity	4 (1.2)	2 (0.6)	0	0	4 (1.2)	1 (0.3)	0	0	1 (0.1)	0	0	0
Face oedema	1 (0.3)	0	0	0	0	0	0	0	0	0	0	0
Lip oedema	1 (0.3)	0	0	0	0	0	0	0	0	0	0	0
Lip swelling	1 (0.3)	0	0	0	0	0	0	0	0	0	0	0
Mouth swelling	1 (0.3)	0	0	0	0	0	0	0	0	0	0	0
Tongue oedema	1 (0.3)	0	0	0	0	0	0	0	0	0	0	0
Type I hypersensitivity	1 (0.3)	0	0	0	0	0	0	0	0	0	0	0
Urticaria	1 (0.3)	1 (0.3)	0	0	0	0	0	0	2 (0.1)	0	0	0
Eyelid oedema	0	0	0	0	1 (0.3)	0	0	0	0	0	0	0
Hypersensitivity	0	0	0	0	1 (0.3)	1 (0.3)	0	0	0	0	0	0
Infusion related reaction	0	0	0	0	0	0	0	0	2 (0.1)	1 (0.1)	0	0
Laryngeal oedema	0	0	0	0	0	0	0	0	1 (0.1)	0	0	0
Rash erythematous	0	0	0	0	0	0	0	0	1 (0.1)	0	0	0
Rash pruritic	0	0	0	0	0	0	0	0	1 (0.1)	0	0	0
Rhinitis allergic	0	0	0	0	0	0	0	0	2 (0.1)	0	0	0
Swelling face	0	0	0	0	0	0	0	0	1 (0.1)	0	0	0

Source: Summary of Clinical Safety Appendix 1 Table 3.1-31

Adverse drug reactions

The following data were used for ADR determination:

- Pivotal Study 306
- 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 306 and Studies 206, 304, 305, and 307, respectively, enrolling patients with various tumor types who received tislelizumab in combination with various regimens of chemotherapy, which were utilised to support ADR determination for the combination treatment.

Therefore, the changes included in section 4.8 of the current procedure II/03 represent the most up-to-date safety pool and a consolidated version that includes also the changes from procedure II/06.

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 update of the 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.

ADR candidates include two types of events, namely pre-qualified ADR candidates and ADR candidates identified through numerical screening rule(s). Prequalified ADR candidates are events that are suspected to be related to the medicinal product based on the known mechanism of action, previous experience collected with the medicinal product, medicinal products in the same class, or any event included in the European Medicines Agency (EMA) Designated Medical Event (DME) list. Other ADR candidates are events for which an excess versus the comparator is observed. These ADR candidates were identified using an algorithm (for more details see Summary of Clinical Safety) based on all TEAEs.

All ADR candidates (both prequalified candidate ADRs and candidate ADRs identified via numerical screening rules) underwent a medical review using the Bradford Hill criteria to assess the plausibility of a causal association between tislelizumab and these candidate ADRs.

An immune-mediated ADR (imADR) was defined as any Preferred Term flagged as ADR and reported as an imTEAE in at least one patient of the pivotal Study 306, the Tislelizumab Monotherapy Pool or the Tislelizumab Combination Therapy Pool.

ADRs for the treatment arms of Study 306 and the Tislelizumab Monotherapy and Combination Therapy Pools are presented below. 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 gastro-oesophageal junction (G/GEJ) adenocarcinoma and oesophageal squamous cell carcinoma

(OSCC) that have been treated with tislelizumab + chemotherapy in Studies 206, 304, 307, 305, and 306.

Table 67: 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

	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)**
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

Immunogenicity

For information on the immunogenicity of tislelizumab, please see Section 4.3.3.

Haematology

The worst post-baseline haematology abnormalities based on CTC grades for T+C, P+C (Study 306), and for tislelizumab monotherapy are presented in Table 68.

Table 68: Worst post-baseline haematology abnormalities based on CTC grades (Safety Set)

	Study 306 T+C N=324		Study 306 P+C N=321		Tislelizumab Monotherapy Pool 200 mg Q3W N=1534	
	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Haemoglobin (g/L) - decrease	315 (97.2)	46 (14.2)	305 (95.0)	47 (14.6)	1067 (69.6)	75 (4.9)
Haemoglobin (g/L) - increase	1 (0.3)	0	6 (1.9)	0	66 (4.3)	2 (0.1)
Leukocytes (10E9/L) - decrease	247 (76.2)	56 (17.3)	237 (73.8)	68 (21.2)	274 (17.9)	14 (0.9)
Leukocytes (10E9/L) - increase	0	0	0	0	0	0
Lymphocytes (10E9/L) - decrease	224 (69.1)	57 (17.6)	214 (66.7)	47 (14.6)	867 (56.5)	178 (11.6)
Lymphocytes (10E9/L) - increase	7 (2.2)	1 (0.3)	11 (3.4)	0	29 (1.9)	1 (0.1)
Neutrophils (10E9/L) - decrease	240 (74.1)	131 (40.4)	235 (73.2)	144 (44.9)	186 (12.1)	29 (1.9)
Platelets (10E9/L) - decrease	143 (44.1)	15 (4.6)	137 (42.7)	13 (4.0)	301 (19.6)	18 (1.2)

- Data cut-off for 306: 28FEB2022.
- Data cut-off for Tisle monotherapy: 001-26AUG2020, 102-31MAY2020, 203-02NOV2020, 204-16SEP2019, 208-30JUN2021,302-01DEC2020, 303-15JUL2021.
Numbers (n) represent counts of subjects. 'All grades' represents subjects 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 v4.03.
Source: [SCS Appendix 1-Table 1.4-1]
Source: Summary of Clinical Safety Table 15

Clinical chemistry

The worst post-baseline chemistry abnormalities based on CTC grades for T+C, P+C (Study 306), and for tislelizumab monotherapy are presented in Table 69.

Table 69: Worst post-baseline chemistry abnormalities based on CTC grades (Safety Set)

	Study 306 T+C N=324		Study 306 P+C N=321		Tislelizumab Monotherapy Pool 200 mg Q3W 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 (U/L) - increase	103 (31.8)	10 (3.1)	78 (24.3)	5 (1.6)	549 (35.8)	34 (2.2)
Albumin (g/L) - decrease	209 (64.5)	1 (0.3)	213 (66.4)	0	684 (44.6)	10 (0.7)
Alkaline Phosphatase (U/L) - increase	118 (36.4)	6 (1.9)	110 (34.3)	4 (1.2)	699 (45.6)	39 (2.5)
Aspartate Aminotransferase (U/L) - increase	127 (39.2)	11 (3.4)	102 (31.8)	4 (1.2)	632 (41.2)	51 (3.3)
Bilirubin (umol/L) - increase	71 (21.9)	2 (0.6)	77 (24.0)	7 (2.2)	319 (20.8)	34 (2.2)
Calcium Corrected (mmol/L) - decrease	57 (17.6)	11 (3.4)	49 (15.3)	8 (2.5)	1 (0.1)	0

	Study 306 T+C N=324		Study 306 P+C N=321		Tislelizumab Monotherapy Pool 200 mg Q3W N=1534	
	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Calcium Corrected (mmol/L) - increase	25 (7.7)	6 (1.9)	15 (4.7)	2 (0.6)	11 (0.7)	7 (0.5)
Creatine Kinase (ukat/L) - increase	73 (22.5)	5 (1.5)	57 (17.8)	1 (0.3)	260 (16.9)	25 (1.6)
Creatinine (umol/L) - increase	108 (33.3)	8 (2.5)	84 (26.2)	5 (1.6)	282 (18.4)	13 (0.8)
Glucose (mmol/L) - decrease	60 (18.5)	3 (0.9)	52 (16.2)	3 (0.9)	153 (10.0)	8 (0.5)
Glucose (mmol/L) - increase	258 (79.6)	23 (7.1)	239 (74.5)	16 (5.0)	972 (63.4)	74 (4.8)
Magnesium (mmol/L) - decrease	103 (31.8)	4 (1.2)	113 (35.2)	5 (1.6)	108 (7.0)	1 (0.1)
Magnesium (mmol/L) - increase	23 (7.1)	8 (2.5)	21 (6.5)	2 (0.6)	98 (6.4)	11 (0.7)
Potassium (mmol/L) - decrease	112 (34.6)	33 (10.2)	96 (29.9)	27 (8.4)	254 (16.6)	38 (2.5)
Potassium (mmol/L) - increase	96 (29.6)	9 (2.8)	90 (28.0)	10 (3.1)	169 (11.0)	13 (0.8)
Sodium (mmol/L) - decrease	231 (71.3)	61 (18.8)	214 (66.7)	34 (10.6)	623 (40.6)	93 (6.1)
Sodium (mmol/L) - increase	19 (5.9)	2 (0.6)	23 (7.2)	1 (0.3)	118 (7.7)	1 (0.1)

- Data cut-off for 306: 28FEB2022.
- Data cut-off for Tisle monotherapy: 001-26AUG2020, 102-31MAY2020, 203-02NOV2020, 204-16SEP2019, 208-30JUN2021,302-01DEC2020, 303-15JUL2021.
Numbers (n) represent counts of subjects. 'All grades' represents subjects 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 v4.03.
Source: [SCS Appendix 1-Table 1.4-2]
Source: Summary of Clinical Safety Table 16

Hepatic laboratory tests

Detailed (categorial) analyses of hepatic laboratory values for T+C, P+C (Study 306), and for tislelizumab monotherapy are presented in the Summary of Clinical Safety; however, the basic information on the impact of treatment on hepatic laboratory values is also included in Table 69 of this Assessment Report. Tislelizumab is known to induce increases in aminotransferases and to be associated with hepatotoxicity/(immune-mediated) hepatitis/drug-induced liver injury (Table 64).

Thyroid panel

In line with the immune-mediated effects of tislelizumab on the thyroid gland (**Table 64**), the incidence rates of altered post-baseline levels of TSH and T4 were higher in the T+C Arm compared to the P+C Arm (hyperthyroidism (4.6% vs. 1.5%), hypothyroidism (9.6% vs. 5.5%); Summary of Clinical Safety). It should be noted that a considerable proportion of these cases did not recover/resolve.

Safety in special populations

No patterns are discernible in terms of safety outcomes in the subgroups of PD-L1 status, gender, hepatic or renal function, race, region, or chemotherapy doublet. The data exhibit random fluctuations with no apparent trend in any of these subgroups (data not shown).

As would be expected, the incidence rates of serious and fatal TEAEs increase with age (<65 years/ ≥65 years up to > 75 years; **Table 70**). In line with this observation, the incidence rates of TEAEs leading to any treatment modification also increase with age. Due to the small sample size of patients ≥ 75 years, no conclusions can be drawn for this patient population; this limitation is reflected in the current SmPC.

Table 70: Overview of treatment-emergent adverse events by age (Safety Set)

	Study 306 T+C N = 324			Study 306 P+C N = 321		
	<65 years N = 175 n (%)	>=65 - <75 years N = 136 n (%)	>=75 years N = 13 n (%)	<65 years N = 160 n (%)	>=65 - <75 years N = 136 n (%)	>=75 years N = 25 n (%)
TEAEs	**174 (99.4)**	**136 (100.0)**	**13 (100.0)**	**158 (98.8)**	**136 (100.0)**	**25 (100.0)**
Treatment-related	166 (94.9)	135 (99.3)	12 (92.3)	152 (95.0)	133 (97.8)	24 (96.0)
Tislelizumab/placebo-related	110 (62.9)	108 (79.4)	8 (61.5)	98 (61.3)	83 (61.0)	14 (56.0)
Chemotherapy-related	166 (94.9)	135 (99.3)	12 (92.3)	152 (95.0)	132 (97.1)	24 (96.0)
TEAEs with grade >=3	**138 (78.9)**	**108 (79.4)**	**9 (69.2)**	**125 (78.1)**	**102 (75.0)**	**22 (88.0)**
Treatment-related	111 (63.4)	98 (72.1)	8 (61.5)	99 (61.9)	91 (66.9)	17 (68.0)
Tislelizumab/placebo-related	46 (26.3)	55 (40.4)	3 (23.1)	28 (17.5)	31 (22.8)	6 (24.0)
Chemotherapy-related	105 (60.0)	90 (66.2)	8 (61.5)	96 (60.0)	91 (66.9)	15 (60.0)
Serious TEAEs	**80 (45.7)**	**70 (51.5)**	**8 (61.5)**	**61 (38.1)**	**56 (41.2)**	**10 (40.0)**
Treatment-related	42 (24.0)	49 (36.0)	4 (30.8)	25 (15.6)	32 (23.5)	5 (20.0)
Tislelizumab/placebo-related	23 (13.1)	38 (27.9)	2 (15.4)	12 (7.5)	14 (10.3)	1 (4.0)
Chemotherapy-related	30 (17.1)	38 (27.9)	3 (23.1)	21 (13.1)	31 (22.8)	5 (20.0)
Fatal serious TEAEs	**10 (5.7)**	**14 (10.3)**	**2 (15.4)**	**13 (8.1)**	**15 (11.0)**	**2 (8.0)**
Treatment-related	1 (0.6)	6 (4.4)	0 (0.0)	3 (1.9)	3 (2.2)	0 (0.0)
Tislelizumab/placebo-related	0 (0.0)	6 (4.4)	0 (0.0)	2 (1.3)	1 (0.7)	0 (0.0)
Chemotherapy-related	1 (0.6)	3 (2.2)	0 (0.0)	3 (1.9)	3 (2.2)	0 (0.0)
TEAEs leading to any treatment discontinuation	**55 (31.4)**	**45 (33.1)**	**4 (30.8)**	**31 (19.4)**	**32 (23.5)**	**9 (36.0)**
Leading to Tislelizumab/placebo discontinuation	24 (13.7)	18 (13.2)	1 (7.7)	9 (5.6)	9 (6.6)	3 (12.0)
Tislelizumab/placebo-related	16 (9.1)	14 (10.3)	1 (7.7)	1 (0.6)	3 (2.2)	1 (4.0)
Chemotherapy-related	10 (5.7)	5 (3.7)	0 (0.0)	3 (1.9)	4 (2.9)	1 (4.0)
Leading to Chemotherapy discontinuation	49 (28.0)	43 (31.6)	4 (30.8)	30 (18.8)	31 (22.8)	9 (36.0)
Tislelizumab/placebo-related	12 (6.9)	13 (9.6)	0 (0.0)	1 (0.6)	7 (5.1)	4 (16.0)
Chemotherapy-related	41 (23.4)	35 (25.7)	4 (30.8)	23 (14.4)	28 (20.6)	7 (28.0)

	Study 306 T+C N = 324			Study 306 P+C N = 321		
	<65 years N = 175 n (%)	>=65 - <75 years N = 136 n (%)	>=75 years N = 13 n (%)	<65 years N = 160 n (%)	>=65 - <75 years N = 136 n (%)	>=75 years N = 25 n (%)
TEAEs leading to any treatment modification	**125 (71.4)**	**112 (82.4)**	**10 (76.9)**	**99 (61.9)**	**108 (79.4)**	**22 (88.0)**
Leading to Tislelizumab/placebo modification	83 (47.4)	78 (57.4)	9 (69.2)	52 (32.5)	63 (46.3)	13 (52.0)
Tislelizumab/placebo-related	37 (21.1)	49 (36.0)	3 (23.1)	12 (7.5)	20 (14.7)	1 (4.0)
Chemotherapy-related	51 (29.1)	51 (37.5)	5 (38.5)	34 (21.3)	44 (32.4)	11 (44.0)
Leading to Chemotherapy modification	121 (69.1)	108 (79.4)	10 (76.9)	94 (58.8)	105 (77.2)	21 (84.0)
Tislelizumab/placebo-related	34 (19.4)	42 (30.9)	2 (15.4)	14 (8.8)	25 (18.4)	4 (16.0)
Chemotherapy-related	110 (62.9)	94 (69.1)	9 (69.2)	79 (49.4)	96 (70.6)	20 (80.0)
Immune-mediated TEAEs	**61 (34.9)**	**48 (35.3)**	**5 (38.5)**	**27 (16.9)**	**29 (21.3)**	**4 (16.0)**
Infusion-Related Reaction	**17 (9.7)**	**8 (5.9)**	**0 (0.0)**	**5 (3.1)**	**10 (7.4)**	**2 (8.0)**

Source: Table 3.23.3 ADSL, ADAE. Data cutoff: 28FEB2022. Data extraction: 06APR2022.

Abbreviations: TEAE, treatment emergent adverse event. Percentages were based on N.

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

For each row category, a patient with two or more adverse events in that category was counted only once.

On the whole, the results from the subgroup analyses of safety outcomes are consistent with the ones reported for the overall population of Study 306.

Safety related to drug-drug interactions and other interactions

Tislelizumab is a humanised monoclonal antibody that is eliminated from the circulation through catabolism. Formal pharmacokinetic interaction studies have not been conducted. As monoclonal antibodies are not metabolised by cytochrome P450 enzymes or other drug metabolising enzymes, inhibition or induction of these enzymes by co-administered medicinal products is not anticipated to affect the pharmacokinetics of tislelizumab. Monoclonal antibodies generally have a low potential for metabolic interactions, therefore, the lack of formal pharmacokinetic interaction studies is considered acceptable.

Discontinuation due to adverse events

The following paragraphs present an overview of TEAEs (including severe TEAEs) by Preferred Term (any component of study treatment, tislelizumab/placebo, any chemotherapy component).

TEAEs of all grades and grade ≥ 3 by Preferred Term leading to **discontinuation of any component of study treatment** for T+C, P+C (Study 306), and for tislelizumab monotherapy are presented in Table 71.

Table 71: Treatment-emergent adverse events all grades and grade ≥ 3 with an incidence ≥ 2% in the T+C Arm leading to discontinuation of any component of study treatment by Preferred Term (Safety Set)

Table 3.1-16 (Page 1 of 18)
Treatment-emergent adverse events all grades and grade >=3 leading to discontinuation of any component of the study treatment, by preferred term
Safety set

	306 Tisle+Chemo N=324		306 Placebo+Chemo N=321		Tisle monotherapy 200 mg Q3W N=1534	
Preferred Term	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	104 (32.1)	55 (17.0)	72 (22.4)	34 (10.6)	199 (13.0)	162 (10.6)
Peripheral sensory neuropathy	23 (7.1)	9 (2.8)	8 (2.5)	4 (1.2)	0	0
Anaemia	8 (2.5)	7 (2.2)	1 (0.3)	1 (0.3)	1 (0.1)	0
Pneumonitis	8 (2.5)	3 (0.9)	2 (0.6)	1 (0.3)	14 (0.9)	9 (0.6)
Hypoaesthesia	6 (1.9)	0	7 (2.2)	0	0	0
Neurotoxicity	5 (1.5)	0	3 (0.9)	1 (0.3)	0	0
Blood creatinine increased	4 (1.2)	1 (0.3)	4 (1.2)	0	1 (0.1)	1 (0.1)
Fatigue	4 (1.2)	2 (0.6)	4 (1.2)	3 (0.9)	1 (0.1)	1 (0.1)
Malaise	4 (1.2)	1 (0.3)	0	0	3 (0.2)	1 (0.1)

Source: Summary of Clinical Safety Appendix 1, excerpt from Table 3.1-16

Treatment-emergent adverse events of all grades and grade ≥ 3 by Preferred Term leading to **discontinuation of tislelizumab/placebo** for T+C, P+C (Study 306), and for tislelizumab monotherapy are presented in Table 72.

Table 72: Treatment-emergent adverse events all grades and grade ≥ 3 leading to tislelizumab/placebo discontinuation by Preferred Term (Safety Set)

ıble 1.3-8 Treatment-emergent adverse events all grades and grade >=3 leading to Tislelizumab/ placebo discontinuation by eferred term (Safety Set)

	306 Tisle+Chemo N=324		306 Placebo+Chemo N=321		Tisle monotherapy 200 mg Q3W N=1534	
Preferred Term	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	43 (13.3)	29 (9.0)	21 (6.5)	17 (5.3)	199 (13.0)	162 (10.6)
Pneumonitis	8 (2.5)	3 (0.9)	2 (0.6)	1 (0.3)	14 (0.9)	9 (0.6)
Asthenia	2 (0.6)	2 (0.6)	0	0	1 (0.1)	0
Fatigue	2 (0.6)	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.1)	1 (0.1)
Gamma-glutamyltransferase increased	2 (0.6)	1 (0.3)	0	0	2 (0.1)	2 (0.1)
Malaise	2 (0.6)	1 (0.3)	0	0	3 (0.2)	1 (0.1)
Pneumonia	2 (0.6)	1 (0.3)	4 (1.2)	4 (1.2)	18 (1.2)	15 (1.0)
Upper gastrointestinal haemorrhage	2 (0.6)	2 (0.6)	0	0	8 (0.5)	8 (0.5)
Alanine aminotransferase increased	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.1)	1 (0.1)
Alpha hydroxybutyrate dehydrogenase increased	1 (0.3)	0	0	0	0	0
Anaemia	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.1)	0
Arthritis	1 (0.3)	1 (0.3)	0	0	1 (0.1)	1 (0.1)
Aspartate aminotransferase increased	1 (0.3)	1 (0.3)	0	0	2 (0.1)	1 (0.1)
Beta 2 microglobulin increased	1 (0.3)	0	0	0	0	0
Blood creatinine increased	1 (0.3)	0	0	0	1 (0.1)	1 (0.1)
Blood lactate dehydrogenase increased	1 (0.3)	1 (0.3)	0	0	0	0
Decreased appetite	1 (0.3)	1 (0.3)	0	0	1 (0.1)	1 (0.1)
Electrolyte imbalance	1 (0.3)	1 (0.3)	0	0	0	0
Enteritis	1 (0.3)	1 (0.3)	0	0	0	0
Erythema	1 (0.3)	1 (0.3)	0	0	0	0
Hyperglycaemia	1 (0.3)	1 (0.3)	0	0	0	0
Hypothyroidism	1 (0.3)	0	0	0	0	0
Immune-mediated dermatitis	1 (0.3)	1 (0.3)	0	0	0	0
Immune-mediated hepatitis	1 (0.3)	1 (0.3)	0	0	0	0
Myocarditis	1 (0.3)	1 (0.3)	0	0	4 (0.3)	0
Myositis	1 (0.3)	0	0	0	2 (0.1)	1 (0.1)
Oesophageal fistula	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)	2 (0.1)	2 (0.1)
Pain in extremity	1 (0.3)	0	0	0	0	0
Paraesthesia	1 (0.3)	1 (0.3)	0	0	0	0
Peripheral ischaemia	1 (0.3)	1 (0.3)	0	0	0	0
Peripheral sensory neuropathy	1 (0.3)	1 (0.3)	0	0	0	0
Pulmonary tuberculosis	1 (0.3)	1 (0.3)	0	0	0	0
Rash	1 (0.3)	1 (0.3)	0	0	1 (0.1)	1 (0.1)
Retinal vasculitis	1 (0.3)	0	0	0	0	0
Sepsis	1 (0.3)	1 (0.3)	0	0	1 (0.1)	1 (0.1)
Tongue neoplasm malignant stage unspecified	1 (0.3)	0	0	0	0	0
Traumatic intracranial haemorrhage	1 (0.3)	1 (0.3)	0	0	0	0
Troponin I increased	1 (0.3)	0	0	0	0	0
Weight decreased	1 (0.3)	0	0	0	0	0
Acquired soft palate fissure	0	0	1 (0.3)	1 (0.3)	0	0
Acquired tracheo-oesophageal fistula	0	0	1 (0.3)	1 (0.3)	1 (0.1)	1 (0.1)
Acute coronary syndrome	0	0	0	0	1 (0.1)	1 (0.1)

Source: Summary of Clinical Safety Appendix 1, excerpt from Table 1.3-8

TEAEs by Preferred Term of all grades and of grade ≥ 3 leading to **discontinuation of any chemotherapy component** for T+C, P+C (Study 306), and for tislelizumab monotherapy are presented in Table 73.

Table 73: Treatment-emergent adverse events all grades and grade ≥ 3 with an incidence ≥ 1% in the T+C Arm leading to discontinuation of any chemotherapy component by Preferred Term (Safety Set)

Table 3.1-17.1 (Page 1 of 8)
Treatment-emergent adverse events all grades and grade >=3 leading to discontinuation of any chemotherapy component, by preferred term
Safety set

	306 Tisle+Chemo N=324		306 Placebo+Chemo N=321	
Preferred Term	All grades n (%)	Grade >=3 n (%)	All grades n (%)	Grade >=3 n (%)
Number of subjects with at least one event	96 (29.6)	49 (15.1)	70 (21.8)	32 (10.0)
Peripheral sensory neuropathy	23 (7.1)	9 (2.8)	8 (2.5)	4 (1.2)
Anaemia	8 (2.5)	7 (2.2)	1 (0.3)	1 (0.3)
Hypoaesthesia	6 (1.9)	0	7 (2.2)	0
Neurotoxicity	5 (1.5)	0	3 (0.9)	1 (0.3)
Pneumonitis	5 (1.5)	2 (0.6)	0	0
Acute kidney injury	3 (0.9)	2 (0.6)	0	0
Asthenia	3 (0.9)	2 (0.6)	0	0
Blood creatinine increased	3 (0.9)	1 (0.3)	4 (1.2)	0
Drug hypersensitivity	3 (0.9)	2 (0.6)	1 (0.3)	1 (0.3)
Fatigue	3 (0.9)	1 (0.3)	3 (0.9)	2 (0.6)

Source: Summary of Clinical Safety Appendix 1, excerpt from Table 3.1-17.1

TEAEs (all grades) leading to discontinuation of any component of study treatment were substantially higher in the T+C Arm than in the P+C Arm (32.1% vs. 22.4%, and 13.0% in the Tislelizumab Monotherapy Pool). Likewise, TEAEs (all grades) leading to discontinuation of tislelizumab/placebo were considerably higher in the T+C Arm than in the P+C Arm (13.3% vs. 6.5%, and 13.0% in the Tislelizumab Monotherapy Pool). tislelizumab. A higher discontinuation rate of tislelizumab due to TEAEs in the T+C Arm, as compared to discontinuation of placebo due to TEAEs in the P+C Arm, can likely be explained by the competing risk of early discontinuation due to progressive disease observed more frequently in P+C Arm as well as tislelizumab induced toxicities.

Post marketing experience

Tislelizumab has been marketed in China for the treatment of patients with various malignancies since 2019; it has been granted marketing authorisation in the EU on 15 September 2023 for the second-line treatment of patients with OSCC.

As of 25 December 2022, there is an equivalent exposure of approximately 109,466.6 patient-years based on a Q3W treatment cycle.

According to the Applicant, up to the cut-off date (28 February 2022), the review of safety data from ongoing clinical trials and ongoing monitoring of post-marketing reports did not reveal any new safety concern that would impact the favourable benefit-risk profile of tislelizumab.

It should be noted that severe IRRs (Grade 3 or higher) have been reported in patients receiving tislelizumab (PBRER submitted to EMA in February 2024). Cases of anaphylaxis, including anaphylactic reaction and anaphylactic shock, have been reported in the post-marketing setting. It is, therefore, recommended in the SmPC that patients should be monitored for signs and symptoms of IRRs.

2.5.1. Discussion on clinical safety

The safety data supporting the Marketing Authorisation Application for tislelizumab in combination with chemotherapy in patients with locally advanced or metastatic oesophageal squamous cell carcinoma (OSCC) were collected in the randomised, placebo-controlled, double-blind phase 3 Study BGB-A317-306 (Study 306). This pivotal study evaluated tislelizumab in combination with chemotherapy (platinum plus a fluoropyrimidine or platinum plus paclitaxel; T+C Arm; N = 324) versus placebo in combination with Investigator´s Choice of Chemotherapy (platinum plus a fluoropyrimidine or platinum plus paclitaxel; P+C Arm; N = 321) as a first-line treatment in this patient population. In addition to the safety data from Study 306, safety data for the Tislelizumab Monotherapy Pool (N = 1534 patients across various malignancies) and, in individual instances, safety data for the Tislelizumab Combination Therapy Pool (N = 838, including patients with NSCLC and patients from pivotal Study 306) are considered in this Assessment Report.

Applications for marketing authorisation have been overlapping for tislelizumab in combination with chemotherapy for the first-line treatment of patients with unresectable, locally advanced or metastatic OSCC (based on Study 306) and for the first-line treatment of patients with unresectable, locally advanced or metastatic G/GEJ adenocarcinoma (based on Study 305)[6]. Therefore, 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 gastro-oesophageal junction (G/GEJ) adenocarcinoma and oesophageal squamous cell carcinoma (OSCC) who have been treated with tislelizumab + chemotherapy in Studies 206, 304, 305, 306, and 307. 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).

The **data cut-off date** for the ongoing pivotal Study 306 was 28 February 2022, and the data cut-off dates for the supportive studies range from 2019 to 2021. Median follow-up in Study 306 was 16.34 months in the T+C Arm and 9.82 months in the P+C Arm. Only a small number of patients in Study 306 remained on treatment at the cut-off date (11.7% vs. 4.7% P+C Arm). In view of these low percentages, data from a more recent cut-off date are not required, as they are not expected to significantly change conclusions with regard to safety outcomes.

As studies included in the Tislelizumab Monotherapy Pool had different treatment-emergent adverse event (**TEAE) definitions**, a harmonised definition was used for the analyses of safety parameters for the Tislelizumab Monotherapy Pool as well as for Study 306, and the analyses were re-run. Due to this approach, there are slight discrepancies in numbers in the Clinical Study Report of Study 306 and in the Summary of Clinical Safety, which is why the safety data presented in this Assessment Report were extracted from the latter.

The available safety data are deemed adequate to describe the safety profile of tislelizumab.

The median **exposure to tislelizumab in combination with chemotherapy** exceeded the median exposure to placebo in combination with chemotherapy in Study 306. The median duration of

[6] Procedures EMEA/H/C/005919/II/0003 and EMEA/H/C/005919/II/0006, respectively

treatment in the T+C Arm was longer than the one in the P+C Arm (6.41 months vs. 4.90 months, and 4.17 months in the Tislelizumab Monotherapy Pool). Likewise, the median number of treatment cycles was higher in the T+C Arm than in the P+C Arm (8.0 cycles vs. 7.0 cycles, and 6.0 cycles in the Tislelizumab Monotherapy Pool). By contrast, the median Relative Dose Intensity (RDI) for tislelizumab and placebo, respectively, was comparable between the two treatment arms (96.19% vs. 97.67%).

Likewise, the median exposure to chemotherapy was essentially comparable between the two treatment arms with respect to the median duration of treatment and the median number of treatment cycles of chemotherapy components. In the chemotherapy regimen of **platinum with a fluoropyrimidine** (5-FU/capecitabine), the median duration of treatment with each active substance was 4.27 months and 5.04 months, respectively, in the T+C Arm; it was 4.11 months and 4.24 months, respectively, in the P+C Arm. The median number of treatment cycles for platinum was 6.0 in the T+C Arm and 5.0 in the P+C Arm. The median number of treatment cycles for a fluoropyrimidine was 6.0 in both treatment arms. In the chemotherapy regimen of **platinum with paclitaxel**, the median duration of treatment with each active substance was 4.14 months and 4.27 months, respectively, in the T+C Arm; it was 4.14 months and 4.14 months, respectively, in the P+C Arm. The median number of treatment cycles for platinum and paclitaxel was 6.0 each in both the T+C Arm and the P+C Arm. Median RDIs were mostly comparable for the chemotherapy components in both treatment arms. The only exception was the median RDI of paclitaxel (platinum + paclitaxel chemotherapy doublet), which was lower by approximately 7% in patients in the T+C Arm compared to those in the P+C Arm. However, this deviation in median RDI is still considered acceptable and is not thought to adversely affect the comparability of exposure *per se*. As exposure to different chemotherapy components was essentially comparable between treatment arms, any observed differences in safety outcomes are more likely attributed to the treatments themselves rather than to variations in exposure to chemotherapy components. This was confirmed by the subgroup analyses by chemotherapy doublet, which showed no effects on safety outcomes.

The proportion of patients treated with the chemotherapy regimen of platinum (cis-/oxaliplatin) with paclitaxel was comparable to the proportion of patients treated with the chemotherapy regimen of platinum (cisplatin/oxaliplatin) with a fluoropyrimidine, the latter being the **European Standard of Care**. This implies, however, that approximately half of the patients in Study 306 did not receive the European Standard of Care and that there may be limitations to a transfer of the trial results to a European patient population/treatment setting.

Furthermore, Study 306 mainly recruited Asian (approximately 75%) and male (approximately 87%) patients. Due to all of these imbalances, the patient population of Study 306 may not be fully representative of a European patient population/treatment setting.

The **most common TEAEs** in both treatment arms are known to be related to chemotherapy and the underlying disease; they include haematologic toxicity and gastrointestinal toxicity. Specifically, the following TEAEs (of all grades) by Preferred Term were common (incidence rate ≥ 30%) in the T+C and P+C Arms: anaemia (60.8% vs. 56.1%, and 28.0% in the Tislelizumab Monotherapy Pool); neutrophil count decreased (47.5% vs. 48.6%, and 4.4% in the Tislelizumab Monotherapy Pool); decreased appetite (44.4% vs. 38.9%, and 15.0% in the Tislelizumab Monotherapy Pool); white blood cell count decreased (44.1% vs. 48.9%, and 6.8% in the Tislelizumab Monotherapy Pool); nausea (38.0% vs. 42.4%, and 10.1% in the Tislelizumab Monotherapy Pool); and constipation (30.2% vs. 31.2%, and 12.6% in the Tislelizumab Monotherapy Pool).

In particular, a difference in incidence rates of ≥ 5% between the T+C Arm and the P+C Arm was observed for decreased appetite, pruritus, and hypothyroidism. The higher incidence rates of decreased appetite, pruritus, and hypothyroidism align with the known safety profile of tislelizumab and are consistent with the one of other PD-1 inhibitors.

The incidence rates of **TEAEs CTCAE grade ≥ 3** were generally similar between the treatment arms (78.7% in the T+C Arm vs. 77.6% in the P+C Arm, and 45.2% in the Tislelizumab Monotherapy Pool). The most commonly reported (≥ 10%) TEAEs grade ≥ 3 by Preferred Term include neutrophil count decreased, hyponatraemia, white blood cell count decreased, and anaemia in the T+C Arm, and neutrophil count decreased, white blood cell count decreased, and anaemia in the P+C Arm (all TEAEs grade ≥ 3 reported for the Tislelizumab Monotherapy Pool were observed in < 10% of patients).

By contrast, the incidence rates of **serious TEAEs** were high in absolute numbers and higher by nearly 10% in the T+C Arm compared to the P+C Arm, reflecting the additive toxicity of tislelizumab (48.8% vs. 39.6%, and 34.7% in the Tislelizumab Monotherapy Pool). The most commonly reported serious TEAEs by SOC with an incidence rate ≥ 5% in any treatment arm were Gastrointestinal disorders, Infections and infestations, Metabolism and nutrition disorders, Respiratory, thoracic and mediastinal disorders, General disorders and administration site conditions, and Blood and lymphatic system disorders. The incidence rates of serious TEAEs by SOC were generally comparable in the two arms except for Gastrointestinal disorders (17.6% in the T+C Arm versus 12.5% in the P+C Arm) and Metabolism and nutrition disorders (8.3% in the T+C Arm and 3.1% in the P+C Arm). Blood and lymphatic system disorders had an incidence rate ≥ 5% in the P+C Arm only (6.5% in the P+C Arm vs. 3.4% in the T+C Arm). Imbalances in the SOCs Gastrointestinal disorders and Metabolism and nutrition disorders, respectively, were not driven by specific Preferred Terms, but rather by small differences in diverse Preferred Terms. The most commonly reported (≥ 2%) serious TEAEs by Preferred Term were dysphagia, pneumonia, diarrhoea, oesophageal stenosis, and pneumonitis. Acute kidney injury, anaemia, decreased appetite, hyponatraemia, and vomiting were all reported at an incidence rate of 1.9% for the T+C Arm. Dysphagia was the only serious TEAE by Preferred Term with a higher incidence rate (difference ≥ 2%) in the T+C Arm than in the P+C Arm (5.2% vs. 2.5%)[7]. While it is acknowledged that oesophageal and respiratory disorders can be symptoms of the underlying disease, their seriousness in combination with their increased frequency in the T+C Arm of Study 306 require in-depth consideration and balancing with the benefits of treatment. No new safety signal in terms of serious TEAEs was identified for tislelizumab in Study 306.

The incidence rate of **deaths** on treatment was comparable in the T+C Arm than in the P+C Arm (6.5% vs. 8.4%, and 7.8% in the Tislelizumab Monotherapy Pool). Adverse events served as the primary cause of death in both treatment arms (4.3% vs. 5.0%, and 3.1% in the Tislelizumab Monotherapy Pool). The disease under consideration was the reason for death for the remaining patients in both the T+C Arm and the P+C Arm (incidence rates were similar for the Tislelizumab Monotherapy Pool, but there was one patient each in the categories concurrent illness, indeterminate, and other).

In Study 306, TEAEs leading to the **discontinuation** of tislelizumab or placebo were more frequent in the T+C Arm compared to the P+C Arm (13.3% vs. 6.5%, and 13.0% in the Tislelizumab Monotherapy Pool). Notably, pneumonitis (2.5% vs. 0.6%, and 0.9% in the Tislelizumab Monotherapy Pool) and pneumonia (0.6% vs. 1.2%, and 1.2% in the Tislelizumab Monotherapy Pool) were the most commonly reported TEAEs leading to the discontinuation of tislelizumab or placebo. This observation, too, requires in-depth consideration and balancing with the benefits of treatment.

TEAEs leading to **dose modification** of tislelizumab or placebo were reported in 52.5% of patients in the T+C Arm and in 39.9% of patients in the P+C Arm (27.2% in the Tislelizumab Monotherapy Pool).

TEAEs assessed as causally **related** to tislelizumab/placebo were experienced by 69.8% of patients in the T+C Arm and by 60.7% of patients in the P+C Arm (74.1% in the Tislelizumab Monotherapy Pool). Furthermore, ≥ 96% of patients experienced more than one TEAE related to any chemotherapy

[7]Pneumonia (5.1%) was the most common serious TEAE in the Tislelizumab Monotherapy Pool.

component in both treatment arms (96.6% in the T+C Arm vs. 96.0% in the P+C Arm). TEAEs grade ≥ 3 related to tislelizumab were reported at a higher incidence rate in the T+C Arm than in the Tislelizumab Monotherapy Pool (32.1% vs. 16.9%). Most TEAEs grade ≥ 3 related to chemotherapy showed comparable incidence rates in the two treatment arms (62.7% in the T+C Arm vs. 62.9% in the P+C Arm). By contrast, the incidence rate of serious TEAEs related to tislelizumab was higher in the T+C Arm than in the Tislelizumab Monotherapy Pool (19.4% vs. 11.8%). The incidence rate of serious TEAEs related to chemotherapy was slightly higher in the T+C Arm compared to the P+C Arm (21.9% vs. 17.8%).

In general, **laboratory findings** in Study 306 reflect the known toxicity profiles of tislelizumab and chemotherapy components, respectively. Increases in liver enzymes (AST, ALT) and abnormalities in the thyroid panel consistent with hypo- and hyperthyroidism were more commonly reported for patients in the T+C Arm than for those in the P+C Arm.

For the retrieval of **immune-mediated TEAEs** (imTEAEs), a new programmatic algorithmic approach was utilised for the Summary of Clinical Safety as agreed with the Competent Authorities (FDA, EMA). The imTEAE profile for tislelizumab in the T+C Arm of Study 306 and in the Tislelizumab Monotherapy Pool was comparable, with slightly more than 30% of patients experiencing at least one imTEAE in each group (35.2% vs. 33.0%). The most common (≥ 1%) imTEAEs by category reported for the T+C Arm included immune-mediated skin adverse reactions (12.7%), immune-mediated hypothyroidism (11.7%), immune-mediated pneumonitis (8.0%), immune-mediated hyperthyroidism (2.8%), immune-mediated colitis (1.5%), immune-mediated adrenal insufficiency (1.5%), immune-mediated pancreatitis (1.5%), and immune-mediated hepatitis (1.2%). Most imTEAEs were of low grades (CTCAE grades 1 or 2) and were manageable with corticosteroids or hormone replacement therapy, either with or without dose modification. However, the incidence rates of imTEAEs grade ≥ 3, serious imTEAEs, imTEAEs leading to discontinuation of treatment with tislelizumab/placebo, and imTEAEs leading to dose modification of tislelizumab/placebo were numerically higher in the T+C Arm than in the P+C Arm (and in the Tislelizumab Monotherapy Pool). A substantial proportion of imTEAEs did not recover/resolve. It should be noted, however, that immune-mediated TEAEs are commonly reported under treatment with PD-1 inhibitors.

Infusion-related reactions (all grades) were reported for 7.7% of patients in the T+C Arm vs. 5.3% of patients in the P+C Arm in Study 306 (and 2.9% in the Tislelizumab Monotherapy Pool).

In patients treated with tislelizumab as monotherapy, infusion-related reactions occurred in 2.9% of patients, including Grade 3 (0.13%) events. Tislelizumab was permanently discontinued in 0.07% of patients and tislelizumab treatment was interrupted in 0.07% of patients. Cases of anaphylaxis, including anaphylactic reaction and anaphylactic shock, have been reported in the post-marketing setting. Patients should be monitored for signs and symptoms of infusion-related reactions (see section 4.4 of the SmPC).

To account for differences in exposure between the T+C and P+C Arms in Study 306 and in the Tislelizumab Monotherapy Pool, an analysis of **exposure-adjusted incidence rates** (EAIRs) was carried out by the Applicant. However, EAIRs were not considered in this Assessment Report due to a potential lack of generalisability, complexity in interpretation, and susceptibility to influence from trial design factors. Suffice it to say that in the exposure-adjusted analysis for Study 306, the EAIRs were comparable or the 95% confidence intervals overlapped between the T+C and P+C Arms in most TEAE categories – except for the imTEAEs category.

Adverse drug reaction (ADR) candidates were identified using an algorithm based on all TEAEs; they included pre-qualified ADR candidates[8] and ADR candidates identified through numerical screening rule(s) identifying an excess of TEAEs versus the comparator. This approach is considered acceptable. The ADR profile of tislelizumab was updated with one new ADR "vitiligo". Furthermore, the Preferred Terms "iridocyclitis" and "chorioretinitis" were added reflecting the already established ADR "uveitis", and "hepatotoxicity" and "drug-induced liver injury" were added reflecting the already established ADR "hepatitis". In the current draft of the SmPC, only the column including ADRs for tislelizumab in combination with chemotherapy is presented. As tislelizumab in combination with chemotherapy is expected to be granted approval for an increasing number of indications, in the future consolidated version of the SmPC, there will be a column reflecting ADRs associated with all approved tislelizumab combination therapies.

No consistent, clinically meaningful differences were observed in the **subgroup analyses** with regard to PD-L1 status, gender, hepatic function, renal function, race, region or chemotherapy doublet. As would be expected, the incidence rates of serious and fatal TEAEs increase with age (<65 years/≥65 years up to > 75 years). In line with this observation, the incidence rates of TEAEs leading to any treatment modification also increase with age. Due to the small sample size of patients ≥ 75 years, no conclusions can be drawn for this patient population.

Overall, the results from these subgroup analyses of safety outcomes are consistent with the ones reported for the overall population of Study 306. However, this assessment is preliminary due to the small sample size in the subgroups of female patients, "Other" patients (as opposed to White or Asian patients), and patients aged ≥ 75 years. This uncertainty is expected to decrease as more patients from these subgroups are exposed to tislelizumab due to upcoming extensions of indications. As was the case for the overall patient population, there was a trend of increased incidence rates of serious TEAEs (including fatal serious TEAES) in subgroups of the T+C Arm compared to those of the P+C Arm.

2.5.2. Conclusions on clinical safety

Despite the treatment of part of the study population with a chemotherapy regimen that does not represent the European Standard of Care and despite the imbalances outlined above, in the absence of any patterns in terms of safety outcomes in the subgroups under consideration (except age), the extrapolation of the safety data observed in the patient population of the global Study 306 to a European patient population / treatment setting can be supported.

Overall, the safety profile (including laboratory values) observed for tislelizumab in combination with platinum-based chemotherapy in adult patients with unresectable, locally advanced or metastatic OSCC in the first-line setting was consistent with the safety profile of chemotherapy (mainly haematological and gastrointestinal toxicity), the safety profile of tislelizumab and PD-1 inhibitors (imTEAEs), the additive toxicity of tislelizumab when given in combination with chemotherapy, and/or the symptoms of the underlying disease (among others oesophageal and respiratory disorders). There are no new safety concerns.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set

[8] Prequalified ADR candidates are events that are suspected to be related to the medicinal product based on the known mechanism of action, previous experience collected with the medicinal product, medicinal products in the same class, or any event included in the European Medicines Agency Designated Medical Event list.

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 74: 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

Pharmacovigilance plan

Not applicable.

Risk minimisation measures

Table 75: 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:	Routine Pharmacovigilance Activities Beyond Adverse Reactions Reporting and Signal Detection: Targeted follow-up checklist Additional Pharmacovigilance Activities: None

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	Restricted medical prescription	
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, 4.5, 4.8 and 5.1 of the SmPC are being updated. The Package Leaflet (PL) is updated accordingly.

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:

No significant changes have been made to the package leaflet. The variation is intended to extend the already existing marketing authorization of Tevimbra (tislelizumab) in 2L OSCC with an indication of tislelizumab in combination with platinum-based chemotherapy "for the first-line treatment of adult patients with unresectable, locally advanced or metastatic oesophageal squamous cell carcinoma". Accordingly, section 1 and section 4 of the package leaflet are amended. The changes do not affect key messages for the safe use of the medicinal product. Thus, the justification for not performing a full user testing is considered acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The approved indication is:

Tevimbra, in combination with platinum-based chemotherapy, is indicated for the first-line treatment of adult patients with unresectable, locally advanced or metastatic OSCC whose tumours express PD L1 with a TAP score ≥ 5% (see section 5.1).

Oesophageal cancer is the eighth most common cancer and the sixth most common cause of cancer-related death worldwide, with an estimated 604,100 new cases and 544,076 deaths (5.5% of all cancer mortality) observed in 2020 (GLOBOCAN 2020). Although EC is a rare disease in Europe (annual incidence approximately 1/13,300, [Orphanet]), it remains a highly fatal disease and a major cause of cancer mortality.

Oesophageal cancers are histologically classified as squamous cell carcinoma (OSCC) or adenocarcinoma (OAC), which differ in their pathology, tumour location, and prognosis.

Oesophageal carcinoma is rare in young people and increases in incidence with age, peaking in the seventh and eighth decades of life. The main risk factors for OSCC in Western countries include tobacco and alcohol consumption.

3.1.2. Available therapies and unmet medical need

Platinum-based doublet chemotherapy (cisplatin/oxaliplatin plus fluoropyrimidines) is usually offered as first-line palliative therapy to advanced or metastatic OSCC patients with good performance status. Unfit patients (ECOG PS > 1) are treated with best supportive care. (Lordick et al. 2016, NCCN 2020. Localized treatments such as radiotherapy (including external radiation or brachytherapy) and endoscopic therapies (stents) are applied for the symptomatic treatment of obstruction and dysphagia.

Recently, Keytruda (pembrolizumab) and Opdivo (nivolumab) were approved in combination with platinum and fluoropyrimidine-based chemotherapy for the first-line treatment of locally advanced unresectable or metastatic OSCC with positive PD-L1 expression (Keytruda: PD-L1 with CPS ≥ 10% Variation Keytruda-H-C-3820-II-97-EC Decision 24/06/2021); Opdivo: TPS ≥ 1% (OPDIVO-H-C/003985/II-0107, EC decision on 01/04/2022). These treatment options have improved survival of patients with advanced unresectable or metastatic OSCC in the first-line setting and therefore have become standard first-line treatment in the respective indication.

3.1.3. Main clinical studies

Study 306 is a global Phase III, randomized, double-blind, placebo-controlled study at the recommended dose of tislelizumab 200 mg administered IV Q3W in combination with platinum-based chemotherapy (platinum [cisplatin or oxaliplatin] + either fluoropyrimidine [5-fluorouracil or capecitabine] or paclitaxel) in patients with unresectable, locally advanced or metastatic OSCC. It includes data from 649 patients randomized worldwide; 326 patients were randomized to tislelizumab in combination with chemotherapy (the T+C arm) and 323 patients were randomized to placebo in combination with chemotherapy (the P+C arm). The study is ongoing, and the data presented within

this application are based on the pre-planned interim analysis with data cut-off date of 28 February 2022, as well as updated OS analyses with data cut-off date 28 April 2023 and 24 November 2023 (3-year follow-up).

3.2. Favourable effects

With 3-year follow-up at the data cut-off 24 November 2023, benefit was demonstrated for patients whose tumours expressed PD-L1 with a TAP score ≥5%; stratified OS HR = 0.62 [95% CI: 0.49, 0.79] with a median OS of 19.1 months (95% CI: 16.1, 24.1) for the tislelizumab + chemotherapy arm vs 10.0 months (95% CI: 8.6, 11.9) for the placebo + chemotherapy arm.

A benefit was also demonstrated on PFS (secondary endpoint) with a stratified HR = 0.50 [95% CI: 0.39, 0.65] and a median PFS of 8.2 months (95% CI: 7.0, 9.8) for the tislelizumab + chemotherapy arm vs 5.5 months (95% CI: 4.3, 6.4) for the placebo + chemotherapy arm.

Favourable effects in the ITT population based on the pre-planned interim analysis with data cut-off date of 28 February 2022 are presented for context. In all patients randomised, the OS HR was 0.66 (95% CI: 0.54, 0.80, 1-sided p-value of < 0.0001), with a median OS of 17.2 months (95% CI: 15.8, 20.1) for the tislelizumab with chemotherapy arm vs. 10.6 months (95% CI: 9.3, 12.1) for the placebo with chemotherapy arm.

3.3. Uncertainties and limitations about favourable effects

Additional subgroup analysis were performed showing no meaningful benefit of tislelizumab + chemotherapy in patients with PD-L1 expression TAP score <5% (N=184):

<5%: stratified OS HR 0.94 (95% CI 0.68, 1.29); median OS 12.3 vs. 10.6 months.

The indication was therefore restricted to patients whose tumours express PD-L1 with a tumour area positivity (TAP) score ⩾ 5%.
Randomisation was not stratified by biomarker status. Overall, 16.5% of patients had PD-L1 status unknown.

A benefit was not apparent in the subgroup of patients ≥75 years old (OS HR=0.91; 95% CI: 0.37, 2.26). However, numbers are too limited (n=38) to draw firm conclusions.

3.4. Unfavourable effects

Nearly all patients in both treatment arms of Study 306 experienced ≥ 1 **TEAE** (99.7% in the T+C Arm vs. 99.4% in the P+C Arm). The most common TEAEs (≥ 30% incidence of all grades) by Preferred Term in both treatment arms of Study 306 included anaemia, neutrophil count decreased, decreased appetite, white blood cell count decreased, nausea, and constipation. A difference of ≥5% between the T+C Arm and P+C Arm was reported for decreased appetite, pruritus, and hypothyroidism.

The incidence rates of **TEAEs grade ≥ 3** was comparable between the two treatment arms (78.7% vs. 77.6%). The most commonly reported (≥ 10%) TEAEs grade ≥ 3 by Preferred Term were neutrophil count decreased, hyponatremia, white blood cell count decreased, and anaemia in the T+C Arm, and neutrophil count decreased, white blood cell count decreased, and anaemia in the P+C Arm.

The incidence rates of **serious TEAEs** was higher in the T+C Arm than in the P+C Arm (48.8% vs. 39.6%), and the most common serious TEAEs (≥2%) by Preferred Term were dysphagia, pneumonia, diarrhoea, oesophageal stenosis, and pneumonitis.

The incidence rate of **deaths on treatment** was numerically lower in the T+C Arm than in the P+C Arm (6.5% vs. 8.4%). Adverse events served as the primary cause of death in both treatment arms (4.3% vs. 5.0). The disease under consideration was the reason for death for the remaining patients in both the T+C Arm and the P+C Arm.

The incidence rate of **TEAEs leading to discontinuation of tislelizumab/placebo** was higher in the T+C Arm than in the P+C Arm (13.3% vs. 6.5%; discontinuation of any component of treatment: 32.1% vs. 22.4%), with pneumonitis and pneumonia the most commonly reported events by Preferred Term.

The incidence rate of **imTEAEs** was higher in the T+C Arm than in the P+C Arm (35.2% vs. 18.7%), and the most common imTEAEs by category (≥ 1%) included immune-mediated skin adverse reaction, immune-mediated hypothyroidism, immune-mediated pneumonitis, immune-mediated colitis, immune-mediated pancreatitis, and immune-mediated hepatitis.

Infusion-related reactions were reported for <10% of patients in Study 306.

3.5. Uncertainties and limitations about unfavourable effects

Uncertainty is associated with the low proportions of patients aged ≥ 75 years (approximately 6%), female patients (approximately 13%), and non-Asian patients (approximately 25%) in Study 306. This uncertainty is expected to decrease as more patients from these subgroups are exposed to tislelizumab due to upcoming extensions of indications. The limitation regarding patients aged ≥ 75 years is reflected in the current SmPC.

3.6. Effects Table

Table 76: Effects Table for Tevimbra (tislelizumab) in combination with platinum-based chemotherapy for 1L treatment of adult patients with unresectable, locally advanced or metastatic OSCC (data cut-off: 28 February 2022)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects (PD-L1 TAP score ⩾5%; data cut-off 24 Nov 2023)						
OS, median	Time from randomization until death	months	19.1	10.0	Updated OS (cut-off date 28-Apr-2023) consistent: stratified HR = 0.69 [95% CI: 0.58 – 0.83] Double-blind study, Results overall consistent between INV and BIRC Consistent benefit in subgroups by region and ICC option – reassuring for applicability of results for EU population Limited number of patients with age ≥75 years	CSR
		HR, 95% CI	0.62 [0.49 – 0.79]			
PFS, median	based on INV per RECIST v1.1	months	8.2	5.5		
		HR, 95% CI	0.50 [0.39 - 0.65]			

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects (ITT population)						
OS, median	Time from randomization until death	months	17.2	10.6		
		HR, 95% CI	0.66 [0.54 – 0.80]			
PFS, median	based on INV per RECIST v1.1	months	7.3	5.6		
		HR, 95% CI	0.62 [0.52 - 0.75]			
Unfavourable Effects						
TEAEs grade ≥ 3	All causality	%	78.7	77.6		SCS
	related	%	67.0	64.5		SCS
Serious TEAEs	All causality	%	48.8	39.6		SCS
	related	%	29.3	19.3		SCS
Deaths	On treatment	%	4.3	5.0		SCS
TEAEs leading to DC	All causality	%	32.1	22.4		SCS
im TEAEs	related	%	35.2	18.7		SCS
IRR	related	%	7.7	5.3		SCS

Abbreviations: 1L=First-line, CR=complete response, CSR=Clinical Study Report, DC= discontinuation, OSCC=oesophageal squamous cell carcinoma, HR=Hazard ratio, ICC=investigator's choice chemotherapy, im=immune-mediated, INV=Investigator, IRR=Infusion-related reaction, PR=partial response, 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

In Study BGB-A317-306, a clinically meaningful improvement in OS was demonstrated for treatment with tislelizumab in combination with platinum-based chemotherapy compared with chemotherapy alone in the subgroup of patients with PD-L1 TAP score ≥ 5%.

Higher incidence rates of serious TEAEs, imTEAEs, and TEAEs leading to discontinuation have been observed for the T+C Arm compared to the P+C Arm. However, the safety data set of study 306 for tislelizumab in combination with platinum-based chemotherapy in patients with unresectable, locally advanced or metastatic OSCC in first-line setting in general reflects 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

The B/R balance of Tevimbra, in combination with platinum-based chemotherapy, is considered positive in the first-line treatment of adult patients with unresectable, locally advanced or metastatic OSCC whose tumours express PD-L1 with a TAP score ≥ 5%.

3.7.3. Additional considerations on the benefit-risk balance

None.

3.8. Conclusions

The overall B/R of Tevimbra in the claimed indication is positive.

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-based chemotherapy the first-line treatment of adult patients with unresectable, locally advanced or metastatic oesophageal squamous cell carcinoma (OSCC) whose tumours express PD-L1 with a tumour area positivity (TAP) score ⩾ 5%for TEVIMBRA, based on results from study BGB-A317-306; this is a multi-regional, randomized, placebo-controlled, double-blind phase 3 study evaluating the efficacy and safety of tislelizumab in combination with chemotherapy compared to placebo in combination with chemotherapy as first-line treatment in patients with unresectable or locally advanced recurrent or metastatic OSCC. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 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 PI.

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.