22 May 2025
EMA/CHMP/194012/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tevimbra

International non-proprietary name: Tislelizumab

Procedure No. EMEA/H/C/005919/II/0017

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 or Special Term	Definition
1L	first line
ADA	antidrug antibodies
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the serum concentration-time curve
BGB-A317	tislelizumab, also known as Tevimbra
AUC	area under the serum concentration-time curve
CI	Confidence interval
CL	clearance
C_{max}	maximum serum concentration
C_{min}	minimum serum concentration
CR	complete response
CSCO	Chinese Society of Clinical Oncology
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DOR	duration of response
EAIR	exposure-adjusted incidence rate
EBV	Epstein-Barr virus
EC	European Commission
ECOG	eastern Cooperative Oncology Group
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EORTC QLQ-H&N35	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Head and Neck-35
ER	exposure-response
ESMO	European Society for Medical Oncology
EU	European Union
FDA	Food and Drug Administration
GC	gemcitabine plus cisplatin
GHS	global health status

Abbreviation or Special Term	Definition
HR	hazard ratio
HRQoL	health-related quality of life
IA	interim analysis
IAR	Immunogenicity assessment report
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICI	immune checkpoint inhibitor
IDMC	independent data monitoring committee
IgG	immunoglobulin G
imAE	immune-mediated adverse event
IRC	independent review committee
IRR	infusion-related reaction
ISI	Integrated summary of immunogenicity
ITT	intent-to-treat (analysis set)
LDH	lactate dehydrogenase
LS	least square
NAb	neutralizing antibody
NCA	noncompartmental PK analysis
NCCN	National Comprehensive Cancer Network
NE	not estimable
NPC	nasopharyngeal carcinoma
ORR	objective response rate
OSCC	oesophageal squamous cell carcinoma (OSCC/ESCC)
OS	Overall survival
pcVPC	prediction-corrected visual predictive check
P+GC placebo + GC	placebo in combination with gemcitabine plus cisplatin
PD-1	programmed cell death protein-1
PD-L1	programmed cell death ligand-1
PFS	progression-free survival
PFS2	second progression/ subsequent progression after initiation of new anticancer therapy
PK	pharmacokinetic(s)
PopPK	population pharmacokinetic(s)
PRO	patient reported outcome
PT	Preferred Term
Q3W	once every 3 weeks
QoL	quality of life

Abbreviation or Special Term	Definition
RECIST	Response Evaluation Criteria in Solid Tumours
RPSFT	rank-preserving structural failure time model
RWE	real-world evidence
$t_{½}$	half-life
TEAE	treatment-emergent adverse event
Tisle+GC	tislelizumab in combination with gemcitabine plus cisplatin
TLR	targeted literature review
US	United States
v	version
V_2, V_3	peripheral volume 2, peripheral volume 3
V_c	central volume (of distribution), volume of the central compartment
WHO	World Health Organization

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 (later changed to BeOne Medicines Ireland Limited) submitted to the European Medicines Agency on 4 November 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, II and IIIB

Extension of indication to include, in combination with gemcitabine and cisplatin, the first-line treatment of adult patients with recurrent or metastatic nasopharyngeal carcinoma (NPC) for TEVIMBRA based on final results from study BGB-A317-309 (study 309). Study 309 was a Phase 3 randomised, double-blind, placebo-controlled, Asia-only study that compared the efficacy and safety of tislelizumab combined with gemcitabine plus cisplatin (GC) versus placebo combined with GC as 1L treatment for recurrent or metastatic NPC. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 2.6 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce editorial and administrative changes to the PI as well as to update the PI in line with the Excipients Guideline.

The variation requested amendments to the Summary of Product Characteristics, Annex II 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 P/0142/2019 on the granting of a product-specific waiver for tislelizumab for all conditions included in the category of malignant neoplasms (except central nervous system, haematopoietic and lymphoid tissue). The waiver applies to all subsets of the paediatric population from birth to less than 18 years of age on the grounds that clinical studies with the specific medicinal product cannot be expected to be of significant therapeutic benefit or fulfil a therapeutic need of the specified paediatric subset.

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 Applicant 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 in the EU.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	4 November 2024
Start of procedure:	30 November 2024
CHMP Rapporteur Assessment Report	24 January 2025
PRAC Rapporteur Assessment Report	30 January 2025
PRAC Outcome	13 February 2025
CHMP members comments	17 February 2025
Updated CHMP Rapporteur(s) (Joint) Assessment Report	20 February 2025
Request for supplementary information (RSI)	27 February 2025
CHMP Rapporteur Assessment Report	22 April 2025
PRAC Rapporteur Assessment Report	23 April 2025
PRAC members comments	n/a
Updated PRAC Rapporteur Assessment Report	n/a
PRAC Outcome	8 May 2025
CHMP members comments	12 May 2025
Updated CHMP Rapporteur Assessment Report	15 May 2025
Opinion	22 May 2025

2. Scientific discussion

2.1. Introduction

Within the current type II variation, the MAH is applying for an extension of indication for *tislelizumab, in combination with gemcitabine and cisplatin, for the first-line treatment of adult patients with recurrent or metastatic nasopharyngeal carcinoma.*

This application is based on clinical data from the completed randomised, double-blind, placebo-controlled, Asia-only phase 3 pivotal trial (Study 309), investigating tislelizumab, in combination with gemcitabine plus cisplatin (GC), as the first-line treatment of adult patients with recurrent or metastatic NPC.

2.1.1. Problem statement

Disease or condition

Nasopharyngeal carcinoma (NPC) is an uncommon type of head and neck cancer with unique epidemiological features. The distribution of the disease demonstrates a clear regional, racial and gender prevalence. In 2022, there were 120,434 new cases of NPC and 73,482 deaths observed worldwide (Globocan 2022[1]).

State the claimed therapeutic indication

Tevimbra, in combination with gemcitabine and cisplatin, is indicated for the first-line treatment of adult patients with recurrent or metastatic NPC.

Epidemiology and risk factors

NPC is rare throughout most of the Western world, but there are areas of the world afflicted with endemic disease. Global incidence rates are highest in Southeast Asia (especially Southern China), Micronesia/Polynesia, Eastern Asia, and North Africa. In recent decades (1970-2007), the incidence of NPC has declined worldwide, with substantial reductions in South and East Asia, North America and the Nordic countries[2].

NPC has several features that differ according to geographic area. For example, age distribution differs in low-incidence areas compared with endemic areas. In low-incidence areas, the incidence of NPC increases with age and has a bimodal peak: the first in adolescents and young adults and the second after 65 years of age, whereas in endemic areas, the incidence increases after 30 years of age, peaks at 40-59 years and decreases thereafter. Incidence is two to three times higher in men than in women[3].

The primary risk factors of NPC include genetic predisposition, EBV infection, tobacco and alcohol use, older age, male gender, and dietary factors such as the consumption of salted fish and preserved food containing volatile N-nitrosamines[4]. The difference in geographical distribution is attributed to multiple factors including EBV infection, genetics, and environmental factors.

Biologic features, aetiology and pathogenesis

NPC is currently classified by the WHO into 3 major histological subtypes: keratinising, non-keratinising (further subdivided into differentiated and undifferentiated), and basaloid cell carcinoma. The non-keratinising NPC is the most common subtype in both high- and low-incidence areas, and is strongly associated with EBV infections in high-incidence areas[5].

Although no actionable mutations in NPC have been identified, a genetic aetiology has been discussed based on the higher rates of disease within specific ethnic groups, patients with first-degree relatives

[1] Ferlay J, Ervik M, Lam F, et al. Global Cancer Observatory: Cancer Today. International Agency for Research on Cancer 2024
[2] Tang L.L. et al., Global trends in incidence and mortality of nasopharyngeal carcinoma. Cancer Lett. 2016
[3] Bray F et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018
[4] Chang E, Ye W, Zeng Y, et al. The evolving epidemiology of nasopharyngeal carcinoma. Cancer Epidemiol Biomarkers Prev. 2021
[5] Stenmark MH, McHugh JB, Schipper M, et al. Nonendemic HPV-positive nasopharyngeal carcinoma: association with poor prognosis. Int J Radiat Oncol Biol Phys. 2014;88(3):580-8.

with the disease, patients with A2 HLA haplotypes, and cytogenetic abnormalities identified within tumour samples[6,7]. Environmental causes must be considered due to the geographical distribution of the disease and association seen in patients who consume a large amount of preserved foods and/or salted fish.

Clinical presentation, diagnosis and prognosis

Symptoms of NPC include nasal bleeding and obstruction, ear infection, deafness and tinnitus, and neck swelling. The first sign of disease is often the appearance of neck nodes. Definitive diagnosis is made by endoscopic-guided biopsy of the primary nasopharyngeal tumour.

More than 80% of NPC patients present with advanced-stage disease and approximately 7% present with metastatic disease at diagnosis[8,9]. The 3-year survival falls to 7 - 40% for patients with metastatic NPC[10,11,12]. The outcome for patients with recurrent disease or de novo metastatic NPC is very poor, with a median OS of about 20 to 22 months.

Management

Cytotoxic chemotherapy has remained the mainstay treatment for recurrent or metastatic NPC, and it was for many years the primary front-line treatment option. Prior to the introduction of anti-PD-1 ICIs, international treatment guidelines recommended the combination of gemcitabine plus cisplatin as the preferred 1L therapy for NPC (ESMO 2021; NCCN 2021), which renders a median PFS of 7 months and an ORR of 64%. However, the long-term benefit of gemcitabine plus cisplatin is limited, with a 12-month PFS rate of only 20% and a median OS of 22 months[13,14].

In the 1L setting, three Phase 3 studies that assessed effects of the anti-PD-1 antibodies tislelizumab (BGB-A317-309), toripalimab (JUPITER-02) and camrelizumab (CAPTAIN-1st), in combination with gemcitabine plus cisplatin, have reported positive outcomes and met their primary endpoints demonstrating longer median PFS for the experimental arms compared to the control arms.

Subsequently, toripalimab (Loqtorzi | European Medicines Agency (EMA)), in combination with gemcitabine and cisplatin was approved for the 1L treatment of adult patients with recurrent, not amenable to surgery or radiotherapy, or metastatic NPC in the EU based on the results from the JUPITER-02 Phase 3 study.

Due to the findings from the aforementioned randomised Phase 3 studies, international clinical guidelines have been updated to recommend treatment with anti-PD-1 antibodies plus chemotherapy

[6] Ung A, Chen CJ, Levine PH, Cheng YJ, Brinton LA, Chen IH, et al. Familial and sporadic cases of nasopharyngeal carcinoma in Taiwan. Anticancer Res. 1999
[7] Lu CC, Chen JC, Tsai ST, Jin YT, Tsai JC, Chan SH, et al. Nasopharyngeal carcinoma-susceptibility locus is localized to a 132 kb segment containing HLA-A using high-resolution microsatellite mapping. Int J Cancer. 2005
[8] Blanchard P, Lee A, Marguet S, et al. Chemotherapy and radiotherapy in nasopharyngeal carcinoma: an update of the MAC-NPC meta-analysis. Lancet Oncol. 2015
[9] Tang LQ, Li CF, Li J, et al. Establishment and validation of prognostic nomograms for endemic nasopharyngeal carcinoma. J Natl Cancer Inst. 2016
[10] Li JX, Huang SM, Wen BX, et al. Prognostic factors on overall survival of newly diagnosed metastatic nasopharyngeal carcinoma. Asian Pac J Cancer Prev. 2014
[11] Xu Y, Huang T, Mao M, et al. Metastatic patterns and prognosis of de novo metastatic nasopharyngeal carcinoma in the United States. Laryngoscope. 2020
[12] Toumi N, Ennouri S, Charfeddine I, et al. Prognostic factors in metastatic nasopharyngeal carcinoma. Braz J Otorhinolaryngol. 2022
[13] Zhang L, Huang Y, Hong S, et al. Gemcitabine plus cisplatin versus fluorouracil plus cisplatin in recurrent or metastatic nasopharyngeal carcinoma: a multicentre, randomised, open-label, phase 3 trial. Lancet. 2016
[14] Hong S, Zhang Y, Yu G, et al. Gemcitabine plus cisplatin versus fluorouracil plus cisplatin as first-line therapy for recurrent or metastatic nasopharyngeal carcinoma: final overall survival analysis of GEM20110714 Phase III study. J Clin Oncol. 2021

as the preferred 1L treatment option for patients with recurrent or metastatic NPC (ESMO 2023; CSCO 2023; NCCN 2024).

2.1.2. About the product

Tislelizumab (BGB-A317) is a humanized immunoglobulin (Ig) G4 variant monoclonal antibody against programmed cell death protein-1 (PD-1), that competitively blocks the binding of both programmed cell death protein ligand-1 (PD-L1) and PD-L2, thereby inhibiting PD-1-mediated negative signalling and enhancing the functional activity of T cells in in-vitro cell-based assays.

Tislelizumab was approved for the treatment of 2L OSCC on 15 September 2023 under the tradename Tevimbra. In February 2024, CHMP recommended an approval for tislelizumab (tradename Tizveni) for the 1L and 2L treatment of NSCLC. Both approvals have been reconciled under the tradename Tevimbra. In October 2024, CHMP adopted a positive opinion for the 1L treatment of HER-2-negative locally advanced unresectable or metastatic gastric or gastroesophageal junction (G/GEJ) adenocarcinoma and for the 1L treatment of unresectable, locally advanced or metastatic oesophageal squamous cell carcinoma (OSCC); both indications were restricted to patients whose tumours express PD-L1 with a tumour area positivity (TAP) score ≥5%. Additionally, an indication in SCLC (small cell lung cancer) was adopted in combination with etoposide and platinum chemotherapy, Tevimbra is indicated for the first-line treatment of adult patients with extensive-stage SCLC.

The applied indication:

Tevimbra, in combination with gemcitabine and cisplatin, is indicated for the first-line treatment of adult patients with recurrent or metastatic NPC.

The adopted indication:

Tevimbra, in combination with gemcitabine and cisplatin, is indicated for the first-line treatment of adult patients with recurrent, not amenable to curative surgery or radiotherapy, or metastatic NPC.

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

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

The MAH did not seek CHMP scientific advice regarding the clinical development this indication.

2.1.4. General comments on compliance with GCP

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

2.2. Non-clinical aspects

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

2.2.1. Ecotoxicity/environmental risk assessment

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

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Table 1-Summary of pivotal study 309

Study Number	Study Status/ Cutoff Date	Study Design	Objectives of the Study	Patient Population (Region)	Treatment Regimen	Patients
Pivotal Study in First Line Recurrent or Metastatic NPC Indication (Efficacy and Safety)						
Study 309	Completed / 26 Mar 2021 (interim analysis); 08 Dec 2023 (study end date)	Phase 3, randomised, double-blind, placebo-controlled	Efficacy assessed by PFS, OS, ORR, DOR, PFS2, and HRQoL; safety and tolerability	1L recurrent or metastatic NPC (China [including Chinese mainland, and Taiwan] and Thailand)	Tisle 200 mg Q3W (Arm Tisle+GC) or matched placebo Q3W (Arm P+GC) + 4 to 6 cycles of gemcitabine on Days 1 and 8 Q3W [a] plus cisplatin on Day 1 Q3W [b]	ITT: Tisle+GC (N = 131) vs P+GC (N = 132) Safety Set: Tisle+GC (N = 133) vs P+GC (N = 130)

2.3.2. Pharmacokinetics

The recommended dose of tislelizumab is the same as the currently approved posology in patients with oesophageal squamous cell carcinoma (OSCC), non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC) and gastric or gastroesophageal junction (G/GEJ) adenocarcinoma.

Pharmacokinetics of tislelizumab, a humanized IgG4 variant mAb against programmed cell death protein-1 (PD-1), have been characterized throughout the initial marketing authorization procedure (EMEA/H/C/005919/0000). In this variation assessment report, only summarized data on tislelizumab ADME, dose proportionality, special populations and interaction studies are presented.

Previously, 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 309, only sparse PK samples were collected at the following time-points: Predose (within 60 minutes before starting infusion) on Day 1 of Cycles 1, 2, 5, 9, and 17; postdose (within 30 minutes after completing infusion) on Day 1 of Cycles 1 and 5. An additional PK sample was collected at the Safety Follow-up Visit.

PK data from Study 309 were not included in the development of the initial PopPK model but were used for external validation to assess the predictive performance and robustness of the population PK model for Study 309.

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]. Bioanalytical methods and assays for quantification of tislelizumab concentration and for determination of ADA response to tislelizumab were found to be adequately validated and overall acceptable for their intended purpose. No new information is provided with the current dossier, as there is no change in bioanalytical methods and assays.

Population PK model

The initial PopPK model analysis included 14,473 measurable tislelizumab concentrations from 2,596 patients. A nonlinear mixed-effects modeling approach with the first-order conditional estimation with interaction (FOCEI) method in NONMEM, Version 7.3.0 (ICON, Maryland) was used for the PopPK analysis.

The PK of tislelizumab in the dose range tested was best described by a 3-compartment model with first-order elimination from the central compartment, and redistribution into the peripheral compartments. The PopPK model was parameterized in terms of clearance (CL) from the central compartment, volume of the central compartment (Vc), distribution clearance from the central to the peripheral compartment (Q2 and Q3), and peripheral volume compartments (V2 and V3). No time-varying CL was identified in this analysis.

Baseline body weight, albumin, tumour size of solid tumours, ADA status (treatment-emergent ADAs), and tumour type were identified as significant covariates on CL. Baseline body weight, sex, and age were identified as significant covariates on Vc.

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.

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.

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-A317-309 (Study 309)

A total of 263 patients were enrolled in this double-blind, randomised, multicentre, Phase 3 study, 131 of whom received 200 mg tislelizumab administered intravenously once every 3 weeks in combination with gemcitabine plus cisplatin. Patients could continue tislelizumab until loss of clinical benefit as assessed by the investigator, withdrawal of consent, study completion by the sponsor, start of a new anticancer therapy, or death, whichever occurred first. The CSR described that PK samples were collected for all randomised patients solely at sites that were able to adequately perform PK sampling and handling.

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 (08-Dec-2023), are presented in Table 2.

Table 2- Summary of Tislelizumab Serum Concentrations (AM ± SD) in Study 309

	Tislelizumab Concentrations (µg/mL)	
Visit	**Predose**	**Postdose**
Cycle 1	NC[a] (n = 129)	74.0 ± 15.37 (n = 131)
Cycle 2	16.9 ± 5.20 (n = 118)	NA
Cycle 5	40.8 ± 12.66 (n = 98)	109.2 ± 24.19 (n = 103)
Cycle 9	59.8 ± 19.63 (n = 63)	NA
Cycle 17	66.1 ± 18.29 (n = 14)	NA

Abbreviation: NA, not available; NC, not calculated.
Population: 131 patients; Sex (M/F): 103/28; Age: 49.0 (26-74); Body weight: 60.0 (37-94.2) kg. 1.7% (12/690) of sample were excluded from the summary due to aberrant sample collection information.
[a] Measurable predose concentration from 1 patient at Cycle 1 was excluded from the summary.

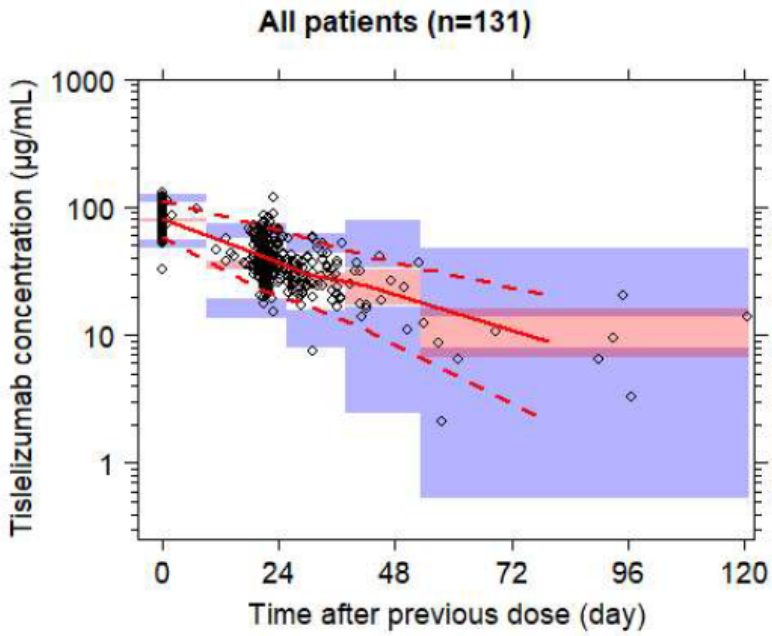
External validation of the final PopPK model for Study 309

The initial tislelizumab PopPK model was externally validated using data from patients in Study 309. The external model validation (EMV) dataset was comprised of 131 patients contributing a total of 672 tislelizumab concentrations. The ability of the existing PopPK model to reproduce the distribution of tislelizumab concentration data over time was evaluated using prediction-corrected visual predictive check (pcVPC) based on 1000 simulated replicates of the Study 309 dataset. Replicates were simulated

using the observed covariates and dose regimens for each subject, the final model parameter estimates, simulated subject-specific random effects, and residual errors. The 95% prediction interval from the 1000 simulated trials of the median, 2.5th, and 97.5th percentiles of the concentration-time profiles, normalized with dose and covariate effects, was overlaid with the corresponding observed data to assess the overall fit of the model predictions.

The pcVPC plot of tislelizumab serum concentration-time profiles is shown in Figure 1.

Figure 1- pcVPC of tislelizumab concentration-time profiles for validation patients in Study 309



Circles are observed tislelizumab serum concentrations, solid red lines represent the median observed value, and dashed red lines represent the 2.5 percentile and 97.5 percentile of the observed values. Pink-shaded areas represent the 95% CI of the predicted median concentrations, and the blue-shaded areas represent the 95% CI of the 2.5 percentile and 97.5 percentile of the predicted concentrations.

A tabular summary of the PopPK-predicted exposure of tislelizumab in Study 309 is presented below.

Table 3-Summary of the PopPK-predicted exposure of tislelizumab in Study 309

Treatment	Summary	$C_{max,ss}$ (µg/mL)	$C_{min,ss}$ (µg/mL)	AUC_{ss} (day.µg/mL)	$C_{avg,ss}$ (µg/mL)
Arm A (N = 131)	n	131	131	131	131
	Geometric Mean (Geometric CV%)	123.35 (17.93)	50.97 (28.22)	1490.67 (22.03)	70.98 (22.03)

Abbreviations: Cmax, ss, Peak Concentration at Steady State; Cmin,ss, Minimum Concentration at Steady State; AUCss, Area Under the Curve at Steady State; Cavg,ss, Average Concentration at Steady State; Arm A, Tislelizumab + Gemcitabine + Cisplatin; CV, Coefficient of Variation.
N is the number of patients in treatment group, n is the number of observations with valid values of the parameter.
Geometric mean was calculated as the exponential of the arithmetic mean for concentrations of study drug in the logarithmic scale.
Geometric CV (%) = sqrt(exp(S2) - 1) * 100, where S2 was the sample variance for concentrations of study drug in the logarithmic scale.
AUCss (day.µg/mL) is equal to Cavg,ss (µg/mL)*21 days.

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.

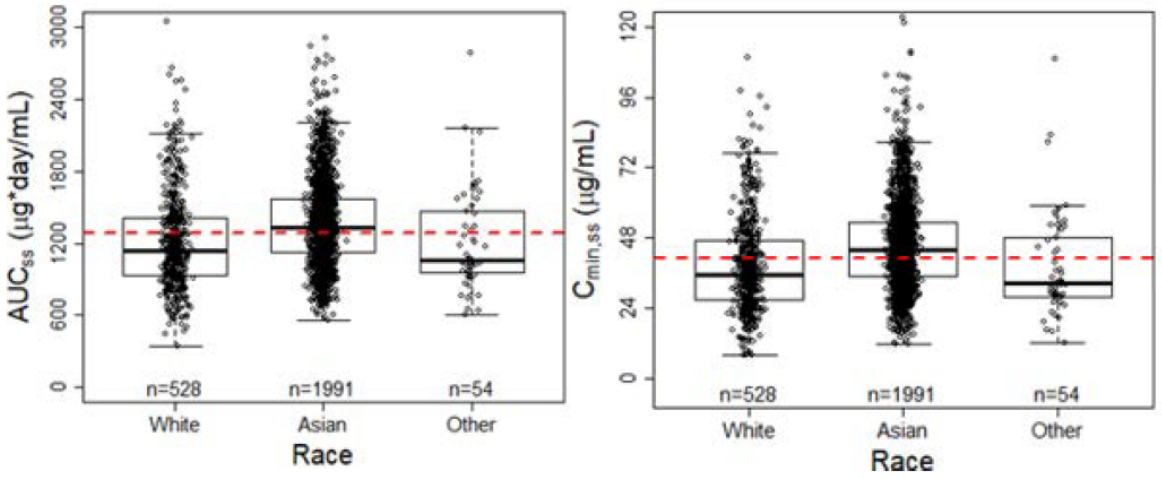
Gender

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. The overall range of tislelizumab exposure after administration of 200 mg once every 3 weeks largely overlapped between the Asian and White patients.

Figure 2-Steady state exposure of tislelizumab by Asian; White and Other following 200 mg Q3W dosing



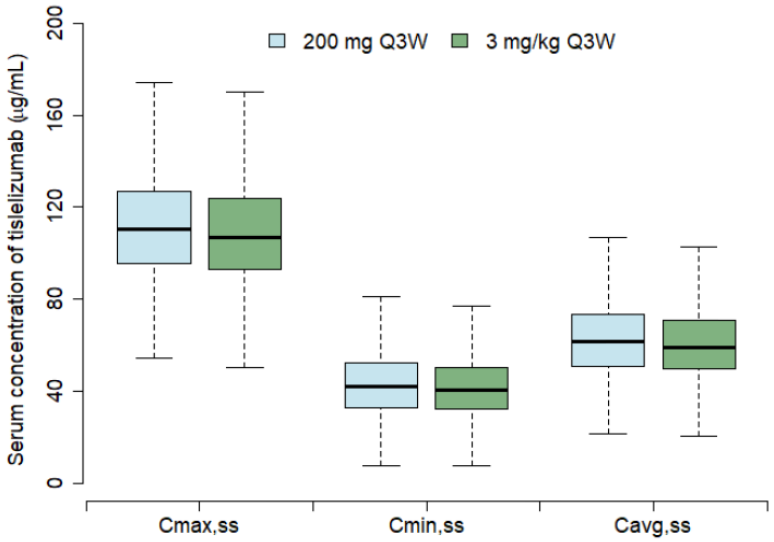
Source: Module 5.3.3.5 PopPK Report (March, 2021), Figure 22.
Abbreviations: AUC_{ss}, area under the serum concentration-time curve at steady state; CL, clearance; $C_{min,ss}$, minimum serum concentration at steady state.
Note: The steady-state exposures ($C_{min,ss}$, AUC_{ss}) of tislelizumab were computed for each patient. AUC_{ss} was calculated as dose/CL. $C_{min,ss}$ was calculated as the minimum concentration at 21 days after 10 consecutive doses of tislelizumab 200 mg once every 3 weeks.
The dashed red horizontal line represents the mean of the overall population

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.

To further explore the impact of flat dosing on PK variability, the exposure range with the clinically recommended dose of 200 mg once every 3 weeks was compared to a hypothetical scenario of body weight-based dosing to assess the impact on the mean and variability in exposure. A 3 mg/kg dose was chosen for this hypothetical scenario as this dose corresponds to a 200 mg dose in a 65-kg patient (median weight in the PopPK dataset). The means and variability in predicted steady-state exposures after 200 mg or 3 mg/kg once every 3 weeks dosing, presented in Figure 4 below, were nearly identical.

Figure 3- Simulated Steady-State Exposures of Tislelizumab at 200 mg Flat Dose and 3 mg/kg Body Weight-Based Dosing Regimen

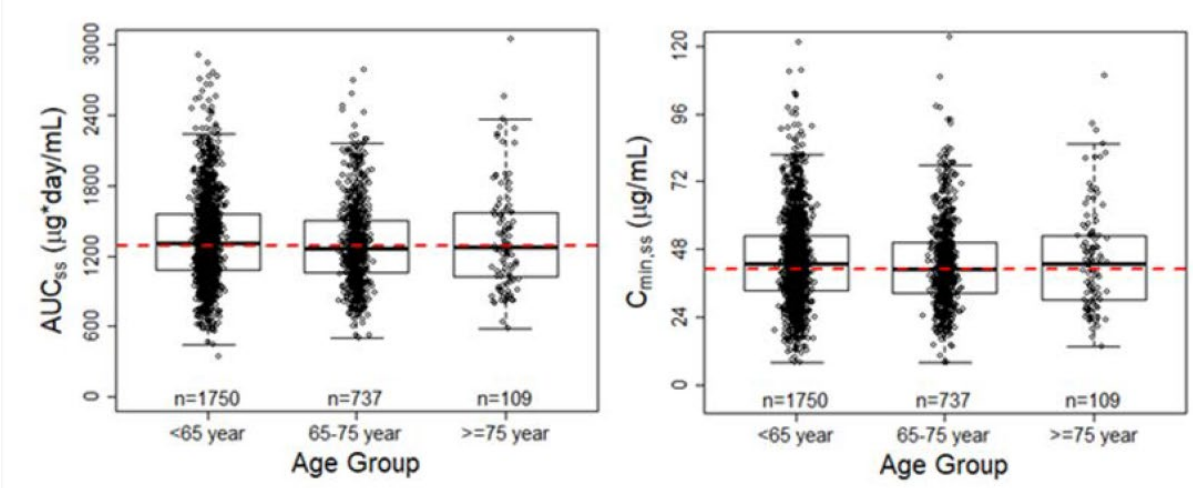


Source: Module 5.3.3.5 PopPK Report (March 2021), Figure 19.
Abbreviations: AUC_{ss}, area under the serum concentration-time curve at steady state; $C_{avg,ss}$, average serum concentration at steady state; $C_{max,ss}$, maximum serum concentration at steady state; $C_{min,ss}$, minimum serum concentration at steady state.

Age

Baseline age was identified as a significant covariate on the Vc of tislelizumab in the final PopPK model. The estimate of Vc at the 10th and 90th percentile of age distribution was within 3% of the typical estimate. The predicted steady-state exposures after administration of 200 mg once every 3 weeks for patients stratified by age groups are presented in Figure 4.

Figure 4-Effect of Age on Steady-State Tislelizumab Exposure



Source: Module 5.3.3.5 PopPK Report (March 2021), Figure 18.
Abbreviations: AUC_{ss}, area under the serum concentration-time curve at steady state; CL, clearance; $C_{min,ss}$, minimum serum concentration at steady state.

Children

Tislelizumab has no study conducted in paediatric subjects.

Pharmacokinetic interaction studies

No formal drug-drug interaction studies have been conducted with tislelizumab.

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 combination therapy 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 309.

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-A317-309.

Immunogenicity of tislelizumab in combination with chemotherapy was assessed as exploratory objective in Study 309.

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 3253 patients treated with tislelizumab at the recommended dose of 200 mg Q3W (regardless of whether received tislelizumab at 400 mg Q6W in adjuvant phase in Study 315) in 15 Phase I to III clinical studies (monotherapy: studies 001, 102, 203, 204, 208, 302, and 303; in combination with chemotherapy: studies 206, 304, 305, 306, 307, 309, 312, and 315) were assessed for treatment-emergent ADA and Nab.

ADA incidence

Overall, the incidence of treatment-emergent ADA was 21.5% (698/3253 ADA evaluable patients). Patients treated with tislelizumab 200 mg Q3W as monotherapy had treatment-emergent ADA incidence of 16.5% (236/1427 evaluable patients). Patients treated with tislelizumab 200 mg Q3W in combination with chemotherapy had a slightly higher incidence of 25.3% (462/1826 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 for the Q3W regimen. NAb were detected in 33 patients (1.0% of 3253 evaluable patients), with a low incidence (< 2%) across most studies that tested the fixed dose of 200 mg Q3W.

Table 4-ADA incidence by dose regimen (ADA evaluable patients)

Dose Regimen	Study	Evaluable Patients N	Treatment-Emergent ADA n (%)	Treatment-Boosted ADA n (%)	Treatment-Induced ADA n (%)	Persistent ADA n (%)	Transient ADA n (%)	NAb-Positive n (%)
0.5 mg/kg Q2W	001	3	1 (33.3)	0 (0.0)	1 (33.3)	0 (0.0)	1 (33.3)	0 (0.0)
2.0 mg/kg Q2W	001	21	6 (28.6)	0 (0.0)	6 (28.6)	2 (9.5)	4 (19.0)	0 (0.0)
5.0 mg/kg Q2W	001	25	5 (20.0)	0 (0.0)	5 (20.0)	4 (16.0)	1 (4.0)	0 (0.0)
10.0 mg/kg Q2W	001	6	1 (16.7)	0 (0.0)	1 (16.7)	1 (16.7)	0 (0.0)	0 (0.0)
2.0 mg/kg Q3W	001	19	6 (31.6)	0 (0.0)	6 (31.6)	3 (15.8)	3 (15.8)	0 (0.0)
5.0 mg/kg Q3W	001	287	44 (15.3)	1 (0.3)	43 (15.0)	21 (7.3)	22 (7.7)	0 (0.0)
Subtotal of Weight-Based Regimen in Study 001		361	63 (17.5)	1 (0.3)	62 (17.2)	31 (8.6)	31 (8.6)	0 (0.0)
200 mg Q3W	001	11	3 (27.3)	0 (0.0)	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 (0.0)	6 (8.6)	4 (5.7)	2 (2.9)	1 (1.4)
200 mg Q3W	204	104	18 (17.3)	1 (1.0)	17 (16.3)	13 (12.5)	4 (3.8)	0 (0.0)
200 mg Q3W	208	231	51 (22.1)	0 (0.0)	51 (22.1)	34 (14.7)	17 (7.4)	4 (1.7)
200 mg Q3W	302	223	32 (14.3)	2 (0.9)	30 (13.5)	19 (8.5)	11 (4.9)	1 (0.4)
200 mg Q3W	303	508	83 (16.3)	3 (0.6)	80 (15.7)	42 (8.3)	38 (7.5)	2 (0.4)
Subtotal of Tislelizumab Monotherapy at 200 mg Q3W		1427	236 (16.5)	8 (0.6)	228 (16.0)	139 (9.7)	89 (6.2)	11 (0.8)
Subtotal of Tislelizumab Monotherapy		1788	299 (16.7)	9 (0.5)	290 (16.2)	170 (9.5)	120 (6.7)	11 (0.6)
200 mg Q3W	206	51	7 (13.7)	0 (0.0)	7 (13.7)	1 (2.0)	6 (11.8)	0 (0.0)
200 mg Q3W	304	213	48 (22.5)	2 (0.9)	46 (21.6)	12 (5.6)	34 (16.0)	2 (0.9)

Dose Regimen	Study	Evaluable Patients N	Treatment-Emergent ADA n (%)	Treatment-Boosted ADA n (%)	Treatment-Induced ADA n (%)	Persistent ADA n (%)	Transient ADA n (%)	NAb-Positive n (%)
200 mg Q3W	305	470	107 (22.8)	1 (0.2)	106 (22.6)	65 (13.8)	41 (8.7)	8 (1.7)
200 mg Q3W	306	300	66 (22.0)	0 (0.0)	66 (22.0)	29 (9.7)	37 (12.3)	1 (0.3)
200 mg Q3W	307	228	63 (27.6)	2 (0.9)	61 (26.8)	28 (12.3)	33 (14.5)	5 (2.2)
200 mg Q3W	309	125	11 (8.8)	1 (0.8)	10 (8.0)	4 (3.2)	6 (4.8)	0 (0.0)
200 mg Q3W	312	220	55 (25.0)	4 (1.8)	51 (23.2)	26 (11.8)	25 (11.4)	0 (0.0)
200mg Q3W&400mg Q6W [a]	315	219	105 (47.9)	2 (0.9)	103 (47.0)	56 (25.6)	47 (21.5)	6 (2.7)
Subtotal of Tislelizumab Combination Therapy		1826	462 (25.3)	12 (0.7)	450 (24.6)	221 (12.1)	229 (12.5)	22 (1.2)
Subtotal of 200 mg Q3W [a]		3253	698 (21.5)	20 (0.6)	678 (20.8)	360 (11.1)	318 (9.8)	33 (1.0)
Total		3614	761 (21.1)	21 (0.6)	740 (20.5)	391 (10.8)	349 (9.7)	33 (0.9)

Immunogenicity in Study 309

ADA samples were collected within 60 minutes before beginning the Day 1 infusion of Cycles 1, 2, 5, 9, and 17 and at the mandatory Safety Follow-up Visit. All samples were drawn at the same time as blood collection for predose PK analysis.

Of the 131 patients in Study Arm A which were dosed with tislelizumab, 125 patients were ADA-evaluable (had a baseline and at least one post-baseline ADA result). Immunogenicity results are presented below.

Table 5-Summary of immunogenicity results for Study 309 (ADA Analysis Set)

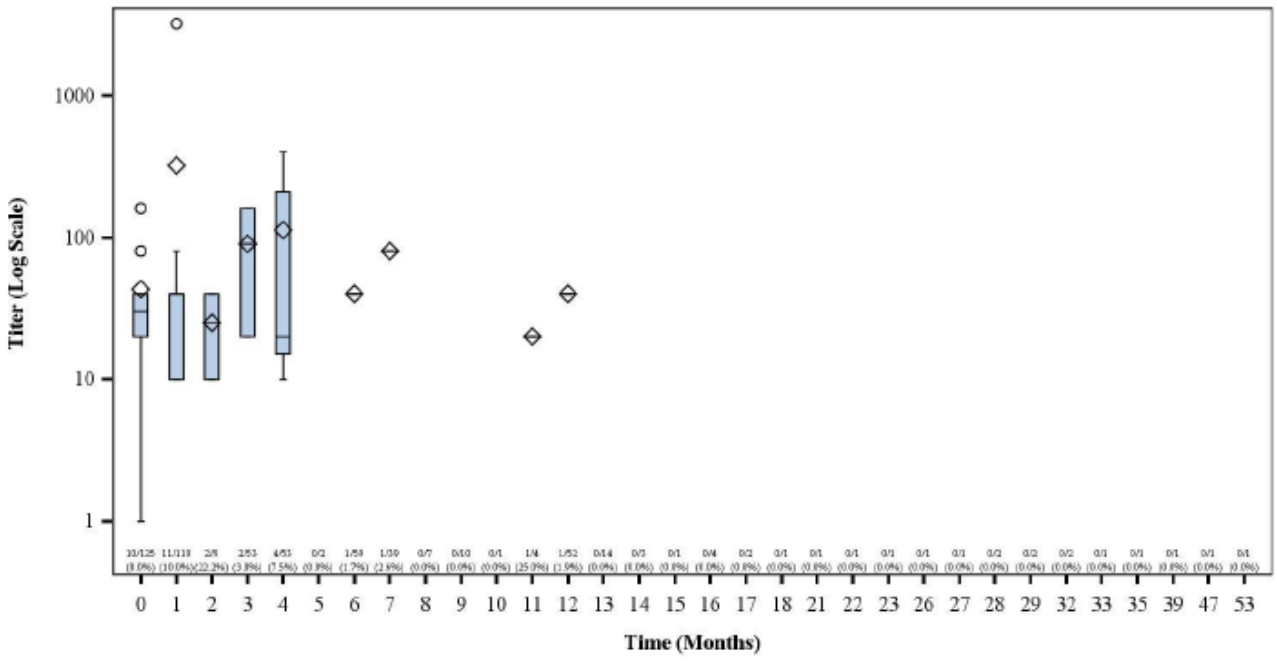
Subgroup	Evaluable Patients: N	Treatment-emergent [a]:n (%)	Treatment-boosted ADA [b]: n (%)	Treatment-induced ADA [c]: n (%)	Persistent ADA [d]: n (%)	Transient ADA [e]: n (%)	NAb Positive [f]: n (%)
Overall	125	11 (8.8)	1 (0.8)	10 (8.0)	4 (3.2)	6 (4.8)	0 (0.0)

[a] Treatment-emergent ADA: Sum of both treatment-induced ADA and treatment-boosted ADA, synonymous with "ADA Incidence".
[b] Treatment-boosted ADA: ADA positive at baseline that is boosted to a 4-fold or higher-level following drug administration.
[c] Treatment-induced ADA: ADA negative at baseline and ADA positive post-baseline following drug administration.
[d] Persistent ADA: Treatment-induced ADA detected at two or more sampling time points during the treatment (including follow-up period if any), where the first and last ADA-positive samples (irrespective of any negative samples in between) are separated by a period of 16 weeks or longer, or treatment induced ADA detected in the last sampling time point.
[e] Transient ADA: Transient ADA is a treatment-induced response that is not considered persistent.
[f] NAb Positive: Treatment-emergent ADA that inhibits or reduces the pharmacological activity.

The overall median ADA onset time was 22 days.

The median titer levels fluctuated between approximately 10 and 100, over 12 months. Over the time course of the study, titer values for most patients did not increase (data not shown).

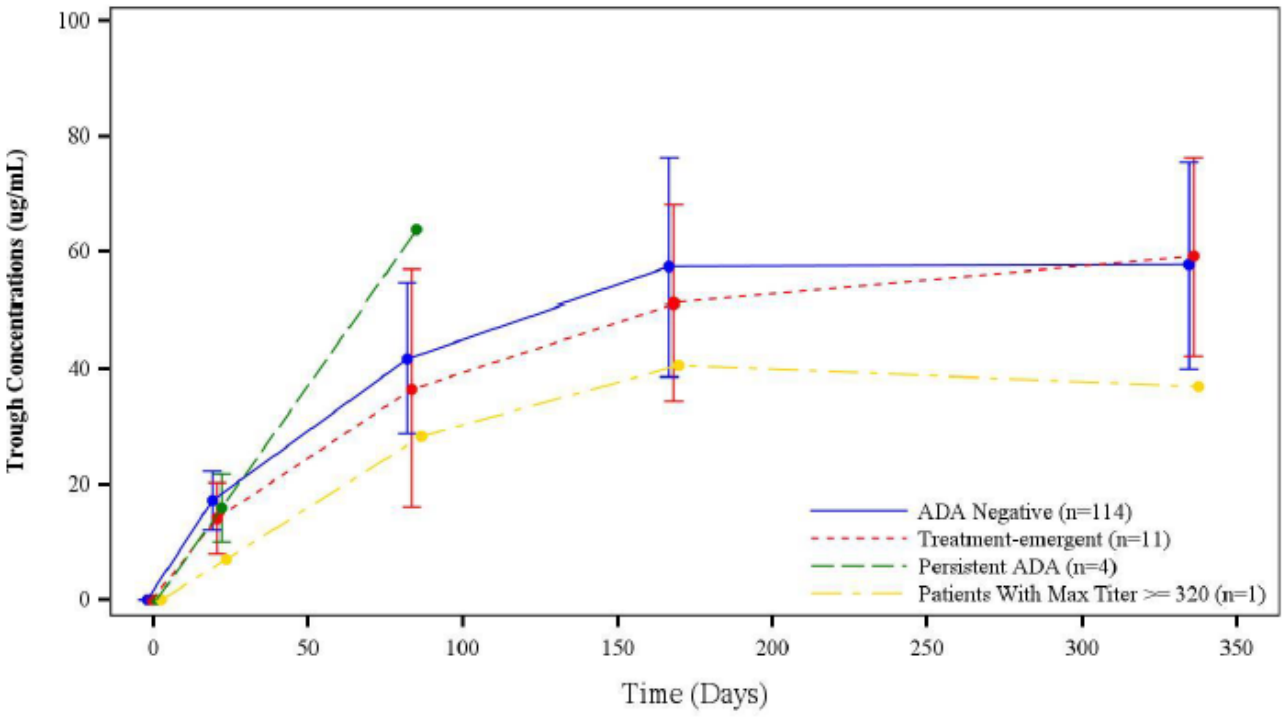
Figure 5-Median and Range of ADA Titers Over Time in Patients Treated with Tislelizumab (ADA Analysis Set)



Impact of ADA on PK (Study 309)

Trough serum tislelizumab concentrations were plotted over time. In the ADA analysis set, the median serum concentrations of tislelizumab were slightly lower in treatment-emergent (ADA positive) patients until Cycle 9 (Day 168) compared to ADA negative patients. However, standard deviation error bars of serum concentrations overlapped at all time points. Serum trough concentrations were numerically lower in the single patient with maximum titers ≥ 320 compared to the ADA-negative population.

Figure 6-ADA Impact on Mean (± SD) Trough Tislelizumab Serum Concentrations by ADA Type (ADA Analysis Set)



Impact of ADA on efficacy (Integrated ADA Analysis)

To estimate the causal treatment effects on survival, the principal stratum strategy based on potential ADA status in both study arms was applied to the primary endpoint of OS in Studies 302, 303, 305, 306, and 312, and PFS in Studies 304 and 307. The results of descriptive subgroup analyses should be interpreted with caution due to the potential bias in comparing between outcome-driven groups based on post-baseline ADA status and due to the variation arising from the small number of patients in the ADA-positive group.

Table 6-Summary of Treatment-Emergent ADA by Disease Response (ADA Evaluable Analysis Set)

	Treatment-Emergent ADA Positive n/N (%)	**Treatment-Emergent ADA Negative n/N (%)**
Tislelizumab Monotherapy		
Study 302 – ESCC		
Objective Response	6/32 (18.8)	32/191 (16.8)
Disease Control	18/32 (56.3)	98/191 (51.3)
Study 303 – NSCLC		

	Treatment-Emergent ADA Positive n/N (%)	Treatment-Emergent ADA Negative n/N (%)
Objective Response	22/83 (26.5)	88/425 (20.7)
Disease Control	51/83 (61.4)	244/425 (57.4)
Clinical Benefit	41/83 (49.4)	191/425 (44.9)
Tislelizumab Combination Therapy		
Study 304 – NSCLC		
Objective Response	28/48 (58.3)	86/165 (52.1)
Disease Control	46/48 (95.8)	151/165 (91.5)
Clinical Benefit	34/48 (70.8)	114/165 (69.1)
Study 305 – G/GEJC		
Objective Response	53/107 (49.5)	182/363 (50.1)
Disease Control	100/107 (93.5)	344/363 (94.8)
Clinical Benefit	69/107 (64.5)	245/363 (67.5)
Study 306 – ESCC		
Objective Response	38/66 (57.6)	139/234 (59.4)
Disease Control	57/66 (86.4)	219/234 (93.6)
Clinical Benefit	43/66 (65.2)	174/234 (74.4)
Study 307 – NSCLC: T+PC		
Objective Response	24/43 (55.8)	50/72 (69.4)
Disease Control	35/43 (81.4)	68/72 (94.4)
Clinical Benefit	27/43 (62.8)	58/72 (80.6)
Study 307 – NSCLC: T+nPC		
Objective Response	10/20 (50.0)	64/93 (68.8)
Disease Control	20/20 (100.0)	88/93 (94.6)
Clinical Benefit	14/20 (70.0)	72/93 (77.4)
Study 309 – NPC		
Objective Response	7/11 (63.6)	83/114 (72.8)
Disease Control	11/11 (100.0)	106/114 (93.0)
Clinical Benefit	7/11 (63.6)	94/114 (82.5)
Study 312 – SCLC		
Objective Response	34/55 (61.8)	121/165 (73.3)
Disease Control	49/55 (89.1)	152/165 (92.1)
Clinical Benefit	35/55 (63.6)	122/165 (73.9)
Study 315 – NSCLC		

	Treatment-Emergent ADA Positive n/N (%)	Treatment-Emergent ADA Negative n/N (%)
Major Pathological Response	62/105 (59.0)	65/114 (57.0)
pathological Complete Response	46/105 (43.8)	46/114 (40.4)

Impact of ADA on efficacy (Study 309)

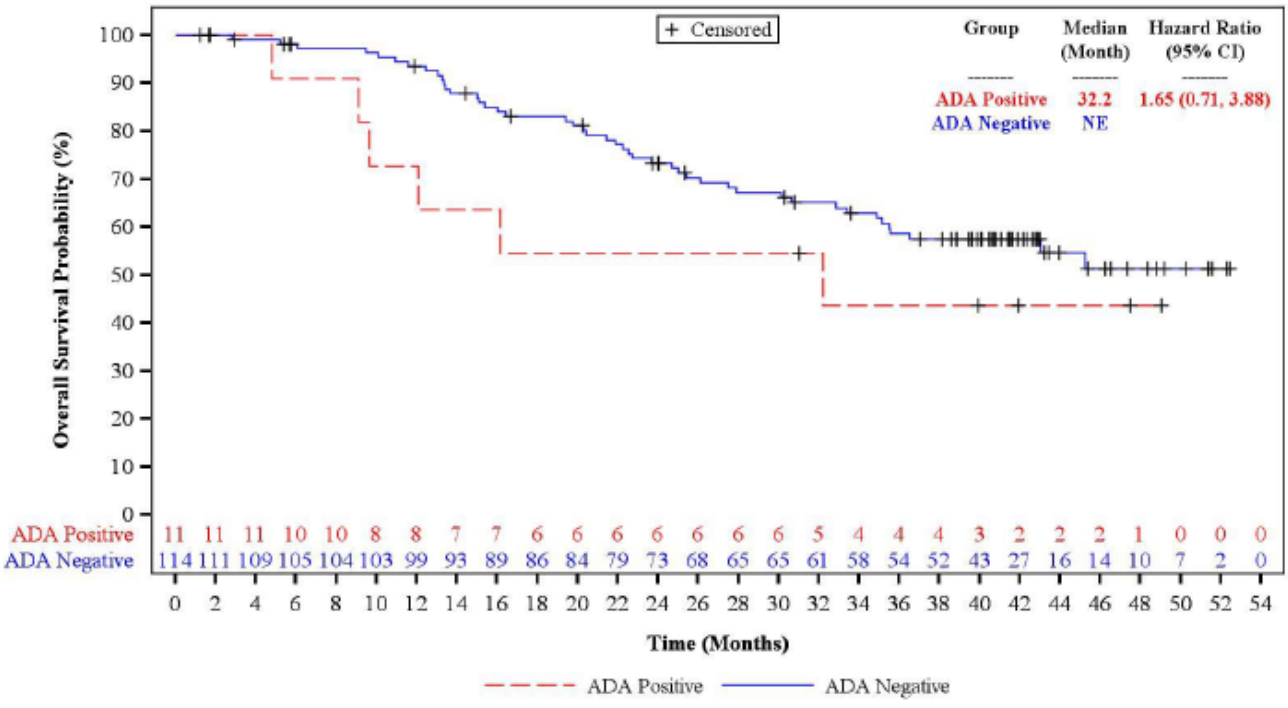
In Study 309, treatment-emergent ADA-positive patients had generally lower clinical response rates compared with ADA-negative patients.

Table 7-Analysis of Clinical Responses by ADA Status in Study 309 (ADA Analysis Set)

		Clinical Response					
		Objective Response		Disease Control		Clinical Benefit	
All Patients							
	Trt-emergent ADA	Yes % (n/N)	No % (n/N)	Yes % (n/N)	No % (n/N)	Yes % (n/N)	No % (n/N)
Total	Yes	63.6 (7/11)	36.4 (4/11)	100 (11/11)	0.0 (0/11)	63.6 (7/11)	36.4 (4/11)
	No	72.8 (83/114)	27.2 (31/114)	93.0 (106/114)	7.0 (8/114)	82.5 (94/114)	17.5 (20/114)
	Total	72.0 (90/125)	28.0 (35/125)	93.6 (117/125)	6.4 (8/125)	80.8 (101/125)	19.2 (24/125)

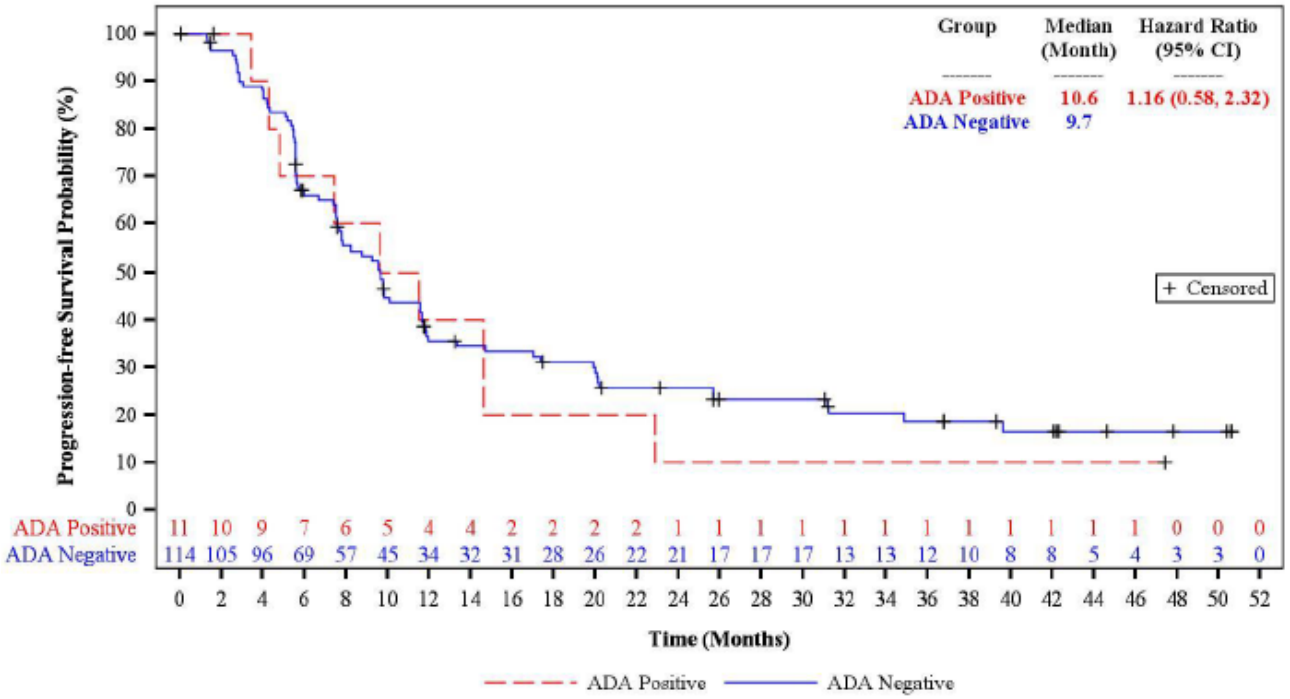
Kaplan-Meier (KM) curves for OS by ADA status are presented below:

Figure 7-Kaplan-Meier Plot of Overall Survival by ADA Status (ADA Analysis Set)



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

Figure 8-Kaplan-Meier Plot of Progression-Free Survival by ADA Status in Patients (ADA Analysis Set)



Potential imbalances in baseline covariates between the ADA-defined subgroups (within the tislelizumab arm) could have confounded the comparisons. In order to account for potential imbalances in baseline characteristics between the two ADA subgroups, a principal stratum method was utilized to provide appropriate controls for each ADA subgroup in Studies 302, 303, 304, 305, 306, 307, 312, and 315. This strategy ensures that the causal effect is attributable only to the treatment by adjusting for potential baseline imbalances in the ADA-defined subgroups compared to the corresponding adjusted controls. As the incidence of ADA in Study 309 was too low, a principal stratum analysis approach was not applied. The results from the principal stratum analysis are shown in Table 8 below:

Table 8-Analyses of the Survival Outcomes Using Principal Stratum Method

Study	Primary Endpoint	Baseline Covariates	Landmark[a]	Variable Selection[b]	ADA-positive HR (95% CI)	ADA-negative HR (95% CI)
302	OS	Age, Sex, Weight, Region, Smoking status, ECOG, PD-L1 expression, Sum of target lesion diameters, Albumin, Lactate dehydrogenase, Neutrophil-to-lymphocyte ratio	No	No	0.56 (0.32, 1.00)	0.62 (0.49, 0.79)
			No	Yes	0.56 (0.32, 1.00)	0.62 (0.49, 0.79)
			Yes	No	0.66 (0.32, 1.33)	0.61 (0.49, 0.77)
			Yes	Yes	0.63 (0.31, 1.28)	0.62 (0.49, 0.78)
303	OS	Age, Sex, Weight, Region, Smoking status, ECOG, Line of therapy, Disease stage, Histology, PD-L1 expression, Liver metastases, Brain metastases, EGFR, ALK, Sum of target lesion diameters, Albumin, Lactate dehydrogenase, Neutrophil-to-lymphocyte ratio	No	No	0.60 (0.37, 0.97)	0.58 (0.47, 0.73)
			No	Yes	0.60 (0.37, 0.96)	0.60 (0.48, 0.74)
			Yes	No	0.67 (0.37, 1.23)	0.59 (0.47, 0.73)
			Yes	Yes	0.70 (0.38, 1.26)	0.59 (0.48, 0.73)
304	PFS	Age, Sex, Weight, Smoking status, ECOG, Disease stage, PD-L1 expression, Bone metastases, ALK, Sum of target lesion diameters, Albumin, Lactate dehydrogenase, Neutrophil	No	No	0.59 (0.32, 1.09)	0.59 (0.41, 0.85)
			No	Yes	0.60 (0.32, 1.12)	0.60 (0.42, 0.85)
			Yes	No	0.58 (0.28, 1.20)	0.58 (0.41, 0.83)
			Yes	Yes	0.61 (0.30, 1.25)	0.58 (0.41, 0.83)
305	OS	Age, Sex, Weight, Region, Smoking status, Alcohol consumption, ECOG, Sum of target lesion diameters, Presence of peritoneal metastasis, Liver metastases, Number of metastatic sites at study entry, Chemotherapy, Albumin, Lactate dehydrogenase, Neutrophil-to-lymphocyte ratio	No	No	0.74 (0.54, 0.99)	0.73 (0.61, 0.86)
			No	Yes	0.71 (0.52, 0.96)	0.74 (0.62, 0.87)
			Yes	No	0.97 (0.65, 1.46)	0.71 (0.61, 0.83)
			Yes	Yes	0.92 (0.61, 1.37)	0.72 (0.61, 0.84)
306	OS	Age, Sex, Weight, Region, Prior definitive therapy, Chemotherapy, Smoking status, Alcohol consumption, ECOG, PD-L1 expression, Sum of target lesion diameters, Number of metastatic sites at study entry, Albumin, Lactate dehydrogenase, Neutrophil-to-lymphocyte ratio	No	No	0.66 (0.43, 1.00)	0.65 (0.51, 0.83)
			No	Yes	0.64 (0.42, 0.97)	0.65 (0.51, 0.83)
			Yes	No	0.68 (0.42, 1.11)	0.65 (0.52, 0.83)
			Yes	Yes	0.74 (0.45, 1.20)	0.65 (0.51, 0.82)
307	PFS		No	No	0.49 (0.31, 0.80)	0.43 (0.30, 0.61)

Study	Primary Endpoint	Baseline Covariates	Landmark[a]	Variable Selection[b]	ADA-positive HR (95% CI)	ADA-negative HR (95% CI)
		Age, Sex, Weight, Smoking status, ECOG, Disease stage, PD-L1 expression, Liver metastases, Bone metastases, EGFR, ALK, Sum of target lesion diameters, Albumin, Lactate dehydrogenase, Neutrophil, chemotherapy type	No	Yes	0.53 (0.33, 0.85)	0.43 (0.31, 0.62)
			Yes	No	0.52 (0.30, 0.90)	0.44 (0.32, 0.62)
			Yes	Yes	0.52 (0.30, 0.89)	0.45 (0.32, 0.63)
312	OS	Age, Sex, ECOG PS, Liver metastasis, LDH, Smoking status, Investigator chosen platinum, AJCC staging at study entry, Body weight	No	No	0.85 (0.61, 1.19)	0.71 (0.57, 0.89)
			No	Yes	0.87 (0.62, 1.21)	0.71 (0.56, 0.88)
			Yes	No	0.85 (0.58, 1.25)	0.72 (0.57, 0.89)
			Yes	Yes	0.84 (0.57, 1.24)	0.72 (0.58, 0.89)
315	EFS	Age group, Sex, Weight, ECOG PS, Disease Stage, Histologic Type, PD-L1 expression, Smoking status, Sum of target lesion diameters, Albumin, Lactate dehydrogenase	No	No	0.46 (0.27, 0.77)	0.67 (0.43, 1.05)
			No	Yes	0.46 (0.28, 0.77)	0.67 (0.42, 1.04)
			Yes	No	0.56 (0.30, 1.04)	0.57 (0.38, 0.85)
			Yes	Yes	0.56 (0.30, 1.04)	0.57 (0.38, 0.85)

ADA, anti-drug antibody; ECOG PS, ALK, alkaline phosphatase; Eastern Cooperative Oncology Group Performance Status; EFS, event-free survival; EGFR, estimated glomerular filtration rate; HR, hazard ratio; OS, overall survival; PD-L1, programmed cell death protein ligand-1; PFS, progression-free survival.

[a] No: ADA status was not defined by landmark; Yes: ADA status was defined by landmark.

[b] No: no variable selection, used all the baseline covariates in the logistic regression; Yes: implemented stepwise variable selection

Table 9-Impact of ADA on safety (Integrated ADA Analysis)

	Treatment-Emergent ADA Positive	Treatment-Emergent ADA Negative
Tislelizumab Monotherapy		
Monotherapy Studies (001, 102, 203, 204, 208, 302, and 303), N	236	1191
Immune-Mediated Adverse Events, n (%)	80 (33.9)	412 (34.6)
Infusion-Related Reactions, n (%)	4 (1.7)	42 (3.5)
TEAEs >= Grade 3, n (%)	124 (52.5)	502 (42.1)
Serious TEAEs, n (%)	92 (39.0)	379 (31.8)
TEAEs Leading to Tislelizumab Discontinuation, n (%)	29 (12.3)	136 (11.4)
TEAEs Leading to Treatment Modification of Tislelizumab, n (%)	71 (30.1)	334 (28.0)
Tislelizumab Combination Therapy		
Combination Therapy Studies (304, 305, 306, 307, 309, 312, 315), N	455	1320
Immune-Mediated Adverse Events, n (%)	191 (42.0)	535 (40.5)
Infusion-Related Reactions, n (%)	35 (7.7)	77 (5.8)
TEAEs >= Grade 3, n (%)	364 (80.0)	1037 (78.6)
Serious TEAEs, n (%)	197 (43.3)	541 (41.0)
TEAEs Leading to Tislelizumab Discontinuation, n (%)	62 (13.6)	178 (13.5)
TEAEs Leading to Treatment Modification of Tislelizumab, n (%)	225 (49.5)	717 (54.3)

Impact of ADA on safety (Study 309)

In Study 309, the incidence of SAEs and IRRs were higher in patients with treatment-emergent ADA, and the remaining safety parameters were overall comparable. However, the small sample size of patients with treatment-emergent ADA must be taken into account.

Table 10-Summary of Treatment-emergent Adverse Events in Patients by ADA Status in Study 309 (ADA Analysis Set)

Treatment-emergent ADA	imAE % (n/N)	IRR % (n/N)	AE Grade >= 3 % (n/N)	SAE % (n/N)	AE Discontinuation % (n/N)	AE Modification % (n/N)	AESI % (n/N)
Yes	45.5 (5/11)	18.2 (2/11)	81.8 (9/11)	63.6 (7/11)	9.1 (1/11)	27.3 (3/11)	45.5 (5/11)
No	55.3 (63/114)	4.4 (5/114)	86.0 (98/114)	30.7 (35/114)	7.9 (9/114)	53.5 (61/114)	56.1 (64/114)
Total	54.4 (68/125)	5.6 (7/125)	85.6 (107/125)	33.6 (42/125)	8.0 (10/125)	51.2 (64/125)	55.2 (69/125)

Most of the AEs including imAEs, IRRs, Grade >3 AEs, SAEs, and AEs leading to dose discontinuation or modification occurred at lower titers (titers ≤ 80) and did not show any trend with toxicity grade in the overall ADA analysis set.

2.3.4. PK/PD modelling

The tislelizumab time-course PK profile was simulated using the Bayesian post-hoc PK parameters from the EMV model for each subject in Study 309. The E-R relationship between the model-predicted tislelizumab exposure and efficacy/safety endpoints from Study 309 was explored.

The previously developed tislelizumab PopPK model was used to obtain empirical Bayes estimates of individual PK parameters of all tislelizumab-treated patients. The tislelizumab time-course PK profile was simulated using the Bayesian post-hoc PK parameters for each subject in study BGB-A317-309.

The following exposure metrics were calculated for 131 patients treated with tislelizumab (200 mg Q3W) from study BGB-A317-309: area under the time-concentration curve of 1st dose interval (AUCdose1), area under the time-concentration curve at steady state (AUCss), and maximum concentration at steady state (Cmax,ss). Both AUCdose1 and AUCss were calculated using the linear up/log down variant of the trapezoidal rule using R software.

Cavg,ss was calculated as AUCss/tau and Cavg,dose1 was calculated as AUCdose1/tau, where tau is 21 days for every 3 weeks (Q3W). As tislelizumab followed linear PK with no time-varying CL and the exposure metrics derived after the first dose and at steady-state are well correlated and, therefore, the model-predicted Cavg,ss, and Cmax,ss were used as the primary exposure endpoint in this E-R safety analysis, while the model-predicted Cavg,dose1 was used as the primary exposure endpoint in this E-R efficacy analysis.

The simulated exposure metrics were merged into the efficacy and safety datasets for E-R analysis.

Exposure-efficacy analysis:

Exposure-efficacy analyses in Study 309 were based on efficacy endpoints (PFS, OS, and ORR) with PFS and ORR assessed by IRC. The exposure-efficacy relationship for tislelizumab was explored using an efficacy dataset containing data from 131 patients who received at least 1 dose of tislelizumab and who had PopPK model predicted Cavg,dose1 for exposure-efficacy.

Exposure versus PFS and OS

The results show that a slightly longer PFS and OS was observed in the higher exposure quartile(s).

Figure 9-Kaplan-Meier Curves of PFS Stratified by Cavg,dose1 Quartiles (Study 309)

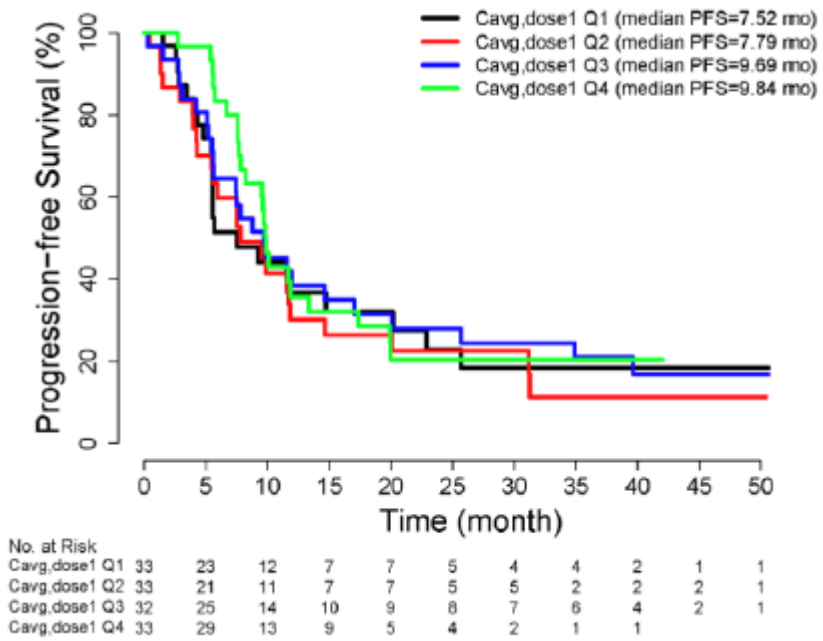
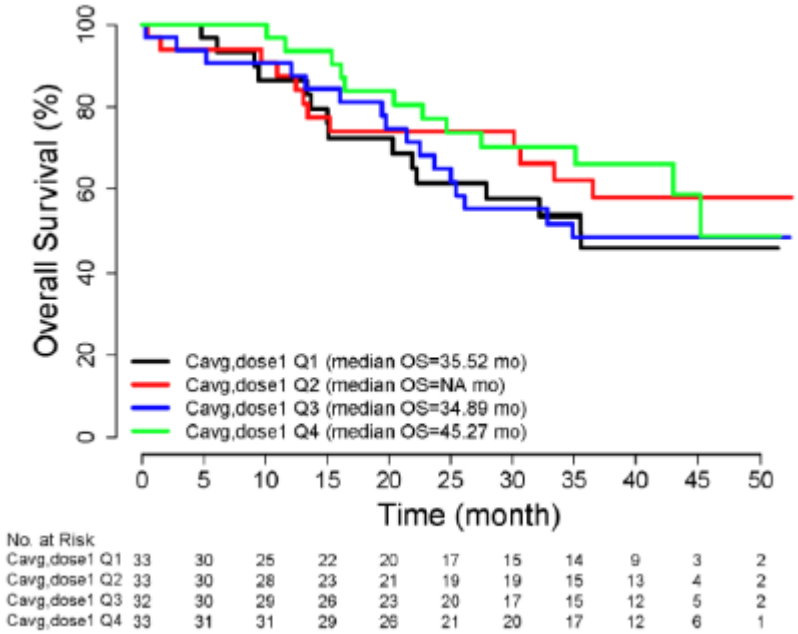


Figure 10-Kaplan-Meier Curves of OS Stratified by Cavg,dose1 Quartiles (Study 309)



To further investigate the effect of prognostic factors on PFS or OS, a Cox proportional hazards model was developed for tislelizumab-treated patients. Tislelizumab Cavg,dose1 as well as prognostic factors were tested in the Cox model as potential predictors of PFS or OS using a two-step forward-addition and backward-elimination method based on the significance level of $p < 0.05$. The Cox proportional-hazards model analysis showed that Cavg.dose1 ($p > 0.05$) was not a significant predictor for PFS or OS.

Table 11-Summary of Cox model parameters for PFS (Study 309)

Predictor	Parameter Estimates		Wald p-value	95% CI for β	
	β	exp(β)		Lower	Upper
$Log(C_{avg,dose1})$	-0.6731	0.5101	0.3231	-2.0082	0.6620

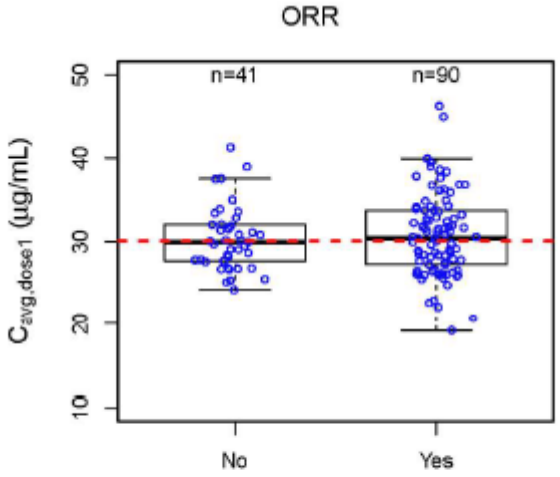
Table 12-Summary of Cox model parameters for OS (Study 309)

Predictor	Parameter Estimates		Wald p-value	95% CI for β	
	β	exp(β)		Lower	Upper
$Log(C_{avg,dose1})$	-1.530	0.2165	0.0941	-3.3211	0.2611

Exposure versus ORR

Based on the summary of PopPK-predicted Cavg,dose1 categorized by response status, the exposure to tislelizumab is similar between responders and non-responders.

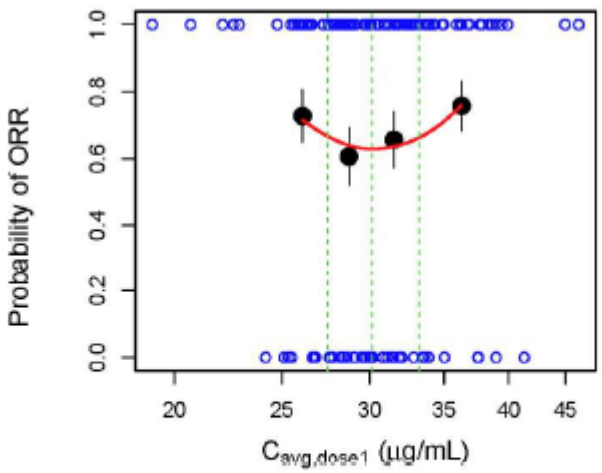
Figure 11-Relationship between tislelizumab exposure and ORR (Study 309)



Open blue circles are the model-predicted exposure matrices. The median is represented by the horizontal black line in the middle of each box. The lower and upper ends of the box plot represent the 25th and 75th percentile (the lower and upper quartiles, respectively). The bars extend to the most extreme data point which is no more than 1.5×IQR from the box. The dashed red horizontal line represents the median value in study BGB-A317-309.

Logistic regression was further used to evaluate the relationship between exposure and response. The probability estimates of major pathologic response versus PopPK predicted Cavg,dose1 were evaluated across four quartiles of Cavg,dose1 Figure 12.

Figure 12-Probability of major pathologic response versus tislelizumab exposure (Study 309)



Open blue circles reflect the observed events. The filled black symbols are the observed probability of events and the error bars are SE [sqrt (P*(1-P)/N)] for quantiles (at 100x(1/4)th percentiles, vertical dotted lines) of exposures (plotted at the median value within each quantile), where P is the probability of event and N is the number of patients in each quantile bin. The red lines are smooth curves to show the relationship between two variables.

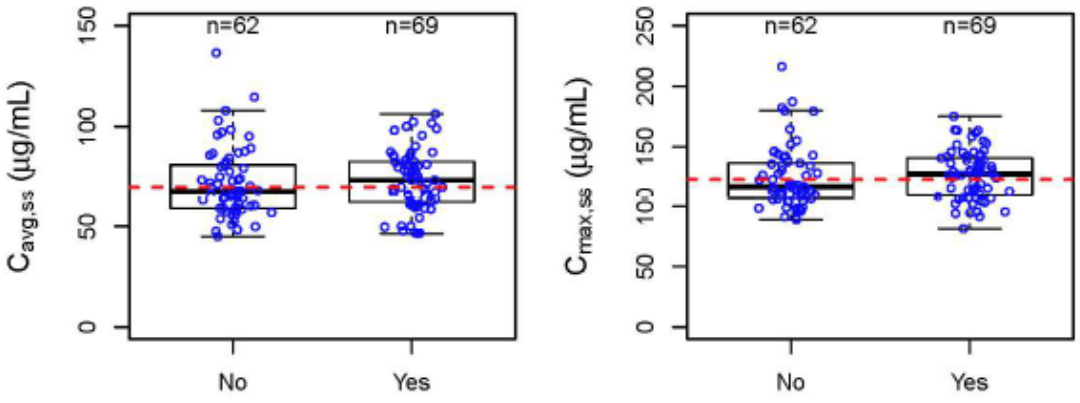
Exposure-safety analysis:

The AESI safety endpoints in Study 309 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

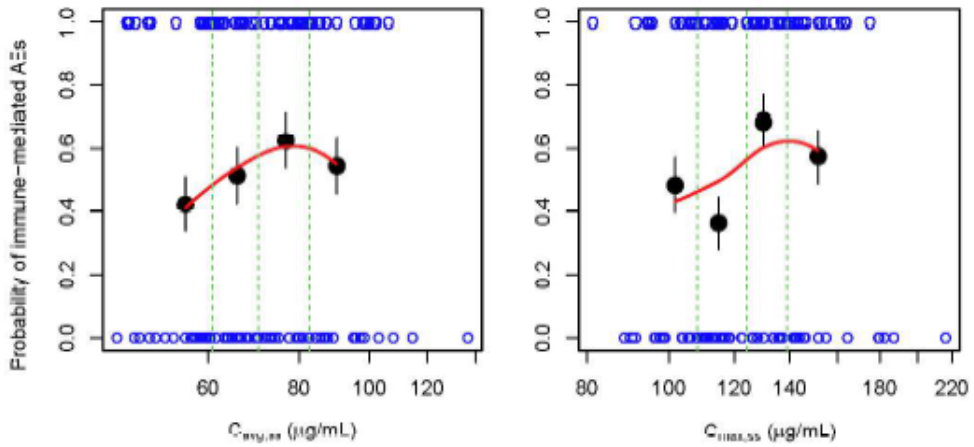
Figure 13-Relationship between exposure and immune-mediated AEs for tislelizumab-treated patients (Study 309)



Open blue circles are the model-predicted exposure. The median is represented by the horizontal black line in the middle of each box. The lower and upper ends of the box plot represent the 25th and 75th percentile (the lower and upper quartiles, respectively). The bars extend to the most extreme data point which is no more than 1.5×IQR from the box. The dashed red horizontal line represents the median value in study BGB-A317-309.

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.

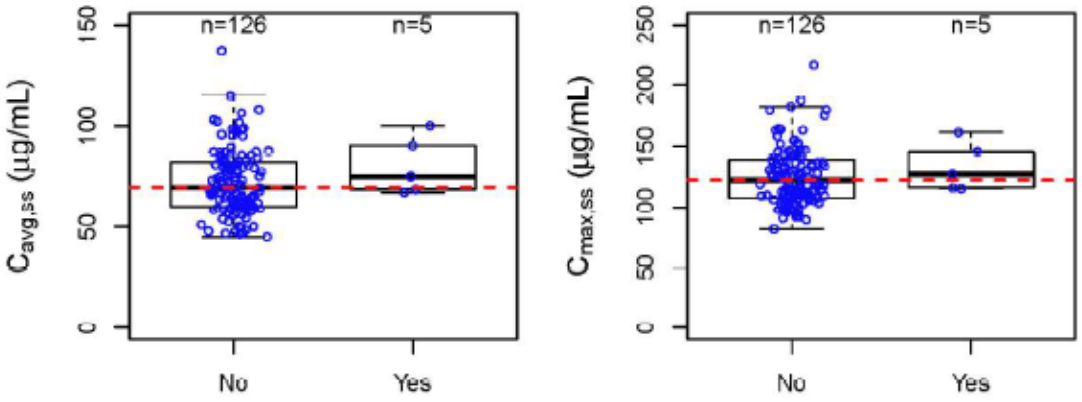
Figure 14-Probability of immune-mediated AEs versus exposure for tislelizumab treated patients (Study 309)



Open blue circles reflect the observed events. The filled black symbols are the observed probability of events and the error bars are SE [sqrt (P*(1-P)/N)] for quantiles (at 100x(1/4)th percentiles, vertical dotted lines) of exposures (plotted at the median value within each quantile), where P is the probability of event and N is the number of patients in each quantile bin. The red lines are smooth curves to show the relationship between two variables.

Infusion-related reactions

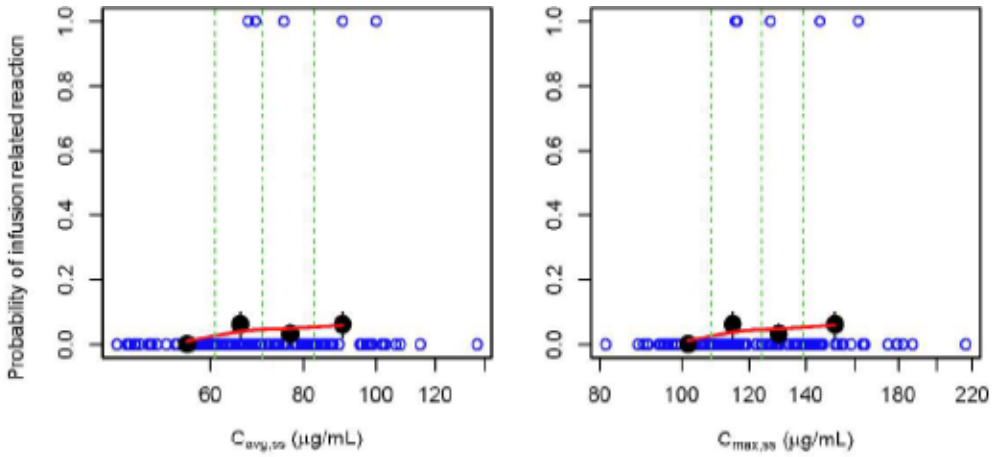
Figure 15-Relationship between exposure and infusion-related reactions (Study 309)



Open blue circles are the model-predicted exposure. The median is represented by the horizontal black line in the middle of each box. The lower and upper ends of the box plot represent the 25th and 75th percentile (the lower and upper quartiles, respectively). The bars extend to the most extreme data point which is no more than 1.5×IQR from the box. The dashed red horizontal line represents the median value in study BGB-A317-309.

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

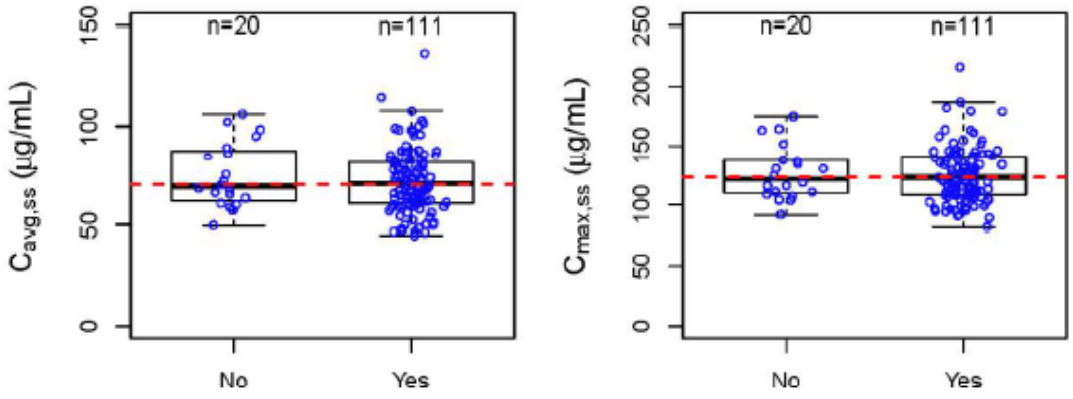
Figure 16-Probability of infusion-related reactions versus tislelizumab exposure (Study 309)



Open blue circles reflect the observed events. The filled black symbols are the observed probability of events and the error bars are SE [sqrt (P*(1-P)/N)] for quantiles (at 100x(1/4)th percentiles, vertical dotted lines) of exposures (plotted at the median value within each quantile), where P is the probability of event and N is the number of patients in each quantile bin. The red lines are smooth curves to show the relationship between two variables.

TEAE with CTCAE grade ≥ 3

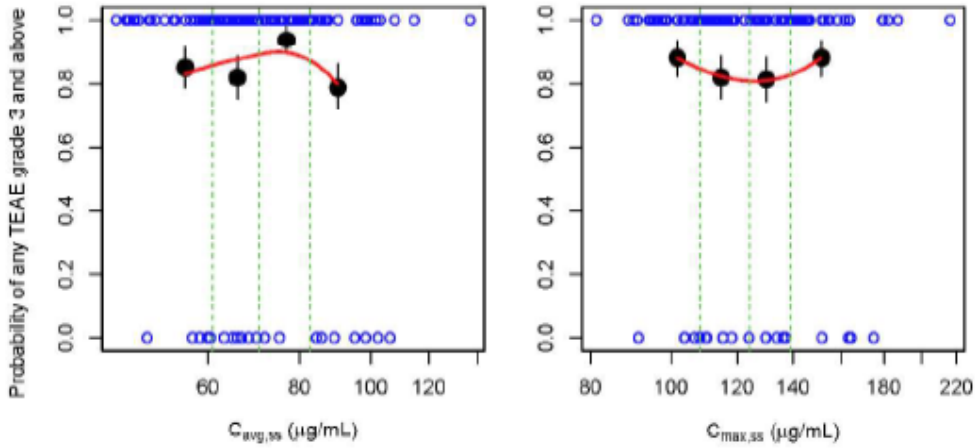
Figure 17-Relationship between exposure and any TEAE grade ≥ 3 for tislelizumab treated patients (Study 309)



Open blue circles are the model-predicted exposure. The median is represented by the horizontal black line in the middle of each box. The lower and upper ends of the box plot represent the 25th and 75th percentile (the lower and upper quartiles, respectively). The bars extend to the most extreme data point which is no more than 1.5×IQR from the box. The dashed red horizontal line represents the median value in study BGB-A317-309.

To further quantify the relationship between exposure and TEAEs with CTCAE grade ≥ 3, logistic regression was conducted to estimate the probability of TEAEs with CTCAE grade ≥ 3 by exposure, as shown below.

Figure 18-Probability of any TEAE grade ≥ 3 versus exposure for tislelizumab treated patients (Study 309)



Open blue circles reflect the observed events. The filled black symbols are the observed probability of events and the error bars are SE [sqrt (P*(1-P)/N)] for quantiles (at 100x(1/4)th percentiles, vertical dotted lines) of exposures (plotted at the median value within each quantile), where P is the probability of event and N is the number of patients in each quantile bin. The red lines are smooth curves to show the relationship between two variables.

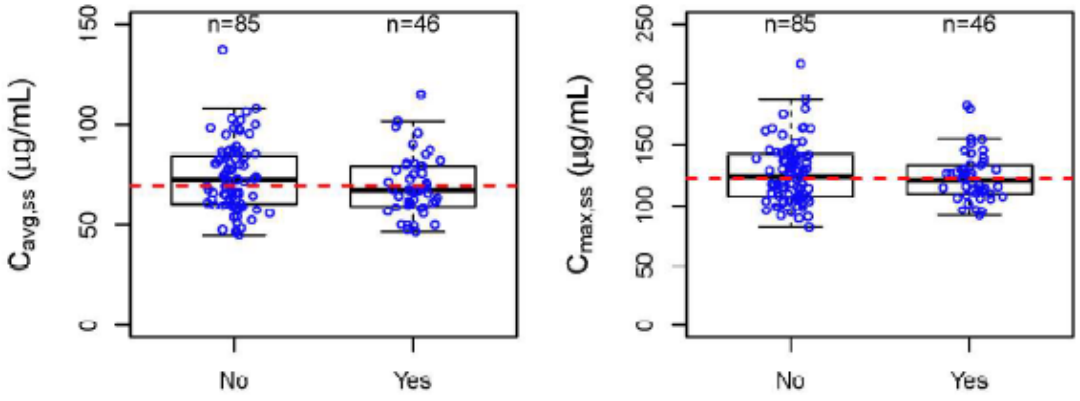
<u>TEAE leading to treatment discontinuation or dose modification of tislelizumab</u>

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).

<u>Serious TEAE</u>

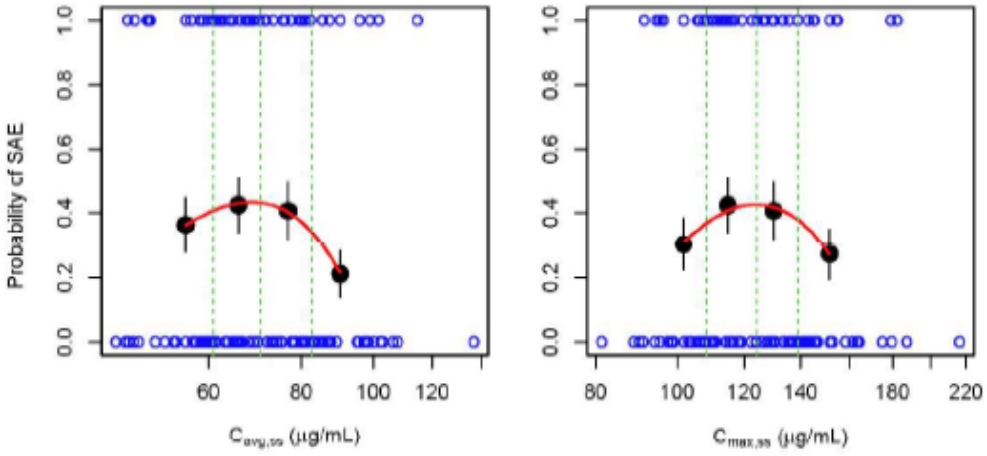
Figure 19-Relationship between exposure and serious TEAEs (Study 309)



Open blue circles are the model-predicted exposure. The median is represented by the horizontal black line in the middle of each box. The lower and upper ends of the box plot represent the 25th and 75th percentile (the lower and upper quartiles, respectively). The bars extend to the most extreme data point which is no more than 1.5×IQR from the box. The dashed red horizontal line represents the median value in study BGB-A317-309.

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.

Figure 20-Probability of serious TEAEs versus tislelizumab exposure (Study 309)



Open blue circles reflect the observed events. The filled black symbols are the observed probability of events and the error bars are SE [sqrt (P*(1-P)/N)] for quantiles (at 100x(1/4)th percentiles, vertical dotted lines) of exposures (plotted at the median value within each quantile), where P is the probability of event and N is the number of patients in each quantile bin. The red lines are smooth curves to show the relationship between two variables.

2.3.5. Discussion on clinical pharmacology

Pharmacokinetics of tislelizumab at the proposed dosing regimen of 200 mg Q3W had already been extensively characterized in previous applications.

In the pivotal study BGB-A317-309 supporting this extension of indication of tislelizumab for 1L treatment of NPC, only sparse PK samples were collected. These data were used for external validation of the predictive performance and robustness of the previously developed population PK model for Study 309. In Study 309 = "PK samples were collected for all randomised patients at sites that were able to adequately perform PK sampling and handling", which implies that there may have been sites without collection of PK samples. The reasons for sites not being able to perform PK sampling and handling have not been specified. Overall, given the size of the PK analysis population, it however seems that all patients have provided PK samples (post-dose Cycle 1 concentrations are available for 131 patients, corresponding to all patients randomised to the tislelizumab + chemotherapy treatment arm). Thus, the validity of PK results is not being put into question.

In general, pre- and post-dose concentrations of tislelizumab in Study 309 were similar to the concentrations reported in previous studies in which tislelizumab was either administered as monotherapy or in combination with chemotherapy. Slightly higher concentrations are noted for pre-dose samples in Cycle 9 and Cycle 17. However, differences in tislelizumab concentrations at these sampling time-points are rather small relative to the overall variability of predose concentrations and are not considered clinically relevant. The means and variability in predicted steady-state exposures after 200 mg or 3 mg/kg once every 3 weeks dosing were nearly identical, supporting the selection of the 200 mg once every 3 weeks flat dose.

The external validation using the data from Study 309 showed that the PopPK model was able to adequately describe the observed PK data from Study 309. The simulated steady state exposure of tislelizumab (Cmaxss, Cminss, AUCss) in Study 309 was comparable to the simulated steady state exposure of tislelizumab in previous studies. The use of the final PopPK model is considered adequate for generation of exposure metrics for subsequent ER analyses.

PK in special populations

In the initial 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. Thus, no dose adjustment is warranted for any of the special subpopulations of patients with NPC or other advanced solid tumours.

Pharmacodynamics

Immunogenicity

In Study 309, the incidence of treatment-emergent ADA (8.8%) was lower than that observed in the Phase 3 monotherapy studies 302 and 303 (14.3% and 16.3%, respectively) as well as in the Phase 3 combination therapy studies 304, 305, 306, and 307 (22.0% to 27.6%). Persistent ADA were detected in 3.2% of patients in Study 309, while no patients were found to be positive for neutralizing ADA (nAb).

The analysis of impact of ADA-positive status on PK revealed reduced exposure of tislelizumab in ADA-positive patients, specifically in one patient with maximum ADA titer (≥320). Similar tendencies have been observed in other tislelizumab combination therapy studies (Study 304, 306 and 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.

However, the analyses of the impact of ADA status on efficacy again reveal also less benefit (response rates and OS) in ADA-positive patients in Study 309. Corresponding analyses in other tislelizumab combination studies (Study 304 and Study 307 in NSCLC, Study 306 in 1L ESCC, Study 312 in SCLC) also indicate a trend towards reduced benefit in patients that were found to be ADA positive. It was discussed that potential imbalances in baseline covariates between the ADA-defined subgroups (i.e. other negative prognostic factors within the tislelizumab arm) could have confounded the comparisons, which is acknowledged. To account for these potential imbalances, a principal stratum method was utilized to provide appropriate controls for each ADA subgroup in Studies 302, 303, 304, 305, 306, 307, 312, and 315. In Study 309, the incidence of ADA was too low to apply the principal stratum analysis approach. Using the principal stratum strategy, the results for the respective primary endpoints used in the studies generally favoured the tislelizumab arm compared to the adjusted control arm in both ADA-positive and ADA-negative subgroups. The 95% CIs for HR estimates largely overlapped for the two ADA subgroups, suggesting likely comparable benefit between the ADA-positive and ADA-negative subgroups of patients.

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 309 (63.6% vs. 30.7%). Similarly, IRRs were observed more frequently in ADA-positive (18.2%) vs. ADA-negative (4.4%) of patients. No increased frequency of imAEs, IRRs, TEAEs with CTCAE grade ≥ 3 and TEAEs leading to dose modification or treatment discontinuation was observed in ADA-positive as compared to ADA-negative patients. Ultimately, the low number of patients determined to be ADA-positive (N=11, 8.8%) in Study 309 needs to be taken into account. It is thus agreed that results of ADA subgroup analyses should be interpreted with caution due to the potential bias in comparing between outcome-driven groups based on post-baseline ADA status and due to the variation arising from the small number of patients in the ADA-positive subgroup.

In the integrated analysis of immunogenicity (including also Study 315), it was further noted that the previously identified signal of higher incidence of TEAEs ≥ grade 3 and serious TEAEs in the ADA-

positive as compared to the ADA-negative population seems less pronounced with the larger database of combination studies (TEAEs ≥ grade 3 80.0% vs. 78.6%, SAEs 43.3% vs. 41.0%). During the initial MAA procedure, higher ADA incidence rates were observed in White vs. Asian patients and patients from Europe/North America vs. Asia, while there was uncertainty regarding a potential differential impact of ADA positivity in race or region subgroups. Back then, no definitive conclusions could be drawn due to the limited size of the database and imbalances in the number of patients in different subgroups. Referring to this matter, the Applicant was further asked to discuss whether differences in ethnicity (with the last studies being China-only studies) may have contributed to the approximation of the ADA impact on safety in ADA-positive vs. ADA-negative patients. In response, the Applicant provided data on treatment-emergent AEs by ADA status, further divided by subgroups of ethnicity (White vs. Asian) and region (Europe/North America vs. Asia). In the tislelizumab combination therapy studies, with the last studies being Asia-only studies, it is obvious that the rates of TEAEs Grade ≥3 and serious TEAEs are similar between ADA-positive and ADA-negative patients in the Asian population (Asian: TEAEs Grade ≥3: 80.1% vs. 79.9%, serious TEAEs: 42.3% vs. 40.9%; Asia: TEAEs Grade ≥3: 80.1% vs. 79.9%, serious TEAEs: 42.3% vs. 40.9), while TEAE rates were different in ADA-positive vs. ADA-negative patients in the White/European population (White: TEAEs Grade ≥3: 78.8% vs. 68.5%, serious TEAEs: 51.5% vs. 40.0%; Europe/NA: TEAEs Grade ≥3: 78.4% vs. 67.8%, serious TEAEs: 54.1% vs. 42.5%). Conclusively, the differences initially observed (and still indicated in the subgroup of White patients and patients from Europe/NA) are less pronounced in the overall population of tislelizumab combination therapy studies. However, the sample size of the subgroups by ADA status in the White/European population is too low to draw reliable conclusions on a potential differential impact of ADA positivity in race or region subgroups.

Exposure-response analyses

The initial PopPK model was used as basis for analyses of the exposure-efficacy and exposure-safety relationship for tislelizumab. Data from 131 patients who had at least one adequately documented tislelizumab administration and a corresponding efficacy or safety measurement after the dose received were utilized.

OS, PFS and ORR 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 of Study 309, KM plots for OS and PFS stratified by PopPK predicted Cavg,dose1 quartiles revealed longer PFS and OS in the higher tislelizumab exposure quartile(s). However, subsequent Cox proportional-hazards model analyses showed that Cavg.dose1 ($p > 0.05$) was not a significant predictor for PFS or OS. In case of ORR, predicted exposures of patients were similar between responders vs. non-responders.

No consistent, clinically relevant E-R relationship was observed between tislelizumab exposure and the probability of experiencing any TEAE grade ≥ 3, immune-mediated AEs, IRRs, TEAEs leading to treatment discontinuation, TEAEs leading to dose modification, and serious TEAEs.

2.3.6. Conclusions on clinical pharmacology

Pharmacokinetics and pharmacodynamics of tislelizumab have been sufficiently characterized. Results from the pivotal study BGB-A317-309 supporting this extension of indication are overall consistent with the analyses provided in previous applications.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

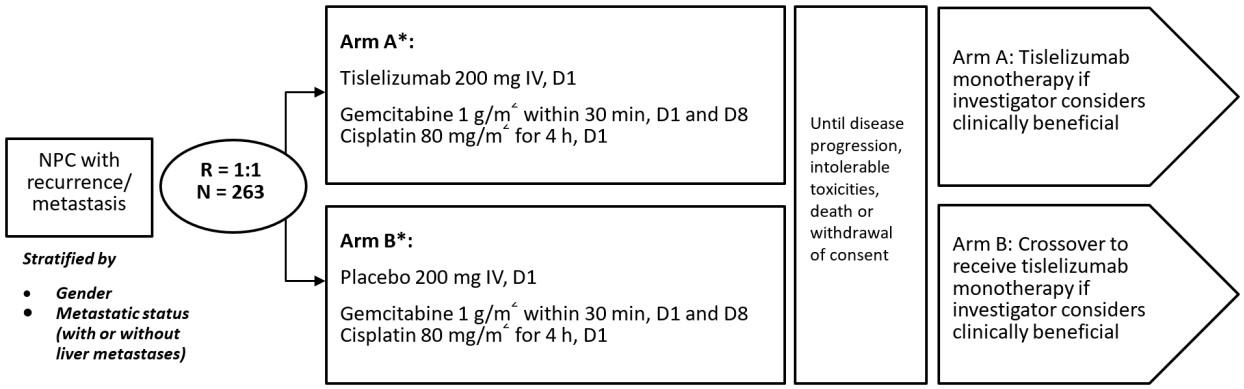
The approved fixed dose regimen of 200 mg IV Q3W was used for tislelizumab in the pivotal study. No additional dose selection studies were performed for this submission.

A Phase 3, multicentre, double-blind, randomised, placebo-controlled study to compare the efficacy and safety of tislelizumab (BGB-A317) combined with gemcitabine plus cisplatin versus placebo combined with gemcitabine plus cisplatin as first-line treatment for recurrent or metastatic nasopharyngeal cancer.

2.4.2. Main study

Methods

Figure 21-*Study Design – Study 309*



A total of 263 patients were randomised; 131 patients were randomised to tislelizumab in combination with gemcitabine + cisplatin and 132 patients were randomised to placebo in combination with gemcitabine + cisplatin.

For patients in placebo + GC arm, crossover to monotherapy with tislelizumab after IRC confirmed disease progression was allowed. At the discretion of the investigator, patients who received tislelizumab could be treated beyond disease progression under protocol defined conditions.

Regular safety monitoring was performed by an IDMC, which also reviewed the pre-planned efficacy interim analysis.

Tumour imaging was performed every 6 weeks (± 7 days) for the first 6 months, every 9 weeks (± 7 days) for the remainder of Year 1, and every 12 weeks (± 7 days) from Year 2 onwards. Responses were assessed by the IRC and by the investigator using RECIST v1.1. The PRO assessments were performed using the EORTC QLQ-C30 and EORTC QLQ H&N35 at baseline, every other cycle through Cycle 12, then every 4 cycles thereafter while on treatment, and at the end of treatment. Survival follow-up was conducted approximately every 3 months after the Safety Follow-up Visit.

Study participants

Key inclusion criteria

- Aged between 18 to 75 years on the day of signing the informed consent form
- Histological or cytological confirmation of NPC with recurrence or metastasis
- ECOG PS ≤ 1
- Treatment-naive for recurrent or metastatic NPC
- Patients who had received prior neoadjuvant, adjuvant chemotherapy, radiotherapy, or chemoradiotherapy with curative intent for nonmetastatic disease must have experienced a treatment-free interval of ≥ 6 months from the last dose of chemotherapy and/or radiotherapy prior to randomisation
- Patients who had received prior neoadjuvant chemotherapy regimen for < 4 cycles
- Life expectancy ≥ 12 weeks
- Adequate organ function as indicated by the following laboratory values obtained ≤ 7 days before randomisation:
    - Absolute neutrophil count ≥ 1.5 x 10^9/L
    - Platelets ≥ 100 x 10^9/L
    - Hemoglobin ≥ 90 g/L.
    - INR or PT ≤ 1.5 x ULN, aPTT ≤ 1.5 x ULN
    - Serum total bilirubin ≤ 1.5 x ULN (total bilirubin must be < 3 x ULN for patients with Gilberts syndrome)
    - AST and ALT ≤ 2.5 x ULN or AST and ALT ≤ 5 x ULN for patients with liver metastases
    - Serum creatinine ≤ 1.5 x ULN or estimated GFR ≥ 60 mL/min/1.73 m^2
- Willing to use highly effective method of birth control through ≥ 120 days after the last dose of study treatment

Key exclusion criteria

- Local recurrence suitable for curative surgery or radiotherapy
- Received any approved systemic anticancer therapy, including hormonal therapy, within 28 days prior to the initiation of study treatment
- Prior treatment with PD-1 or PD-L1 therapy
- Active leptomeningeal disease or uncontrolled, untreated brain metastasis
    - *Note:* Patients with a history of treated and, at the time of screening, asymptomatic CNS metastases are eligible
    - *Note:* Patients with new asymptomatic CNS metastases detected at the screening scan must have received radiation therapy and/or surgery for CNS metastases
- Active autoimmune diseases or history of autoimmune diseases that may relapse
- With a history of interstitial lung disease, non-infectious pneumonitis, or uncontrolled systemic diseases, including pulmonary fibrosis, acute lung diseases, hypertension, etc.
- Severe chronic or active infections requiring systemic antibacterial, antifungal, or antiviral therapy within 2 weeks before randomisation

- Patients with cardiovascular risk factors such as cardiac chest pain or symptomatic pulmonary embolism ≤ 28 days before randomisation, history of acute myocardial, heart failure (NYHA III or IV), ventricular arrhythmia ≥ Grade 2, or cerebrovascular accident ≤ 6 months before randomisation
- Prior allogeneic stem cell transplantation or organ transplantation

Treatments

Table 13-Selection and Timing of Dose for Each Patient

Study drug	Dose	Frequency of administration	Route of administration
Tislelizumab or placebo	200 mg	Day 1 of each cycle	Intravenous infusion
Gemcitabine	1 g/m^2	Day 1 and Day 8 of each cycle	
Cisplatin	80 mg/m^2	Day 1 of each cycle	

Chemotherapy was administered on a 3-week cycle.
The number of treatment cycles (4 to 6) was at the discretion of the investigator.

Tislelizumab 200 mg was administered on Day 1 of each 21-day cycle once every 3 weeks by intravenous infusion delivered over 60 minutes; if it was well-tolerated, subsequent infusions could be administered over 30 minutes.

For each cycle, tislelizumab or placebo was administered before chemotherapy drugs.

Chemotherapy was given for 4 – 6 cycles at the investigator's discretion. Handling and administration of gemcitabine and cisplatin was in accordance with relevant local guidelines and/or prescribing information.

Study treatment could continue until documented disease progression per RECIST v1.1, loss of clinical benefit as assessed by the investigator, withdrawal of consent, study termination by sponsor, start of a new anticancer therapy, or death, whichever occurred first.

Objectives

Primary objective

- To compare progression-free survival (**PFS**) as assessed by the Independent Review Committee (IRC) per RECIST v1.1 in the ITT Analysis Set between tislelizumab combined with gemcitabine + cisplatin and placebo + gemcitabine + cisplatin in patients with recurrent or metastatic NPC.

Secondary objectives

- To compare objective response rate (**ORR**) as assessed by the IRC per RECIST v1.1 between tislelizumab combined with gemcitabine + cisplatin and placebo + gemcitabine + cisplatin.
- To compare duration of response (**DOR**) as assessed by the IRC per RECIST v1.1 between tislelizumab combined with gemcitabine + cisplatin and placebo + gemcitabine + cisplatin.
- To compare overall survival (**OS**) between tislelizumab combined with gemcitabine + cisplatin and placebo + gemcitabine + cisplatin in the ITT Analysis Set.

- To compare **PFS** as assessed by the investigator per RECIST v1.1 between tislelizumab combined with gemcitabine + cisplatin and placebo + gemcitabine + cisplatin in the ITT Analysis Set.
- To evaluate the PFS after the next line of treatment (**PFS2**) as assessed by the investigator per RECIST v1.1.
- To compare health-related quality of life (**HRQo**L) between tislelizumab combined with gemcitabine + cisplatin and placebo + gemcitabine + cisplatin.
- To evaluate the **safety and tolerability** of tislelizumab combined with gemcitabine + cisplatin compared with placebo + gemcitabine + cisplatin.

Exploratory Objectives

- To compare **ORR** as assessed by the investigator per RECIST v1.1 between tislelizumab combined with gemcitabine + cisplatin and placebo + gemcitabine + cisplatin.
- To compare **DOR** as assessed by the investigator per RECIST v1.1 between tislelizumab combined with gemcitabine + cisplatin and placebo + gemcitabine + cisplatin.
- To compare tumour assessment outcomes (eg, disease control rate [**DCR**], time to response [**TTR**]) between tislelizumab combined with gemcitabine + cisplatin and placebo + gemcitabine + cisplatin assessed by the investigator per RECIST v1.1.
- To evaluate the correlation between **PD-L1 expression** levels by immunohistochemistry and antitumour activity of tislelizumab combined with gemcitabine + cisplatin compared with placebo + gemcitabine + cisplatin.
- To assess tumour and blood-based **biomarkers** of tislelizumab response, resistance, and patient prognosis. To explore potential predictive biomarkers including any association with response to study treatment and mechanism(s) of resistance.
- To characterize the **PK** of tislelizumab when given in combination with gemcitabine + cisplatin.
- To assess **immunogenicity** against tislelizumab.

Outcomes/endpoints

Primary efficacy endpoint

The primary efficacy endpoint was **IRC-assessed PFS** in the ITT Analysis Set, which was defined as the time from randomisation to the first objectively documented disease progression as assessed by the IRC with the use of RECIST v1.1 or death from any cause, whichever occurred first.

Secondary efficacy endpoints

OS was defined as the time from randomisation to death from any cause.

PFS per the investigator was defined as the time from randomisation to the first objectively documented disease progression or death from any cause, whichever occurred first, as determined per RECIST v1.1 in the ITT Analysis Set.

ORR was the proportion of patients who had CR or PR as assessed **by the IRC** per RECIST v1.1 in the ITT Analysis Set.

DOR per the IRC was defined as the time from the first documented objective response to documented disease progression as assessed by the IRC using RECIST v1.1 or death from any cause, whichever occurred first.

PFS2 per the investigator, defined as the time from randomisation to second/subsequent disease progression after initiation of new anticancer therapy or death from any cause, whichever occurred first.

HRQoL analyses: global health status/quality of life (GHS/QoL), functional/symptom scales of QLQ-C30 and the symptom scales and index score of H&N35.

Exploratory efficacy endpoints

ORR and DOR per the investigator

Disease Control Rate (DCR) per the Investigator was defined as the proportion of patients with objective response (CR or PR) or SD maintained for ≥ 6 weeks as assessed by the investigator using RECIST v1.1.

Time to response (TTR) was defined as the time from randomisation to the first occurrence of a CR or PR as assessed by the investigator using RECIST v1.1.

PD-L1 expression level was examined in the ITT Analysis Set. Applicable association between PD-L1 expression and treatment effect in PFS per IRC was explored.

Distribution of **EBV DNA level** was examined in the ITT Analysis Set. Applicable association between EBV DNA level and treatment effect in PFS per IRC was explored.

Biomarker

PD-L1 expression was determined on tumour cells by central IHC analysis using the VENTANA PD-L1 (SP263) assay.

Sample size

The sample size calculation was based on the number of PFS events required to demonstrate the PFS superiority of Arm A to Arm B in the ITT Analysis Set. Exponential distribution was assumed for PFS. The estimates of the number of events required to demonstrate superior efficacy with regards to PFS were based on the following assumptions:

1. Median PFS of 7 months in Arm B

2. At a 1-sided α of 0.025, 82% power to detect a difference, assuming an HR of 0.65, corresponding to an improvement in median PFS from 7 months to 10.8 months, in the PFS of Arm A versus Arm B comparison

3. Randomisation ratio: 1:1

4. PFS evaluation dropout rate of 5% per 12 months

5. A steady-state enrolment rate of 20 patients per month and enrolment ramp-up duration of 3 months, i.e., enrolment rate of 5 patients per month from study month 0 to month 1, 10 patients per month from month 1 to 2, 15 patients per month from month 2 to month 3, and 20 patients per months afterwards.

6. One interim analysis was planned when approximately 70% of total PFS events occurred, with Lan-DeMets O'Brien-Fleming approximation spending function

With these assumptions, a total of 181 PFS events were planned to be required for final analysis of PFS and an interim analysis was planned to be performed when approximately 127 PFS events will have been observed.

It was planned that 256 patients were to be enrolled over a 14.3-month period, and that the final analysis would then occur approximately 21.5 months after the first patient was randomised

Randomisation

Patients were randomised in a 1:1 ratio and treated with either tislelizumab combined with gemcitabine + cisplatin (Arm A) or placebo combined with gemcitabine + cisplatin (Arm B) using an interactive response technology (IRT) system by permuted block stratified randomisation per the following stratification factors: gender (male versus female) and liver metastases (yes versus no).

Blinding (masking)

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

Statistical methods

Analysis Populations/Sets

The intent-to-treat (ITT) analysis set was planned to include all randomised patients. Patients were planned to be analysed according to their randomised treatment arms. This was planned to be the primary analysis set for all efficacy analysis, including analyses of PFS and OS endpoints.

Per-Protocol analysis set (PP) was planned to include patients in the ITT analysis set who had no critical protocol deviations. Critical protocol deviations were defined as a subset of major protocol deviations impacting efficacy analysis. Criteria for exclusion from the PP were planned to be determined and documented before the database lock for the primary analysis. This was planned to be the secondary analysis set for efficacy analysis when there are over 10% ITT patients who had critical protocol deviations.

Primary Endpoint(s) / Primary Estimand(s)

PFS per the IRC was defined as the time from randomisation to the first documented disease progression as assessed by the IRC with the use of RECIST v1.1, or death from any cause, whichever occurs first. The actual tumour assessment visit date will be used to calculate PFS. Data for patients without disease progression or death at the time of analysis were planned to be censored at the time of the last valid tumour assessment. Data for patients without postbaseline tumour assessment were planned to be censored at the time of randomisation. Data for patients who start to receive new anticancer therapy or are lost to follow-up were planned be censored at the last valid tumour assessment date prior to the introduction of new therapy or loss to follow-up.

PFS per the IRC was planned to be compared between tislelizumab + gemcitabine + cisplatin (Arm A) and placebo + gemcitabine + cisplatin (Arm B) at a 1-sided α of 2.5% using stratified log-rank test methodology. The hypothesis test was planned to be formed as follows:

The null hypothesis to be tested is: H0: PFS in Arm A ≤ PFS in Arm B

Against the alternative hypothesis: Ha: PFS in Arm A > PFS in Arm B

The p-value from a stratified log-rank test was planned to be presented using stratification factors with actual values as recorded in the electronic data capture (EDC) system at randomisation. The median PFS was planned to be calculated for each treatment arm and presented with two-sided 95% CIs. Kaplan-Meier survival probabilities for each arm were planned to be plotted over time. The HR for PFS was planned to be estimated using a stratified Cox regression model, with treatment arm as a factor and stratified by the actual value of the stratification factors as recorded in eCRF. The 95% CI for the HR was planned to be provided. Unstratified analysis was also planned to be presented for descriptive purposes.

Sensitivity Analyses for Primary Endpoint

In order to evaluate the robustness of the analysis of PFS per IRC, it was planned to perform possible sensitivity analyses with different censoring rules if the number of patients with censor reason would be greater than or equal to 5% of patients in the ITT analysis set. If the patient met multiple situations in Appendix 10.1 of the Statistical Analysis Plan (SAP), the censor reason was planned to be the earliest situation.

The sensitivity analysis 1 was planned to be the same as the primary analysis except that it progressed at date of documented progression with protocol specified continued follow-up in all treatment arms or died at date of death whichever was earlier when new anticancer therapy was started.

The sensitivity analysis 2 was planned to be the same as the primary analysis except that it progressed at date of documented progression or died at date of death whichever is earlier after 2 missed tumour assessment.

When there would be over 10% ITT patients who had critical protocol deviations, sensitivity analysis 3 in PP analysis set was planned to be implemented using primary PFS censoring rule.

Sensitivity analysis 4 in ITT analysis set was planned to be implemented using primary PFS censoring rule when randomisation error in stratification factor from IWRS was high.

If necessary, restricted mean survival time (RMST) was planned to be performed to account for the possible non-proportional hazard effects.

Secondary Endpoints / Secondary Estimand(s)

Objective Response Rate per the IRC

ORR (confirmation not required according to RECIST v1.1) was defined as the proportion of patients who had a CR or PR as assessed by the IRC per RECIST v1.1 in all randomised patients with measurable disease at baseline. Patients without any postbaseline assessment were planned to be considered non-responders. The difference in ORR between Arm A and Arm B in the ITT analysis set was planned to be evaluated using the Cochran-Mantel-Haenszel chi-square test with the actual stratification factors as strata. The two-sided 95% CIs for the odds ratio and the difference in ORR were planned to be calculated, as well as Clopper-Pearson 95% CIs for the ORR within each arm.

Duration of Response per the IRC

DOR per the IRC is defined as the time from the first documented objective response to documented disease progression as assessed by the IRC using RECIST v1.1, or death from any cause, whichever occurs first. Data for patients who are alive and who have not experienced disease progression at the time of analysis were planned to be censored at the date of the last tumour assessment. If no tumour assessments were performed after the date of the first occurrence of the objective response (CR or PR), DOR was planned to be censored at the date of the first occurrence of the objective response. DOR was planned to be estimated using Kaplan-Meier methodology. Comparison between Arm A and Arm B was planned to be made using the stratified and unstratified log-rank test for descriptive purposes only.

Overall Survival

OS is defined as the time from randomisation to death from any cause. Data for patients who are not reported as having died at the time of analysis were planned to be censored at the date last known to be alive. Data for patients who do not have postbaseline information were planned to be censored at the date of randomisation. Similar methodology used to evaluate PFS per the IRC was planned to be applied to OS analysis.

Based on the 08 December 2023 data cut-off, 2 (not pre-specified) supportive analyses were conducted to assess the impact of crossover on the OS results using two model-based approaches:

- The rank-preserving structural failure time (RPSFT) model (Robins and Tsiatis 1991) estimated the shrink parameter by creating the counterfactual survival time to the portion of survival time when the patient was receiving tislelizumab during the crossover period, with the assumption that the counterfactual survival times are balanced between 2 treatment groups in the absence of treatment effect. The re-censoring approach was implemented to break the dependence between the censoring time and treatment received. The estimated shrink parameter reflects the degree of adjustment to patients' survival time after receiving tislelizumab during the crossover. The counterfactual survival time of patients in the control arm (placebo + GC) who crossed over to receive tislelizumab and the observed survival time for other patients were then fitted into a Cox proportional hazard model; with treatment arm being the only covariate
- The two-stage method (Latimer et al 2014) was also performed to estimate the in-study crossover effect on the post-progression survival using data from patients who progressed per IRC assessment before any subsequent anticancer therapy in the control arm only. The shrink parameter was estimated and indicated the survival time following progression. For patients in the placebo + GC arm with disease progression, baseline risk factors (age, sex, liver metastases, ECOG PS, EBV-DNA, smoking status), and the time of disease progression were fitted in an accelerated failure time model to estimate the effect of crossover. A counterfactual survival time was then derived for patients in the placebo + GC arm who crossed over to receive tislelizumab, which was based on the time to disease progression and post-progression survival and was adjusted for the crossover effect estimated from the accelerated failure time model. The re-censoring approach was implemented to break the dependence between censoring time and the treatment received. The stratified HR based on the counterfactual survival time of patients in the placebo + GC arm who crossed over to receive tislelizumab and the observed survival times in the rest of the patients were estimated from a Cox proportional hazard model.

Progression-Free Survival per the Investigator

PFS per the investigator was defined as the time from randomisation to the first objectively documented disease progression, or death from any cause, whichever occurs first, as determined per RECIST v1.1 in an ITT analysis set. Similar methodology used to evaluate PFS per the IRC was planned to be applied to analysis of PFS per the investigator.

Interim Analyses

It was planned to perform one interim efficacy analysis of PFS in the ITT analysis set. The interim efficacy analysis was planned to be performed when approximately 127 PFS events (70% of the target number of 181 PFS events) are observed. It was estimated that it would take approximately 15.6 months to reach time of interim analysis. The interim boundary for each comparison was based on Lan-DeMets O'Brien-Fleming approximation spending function. The interim and final analysis timing, and stopping boundaries are summarized in Table 14 below.

Table 14-Analysis timing and stopping boundaries for PFS in each of the primary tests at a 1-sided α=0.025

Type of analysis	Time (months)	Number of events	Testing boundary	
			P-value boundary	Approximate hazard ratio threshold
Interim analysis	15.6	127	0.007	0.649
Final analysis	21.5	181	0.023	0.743

Subgroup Analyses

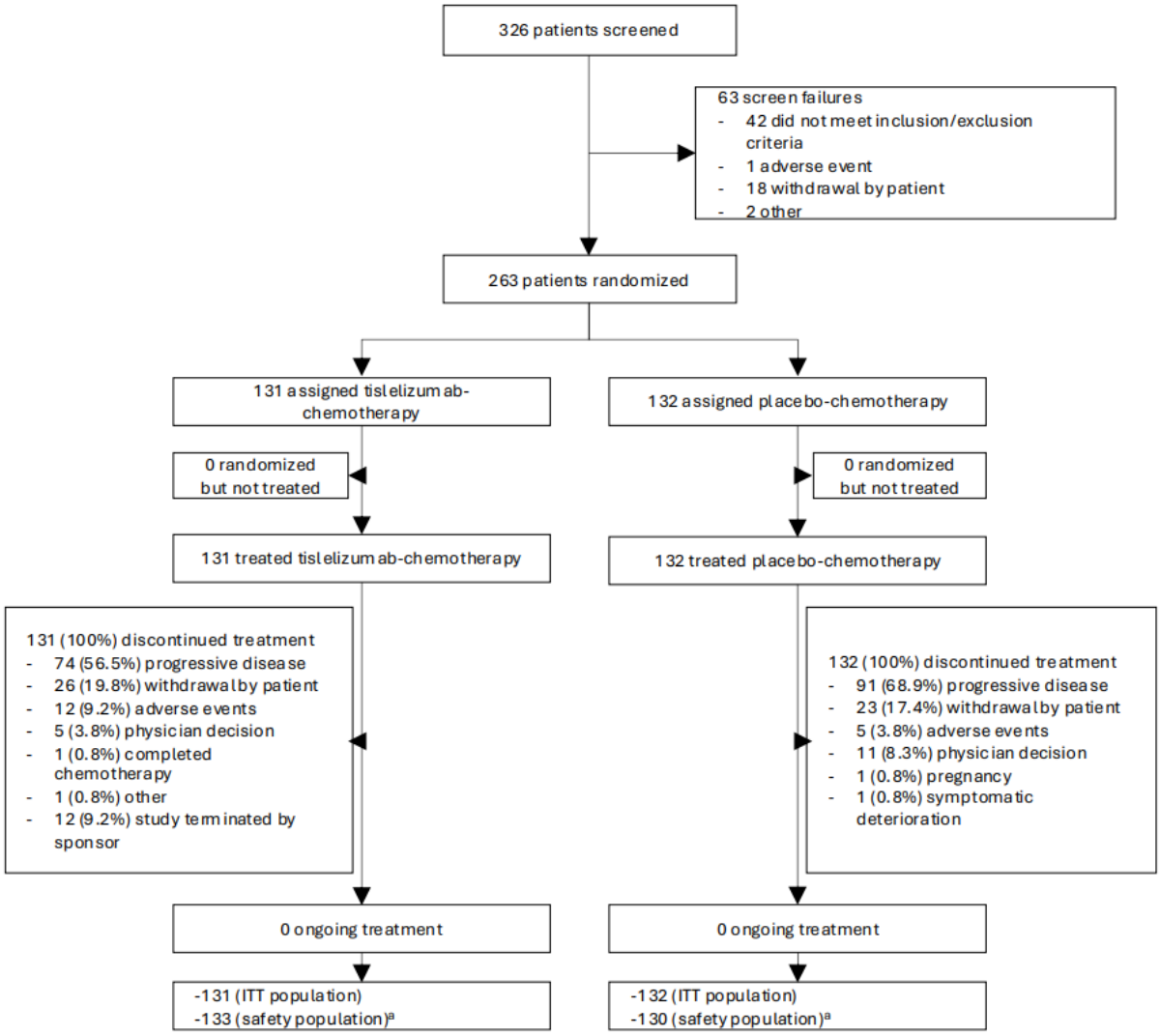
Subgroup analyses of the primary endpoint PFS per the IRC were planned to be conducted to determine whether the treatment effect is consistent across various subgroups, and the HR estimates of PFS and its 95% CI were planned to be estimated and plotted within each category of the following variables: metastatic status (liver versus other organ), ECOG performance status (0 versus 1), age (≤ 65 versus > 65 years), gender (female versus male), smoking status (former versus current versus never), etc.

Results

Participant flow

A total of 263 eligible patients were randomised 1:1 to tislelizumab plus chemotherapy (Arm Tisle+GC, 131 patients) or placebo plus chemotherapy (Arm P+GC, 132 patients). All patients received ⩾ 1 dose of assigned study treatment.

Figure 22-Patient Disposition Study 309



Data cutoff: December 8, 2023. All percentages are calculated based on n=131 for tislelizumab-chemotherapy and n=132 for placebo-chemotherapy arms. a For the safety analysis set, 2 patients initially randomized to the placebo-chemotherapy arm but who erroneously received 100 mg tislelizumab were included in the tislelizumab-chemotherapy arm. ITT, intention-to-treat.

Most patients had discontinued from study treatment prior to the study end date.

As of the 26 March 2021 IA data cutoff, 5 patients (3.8%) continued tislelizumab treatment beyond disease progression in Arm Tisle+GC and 51 patients (38.6%) in Arm P+GC crossed over to receive tislelizumab monotherapy after disease progression.

As of the study end date of 08 December 2023, 49 patients (18.6%) had discontinued study treatment because of "withdrawal by subject". The specific reasons for these withdrawals were not collected in the study database. To better understand the potential underlying reasons for patient withdrawal, a retrospective exploration based on both data on file and medical records was performed to explore any chronological events potentially related to treatment withdrawal. Among these 49 patients:

- 10 patients (20.4%), 3 in Arm Tisle+GC and 7 in Arm P+GC, experienced investigator-assessed disease progression and decided to end study treatment prior to disease progression confirmation by IRC. All these cases would have been assessed as progressive disease if patients had agreed to wait a bit longer for the blinded independent review assessment of tumour scans.
- 5 patients (10.2%) in Arm Tisle+GC achieved objective responses with the earliest response

observed at Week 6 and the responses lasting until Week 99 to Week 219 (corresponding to 23 to 51 months) and had not progressed prior to study treatment discontinuation, as assessed by investigators. It is worth noting that while there was no treatment cap for tislelizumab in Study 309, it is common practice in clinical trials, as well as in the real world, to treat cancer patients with ICIs for up to 2 years, particularly in cases like these where long-term treatment benefit has been achieved. Among these 5 patients, 2 concurrently discontinued study treatment and permanently withdrew from the study, while 3 patients remained on study and continued to provide survival follow-up information after treatment discontinuation.

- 1 patient (2.0%) in Arm Tisle+GC decided to withdraw due to an adverse event of creatinine increased related to cisplatin that did not recover by the end of treatment, per medical records.
- 1 patient (2.0%) in Arm P+GC received a herbal anticancer treatment (listed as ground for treatment discontinuation, per Study 309 Protocol Section 3.6.1) and had early withdrawal on Study Day 56.
- The remaining 32 patients (65.3%) withdrew for reasons not captured in the study database (which was assessed as patient decision); however, 23 of these 32 patients (71.9%) agreed to provide further survival information after permanent treatment discontinuation.

Table 15-Patient Disposition and Reasons for Discontinuation (ITT) – Study 309

	IA			Closeout		
	Tislelizumab + Chemotherapy (N = 131) n (%)	**Placebo + Chemotherapy (N = 132) n (%)**	**Total (N = 263) n (%)**	**Tislelizumab + Chemotherapy (N = 131) n (%)**	**Placebo + Chemotherapy (N = 132) n (%)**	**Total (N = 263) n (%)**
Number of Patients Randomised	131 (100.0)	132 (100.0)	263 (100.0)	131 (100.0)	132 (100.0)	263 (100.0)
Patients Randomised, but not Treated	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Number of Patients Treated	131 (100.0)	132 (100.0)	263 (100.0)	131 (100.0)	132 (100.0)	263 (100.0)
Number of Patients Discontinued from All Study Drugs	68 (51.9)	95 (72.0)	163 (62.0)	131 (100.0)	132 (100.0)	263 (100.0)
Primary Reason for Treatment Discontinuation [a]						
Progressive disease	36 (27.5)	63 (47.7)	99 (37.6)	74 (56.5)	91 (68.9)	165 (62.7)
Withdrawal by subject	20 (15.3)	20 (15.2)	40 (15.2)	26 (19.8)	23 (17.4)	49 (18.6)
Adverse event	8 (6.1)	5 (3.8)	13 (4.9)	12 (9.2)	5 (3.8)	17 (6.5)
Physician decision	2 (1.5)	5 (3.8)	7 (2.7)	5 (3.8)	11 (8.3)	16 (6.1)
Study terminated by sponsor	NA	NA	NA	12 (9.2)	0 (0.0)	12 (4.6)
Complete chemotherapy	1 (0.8)	0 (0.0)	1 (0.4)	1 (0.8)	0 (0.0)	1 (0.4)
Pregnancy	0 (0.0)	1 (0.8)	1 (0.4)	0 (0.0)	1 (0.8)	1 (0.4)
Symptomatic deterioration	0 (0.0)	1 (0.8)	1 (0.4)	0 (0.0)	1 (0.8)	1 (0.4)
Lost to follow-up	1 (0.8)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.4)
Number of Patients Remained on Treatment	63 (48.1)	37 (28.0)	100 (38.0)	0 (0.0)	0 (0.0)	0 (0.0)
Number of Patients Discontinued from Study	27 (20.6)	29 (22.0)	56 (21.3)	131 (100.0)	132 (100.0)	263 (100.0)
Primary Reason for Study Discontinuation						
Death	18 (13.7)	16 (12.1)	34 (12.9)	57 (43.5)	66 (50.0)	123 (46.8)
Study terminated by sponsor	NA	NA	NA	51 (38.9)	41 (31.1)	92 (35.0)
Withdrawal by subject	6 (4.6)	12 (9.1)	18 (6.8)	15 (11.5)	20 (15.2)	35 (13.3)
Lost to follow-up	3 (2.3)	1 (0.8)	4 (1.5)	7 (5.3)	5 (3.8)	12 (4.6)
Other	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.4)
Number of Patients Remained on Study	104 (79.4)	103 (78.0)	207 (78.7)	0 (0.0)	0 (0.0)	0 (0.0)
Study Follow-up Time (months) [b]						
n	131	132	263	131	132	263

	IA			Closeout		
	Tislelizumab + Chemotherapy (N = 131) n (%)	**Placebo + Chemotherapy (N = 132) n (%)**	**Total (N = 263) n (%)**	**Tislelizumab + Chemotherapy (N = 131) n (%)**	**Placebo + Chemotherapy (N = 132) n (%)**	**Total (N = 263) n (%)**
Mean (SD)	10.81 (4.584)	10.27 (4.359)	10.54 (4.472)	29.21 (15.210)	25.43 (15.109)	27.31 (15.249)
Median	10.25	9.77	10.02	33.25	25.00	27.50
Min, Max	0.3, 23.3	0.1, 20.9	0.1, 23.3	0.3, 52.4	0.1, 53.0	0.1, 53.0

Data cutoff: IA-26Mar2021; Closeout (refers to the data cutoff of the final CSR) -08DEC2023. Data extraction: IA-29Apr2021; Closeout-26JAN2024.
Abbreviations: NA, Not Applicable.
Tislelizumab + Chemotherapy: tislelizumab in combination with gemcitabine plus cisplatin.
Placebo + Chemotherapy: placebo in combination with gemcitabine plus cisplatin.
[a] Primary reason for treatment discontinuation referred to primary reason of study drug which discontinued last.
[b] Study follow-up time is defined as the time from the randomisation date to date of death or end of study date (whichever occurs first) for patient discontinued from the study or the database cutoff date for ongoing patients.
No patient had treatment/study discontinuation related to COVID-19.

Overall, 69/132 patients (52.3%) in placebo + GC arm crossed over to receive tislelizumab monotherapy after disease progression confirmed by the IRC. The most common reason for treatment discontinuation after crossover was radiographic disease progression (72.5%).

Table 16-Patient Disposition and Reasons for Discontinuation (Crossover Analysis Set) – Study 309 (DCO: 08 Dec 2023)

	Tislelizumab (N = 69) n (%)
Number of Patients Treated with Tislelizumab after Crossover	69 (100.0)
Number of Patients Discontinued from Tislelizumab after Crossover	69 (100.0)
Primary Reason for Tislelizumab Discontinuation	
Progressive disease	50 (72.5)
Withdrawal by subject	6 (8.7)
Adverse event	4 (5.8)
Study terminated by sponsor	4 (5.8)
Physician decision	2 (2.9)
Symptomatic deterioration	2 (2.9)
Other	1 (1.4)

Data cutoff: 08DEC2023. Data extraction: 26JAN2024.
Percentages were based on number of patients who crossed over from control arm.
Patients who met the criteria to continue/crossover Tislelizumab monotherapy and had IRC assessed PD before crossover visit were included in this table.

Recruitment

Study 309 was conducted at 37 sites in 3 countries/regions including China, Taiwan, and Thailand.

The first patient enrolled in Study BGB-A317-309 was randomised on 17 April 2019; the last patient was randomised on 30 September 2020.

Data cut-off date of the prespecified IA is 26 March 2021. The study has been completed with study end date (LPLV) 8 December 2023 (final database lock: 26 January 2024).

As of the 26 March 2021 IA data cutoff, the median study follow-up time was 10.25 months in Arm Tisle+GC and 9.77 months in Arm P+GC. As of the study end date of 08 December 2023, the median study follow-up time was 33.25 months in Arm Tisle+GC and 25.00 months in Arm P+GC.

Conduct of the study

Protocol amendments

The original protocol for this study was dated 28 November 2018. The protocol was amended twice before the study end date. Protocol amendment version 0.1 (dated 30 July 2019) was issued with the primary purpose to extend the study in the Asia-Pacific region. Protocol amendment 1.0 (26 March 2021) included editorial changes as well as changes to keep consistency across all Beigene protocols. No changes were made to the planned analyses and none of the changes implemented in the two protocol amendments were assessed as substantial.

Protocol deviations

In the ITT Analysis Set, a total of 61 patients (23.2%), including 28 patients (21.4%) in Arm A and 33 patients (25.0%) in Arm B, had important protocol deviations. The most common important protocol

deviations were those concerning informed consent in both arms (21 patients [16.0%] in Arm A and 22 patients [16.7%] in Arm B).

Table 17-Important Protocol Deviations (ITT Analysis Set)

	ARM A (N = 131) n (%)	ARM B (N = 132) n (%)	Total (N = 263) n (%)
Patients with any Important Protocol Deviation	28 (21.4)	33 (25.0)	61 (23.2)
Informed Consent	21 (16.0)	22 (16.7)	43 (16.3)
Laboratory	5 (3.8)	7 (5.3)	12 (4.6)
Principal Investigator Oversight	2 (1.5)	2 (1.5)	4 (1.5)
Concomitant Medication	1 (0.8)	0 (0.0)	1 (0.4)
Efficacy Criteria	1 (0.8)	0 (0.0)	1 (0.4)
Entry Criteria	1 (0.8)	0 (0.0)	1 (0.4)
Investigational Product	0 (0.0)	3 (2.3)	3 (1.1)
Pregnancy	0 (0.0)	1 (0.8)	1 (0.4)
Others	2 (1.5)	2 (1.5)	4 (1.5)

Source: ADDV. Data cutoff: 08DEC2023. Data extraction: 26JAN2024.
Abbreviations: ARM A, Tislelizumab + Gemcitabine + Cisplatin; ARM B, Placebo + Gemcitabine + Cisplatin.
A patient was counted only once within each category, but may be counted in multiple categories.
unblind/bgb_a317/bgb_a317_309/csr_20231208_final/dev/pgm/tlfs/t-pd1.sas 27FEB2024 18:45 t-14-1-1-4-1-pd1-maj-i.rtf

Critical protocol deviations (with impact on efficacy analysis) were identified in 6 patients (2.3%) (including 1 patient [0.8%] in Arm A and 5 patients [3.8%] in Arm B) in the ITT Analysis Set. Critical protocol deviations were e.g. related to eligibility criteria (1 patient in Arm A, who received capecitabine 5 months before randomisation), investigational product (1 patient in Arm B received a 30% above planned dose at Cycle 1 Day 1), laboratory assessments (2 patients in Arm B), pregnancy (1 patient in Arm B).

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

The study started in April 2019, which included the period during which the COVID-19 pandemic was occurring globally. The period impacted by the COVID-19 pandemic was from January 2020 through the data cutoff date. The study continued despite the COVID-19 pandemic. A total of 198 patients were randomised from 01 January 2020 until enrolment was closed on 30 September 2020. Among the 162 patients who were tested for COVID-19, no patients presented a positive result.

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.

- A total of 39 patients (14.8%) experienced ≥ 1 missed dose due to COVID-19 (20 patients [15.3%] in Arm A and 19 patients [14.4%] in Arm B); a total of 10 patients (3.8%) experienced ≥ 3 missed doses due to COVID-19 (6 patients [4.6%] in Arm A and 4 patients [3.0%] in Arm B).
- A total of 20 patients (7.6%) experienced ≥ 1 missed tumour assessment due to COVID-19 (11 patients [8.4%] in Arm A and 9 patients [6.8%] in Arm B); a total of 5 patients (1.9%) with 2 missed tumour assessments due to COVID-19 (2 patients [1.5%] in Arm A and 3 patients [2.3%] in Arm B); no patient experienced ≥ 3 missed tumour assessments 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. Major protocol deviations related to COVID-19 were identified in 2 patients (0.8%), with 1 patient in each arm reporting a deviation concerning laboratory (missing

tumour assessments at Weeks 12 and 18, and missing tumour assessment at Week 24). Among these, one major protocol deviation was reported as critical protocol deviation concerning laboratory related to COVID-19 (missing tumour assessment at Week 24).

No delayed serious adverse event reporting was identified to be due to COVID-19 pandemic.

Baseline data

Table 18-Patient Demographics, Baseline Characteristics and Disease History at Baseline (ITT); DCO: 26 March 2021

	Tislelizumab + Chemotherapy (N = 131)	Placebo + Chemotherapy (N = 132)	Total (N = 263)
Age (years)			
Median	50.0	50.0	50.0
Min, Max	26, 74	23, 73	23, 74
Age Group 1, n (%)			
< 65 years	121 (92.4)	120 (90.9)	241 (91.6)
≥ 65 years	10 (7.6)	12 (9.1)	22 (8.4)
Age Group 2, n (%)			
< 50 years	63 (48.1)	64 (48.5)	127 (48.3)
≥ 50 years	68 (51.9)	68 (51.5)	136 (51.7)
Sex, n (%)			
Male	103 (78.6)	103 (78.0)	206 (78.3)
Female	28 (21.4)	29 (22.0)	57 (21.7)
Ethnicity, n (%)			
Not Hispanic or Latino	131 (100.0)	132 (100.0)	263 (100.0)
Race, n (%)			
Asian	131 (100.0)	132 (100.0)	263 (100.0)
Region, n (%)			
China	122 (93.1)	126 (95.5)	248 (94.3)
Thailand	5 (3.8)	1 (0.8)	6 (2.3)
Taiwan, China	4 (3.1)	5 (3.8)	9 (3.4)
BMI (kg/m^2)			
Median	21.94	22.21	22.06
Min, Max	14.7, 36.8	14.5, 34.3	14.5, 36.8
ECOG Performance Status, n (%)			
0	51 (38.9)	46 (34.8)	97 (36.9)
1	80 (61.1)	86 (65.2)	166 (63.1)
Smoking Status, n (%)			
Never	74 (56.5)	66 (50.0)	140 (53.2)
Current	7 (5.3)	6 (4.5)	13 (4.9)
Former	50 (38.2)	60 (45.5)	110 (41.8)
Baseline Target Lesions Sum of Diameters by Investigator (mm)			
Median	51.00	45.35	47.40
Min, Max	10.0, 320.0	10.0, 168.1	10.0, 320.0
Time from Initial Diagnosis to Study Entry (months) [a]			
Median	14.49	17.54	15.11
Min, Max	0.1, 198.2	0.2, 182.8	0.1, 198.2
Histology, n (%)			

	Tislelizumab + Chemotherapy (N = 131)	Placebo + Chemotherapy (N = 132)	Total (N = 263)
Undifferentiated non-keratinised	97 (74.0)	95 (72.0)	192 (73.0)
Differentiated non-keratinised	17 (13.0)	18 (13.6)	35 (13.3)
Keratinised squamous carcinoma	9 (6.9)	8 (6.1)	17 (6.5)
Unclassified	8 (6.1)	11 (8.3)	19 (7.2)
Location of Metastases, n (%)			
Bone	59 (45.0)	58 (43.9)	117 (44.5)
Liver	56 (42.7)	57 (43.2)	113 (43.0)
Lung	59 (45.0)	62 (47.0)	121 (46.0)
Brain	3 (2.3)	3 (2.3)	6 (2.3)
Lymph nodes	82 (62.6)	69 (52.3)	151 (57.4)
Other	14 (10.7)	14 (10.6)	28 (10.6)
Current Disease Stage, n (%)			
Local Recurrent	5 (3.8)	8 (6.1)	13 (4.9)
Metastatic	126 (96.2)	124 (93.9)	250 (95.1)
Primary	46 (35.1)	40 (30.3)	86 (32.7)
Recurrent	80 (61.1)	84 (63.6)	164 (62.4)
EBV DNA Level, n (%)			
< 500 IU/mL	26 (19.8)	37 (28.0)	63 (24.0)
≥ 500 IU/mL	105 (80.2)	95 (72.0)	200 (76.0)
PD-L1 Expression on Tumour Cell, n (%) [b]			
PD-L1 ≥ 10%	80 (61.1)	84 (63.6)	164 (62.4)
PD-L1 < 10%	42 (32.1)	33 (25.0)	75 (28.5)
Not Evaluable	9 (6.9)	15 (11.4)	24 (9.1)
Patients with any Prior Anticancer Drug Therapy, n (%)	83 (63.4)	88 (66.7)	171 (65.0)
Type of Prior Anticancer Drug Therapy, n (%) [cd]			
Adjuvant	36 (43.4)	32 (36.4)	68 (39.8)
Neoadjuvant	55 (66.3)	59 (67.0)	114 (66.7)
Concurrent with radiotherapy	61 (73.5)	67 (76.1)	128 (74.9)
Other	6 (7.2)	4 (4.5)	10 (5.8)
Patients with any Prior Anticancer Surgeries, n (%)	6 (4.6)	4 (3.0)	10 (3.8)
Patients with any Prior Anticancer Radiotherapy, n (%)	84 (64.1)	91 (68.9)	175 (66.5)

Data cutoff: 26Mar2021. Data extraction: 29Apr2021.
Abbreviations: BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; EBV, Epstein-Barr virus; PD-L1, programmed cell death protein ligand-1.
a Study Entry date referred to randomisation date in this study.
b PD-L1 expression level on tumour cells (centrally evaluated) was determined by SP263 IHC. Not evaluable: Samples for which a PD-L1 expression level could not be determined due to technical reasons.
c A patient was counted only once within each category, but may be counted in multiple categories.
d Percentages were based on the number of patients with any prior anticancer drug therapy.

Baseline disease burden of metastatic NPC was 95.1%. The most common distant metastases reported were in the lymph nodes, lung, bone, and liver. All patients with non-metastatic disease at study entry (13 patients, 4.9%) were confirmed to have recurrent disease and were deemed by the investigators to be unsuitable to receive locoregional therapy for recurrent disease.

A total of 78 patients (59.5%) in the T + GC arm and 32 patients (24.2%) in the P + GC arm received subsequent systemic anticancer therapies. Of note, patients in the P + GC arm who crossed over to receive tislelizumab (69 patients, 52.3%) were not included in the analysis.

Table 19-Subsequent Anticancer Systemic Therapies Used by ⩾ 2% of Patients in Any Arm (ITT); DCO: 08 December 2023

Category WHO Drug Dictionary Preferred Term	Tislelizumab + Chemotherapy (N = 131) n (%)	Placebo + Chemotherapy (N = 132) n (%)
Patients Who Received any Subsequent Anticancer Systemic Therapy	78 (59.5)	32 (24.2)
Chemotherapy	62 (47.3)	26 (19.7)
Capecitabine	26 (19.8)	8 (6.1)
Paclitaxel Nanoparticle Albumin-Bound	25 (19.1)	9 (6.8)
Cisplatin	16 (12.2)	8 (6.1)
Carboplatin	12 (9.2)	5 (3.8)
Docetaxel	9 (6.9)	1 (0.8)
Nedaplatin	7 (5.3)	6 (4.5)
Paclitaxel	7 (5.3)	6 (4.5)
Gemcitabine	4 (3.1)	3 (2.3)
Gimeracil;oteracil Potassium;tegafur	4 (3.1)	3 (2.3)
Immunotherapy	31 (23.7)	18 (13.6)
Toripalimab	9 (6.9)	5 (3.8)
Shr 1701	6 (4.6)	2 (1.5)
Camrelizumab	5 (3.8)	2 (1.5)
Tislelizumab	4 (3.1)	5 (3.8)
Pembrolizumab	3 (2.3)	0 (0.0)
Ql 1706	3 (2.3)	0 (0.0)
Sintilimab	2 (1.5)	3 (2.3)
Target therapy	28 (21.4)	13 (9.8)
Catequentinib Hydrochloride	7 (5.3)	3 (2.3)
Nimotuzumab	7 (5.3)	6 (4.5)
Catequentinib	4 (3.1)	0 (0.0)
Rivoceranib Mesylate	3 (2.3)	0 (0.0)
Chinese herb medicine	7 (5.3)	5 (3.8)
Unspecified Herbal And Traditional Medicine	5 (3.8)	2 (1.5)
Antibody-drug conjugate	5 (3.8)	0 (0.0)
Mrg 003	3 (2.3)	0 (0.0)

Data cutoff: 08DEC2023. Data extraction: 26JAN2024.
Tislelizumab + Chemotherapy: tislelizumab in combination with gemcitabine plus cisplatin.
Placebo + Chemotherapy: placebo in combination with gemcitabine plus cisplatin.
A patient was counted only once within a category.
Medication terms were coded using World Health Organization Drug Dictionary Global-B3.

Numbers analysed

All 263 patients who were randomised to the study were included in the ITT Analysis Set, the Safety Analysis Set and the HRQoL Analysis Set. All 131 patients (100.0%) in Arm A who received any dose of tislelizumab were included in the PK Analysis Set.

Table 20-Analysis Sets (ITT Analysis Set)

	ARM A (N = 131) n (%)	ARM B (N = 132) n (%)	Total (N = 263) n (%)
ITT Analysis Set [a]	131 (100.0)	132 (100.0)	263 (100.0)
Safety Analysis Set [b]	133 (101.5)	130 (98.5)	263 (100.0)
PK Analysis Set [c]	131 (100.0)	NA	131 (49.8)
ADA Analysis Set [d]	125 (95.4)	NA	125 (47.5)
HRQoL Analysis Set [e]	131 (100.0)	132 (100.0)	263 (100.0)

Source: ADSL. Data cutoff: 08DEC2023. Data extraction: 26JAN2024.
Abbreviations: ARM A, Tislelizumab + Gemcitabine + Cisplatin; ARM B, Placebo + Gemcitabine + Cisplatin; NA, Not applicable.
A patient was counted only once within each category, but may be counted in multiple categories.
[a] ITT Analysis Set included all patients randomized to the study.
[b] Safety Analysis Set included all randomized patients who received any dose of any study drug.
[c] PK Analysis Set included all patients who received at least one dose of tislelizumab per the protocol, for whom any post-baseline PK data were available.
[d] ADA Analysis Set included all patients who received at least one dose of tislelizumab for whom both baseline ADA and at least one post-baseline ADA results are available.
[e] HRQoL Analysis Set included all randomized patients who received at least one dose of study drug and completed at least one HRQoL assessment.
Source: Table 5, CSR Study 309 (DCO 08 December 2023)

Outcomes and estimation

The efficacy results of the primary analysis are based on the pre-planned interim analysis conducted at the cut-off date of 26 March 2021, at which time a total 152 (57.8%) PFS events per RECIST v 1.1 by the IRC in the ITT Analysis Set (65 events in Arm A and 87 events in Arm B) had occurred.

Furthermore, updated efficacy information with approximately 17 additional months of median study follow-up as of the study end date of 08 December 2023 was provided.

Primary efficacy endpoint

PFS per IRC in the ITT Analysis Set

Median PFS per the IRC for Arm A was significantly longer than PFS for Arm B, with a 1-sided stratified log-rank test p-value of < 0.0001, which was less than the p-value boundary of 0.014449 using the prespecified Lan-DeMets spending function to approximate O'Brien-Fleming stopping boundary based on the actual number of PFS events for the interim analysis.

The median study follow-up time was 10.25 months (range: 0.3 to 23.3 months) for Arm A and 9.77 months (range: 0.1 to 20.9 months) for Arm B.

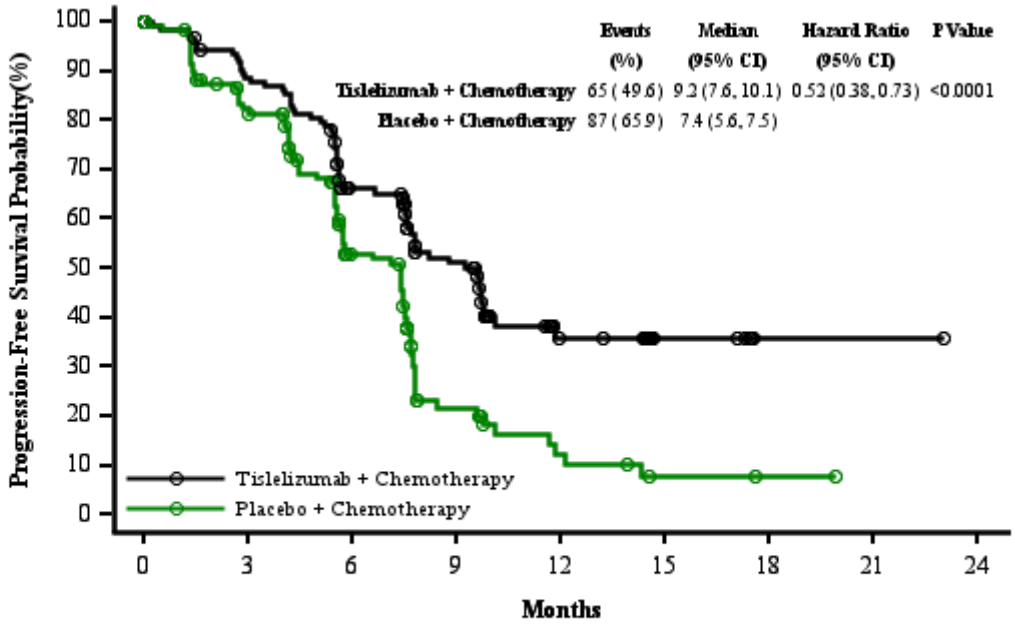
Table 21-Progression-Free Survival Assessed by IRC (ITT) – Study 309

	IA		Closeout	
	Tislelizumab + Chemotherapy (N = 131) n (%)	Placebo + Chemotherapy (N = 132) n (%)	Tislelizumab + Chemotherapy (N = 131) n (%)	Placebo + Chemotherapy (N = 132) n (%)
Progression-Free Survival				
Events, n (%)	65 (49.6)	87 (65.9)	95 (72.5)	106 (80.3)
Progressive Disease	58 (44.3)	85 (64.4)	87 (66.4)	104 (78.8)
Death	7 (5.3)	2 (1.5)	8 (6.1)	2 (1.5)
Censored, n (%)	66 (50.4)	45 (34.1)	36 (27.5)	26 (19.7)
No Baseline Assessment	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.8)

	IA		Closeout	
	Tislelizumab + Chemotherapy (N = 131) n (%)	**Placebo + Chemotherapy (N = 132) n (%)**	**Tislelizumab + Chemotherapy (N = 131) n (%)**	**Placebo + Chemotherapy (N = 132) n (%)**
No Post-Baseline	7 (5.3)	4 (3.0)	7 (5.3)	4 (3.0)
New Anti-Cancer Therapy	5 (3.8)	8 (6.1)	12 (9.2)	8 (6.1)
Missing >= 2 Assessments	0 (0.0)	3 (2.3)	1 (0.8)	5 (3.8)
Withdraw Consent	2 (1.5)	2 (1.5)	4 (3.1)	2 (1.5)
Study Terminated by Sponsor	0 (0.0)	0 (0.0)	11 (8.4)	6 (4.5)
On-Going Without Events	52 (39.7)	27 (20.5)	0 (0.0)	0 (0.0)
Study Discontinuation due to Other Reasons	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
One-sided stratified log-rank test p-value [a]	<0.0001	-	-	-
Stratified Hazard Ratio (95% CI) [a]	0.52 (0.38, 0.73)	-	0.53 (0.39, 0.71)	-
One-sided unstratified log-rank test p-value	<0.0001	-	-	-
Unstratified Hazard Ratio (95% CI)	0.51 (0.37, 0.71)	-	0.55 (0.41, 0.73)	-
Progression-Free Survival (months)				
Median (95% CI)	9.2 (7.6, 10.1)	7.4 (5.6, 7.5)	9.6 (7.6, 11.6)	7.4 (5.6, 7.6)
Event Free Rate at, % (95% CI)				
6 month (95% CI)	66.1 (56.9, 73.8)	53.0 (43.4, 61.8)	64.7 (55.5, 72.5)	54.8 (45.3, 63.3)
12 month (95% CI)	35.7 (25.2, 46.4)	12.2 (5.6, 21.4)	35.1 (26.6, 43.8)	10.2 (5.4, 16.8)
24 month (95% CI)	NE (NE, NE)	NE (NE, NE)	23.5 (16.1, 31.7)	7.3 (3.4, 13.3)

Data cutoff: IA-26Mar2021; Closeout-08DEC2023. Data extraction: IA-29Apr2021; Closeout-26JAN2024.
Abbreviations: NE, Not Estimable; NR, Not Reached.
Medians and other quartiles were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley.
Event free rates were estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula.
Placebo + Gemcitabine + Cisplatin arm was the reference group for hazard ratio.
a Stratified by stratification factors: gender (male versus female) and liver metastases status (yes versus no).
Source: Table 8, SCE

Figure 23-Kaplan-Meier Plot of PFS by IRC (ITT) – Study 309 (Interim Analysis, DCO: 26 March 2021)

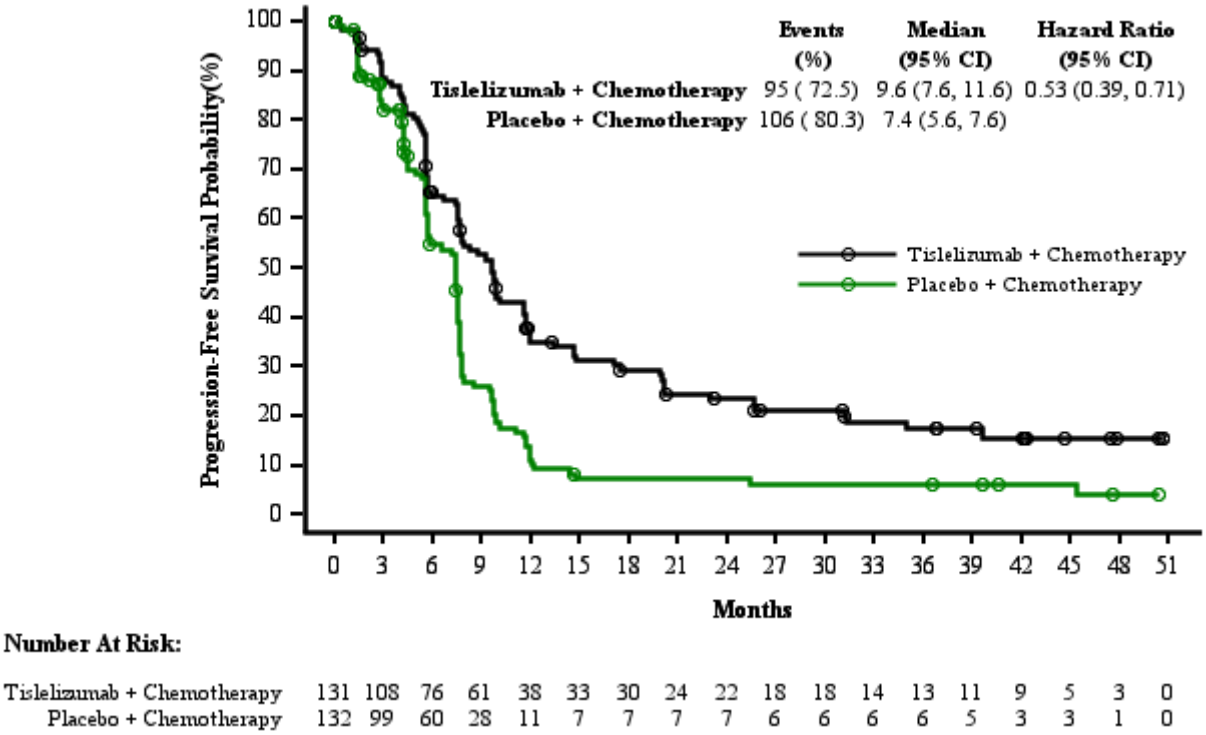


Number At Risk:

Tislelizumab + Chemotherapy	131	108	70	42	13	6	1	1	0
Placebo + Chemotherapy	132	98	50	14	6	2	1	0	0

Data cutoff: 26Mar2021. Data extraction: 29Apr2021.
Abbreviations: CI, confidence interval; IRC, independent review committee; ITT, intent-to-treat; PFS, progression-free survival.
Tislelizumab + Chemotherapy: tislelizumab in combination with gemcitabine plus cisplatin.
Placebo + Chemotherapy: placebo in combination with gemcitabine plus cisplatin.
Hazard ratio was estimated from stratified Cox model with Placebo + Gemcitabine + Cisplatin group as reference group.

Figure 24- Kaplan-Meier Plot of PFS by IRC (ITT) – Study 309 (Closeout, DCO: 08 December 2023)



Data cutoff: 08DEC2023. Data extraction: 26JAN2024.
Abbreviations: CI, confidence interval; IRC, independent review committee; ITT, intent-to-treat; PFS, progression-free survival.
Tislelizumab + Chemotherapy: tislelizumab in combination with gemcitabine plus cisplatin.
Placebo + Chemotherapy: placebo in combination with gemcitabine plus cisplatin.
Hazard ratio was estimated from stratified Cox model with Placebo + Gemcitabine + Cisplatin group as reference group.
Source: Figure 3, SCE

Secondary endpoints

All the secondary efficacy endpoints are presented for the prespecified IA, data cutoff of 26 March 2021 in the following sections. Additionally, updated efficacy analyses for OS, PFS2, and PRO are presented based on data up to the study end date of 08 December 2023.

Overall Survival

As of the **DCO date of the IA**, the median follow-up time was 10.3 months (95% CI: 9.8 to 11.2 months) in Arm A and 9.8 months (95% CI: 9.3 to 10.5 months) in Arm B; OS data were not mature. A total of 34 (12.9%) deaths occurred in the ITT Analysis Set (18 in Arm A and 16 in Arm B). The median OS was not reached in either arm. The estimated stratified HR was 0.97 (95% CI: 0.49 to 1.92). More than 80% of patients were censored in each arm (86.3% in Arm A and 87.9% in Arm B).

As of the **study end date** of 08 December 2023, with a median survival follow up of approximately 41 months, 119 OS events (45.2%) had been reported in the ITT Analysis Set (42.0% in Arm Tisle+GC versus 48.5% in Arm P+GC).

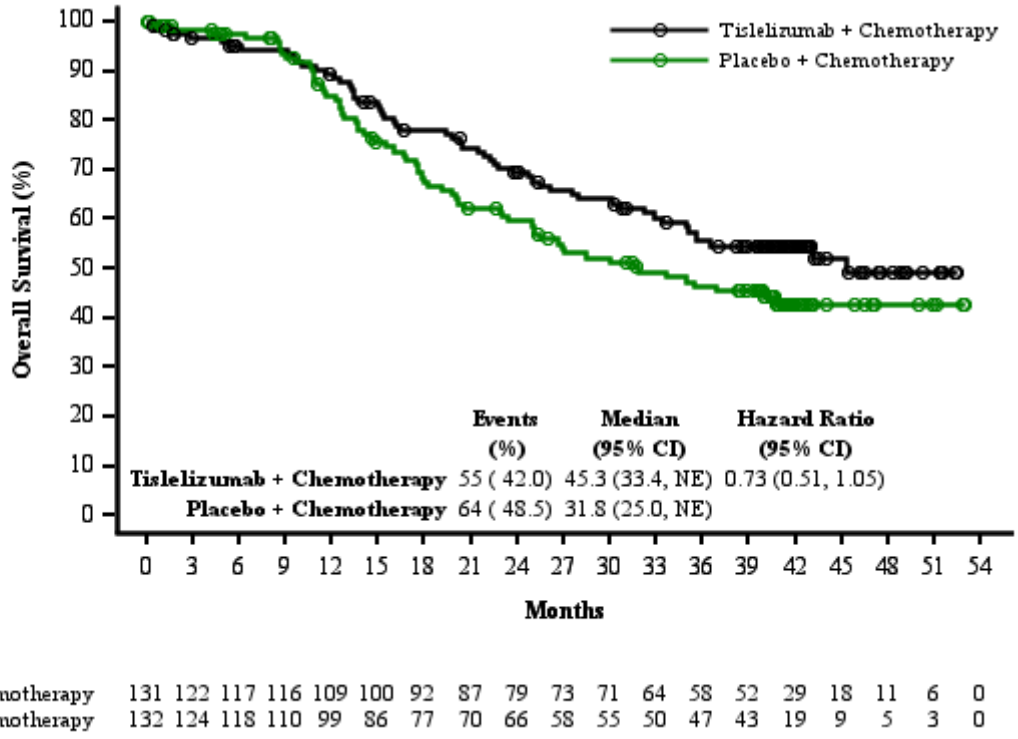
Table 22-Overall Survival (ITT) – Study 309 (Closeout, DCO: 08 December 2023)

	Tislelizumab + Chemotherapy (N = 131)	Placebo + Chemotherapy (N = 132)
Overall Survival		
Death, n (%)	55 (42.0)	64 (48.5)

	Tislelizumab + Chemotherapy (N = 131)	Placebo + Chemotherapy (N = 132)
Censored, n (%)	76 (58.0)	68 (51.5)
Lost to Follow-up	7 (5.3)	5 (3.8)
Withdrawal by Subject	15 (11.5)	20 (15.2)
Study Terminated by Sponsor	51 (38.9)	41 (31.1)
Partial Death Date*	2 (1.5)	2 (1.5)
Study Discontinuation Due to Other Reasons	1 (0.8)	0 (0.0)
Stratified Hazard Ratio (95% CI) [a]	0.73 (0.51, 1.05)	-
Unstratified Hazard Ratio (95% CI)	0.74 (0.52, 1.06)	-
Overall Survival (months)		
Median (95% CI)	45.3 (33.4, NE)	31.8 (25.0, NE)
Event Free Rate at, % (95% CI)		
6 month (95% CI)	95.3 (89.9, 97.9)	97.6 (92.9, 99.2)
12 month (95% CI)	89.6 (82.8, 93.8)	84.9 (77.1, 90.2)
24 month (95% CI)	69.4 (60.4, 76.8)	59.6 (50.1, 67.9)
48 month (95% CI)	49.2 (38.0, 59.5)	42.7 (33.2, 51.9)
Follow-up Time (months)		
Median (95% CI)	41.4 (40.1, 42.2)	40.8 (39.8, 41.7)

Abbreviations: NE, Not Estimable; NR, Not Reached.
Tislelizumab + Chemotherapy: tislelizumab in combination with gemcitabine plus cisplatin.
Placebo + Chemotherapy: placebo in combination with gemcitabine plus cisplatin.
Median follow-up time was estimated by the reverse Kaplan-Meier method. Medians and other quartiles were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley.
Event free rates were estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula.
Placebo + Gemcitabine + Cisplatin arm was the reference group for hazard ratio.
a Stratified by stratification factors: gender (male versus female) and liver metastases status(yes versus no).

Figure 25-Kaplan-Meier Plot of Overall Survival (ITT) – Study 309 (Closeout, DCO: 08 December 2023)



Abbreviations: CI, confidence interval; ITT, intent-to-treat; NE, Not Estimable.
Tislelizumab + Chemotherapy: tislelizumab in combination with gemcitabine plus cisplatin.

Placebo + Chemotherapy: placebo in combination with gemcitabine plus cisplatin.
Hazard ratio was estimated from stratified Cox model with Placebo + Gemcitabine + Cisplatin group as reference group.

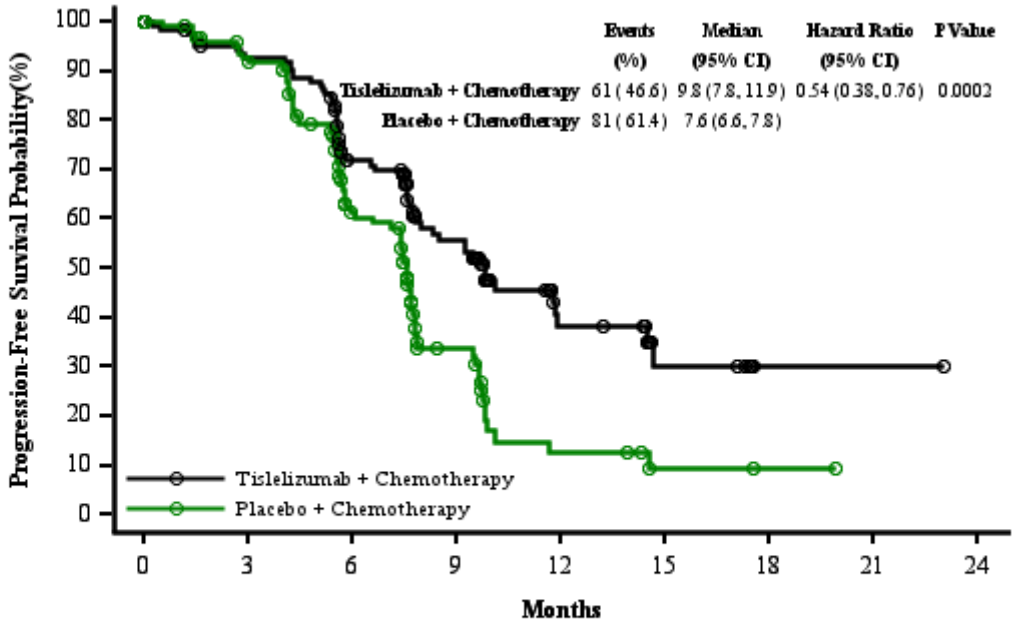
PFS Assessed by Investigator

Table 23-Progression-Free Survival by Investigator (ITT) – Study 309 (Interim Analysis, DCO: 26 March 2021)

	Tislelizumab + Chemotherapy (N = 131)	Placebo + Chemotherapy (N = 132)
Progression-Free Survival		
Events, n (%)	61 (46.6)	81 (61.4)
Progressive Disease	54 (41.2)	78 (59.1)
Death	7 (5.3)	3 (2.3)
Censored, n (%)	70 (53.4)	51 (38.6)
No Post-Baseline	6 (4.6)	5 (3.8)
New Anti-Cancer Therapy	5 (3.8)	5 (3.8)
Missing >= 2 Assessments	1 (0.8)	3 (2.3)
Withdraw Consent	0 (0.0)	3 (2.3)
On-Going Without Events	58 (44.3)	35 (26.5)
One-sided stratified log-rank test p-value [a]	0.0002	-
Stratified Hazard Ratio (95% CI) [a]	0.54 (0.38, 0.76)	-
One-sided unstratified log-rank test p-value	0.0001	-
Unstratified Hazard Ratio (95% CI)	0.53 (0.38, 0.75)	-
Progression-Free Survival (months)		
Median (95% CI)	9.8 (7.8, 11.9)	7.6 (6.6, 7.8)
Event Free Rate at, % (95% CI)		
6 month (95% CI)	71.8 (62.9, 79.0)	61.2 (51.7, 69.5)
12 month (95% CI)	38.1 (26.5, 49.6)	12.7 (5.7, 22.7)

Abbreviations: NE, Not Estimable; NR, Not Reached.
Tislelizumab + Chemotherapy: tislelizumab in combination with gemcitabine plus cisplatin.
Placebo + Chemotherapy: placebo in combination with gemcitabine plus cisplatin.
One-sided p-value was estimated from log rank test for descriptive purpose only.
Medians and other quartiles were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley.
Event free rates were estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula.
Placebo + Gemcitabine + Cisplatin arm was the reference group for hazard ratio.
a Stratified by stratification factors: gender (male versus female) and liver metastases status (yes versus no).

Figure 26-Kaplan-Meier Plot of PFS by Investigator (ITT) – Study 309 (Interim Analysis, DCO: 26 March 2021)



Abbreviations: CI, confidence interval; ITT, intent-to-treat.
Tislelizumab + Chemotherapy: tislelizumab in combination with gemcitabine plus cisplatin.
Placebo + Chemotherapy: placebo in combination with gemcitabine plus cisplatin.
Hazard ratio was estimated from stratified Cox model with Placebo + Gemcitabine + Cisplatin group as reference group.

Objective Response Rate Assessed by IRC

Table 24-Objective Response Rate by IRC (ITT) – Study 309 (Interim Analysis, DCO: 26 March 2021)

	Tislelizumab + Chemotherapy (N = 131)	Placebo + Chemotherapy (N = 132)
Best Overall Response, n (%)		
Complete Response	21 (16.0)	9 (6.8)
Partial Response	70 (53.4)	64 (48.5)
Stable Disease	19 (14.5)	34 (25.8)
Non-CR/Non-PD	7 (5.3)	5 (3.8)
Progressive Disease	4 (3.1)	14 (10.6)
Could not be Determined	10 (7.6)	6 (4.5)
Objective Response Rate (ORR), n (%)	91 (69.5)	73 (55.3)
95% CI	(60.8, 77.2)	(46.4, 64.0)
Odds Ratio (95% CI)	1.85 (1.11, 3.07)	-
ORR Difference, % (95% CI)	14.2 (2.7, 25.8)	-
Disease Control Rate, n (%)	117 (89.3)	112 (84.8)
95% CI	(82.7, 94.0)	(77.6, 90.5)
Clinical Benefit Rate [a], n (%)	101 (77.1)	85 (64.4)
95% CI	(68.9, 84.0)	(55.6, 72.5)

Tislelizumab + Chemotherapy: tislelizumab in combination with gemcitabine plus cisplatin.
Placebo + Chemotherapy: placebo in combination with gemcitabine plus cisplatin.
95% CI was calculated using Clopper-Pearson method.
Objective response rate differences and odds ratios between arms were calculated using the Cochran-Mantel-Haenszel Chi-square test with actual stratification factors as strata.

Placebo + Gemcitabine + Cisplatin arm was the reference group.
Best overall response of could not be determined included patients who had post-baseline tumour assessment, none of which were evaluable; or patients who had no post-baseline tumour assessments due to death, withdrawal of consent, lost to follow up or any other reasons.
Non-CR/non-PD was due to no measurable target lesion per IRC.
a Included patients with BOR in CR or PR or >=24 weeks SD or Non-CR/Non-PD.

Table 25-Objective Response Rate by IRC (ITT) – Study 309 (Closeout, DCO: 08 December 2023)

	Tislelizumab + Chemotherapy (N = 131)	Placebo + Chemotherapy (N = 132)
Best Overall Response, n (%)		
Complete Response	28 (21.4)	10 (7.6)
Partial Response	62 (47.3)	63 (47.7)
Stable Disease	19 (14.5)	33 (25.0)
Non-CR/Non-PD	8 (6.1)	7 (5.3)
Progressive Disease	4 (3.1)	13 (9.8)
Could not be Determined	10 (7.6)	6 (4.5)
Objective Response Rate (ORR), n (%)	90 (68.7)	73 (55.3)
95% CI	(60.0, 76.5)	(46.4, 64.0)
Odds Ratio (95% CI)	1.78 (1.08, 2.96)	-
ORR Difference, % (95% CI)	13.4 (1.9, 25.0)	-
Disease Control Rate, n (%)	117 (89.3)	113 (85.6)
95% CI	(82.7, 94.0)	(78.4, 91.1)
Clinical Benefit Rate [a], n (%)	101 (77.1)	87 (65.9)
95% CI	(68.9, 84.0)	(57.2, 73.9)

95% CI was calculated using Clopper-Pearson method.
Objective response rate differences and odds ratios between arms were calculated using the Cochran-Mantel-Haenszel Chi-square test with actual stratification factors as strata.
Placebo + Gemcitabine + Cisplatin arm was the reference group.
Best overall response of could not be determined included patients who had post-baseline tumour assessment, none of which were evaluable; or patients who had no post-baseline tumour assessments due to death, withdrawal of consent, lost to follow up or any other reasons.
Non-CR/non-PD was due to no measurable target lesion per IRC.
a Included patients with BOR in CR or PR or >=24 weeks SD or Non-CR/Non-PD.
Source: Table 14.2.2.3.2, SCE Appendix 1

Duration of Response Assessed by IRC

Table 26-Duration of Response by IRC (ITT) – Study 309 (Interim Analysis, DCO: 26 March 2021)

	Tislelizumab + Chemotherapy (N = 131)	Placebo + Chemotherapy (N = 132)
Number of Responders	91	73
Events, n (%)	39 (42.9)	49 (67.1)
Progressive Disease	38 (41.8)	49 (67.1)
Death	1 (1.1)	0 (0.0)
Censored, n (%)	52 (57.1)	24 (32.9)
Duration of Response (months)		
Median (95% CI)	8.5 (6.5, NE)	6.1 (4.7, 6.2)
Event Free Rate at, % (95% CI)		
6 month (95% CI)	73.3 (62.6, 81.5)	52.0 (38.9, 63.7)
12 month (95% CI)	44.5 (30.5, 57.5)	4.8 (0.4, 18.5)

Abbreviations: NE, Not Estimable; NR, Not Reached.
Tislelizumab + Chemotherapy: tislelizumab in combination with gemcitabine plus cisplatin.
Placebo + Chemotherapy: placebo in combination with gemcitabine plus cisplatin.
Percentages were based on number of responders.
Duration of response analysis included patients with objective response.
Medians and other quartiles were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and

Crowley.
Event free rates were estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula.

PFS2 Assessed by Investigator

As of the IA data cutoff, PFS2 results were immature with only 51 PFS2 events (19.4%) reported in the ITT Analysis Set (19 events (14.5%) in Arm Tisle+GC and 32 events (24.2%) in Arm P+GC). The median PFS2 was not reached (95% CI: 16.1, NE) for Arm Tisle+GC and 16.1 months (95% CI: 12.5, NE) for Arm P+GC.

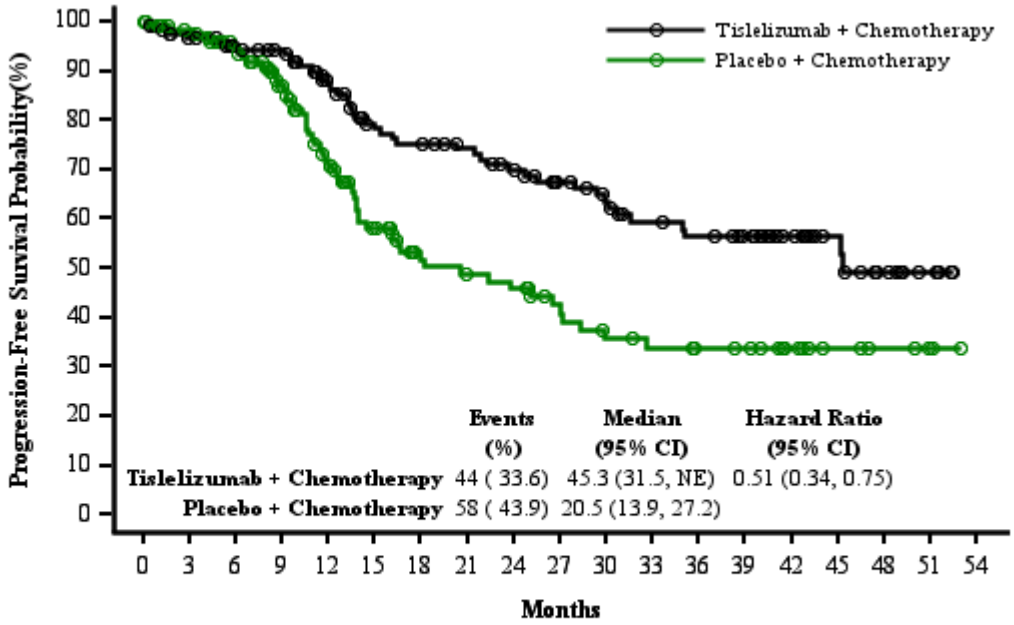
As of the study end date of 08 December 2023, an improvement in PFS2 per investigator was observed with Tisle + GC compared to placebo + GC, see below.

Table 27-PFS2 per RECIST Version 1.1 by Investigator – Study 309 (Closeout, DCO: 08 December 2023)

	Tislelizumab + Chemotherapy (N = 131)	Placebo + Chemotherapy (N = 132)
Progression-Free Survival		
Events, n (%)	44 (33.6)	58 (43.9)
Progressive Disease	11 (8.4)	39 (29.5)
Death	33 (25.2)	19 (14.4)
Censored, n (%)	87 (66.4)	74 (56.1)
Progression-Free Survival (months)		
Median (95% CI)	45.3 (31.5, NE)	20.5 (13.9, 27.2)
Event Free Rate at, % (95% CI)		
6 month (95% CI)	95.3 (89.8, 97.9)	95.2 (89.5, 97.8)
12 month (95% CI)	87.2 (79.7, 92.1)	70.9 (61.2, 78.7)
24 month (95% CI)	69.8 (59.9, 77.7)	45.9 (35.0, 56.0)
48 month (95% CI)	49.3 (35.9, 61.4)	33.8 (23.1, 44.8)

Abbreviations: NE, Not Estimable.
Tislelizumab + Chemotherapy: tislelizumab in combination with gemcitabine plus cisplatin.
Placebo + Chemotherapy: placebo in combination with gemcitabine plus cisplatin.
Medians and other quartiles were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley.
Event free rates were estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula.

Figure 27-Kaplan-Meier Plot of PFS2 by Investigator (ITT) – Study 309 (Closeout, DCO: 08 December 2023)



Abbreviations: CI, confidence interval; ITT, intent-to-treat; NE, Not Estimable.
Tislelizumab + Chemotherapy: tislelizumab in combination with gemcitabine plus cisplatin.
Placebo + Chemotherapy: placebo in combination with gemcitabine plus cisplatin.
Hazard ratio was estimated from unstratified Cox model with Placebo + Gemcitabine + Cisplatin as reference group.

Patient-Reported Outcomes

Health-Related Quality of Life was assessed based on descriptive analyses using EORTC QLQ-C30 and its NPC module (QLQ-H&N35). The scores of the EORTC QLQ-C30 and QLQ-H&N35 questionnaires were summarised for each assessment timepoint and treatment arm.

As of the study end date of 08 December 2023, adjusted compliance rates *(defined as the proportion of the actual number of questionnaires received out of the expected number of questionnaires to be received at each assessment timepoint)* were 99.1% – 100.0% in both arms at baseline and the key cycles (Cycle 4 and Cycle 8).

Baseline scores in EORTC QLQ-C30 were slightly higher in Arm B (mean score = 67.6) as compared to Arm A (mean score = 62.9), but were similar in QLQ-H&N35 between both arms.

Changes from baseline

Table 28-Summary of the mean changes in scores from baseline to Cycle 8 -*extract*

Questionnaire/ Parameter - Mean change (standard deviation)	**Tislelizumab + Chemotherapy**	**Placebo + Chemotherapy**
EORTC QLQ-C30		
GHS (Global Health Status)/QoL	4.6 (26.33)	3.4 (21.80)
Physical functioning	-2.2 (14.03)	0.0 (13.37)
QLQ-H&N35		
QLQ-H&N35 index score	-1.3 (7.01)	-1.4 (6.25)

Pain	-2.1 (8.65)	-0.1 (8.66)
Swallowing	-1.1 (7.53)	-0.4 (6.95)
Senses	-3.3 (16.21)	-0.3 (12.57)
Speech	-1.0 (10.45)	-0.2 (9.70)

Least square mean changes from baseline by cycle 6 (based on the mixed-effects model analysis)

Table 29-Summary of Least Square (LS) Mean Changes From Baseline (95% CI) from baseline to Cycle 8-*extract*

Questionnaire/ Parameter – LS Mean Score change from baseline (95% CI)	**Tislelizumab + Chemotherapy**	**Placebo + Chemotherapy**
EORTC QLQ-C30		
GHS (Global Health Status)/QoL	2.72 (-0.98, 6.43)	3.03 (-0.80, 6.86)
Physical functioning	-2.82 (-5.01, -0.62)	-1.37 (-3.62, 0.87)
QLQ-H&N35		
QLQ-H&N35 index score	-1.66 (-2.80, -0.52)	-1.43 (-2.60, -0.26)
Pain	-2.78 (-4.16, -1.40)	-0.38 (-1.81, 1.05)
Senses	-2.86 (-5.07, -0.64)	-0.11 (-2.40, 2.17)
Speech	-0.70 (-2.41, 1.01)	0.22 (-1.54, 1.98)

Source: SCE Appendix 1, Table 14.2.2.7.5

Time to Deterioration (TTD)

Deterioration was defined as a ≥ 10-point decrease in global health status/QoL of the EORTC QLQ-C30 and a ≥ 10-point increase in index score of QLQ-H&N35 from baseline. TTD was calculated using Kaplan-Meier estimates, and presented with 2-sided 95% CIs.

The number and percentages of patients with events for GHS/QoL for Arm A was 33 (26.4%) and 41 (32.0%) for Arm B, but the median time to deterioration was not reached at the cutoff of -10 points despite Arm B having more events. Similarly, the median time to deterioration was not reached for the EORTC QLQ-H&N35 index score in either arm. Both arms experienced similar and few numbers of events, with 3 patients (2.4%) with events in Arm A and 3 patients (2.3%) with events in Arm B.

Overall, the results indicate that patients in both arms were at similar risk of worsening of

- GHS/QoL score: HR of 0.78 [95% CI: 0.500 to 1.206],
- physical functioning: HR of 0.97 [95% CI: 0.607 to 1.536],
- pain: HR of 0.94 [95% CI: 0.432 to 2.032],
- senses: HR of 0.99 [95% CI: 0.600 to 1.640],
- speech: HR of 0.74 [95% CI: 0.266 to 2.083].

Exploratory endpoints

Objective Response Rate per the Investigator

The ORR per RECIST v 1.1 as assessed by the investigator was 77.9% (95% CI: 69.8% to 84.6%) in Arm A versus 67.4% (95% CI: 58.7% to 75.3%) in Arm B, with similar ORR improvements as that assessed by the IRC. Odds Ratio (95% CI) was 1.73 (0.99, 3.03) and ORR Difference (95% CI) was 10.4% (-0.1, 20.9).

Duration of Response per the Investigator

The median DOR was longer in Arm A than Arm B (10.6 months [95% CI: 6.9 months to not estimable] and 6.2 months [95% CI: 6.0 to 6.7 months], respectively). The DOR by the investigator was consistent with that assessed by the IRC.

Ancillary analyses

Sensitivity Analyses of PFS

In order to evaluate the robustness of the PFS assessed per the IRC, 4 sensitivity analyses were planned: 2 sensitivity analyses with different censoring rules were performed; as described below, the sensitivity analysis in the PP Analysis Set was not performed per SAP due to < 10% of patients in the ITT Analysis Set having critical protocol deviations; and 1 additional sensitivity analysis to evaluate the impact of discordance rate for stratification factors between IRT and EDC was also not performed due to the concordance rate of 100%.

Sensitivity Analysis 1

Sensitivity Analysis 1 evaluated the impact of new anticancer treatment on the primary endpoint. This analysis was the same as the primary analysis with regard to the censoring rules except for the handling of new anticancer treatment: PFS was derived without considering the occurrence of new anticancer treatment.

Sensitivity Analysis 1 showed a stratified HR of 0.53 (95% CI: 0.38 to 0.74).

Sensitivity Analysis 2

Sensitivity Analysis 2 evaluated the impact of ≥ 2 consecutive missing tumour assessments on primary endpoint. This analysis was the same as the primary analysis with regard to the censoring rules except for the handling of ≥ 2 consecutive missing tumour assessments: PFS was derived regardless of ≥ 2 missed tumour assessments.

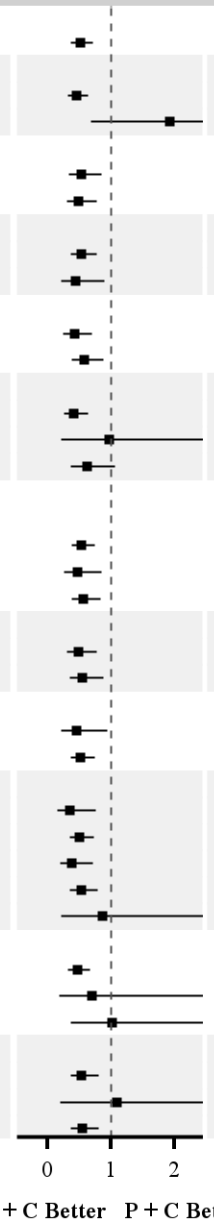
The estimated stratified HR of Sensitivity Analysis 2 was 0.53 (95% CI: 0.38 to 0.73).

Subgroup Analyses of PFS Assessed by IRC

The consistency of the PFS treatment effect was evaluated in the ITT Analysis Set across key relevant clinical subgroups.

Table 30-Subgroup Analysis: PFS Assessed by IRC (ITT) – Study 309 (Interim Analysis, DCO: 26 March 2021)

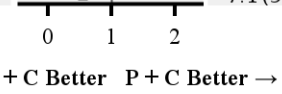
Subgroup	Events/ Total T + C	Events/ Total P + C	Median (95% CI) T + C	Hazard Ratio (95% CI)	Median (95% CI) P + C	Hazard Ratio (95% CI)
Overall	65/131	87/132	9.2 (7.6, 10.1)		7.4 (5.6, 7.5)	0.51 (0.37, 0.71)
Age Group 1						
< 65 years	57/121	80/120	9.6 (7.7, 11.8)		7.4 (5.6, 7.5)	0.46 (0.32, 0.64)
≥ 65 years	8/10	7/12	4.6 (1.5, 9.6)		7.1 (4.4, 11.9)	1.93 (0.69, 5.38)*
Age Group 2						
< 50 years	34/63	46/64	8.2 (7.4, 11.8)		7.4 (5.6, 7.7)	0.54 (0.34, 0.84)
≥ 50 years	31/68	41/68	9.6 (7.6, NE)		7.4 (5.5, 7.5)	0.48 (0.30, 0.77)
Sex						
Male	50/103	68/103	9.6 (7.5, 11.8)		6.6 (5.5, 7.6)	0.53 (0.37, 0.77)
Female	15/28	19/29	8.2 (6.7, NE)		7.4 (5.5, 7.7)	0.44 (0.22, 0.89)
ECOG Performance Status						
0	27/51	35/46	9.6 (7.5, 11.8)		5.8 (5.4, 7.4)	0.42 (0.25, 0.70)
1	38/80	52/86	9.2 (5.7, NE)		7.4 (5.6, 7.8)	0.58 (0.38, 0.88)
Smoking Status						
Never	38/74	45/66	9.6 (7.6, NE)		7.4 (5.5, 7.5)	0.40 (0.26, 0.63)
Current	4/7	4/6	5.7 (5.6, NE)		5.7 (1.3, NE)	0.97 (0.22, 4.35)*
Former	23/50	38/60	8.8 (7.5, NE)		7.1 (5.5, 7.8)	0.63 (0.37, 1.05)
Current Disease Stage						
Local Recurrent	1/5	4/8	NR (9.6, NE)		5.5 (0.6, NE)	NE (NE, NE)
Metastatic	64/126	83/124	8.8 (7.6, 9.8)		7.4 (5.7, 7.5)	0.53 (0.38, 0.74)
Primary	23/46	25/40	9.2 (7.5, 11.8)		7.4 (5.5, 7.7)	0.48 (0.27, 0.85)
Recurrent	41/80	58/84	8.2 (5.6, NE)		7.1 (5.6, 7.6)	0.56 (0.37, 0.84)
Liver Metastases at Baseline						
Yes	33/56	46/57	7.5 (5.6, 9.7)		5.7 (4.5, 7.4)	0.48 (0.31, 0.77)
No	32/75	41/75	9.7 (7.8, NE)		7.6 (5.7, 7.8)	0.55 (0.34, 0.87)
EBV DNA Level						
< 500 IU/mL	11/26	20/37	9.8 (7.7, NE)		7.5 (4.4, 11.7)	0.45 (0.21, 0.94)
≥ 500 IU/mL	54/105	67/95	7.8 (5.7, 9.8)		7.1 (5.6, 7.4)	0.52 (0.36, 0.75)
PD-L1 Expression in TC						
< 1% TC	14/27	15/21	7.8 (5.5, 9.8)		4.3 (3.0, 7.6)	0.35 (0.16, 0.76)
≥ 1% TC	48/95	65/96	9.6 (7.6, 11.8)		7.4 (5.7, 7.6)	0.50 (0.34, 0.73)
< 10% TC	20/42	23/33	7.8 (7.4, NE)		5.5 (4.2, 7.4)	0.38 (0.20, 0.72)
≥ 10% TC	42/80	57/84	9.6 (7.5, 11.8)		7.4 (5.7, 7.6)	0.53 (0.35, 0.79)
Not Evaluable	3/9	7/15	NR (3.4, NE)		7.8 (5.6, NE)	0.87 (0.22, 3.49)*
Histology Subtype						
Non-keratinizing	54/114	73/113	9.6 (7.8, 11.8)		7.4 (5.7, 7.5)	0.47 (0.33, 0.67)
Keratinizing	5/9	4/8	5.6 (2.8, NE)		5.5 (1.7, NE)	0.70 (0.19, 2.61)*
Unknown	6/8	10/11	4.7 (2.7, NE)		7.6 (4.1, 7.8)	1.02 (0.37, 2.82)*
Prior Anticancer Therapies						
Drug	41/83	59/88	9.6 (7.6, NE)		7.1 (5.5, 7.6)	0.54 (0.36, 0.81)
Surgeries	4/6	2/4	4.9 (2.8, NE)		4.4 (4.2, NE)	1.09 (0.20, 6.05)*
Radiotherapy	42/84	61/91	8.8 (7.6, NE)		7.1 (5.5, 7.6)	0.54 (0.36, 0.81)



Abbreviations: T + C, Tislelizumab + Chemotherapy; P + C, Placebo + Chemotherapy; NE, Not Estimable; NR, Not Reached; EBV, Epstein-Barr virus; PD-L1, programmed cell death protein ligand-1.
Hazard ratio and its 95% CI was estimated from unstratified Cox model with Placebo + Gemcitabine + Cisplatin group as reference group.
PD-L1 expression level on tumour cells was centrally determined by SP263 IHC. Not evaluable: Samples for which a PD-L1 expression level could not be determined due to technical reasons.
* The confidence interval of this subgroup is not shown completely due to space limit.

Table 31-Subgroup Analysis: PFS Assessed by IRC (ITT) – Study 309 (Closeout, DCO: 08 December 2023)

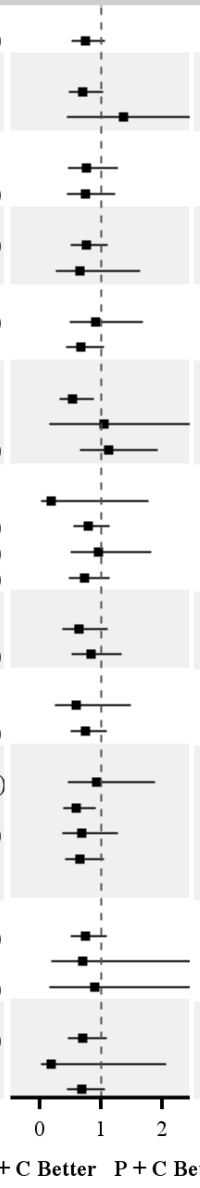
Subgroup	Events/ Total T + C	Events/ Total P + C	Median (95% CI) T + C	Hazard Ratio (95% CI)	Median (95% CI) P + C	Hazard Ratio (95% CI)
Overall	95/131	106/132	9.6 (7.6, 11.6)		7.4 (5.6, 7.6)	0.55 (0.41, 0.73)
Age Group 1						
< 65 years	85/121	97/120	9.8 (7.7, 11.7)		7.4 (5.7, 7.6)	0.50 (0.37, 0.68)
≥ 65 years	10/10	9/12	5.1 (1.5, 9.6)		6.4 (4.4, 11.9)	1.89 (0.74, 4.83)*
Age Group 2						
< 50 years	49/63	56/64	9.2 (6.7, 11.7)		7.4 (5.6, 7.7)	0.54 (0.36, 0.80)
≥ 50 years	46/68	50/68	9.6 (7.5, 11.9)		7.4 (5.5, 7.6)	0.56 (0.37, 0.85)
Sex						
Male	73/103	84/103	9.7 (7.5, 11.7)		7.1 (5.6, 7.6)	0.57 (0.41, 0.78)
Female	22/28	22/29	8.9 (6.7, 13.3)		7.5 (5.5, 7.8)	0.42 (0.22, 0.81)
ECOG Performance Status						
0	38/51	37/46	9.6 (7.5, 11.5)		7.1 (5.5, 7.6)	0.54 (0.34, 0.86)
1	57/80	69/86	9.9 (5.7, 14.7)		7.4 (5.6, 7.7)	0.53 (0.37, 0.76)
Smoking Status						
Never	58/74	53/66	9.6 (7.6, 11.9)		7.4 (5.5, 7.6)	0.39 (0.26, 0.59)
Current	5/6	6/6	5.6 (4.0, NE)		6.6 (1.3, NE)	0.68 (0.19, 2.45)*
Former	32/51	47/60	9.7 (5.7, 11.7)		7.4 (5.5, 7.7)	0.66 (0.42, 1.04)
Current Disease Stage						
Local Recurrent	3/5	5/7	11.9 (11.6, NE)		2.8 (0.6, NE)	0.11 (0.01, 0.96)
Metastatic	92/126	101/125	9.6 (7.5, 11.5)		7.4 (5.7, 7.6)	0.57 (0.43, 0.77)
Primary	35/46	31/40	9.6 (7.4, 11.5)		7.4 (5.6, 7.7)	0.55 (0.33, 0.90)
Recurrent	57/80	70/85	8.8 (5.7, 13.3)		7.4 (5.6, 7.6)	0.58 (0.40, 0.82)
Liver Metastases at Baseline						
Yes	43/56	51/56	7.5 (5.6, 11.5)		5.7 (4.5, 7.4)	0.44 (0.28, 0.69)
No	52/75	55/76	9.9 (7.8, 11.9)		7.6 (5.8, 7.8)	0.63 (0.43, 0.92)
EBV DNA Level						
< 500 IU/mL	19/26	26/37	13.3 (7.7, 31.2)		7.7 (5.4, 11.7)	0.60 (0.33, 1.08)
≥ 500 IU/mL	76/105	80/95	8.8 (5.9, 9.9)		7.1 (5.6, 7.5)	0.51 (0.37, 0.71)
PD-L1 Expression in TC						
< 1% TC	22/27	16/22	7.7 (5.5, 11.6)		4.3 (3.0, 7.6)	0.53 (0.27, 1.04)
≥ 1% TC	70/96	79/97	9.7 (7.6, 11.7)		7.4 (5.7, 7.6)	0.51 (0.36, 0.71)
< 10% TC	34/42	27/35	7.6 (5.6, 11.6)		5.5 (4.2, 7.4)	0.55 (0.33, 0.93)
≥ 10% TC	58/81	68/84	9.7 (7.8, 11.8)		7.4 (5.7, 7.7)	0.49 (0.34, 0.71)
Not Evaluable	3/8	11/13	NR (3.4, NE)		8.8 (1.4, 11.9)	0.62 (0.17, 2.24)*
Histology Subtype						
Non-keratinizing	84/116	94/117	9.6 (7.6, 11.7)		7.4 (5.7, 7.6)	0.54 (0.40, 0.73)
Keratinizing	5/8	7/10	8.6 (2.8, NE)		5.5 (1.7, 10.1)	0.52 (0.16, 1.67)
Unknown	6/7	5/5	5.9 (2.7, 11.6)		5.6 (1.4, NE)	0.48 (0.13, 1.82)
Prior Anticancer Therapies						
Drug	58/83	72/88	9.7 (5.9, 11.9)		7.4 (5.5, 7.6)	0.54 (0.38, 0.77)
Surgeries	5/6	2/4	5.8 (2.8, NE)		4.4 (4.2, NE)	0.94 (0.17, 5.25)*
Radiotherapy	59/84	74/91	9.7 (5.9, 11.9)		7.4 (5.6, 7.6)	0.55 (0.39, 0.78)



Source: ADTTE. Data cutoff: 08DEC2023. Data extraction: 26JAN2024.
Abbreviations: T + C, Tislelizumab + Chemotherapy; P + C, Placebo + Chemotherapy; NE, Not Estimable; NR, Not Reached; EBV, Epstein-Barr virus; PD-L1, programmed cell death protein ligand-1.
Hazard ratio and its 95% CI was estimated from unstratified Cox model with Placebo + Gemcitabine + Cisplatin group as reference group.
PD-L1 expression level on tumour cells was centrally determined by SP263 IHC. Not evaluable: Samples for which a PD-L1 expression level could not be determined due to technical reasons.
* The confidence interval of this subgroup is not shown completely due to space limit.

Table 32-Subgroup Analysis of OS - Study 309 (Closeout, DCO: 08 December 2023)

Subgroup	Events/ Total T + C	Events/ Total P + C	Median (95% CI) T + C	Hazard Ratio (95% CI)	Median (95% CI) P + C	Hazard Ratio (95% CI)
Overall	55/131	64/132	45.3 (33.4, NE)		31.8 (25.0, NE)	0.74 (0.52, 1.06)
Age Group 1						
< 65 years	49/121	58/120	NR (35.1, NE)		31.8 (23.4, NE)	0.70 (0.48, 1.03)
≥ 65 years	6/10	6/12	21.9 (4.8, NE)		25.1 (11.4, NE)	1.36 (0.44, 4.24)*
Age Group 2						
< 50 years	27/63	33/64	NR (30.1, NE)		31.8 (23.0, NE)	0.76 (0.46, 1.27)
≥ 50 years	28/68	31/68	45.3 (30.7, NE)		30.0 (18.2, NE)	0.74 (0.44, 1.23)
Sex						
Male	47/103	54/103	45.3 (30.7, NE)		28.4 (22.8, 40.6)	0.75 (0.51, 1.11)
Female	8/28	10/29	NR (23.7, NE)		NR (16.6, NE)	0.65 (0.25, 1.64)
ECOG Performance Status						
0	22/51	19/46	45.3 (30.1, NE)		NR (25.1, NE)	0.91 (0.49, 1.68)
1	33/80	45/86	NR (27.9, NE)		27.0 (18.2, 40.6)	0.67 (0.42, 1.04)
Smoking Status						
Never	28/74	34/66	NR (35.5, NE)		30.0 (15.4, NE)	0.53 (0.32, 0.88)
Current	2/6	2/6	NR (13.3, NE)		NR (17.5, NE)	1.05 (0.15, 7.44)*
Former	25/51	28/60	30.7 (21.9, NE)		31.6 (25.0, NE)	1.12 (0.65, 1.92)
Current Disease Stage						
Local Recurrent	1/5	4/7	NR (32.9, NE)		15.5 (0.6, NE)	0.18 (0.02, 1.77)
Metastatic	54/126	60/125	45.3 (33.4, NE)		33.6 (25.0, NE)	0.79 (0.54, 1.14)
Primary	20/46	17/40	43.0 (22.7, NE)		39.9 (26.7, NE)	0.95 (0.50, 1.81)
Recurrent	34/80	43/85	45.3 (34.9, NE)		27.0 (20.5, NE)	0.73 (0.46, 1.14)
Liver Metastases at Baseline						
Yes	23/56	29/56	NR (22.5, NE)		26.7 (17.4, NE)	0.64 (0.37, 1.10)
No	32/75	35/76	45.3 (32.9, NE)		36.8 (25.0, NE)	0.83 (0.51, 1.34)
EBV DNA Level						
< 500 IU/mL	7/26	14/37	NR (43.0, NE)		NR (23.4, NE)	0.60 (0.24, 1.48)
≥ 500 IU/mL	48/105	50/95	35.5 (27.5, NE)		26.9 (19.1, 40.6)	0.74 (0.50, 1.10)
PD-L1 Expression in TC						
< 1% TC	17/27	14/22	25.4 (13.1, 43.0)		18.3 (10.8, NE)	0.92 (0.45, 1.87)
≥ 1% TC	34/96	46/97	NR (45.3, NE)		31.8 (23.4, NE)	0.59 (0.38, 0.91)
< 10% TC	19/42	20/35	43.0 (25.4, NE)		25.1 (16.6, NE)	0.68 (0.36, 1.27)
≥ 10% TC	32/81	40/84	NR (32.2, NE)		31.6 (20.5, NE)	0.66 (0.41, 1.05)
Not Evaluable	4/8	4/13	24.5 (9.1, NE)		NR (25.0, NE)	2.95 (0.73, NE)
Histology Subtype						
Non-keratinizing	48/116	57/117	45.3 (34.9, NE)		33.6 (25.0, NE)	0.74 (0.50, 1.08)
Keratinizing	4/8	5/10	27.9 (2.8, NE)		25.0 (1.7, NE)	0.71 (0.19, 2.65)*
Unknown	3/7	2/5	32.2 (16.0, NE)		NR (17.8, NE)	0.89 (0.15, 5.41)*
Prior Anticancer Therapies						
Drug	35/83	45/88	45.3 (33.4, NE)		26.9 (20.5, NE)	0.70 (0.45, 1.09)
Surgeries	2/6	2/4	NR (2.8, NE)		17.4 (14.4, NE)	0.18 (0.02, 2.05)*
Radiotherapy	35/84	47/91	NR (34.9, NE)		26.9 (20.1, NE)	0.68 (0.44, 1.06)



Exploratory Analyses by PD-L1 Expression Levels

PFS

The impact of baseline tumour cell PD-L1 expression levels on PFS outcomes was evaluated as an exploratory analysis, using both the DCO date of the IA (26 March 2021) and the study end date of 8 December 2023.

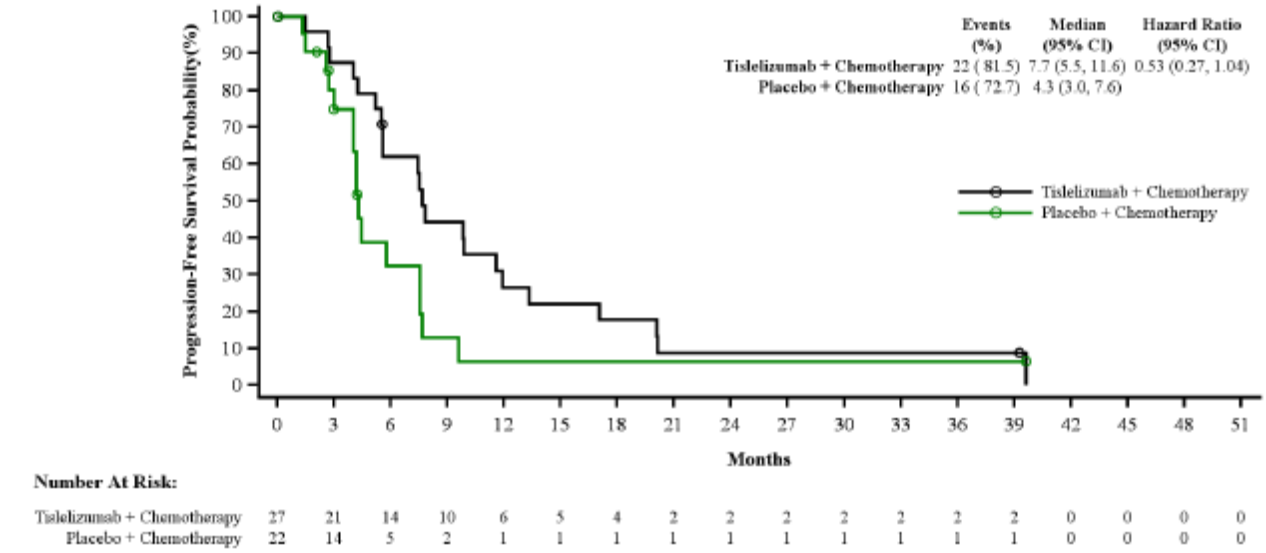
Table 33-PFS by PD-L1 Expression Levels (ITT Analysis Set) – Study 309

Subgroup	Event/Total (%) Arm Tisle+GC	Event/Total (%) Arm P+GC	Median (95%CI) Arm Tisle+GC	Median (95%CI) Arm P+GC	Hazard Ratio (95%CI)
DCO: 26 Mar 2021					

Subgroup	Event/Total (%) Arm Tisle+GC	Event/Total (%) Arm P+GC	Median (95%CI) Arm Tisle+GC	Median (95%CI) Arm P+GC	Hazard Ratio (95%CI)
PD-L1 < 1%	14/27 (51.9)	15/21 (71.4)	7.8 (5.5, 9.8)	4.3 (3.0, 7.6)	0.35 (0.16, 0.76)
PD-L1 ≥ 1%	48/95 (50.5)	65/96 (67.7)	9.6 (7.6, 11.8)	7.4 (5.7, 7.6)	0.50 (0.34, 0.73)
PD-L1 < 10%	20/42 (47.6)	23/33 (69.7)	7.8 (7.4, NE)	5.5 (4.2, 7.4)	0.38 (0.20, 0.72)
PD-L1 ≥ 10%	42/80 (52.5)	57/84 (67.9)	9.6 (7.5, 11.8)	7.4 (5.7, 7.6)	0.53 (0.35, 0.79)
DCO: 08 Dec 2023					
PD-L1 < 1%	22/27 (81.5)	16/22 (72.7)	7.7 (5.5, 11.6)	4.3 (3.0, 7.6)	0.53 (0.27, 1.04)
PD-L1 ≥ 1%	70/96 (72.9)	79/97 (81.4)	9.7 (7.6, 11.7)	7.4 (5.7, 7.6)	0.51 (0.36, 0.71)
PD-L1 < 10%	34/42 (81.0)	27/35 (77.1)	7.6 (5.6, 11.6)	5.5 (4.2, 7.4)	0.55 (0.33, 0.93)
PD-L1 ≥ 10%	58/81 (71.6)	68/84 (81.0)	9.7 (7.8, 11.8)	7.4 (5.7, 7.7)	0.49 (0.34, 0.71)

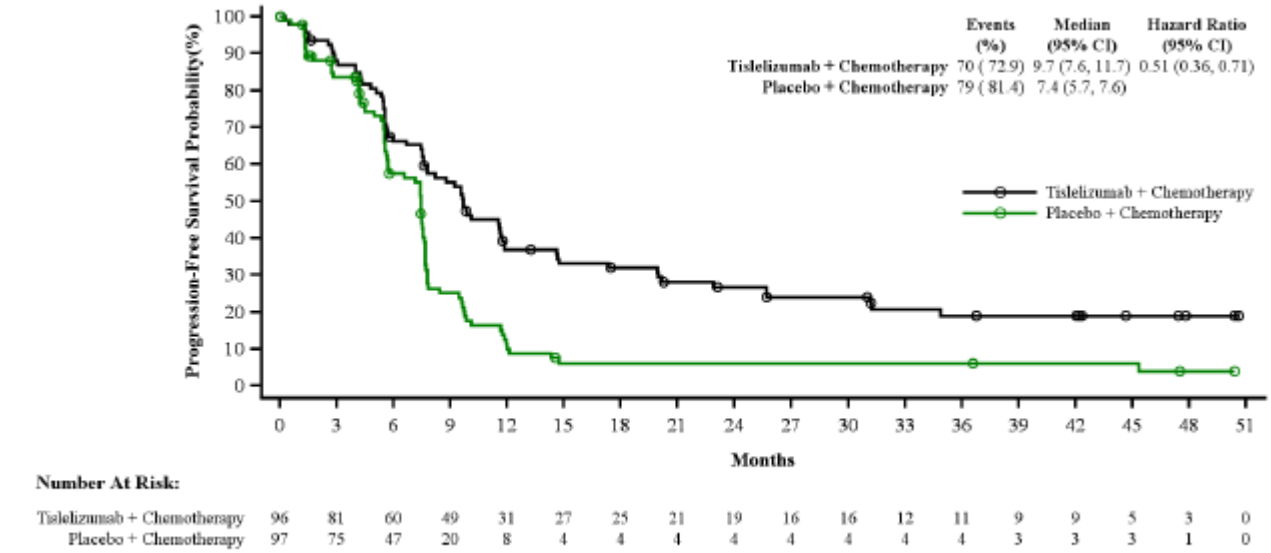
PD-L1 expression level on tumour cells was centrally determined by SP263 IHC.
Abbreviations: DCO, data cutoff; IHC, immunohistochemistry; ITT, Intent-to-Treat (Analysis Set); NE, not estimable; P+GC, placebo in combination with gemcitabine plus cisplatin; PD-L1, programmed cell death ligand-1; PFS, progression-free survival; Tisle+GC, tislelizumab in combination with gemcitabine plus cisplatin.
Source: Table 9, SCE

Figure 28-Kaplan-Meier Plot of PFS per RECIST version 1.1 by IRC for Patients with PD-L1 Expression < 1%, ITT Analysis Set (Closeout, DCO 8 December 2023)



Source: ADTTE. Data cutoff: 08DEC2023. Data extraction: 26JAN2024.
Hazard ratio and its 95% CI was estimated from unstratified Cox model with Placebo + Gemcitabine + Cisplatin group as reference group.
unblind/bgb_a317/filing_npc309/npc309_2024_sce_eu/dev/pgm/tlfs/f-subpfs.sas 05AUG2024 00:15 f-14-2-1-1-1-5-1-subpfs-irc-1a.rtf

Figure 29-Kaplan-Meier Plot of PFS per RECIST version 1.1 by IRC for Patients with PD-L1 Expression ⩾ 1%, ITT Analysis Set (Closeout, DCO 8 December 2023)



Source: ADTTE. Data cutoff: 08DEC2023. Data extraction: 26JAN2024.
Hazard ratio and its 95% CI was estimated from unstratified Cox model with Placebo + Gemcitabine + Cisplatin group as reference group.
unblind/bgb_a317/filing_npc309/npc309_2024_sce_eu/dev/pgm/tlfs/f-subpfs.sas 05AUG2024 00:15 f-14-2-1-1-1-5-2-subpfs-irc-1b.rtf

OS

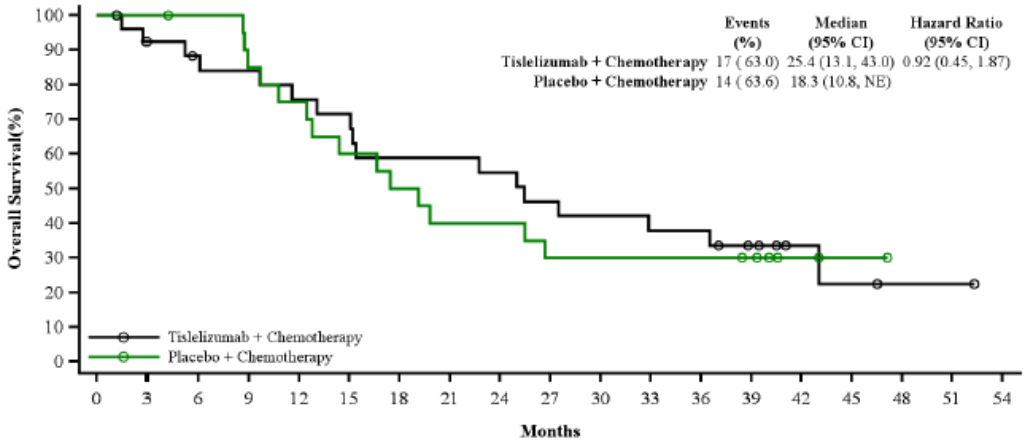
The impact of baseline PD-L1 expression levels on OS outcomes was evaluated as an exploratory analysis, using the study end date of 08 December 2023.

Table 34-OS by PD-L1 Expression Levels (ITT Analysis Set) – Study 309 (Closeout, DCO: 08 December 2023)

Subgroup	Event/Total (%) Arm Tisle+GC	Event/Total (%) Arm P+GC	Median (95%CI) Arm Tisle+GC	Median (95%CI) Arm P+GC	Hazard Ratio (95%CI)
PD-L1 < 1%	17/27 (63.0)	14/22 (63.6)	25.4 (13.1, 43.0)	18.3 (10.8, NE)	0.92 (0.45, 1.87)
PD-L1 ≥ 1%	34/96 (35.4)	46/97 (47.4)	NR (45.3, NE)	31.8 (23.4, NE)	0.59 (0.38, 0.91)
PD-L1 < 10%	19/42 (45.2)	20/35 (57.1)	43.0 (25.4, NE)	25.1 (16.6, NE)	0.68 (0.36, 1.27)
PD-L1 ≥ 10%	32/81 (39.5)	40/84 (47.6)	NR (32.2, NE)	31.6 (20.5, NE)	0.66 (0.41, 1.05)

PD-L1 expression level on tumour cells was centrally determined by SP263 IHC.
Abbreviations: IHC, immunohistochemistry; ITT, Intent-to-Treat (Analysis Set); NE, not estimable; NR, not reached; OS, overall survival; P+GC, placebo in combination with gemcitabine plus cisplatin; PD-L1, programmed cell death ligand-1; Tisle+GC, tislelizumab in combination with gemcitabine plus cisplatin.

Figure 30-Kaplan-Meier Plot of OS for Patients with PD-L1 Expression < 1%, ITT Analysis Set (Closeout, DCO 8 December 2023)

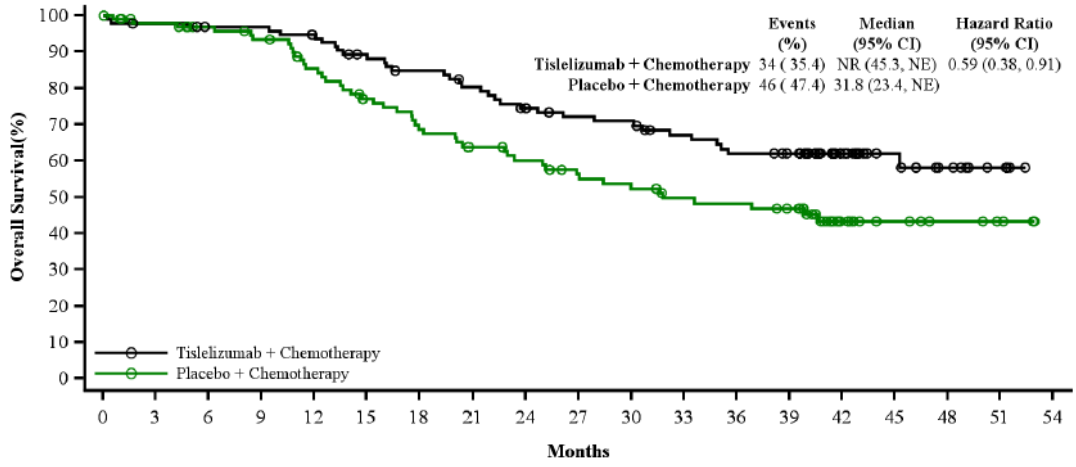


Number At Risk:

Tislelizumab + Chemotherapy	27	23	21	20	18	17	14	14	13	11	10	9	9	6	3	2	1	1	0
Placebo + Chemotherapy	22	21	20	17	15	12	10	8	8	6	6	6	6	5	2	1	0	0	0

Source: ADTTE. Data cutoff: 08DEC2023. Data extraction: 26JAN2024.
Abbreviations: NE, Not Estimable.
Hazard ratio and its 95% CI was estimated from unstratified Cox model with Placebo + Gemcitabine + Cisplatin group as reference group.
unblind/bgb_a317/filing_npc309/npc309_2024_sce_eu/dev/pgm/tlfs/f-subos.sas 05AUG2024 00:34 f-14-2-2-1-5-1-1-subos-1a.rtf

Figure 31 Kaplan-Meier Plot of OS for Patients with PD-L1 Expression ≥ 1%, ITT Analysis Set (Closeout, DCO 8 December 2023)



Number At Risk:

Tislelizumab + Chemotherapy	96	93	90	90	87	80	75	70	63	59	58	52	48	45	26	16	10	5	0
Placebo + Chemotherapy	97	91	86	82	73	64	57	52	48	43	40	36	35	32	14	8	5	3	0

Source: ADTTE. Data cutoff: 08DEC2023. Data extraction: 26JAN2024.
Abbreviations: NE, Not Estimable; NR, Not Reached.
Hazard ratio and its 95% CI was estimated from unstratified Cox model with Placebo + Gemcitabine + Cisplatin group as reference group.
unblind/bgb_a317/filing_npc309/npc309_2024_sce_eu/dev/pgm/tlfs/f-subos.sas 05AUG2024 00:34 f-14-2-2-1-5-1-2-subos-1b.rtf

Crossover to Tislelizumab Monotherapy and Impact on OS

To adjust for the effect of crossover, and to estimate the benefit of tisle + GC on OS assuming no control arm patients had crossed over to receive tislelizumab after disease progression, 2 supplementary OS analyses were performed, using an RPSFT model and the two-stage method (for details on the methods see 2.4.2. Statistical methods) based on the study end date of 08 December 2023. The results from the 2 supportive analyses are shown below.

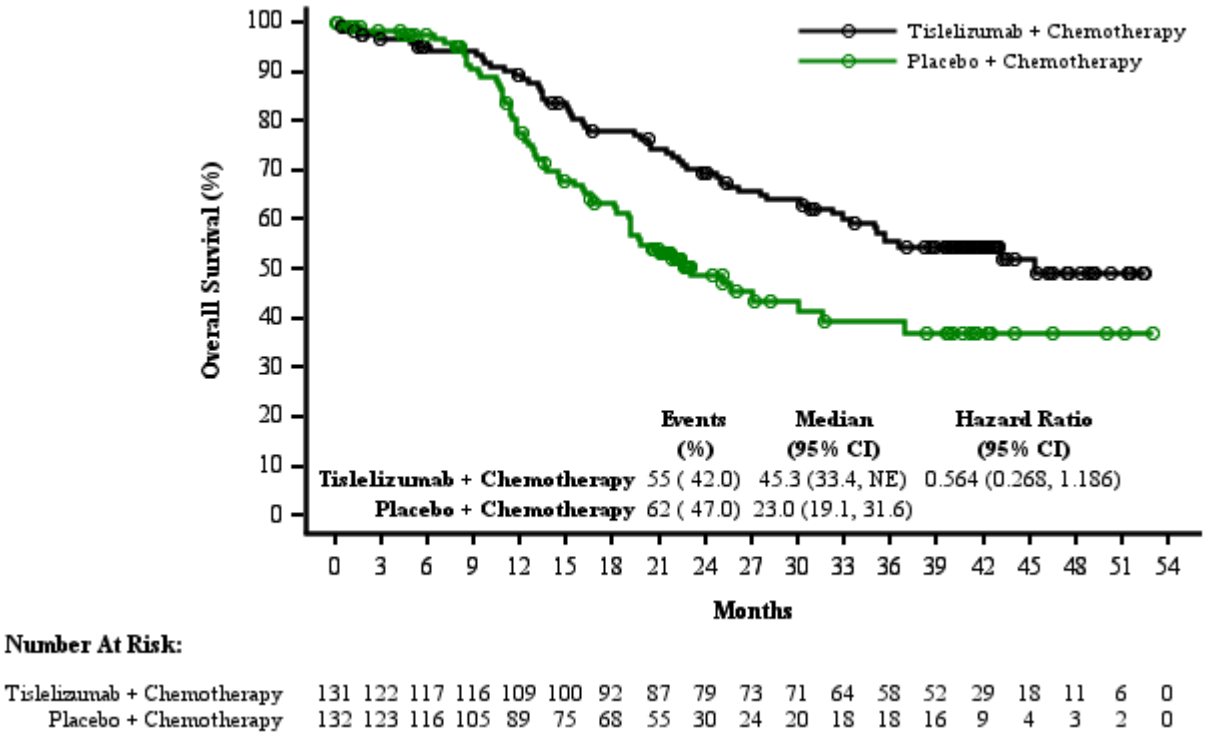
Rank-Preserving Structural Failure Time (RPSFT) Method

Table 35-Overall Survival (ITT) – Supportive Analysis Using RPSFT Method Without Multivariate Adjustments (Adjusted for Crossover Patients Only) – Study 309 (08 December 2023 Cutoff)

	Tislelizumab + Chemotherapy (N = 131)	Placebo + Chemotherapy (N = 132)
Overall Survival		
Death, n (%)	55 (42.0)	62 (47.0)
Censored, n (%)	76 (58.0)	70 (53.0)
Stratified Hazard Ratio (95% CI) [a]	0.564 (0.268, 1.186)	
Overall Survival (month)		
Median (95% CI)	45.3 (33.41, NE)	23.0 (19.13, 31.61)
Event Free Rate at, % (95% CI)		
6 month (95% CI)	95.3 (89.87, 97.87)	97.6 (92.83, 99.23)
12 month (95% CI)	89.6 (82.78, 93.84)	77.8 (69.05, 84.28)
24 month (95% CI)	69.4 (60.35, 76.83)	48.9 (38.96, 58.20)
48 month (95% CI)	49.2 (37.98, 59.53)	37.2 (26.24, 48.09)

Abbreviations: NE, Not Estimable; NR, Not Reached.
Medians and other quartiles were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley. Event free rates were estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula. Placebo + Gemcitabine + Cisplatin arm was the reference group for hazard ratio. a Stratified by stratification factors: gender (male versus female) and liver metastases status(yes versus no). 95% CIs for HR was obtained by inflating the standard error of the log-hazard ratio to preserve the ITT p-value.
Shrinking factor obtained from accelerated failure time model by comparing PPS between switcher and non-switcher in the control group is 0.5331, which was used to calculate counterfactual survival times. Hazard ratio was estimated from Cox model with Placebo + Gemcitabine + Cisplatin arm as reference group without multivariate adjustments.

Figure 32-Kaplan-Meier Plot of Overall Survival – – Supportive Analysis Using RPSFT Method Without Multivariate Adjustments (Adjusted for Crossover Patients Only) – Study 309 (08 December 2023 Cutoff)



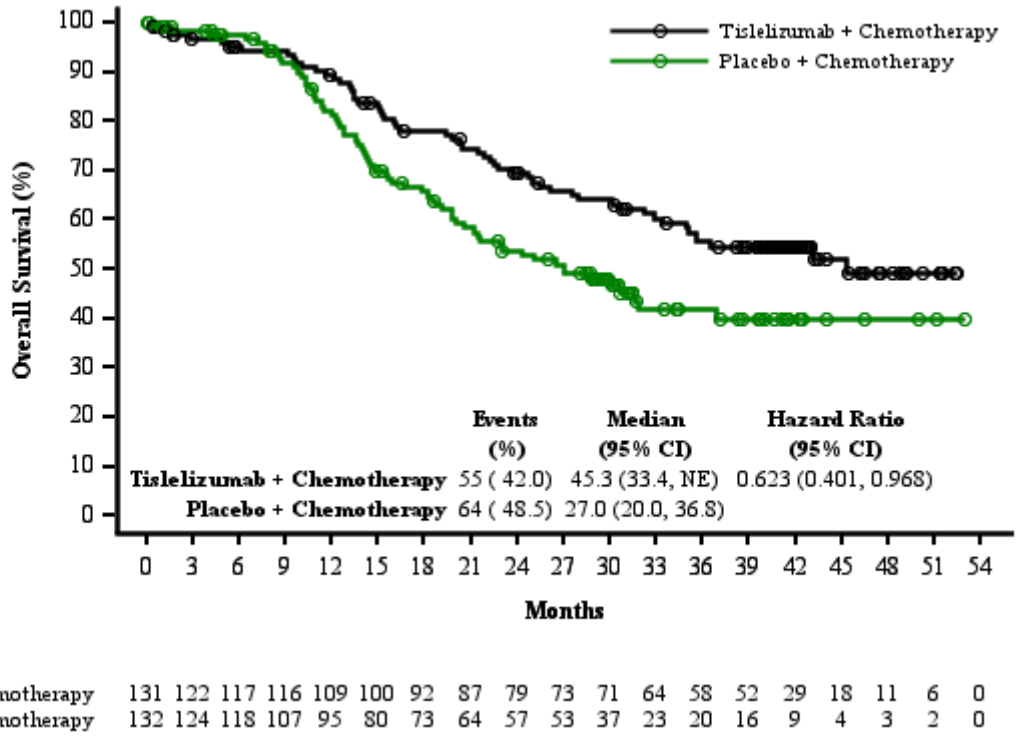
Two Stage Method

Table 36-Overall Survival (ITT) – Supportive Analysis Using Two Stage Method (Adjusted for Crossover Patients Only) – Study 309 (08 December 2023 Cutoff)

	Tislelizumab + Chemotherapy (N = 131)	Placebo + Chemotherapy (N = 132)
Overall Survival		
Death, n (%)	55 (42.0)	64 (48.5)
Censored, n (%)	76 (58.0)	68 (51.5)
Stratified Hazard Ratio (95% CI) [a]	0.623 (0.401, 0.968)	
Overall Survival (month)		
Median (95% CI)	45.3 (33.41, NE)	27.0 (19.98, 36.83)
Event Free Rate at, % (95% CI)		
6 month (95% CI)	95.3 (89.87, 97.87)	97.6 (92.83, 99.23)
12 month (95% CI)	89.6 (82.78, 93.84)	82.3 (74.08, 88.06)
24 month (95% CI)	69.4 (60.35, 76.83)	53.8 (44.21, 62.46)
48 month (95% CI)	49.2 (37.98, 59.53)	39.7 (29.45, 49.72)

Abbreviations: NE, Not Estimable; NR, Not Reached.
Tislelizumab + Chemotherapy: tislelizumab in combination with gemcitabine plus cisplatin.
Placebo + Chemotherapy: placebo in combination with gemcitabine plus cisplatin.
Medians and other quartiles were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley. Event free rates were estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula. Placebo + Gemcitabine + Cisplatin arm was the reference group for hazard ratio.
a Stratified by stratification factors: gender (male versus female) and liver metastases status (yes versus no). 95% CIs for HR was obtained by inflating the standard error of the log-hazard ratio to preserve the ITT p-value.
Shrinking factor obtained from accelerated failure time model by comparing PPS between switcher and non-switcher in the control group is 0.7305, which was used to calculate counterfactual survival times.

Figure 33-Kaplan-Meier Plot of Overall Survival – Supportive Analysis Using Two Stage Method (Adjusted for Crossover Patients Only) – Study 309 (08 December 2023 Cutoff)



Applicability of Study 309 Data to the EU Patient Population

Comparison of Baseline and Disease Characteristics Between Study 309 and EU NPC Patient Population

An initial review and analysis of scientific and medical literature on European NPC patients' baseline and disease characteristics was conducted and found consistent features across Central, Eastern, and Western Europe. Comparison with the Study 309 NPC population was provided, see Table 37.

Table 37-Comparison of Baseline and Disease Characteristics Between Study 309 and EU NPC Patient Population

Characteristics	BGB-A317-309 Patient Population (N=263)	EU Patient Population*
Age (years), median	50.0	50.2
Gender male (%)	78.3	70.9
Smoking status current/former (%)	46.8	49.9
Clinical TNM stage 7th [a] (%)		
Stage I, II, III	4.9	52.2
Stage IV	95.1	44.6
Histology within NPC [b] (%)		
Non-keratinising	86.3	85.9
Keratinising	6.5	11.0
Basaloid/unknown	7.2	1.0
EBV expression (%)		
EBV positive	76.0	38.9
EBV negative	24.0	36.5
EBV unknown	0	24.6

Literature search criteria of "nasopharyngeal carcinoma, European" without any specific criteria were used.
The following pooling strategy was applied to selected literature: 1) age at randomisation and age at diagnosis were combined; 2) disease Stage IVA, IVB (if applicable) were combined into Stage IV.
Each characteristic was summarised based on available literature.
Liver metastasis was not summarised as reported in only one paper in EU population, which reported as 24%.
a Stage I, II, III was combined under this category to align with the target population in Study 309.
b Differentiated non-keratinising (WHO TYPE II) and undifferentiated non-keratinising (WHO TYPE III) was combined under this category as this two histology are subtype in non-keratinising squamous cell per 2018 WHO histology classification.
*Sources: d'Espiney et al 2009; Eduardo et al 2010; Arnold et al 2013; Robinson et al 2013; Li et al 2014; Svajdler et al 2016; Ruuskanen et al 2018; Bossi et al 2019; Ruuskanen et al 2019; Economopoulou et al 2022; Grønlund van et al 2021; Simon et al 2022; van Velsen et al 2024.

Differences were noted in EBV infection rates, disease histology and clinical stages and were discussed by the Applicant as follows:

- EBV Status

The oncogenic role of EBV in the genesis of NPC is universally recognized, especially in endemic regions (Li et al 2002; Tsao et al 2017). The NPC pooled analysis in European patients showed an EBV infection rate of 39%, which is lower than the 76% described in Study 309, though EBV status was reported as unknown in approximately 25% of European patients with available data (d'Espiney et al 2009; Eduardo et al 2010; Arnold et al 2013; Ruuskanen et al 2018; Grønlund et al 2021), which may have contributed to the observed differences.

Despite these differences, the treatment recommendations for non-EBV-associated NPC are identical to EBV-associated disease.

Results from the Study 309 subgroup analysis also align with this approach and show improved PFS

clinical benefit with tisle + GC versus placebo + GC in both EBV-negative (DNA level < 500 IU/mL, HR: 0.45 (95% CI: 0.21, 0.94) and EBV-positive patients (DNA level ⩾ 500 IU/mL; HR: 0.52 (95% CI: 0.36, 0.75), supporting treatment of recurrent/metastatic NPC with tislelizumab plus chemotherapy, regardless of EBV status (Table 13-Selection and Timing of Dose for Each Patient*2*).

- Clinical Stage

There are no reports indicating differences in terms of disease staging patterns between endemic and non-endemic areas, with the International Union Against Cancer (UICC) and American Joint Committee on Cancer (AJCC) as the most frequently used staging systems for NPC across the world.

Clinical data from 2629 Asian NPC patients reported overall disease stage distribution as Stage I: 4.6%, Stage II: 14.7%, Stage III: 53.2%, and Stage IV: 27.5% of NPC patients (Li et al 2014), which is consistent with that reported in Europe, with more than 70% of NPC patients diagnosed with advanced-stage disease (Mao et al 2009; Lai et al 2011; Lee et al 2014).

The observed differences in clinical stages noted between the European pooled analysis and Study 309 could be due to the fact that the latter excluded patients with early stage or local recurrence suitable for curative surgery or radiotherapy (resulting in a high percentage of Stage IV patients), whereas no clinical stage restriction was applied to the European pooled analysis of NPC retrieved in the literature review, given the limited data reported in the EU, where NPC is rare. While the European NPC literature is very limited, clinical staging incidence was generally consistent with that reported in endemic areas (d'Espiney et al 2009; Eduardo et al 2010; Arnold et al 2013; Robinson et al 2013; Li et al 2014; Ruuskanen et al 2018; Ruuskanen et al 2019; Economopoulou et al 2022; van Velsen et al 2024), further supporting applicability of Study 309 data to the European NPC population.

- Minor Differences in Histology

Based on literature review, the non-keratinising NPC subtype comprises the vast majority of cases in both endemic countries (ranging from 97% to 98%) (Wang et al 2011; Wang et al 2016; Wei and Sham 2005) and non-endemic areas, including European countries like the Netherlands, Finland, Italy, Greece, Portugal, Norway, Slovakia, Czech Republic, and the United Kingdom.

Whereas the rate of keratinising histology is more prevalent in non-endemic compared to endemic areas, where it ranges from 2% to 3% (Wei and Sham 2005; Wang et al 2011; Wang et al 2016), this is still a less prevalent histological subtype in low-incidence regions, including Europe (11%), with incidence ranging from 0.8% to 22%.

Study 309 post-hoc analysis by histological subtypes showed that patients with both keratinising and non-keratinising histologies benefited from treatment with tisle + GC over placebo + GC, with PFS HR of 0.70 (95% CI: 0.19, 2.61) and 0.47 (95% CI: 0.33, 0.67), respectively, though these data should be interpreted with caution due to the limited sample size in the keratinising histology subgroup.

Similarly, favourable objective antitumour responses in the tislelizumab plus chemotherapy arm were observed, regardless of histology, with higher confirmed ORR per IRC reported in Arm Tisle+GC versus Arm P+GC (55.6% versus 37.5% in patients with keratinising NPC, and 71.1% versus 57.5% in those with non-keratinising NPC, respectively).

To further evaluate the applicability of Study 309 to European patients with recurrent/metastatic NPC in the 1L setting,

- **a protocol-driven targeted-literature review (TLR),**
- **NPC clinician interviews** (results not shown)**,** and
- **statistical analyses**

were conducted.

Targeted-literature review (TLR)

Methods

A TLR was conducted across various data sources (eg, Embase® and MEDLINE databases, ClinicalTrials.gov registry) to identify peer-reviewed articles reporting data relevant to the predefined research questions.

The study selection process involved evaluating publications retrieved by the searches against predetermined PICOS criteria.

Results

No interventional studies were found in the relevant NPC patient setting, as none investigated anti-PD-(L)1 ICIs and/or reported characteristics and outcomes in European 1L NPC patients.

Data were extracted from 3 real-world observational studies (Netto 2020; Economopoulou 2022; Rampinelli 2023) reporting characteristics and/or outcomes among 1L recurrent or metastatic NPC patients in Europe. Two of these studies were "near-miss" as they did not report characteristics/outcomes among 1L recurrent or metastatic NPC patients separately.

When comparing baseline characteristics between the European RWE studies and Study 309, some differences in race, histology, smoking status, and recurrent or metastatic status were observed.

- The findings from the RWE studies were generally consistent with the initial literature review (Section 3.2), except for a higher proportion of current smokers (30% versus 5%) and a lower proportion of former smokers (24% versus 42%) reported among patients from Greece/Italy from the RWE study compared to Study 309, respectively, which may account for country-specific differences. However, the overall proportion of current and former smokers combined encompassed nearly half the overall population and was comparable to that reported in Study 309 (54% versus 47%, respectively), and was consistent with the initial literature review.

Overall, as the TLR data from European recurrent or metastatic NPC patients treated in the 1L setting were very limited, direct conclusions on comparability with Study 309 were challenging.

Statistical Analysis to Extrapolate Treatment Effects Observed in Study 309 Relative to European NPC Patients

Methods

- The 3 RWE studies conducted in Europe that were identified in the TLR were screened against the predetermined PICOS criteria to identify the relevant NPC target population for the statistical analysis.
- Information gathered during the interviews with the NPC clinical experts was incorporated into the analysis to aid the selection of effect modifiers and prognostic factors (age, EBV status, liver metastases, and disease stage). Two studies were selected for statistical analyses based on the availability of patient characteristics identified as potential effect modifiers and prognostic factors:
    - Base case: Rampinelli 2023 study population was used, since it included 1L recurrent or metastatic NPC patients and provided data on most of the selected effect modifiers.
    - Sensitivity analysis: Economopoulou 2022 study population was used, as patients included in this publication were a mix of NPC treatment lines.

An outcome regression approach was used. Therefore, a Cox proportional hazard (PH) regression model for the conditional mean response (or outcome) for a given treatment was fitted, with observed covariates (age, EBV status, liver metastases, and disease stage), and their interactions included. This regression model was then used to predict the treatment effect (PFS and OS) in the target population

(the population observed in the RWE studies) using its published aggregated characteristics as inputs in the predictive equation.

Results

Disease stage was prespecified as an effect modifier. As only seven out of 263 patients in RATIONALE-309 had disease stage I-III at baseline and the inclusion of disease stage (stage I-III vs stage IV) as an effect modifier resulted in convergence issues in the models, only the main effect of disease stage remained in the model. The regression model for the base case included adjustment for age and EBV as effect modifiers, as well as disease stage and liver metastases (for PFS only) as prognostic factors. The regression model for the sensitivity analysis included adjustment for age, EBV and liver metastases as effect modifiers, as well as disease stage as a prognostic factor.

- PFS

For PFS, outcome regressions were conducted using Cox PH models, and were based on 263 patients with 201 events for both the base case and sensitivity analyses.

For the base case, effect modifiers included age and EBV positivity; liver metastases and ECOG status could not be included as effect modifiers due to lack of data reported in the target population, while disease stage was not included as an effect modifier due to issues with convergence. Disease stage was, however, included as a prognostic factor, alongside liver metastases. Smoking status, histology and ECOG status were not included as prognostic factors as they did not improve model fit based on AIC and BIC.

For the sensitivity analysis, effect modifiers included age, EBV positivity and liver metastases; disease stage was similarly not included due to issues with convergence. Disease stage was, however, included as a prognostic factor. Smoking status, histology and ECOG status were not included as prognostic factors as they did not improve model fit (AIC and BIC increased).

Table 38-PFS results predicted for the European target population

Population	PFS HR (95% CI)
RATIONALE-309	0.53 (0.39, 0.71)
Base Case (Based on Rampinelli 2023)[1]	0.49 (0.36, 0.68)
Sensitivity Analysis (Based on Economopoulou 2022)[2]	0.67 (0.47, 0.97)

[1] Effect modifiers: age, EBV positivity; prognostic factors: disease stage, liver metastases
[2] Effect modifiers: age, EBV positivity, liver metastases; prognostic factors: disease stage
Abbreviations: CI = confidence interval; EBV = Epstein-Barr viral; HR = hazard ratio; PFS = progression-free survival.

- OS

For OS, outcome regressions were conducted using Cox PH models, and were based on 263 patients and 119 events for both the base case and sensitivity analyses.

For the base case, effect modifiers included age and EBV positivity; liver metastases and ECOG status could not be included as effect modifiers due to lack of data reported in the target population, while disease stage was not included as an effect modifier due to issues with convergence. Disease stage was, however, included as a prognostic factor. Smoking status, histology, liver metastases and ECOG status were not included as prognostic factors as they did not improve model fit based on AIC and BIC values.

For the sensitivity analysis, effect modifiers included age, EBV positivity and liver metastases; disease stage was similarly not included due to issues with convergence. Disease stage was, however, included

as a prognostic factor. Smoking status, histology and ECOG status were not included as prognostic factors as they did not improve model fit (both AIC and BIC increased).

Table 39-OS results predicted for the European target population

Population	OS HR (95% CI)
RATIONALE-309	0.73 (0.51, 1.05)
Base Case (Based on Rampinelli 2023)[1]	0.75 (0.50, 1.11)
Sensitivity Analysis (Based on Economopoulou 2022)[2]	0.79 (0.48, 1.29)

[1] Effect modifiers: age, EBV positivity; prognostic factors: disease stage
[2] Effect modifiers: age, EBV positivity, liver metastases; prognostic factors: disease stage
Abbreviations: CI = confidence interval; EBV = Epstein-Barr viral; HR = hazard ratio; OS = overall survival.

Summary of main study(ies)

The following table summarises the efficacy results from Study BGB-A317-309 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 40-Summary of Efficacy for Trial BGB-A317-309

Title: A Phase 3, Multicentre, Double-Blind, Randomised, Placebo-controlled Study to Compare the Efficacy and Safety of Tislelizumab (BGB-A317) Combined With Gemcitabine Plus Cisplatin Versus Placebo Combined With Gemcitabine Plus Cisplatin as First-Line Treatment for Recurrent or Metastatic Nasopharyngeal Cancer		
Study identifier	BGB-A317-309	
Design	Phase 3, Double-Blind, Placebo-Controlled, Randomised	
	Duration of main phase:	Not applicable, event driven
	Duration of Run-in phase:	Not applicable
	Duration of Extension phase:	Not applicable
Hypothesis	Superiority	
Treatments groups	Arm Tisle+GC (tislelizumab + gemcitabine + cisplatin)	Tislelizumab 200 mg IV Q3W+GC; GC regimen: 4 to 6 cycles of gemcitabine 1 g/m^2 IV on Days 1 and 8 Q3W plus cisplatin 80 mg/m^2 IV on Day 1 Q3W. <u>Duration:</u> Treatment continued until disease progression, intolerable toxicity, death, or withdrawal of consent. <u>Number of randomised patients:</u> 131

	Arm P+GC (placebo + gemcitabine + cisplatin)		Placebo 200 mg IV Q3W+GC; GC regimen: 4 to 6 cycles of gemcitabine 1 g/m^2 IV on Days 1 and 8 Q3W plus cisplatin 80 mg/m^2 IV on Day 1 Q3W. <u>Duration:</u> Treatment continued until disease progression, intolerable toxicity, death, or withdrawal of consent. Crossover to tislelizumab monotherapy after IRC-confirmed disease progression was allowed. <u>Number of randomised patients:</u> 132
Endpoints and definitions	Primary endpoint	PFS by IRC	The time from randomisation to the first objectively documented disease progression by the IRC per RECIST v1.1, or death from any cause, whichever occurs first.
	Secondary endpoints	OS	The time from randomisation to death from any cause.
		ORR by IRC	The proportion of patients who have a BOR of CR or PR by the IRC per RECIST v1.1. Confirmation of response is required.
		DOR by IRC	The time from the first documented objective response to documented disease progression by the IRC per RECIST v1.1, or death from any cause, whichever occurs first, for responder patients.
		PFS by INV	The time from randomisation to the first objectively documented disease progression by the investigator per RECIST v1.1, or death from any cause, whichever occurs first.
		PFS2	The time from randomisation to second/subsequent disease progression after initiation of new anticancer therapy, or death from any cause, whichever occurs first.
Database lock	26 January 2024 (end of study analysis)		

Results and Analysis

Analysis description	**Interim Analysis (Primary Analysis)**		
Analysis population and time point description	Intent to treat=263, when 152 (57.8%) PFS events were observed DCO: 26 March 2021		
Descriptive statistics and estimate variability	**Primary Endpoint**		
	Treatment group	Arm Tisle+GC	Arm P+GC
	Number of subjects	131	132
	Median PFS by IRC, months	9.2	7.4
	95% CI	7.6, 10.1	5.6, 7.5
Effect estimate per comparison	PFS by IRC	Comparison groups	Tisle+GC vs P+GC
		Stratified Hazard Ratio	0.52
		95% CI	0.38, 0.73

		One-sided stratified log-rank test p-value	<0.0001
Descriptive statistics and estimate variability	**Secondary Endpoints**		
	Treatment group	Arm Tisle+GC	Arm P+GC
	Number of subjects	131	132
	Median PFS by INV, months	9.8	7.6
	95% CI	7.8, 11.9	6.6, 7.8
	ORR by IRC, %	69.5	55.3
	95% CI	60.8, 77.2	46.4, 64.0
	Median DOR by IRC, months	8.5	6.1
	95% CI	6.5, NE	4.7, 6.2
	Median PFS2 by INV, months	45.3	20.5
	95% CI	31.5, NE	13.9, 27.2
Effect estimate per comparison		Comparison groups	Tisle+GC vs P+GC
	PFS by INV	Stratified Hazard Ratio	0.54
		95% CI	0.38, 0.76
	ORR by IRC	Odds ratio	1.85
		95% CI	1.11, 3.07
		ORR Difference, %	14.2
		95% CI	2.7, 25.8
Analysis description	**End of Study Analysis**		
Analysis population and time point description	Intent to treat=263. DCO: 08 December 2023		
Descriptive statistics and estimate variability	Treatment group	Arm Tisle+GC	Arm P+GC
	Number of subjects	131	132
	Median OS, months	45.3	31.8
	95% CI	33.4, NE	25.0, NE
	Median PFS by IRC, months	9.6	7.4
	95% CI	7.6, 11.6	5.6, 7.6
Effect estimate per comparison		Comparison groups	Tisle+GC vs P+GC
	OS	Stratified Hazard Ratio	0.73
		95% CI	0.51, 1.05
	PFS by IRC	Stratified Hazard Ratio	0.53
		95% CI	0.39, 0.71
Notes	The primary endpoint has been met.		

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

N/A

Clinical studies in special populations

Table 41-Nr of patients per age group*:-extract from "Table 6: Patient Demographics, Baseline Characteristics and Disease History at Baseline (ITT) –Study 309 (26 March 2021Cutoff)"*

	Tislelizumab + Chemotherapy (N = 131)	Placebo + Chemotherapy (N = 132)	Total (N = 263)
Age (years)			
Median	50.0	50.0	50.0
Min, Max	26, 74	23, 73	23, 74
Age Group 1, n (%)			
< 65 years	121 (92.4)	120 (90.9)	241 (91.6)
≥ 65 years	10 (7.6)	12 (9.1)	22 (8.4)
Age Group 2, n (%)			
< 50 years	63 (48.1)	64 (48.5)	127 (48.3)
≥ 50 years	68 (51.9)	68 (51.5)	136 (51.7)

Source: ADSL, ADBASE. Data cutoff: 26Mar2021. Data extraction: 29Apr2021.

Supportive study(ies)

N/A

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The pivotal phase 3 study BGB-A317-309 (Study 309) supporting this application for extension of indication was a double-blind, randomised, placebo-controlled Asia-only study evaluating the efficacy and safety of tislelizumab combined with gemcitabine plus cisplatin (GC; Arm A) versus placebo combined with GC (Arm B) as first-line treatment in adult patients with recurrent or metastatic nasopharyngeal cancer (NPC). Stratification factors for this study were gender (male vs. female) and presence of liver metastases (yes vs. no), which have been described as negative prognostic factor as compared to other metastases located elsewhere. Overall, the study design is considered adequate.

Patient population

The study enrolled 263 patients with recurrent or metastatic NPC from Asia only (including sites in China, Taiwan, and Thailand). Patients with local recurrence amenable to curative approaches such as surgery or radiotherapy were excluded, which is now adequately reflected in the indication wording. The study excluded patients with local recurrence suitable for curative surgery or radiotherapy, and patients who received prior therapies targeting PD-1 or PD-L1.

Overall, the applied eligibility criteria adequately defined a population that is representative of a patient population eligible for 1L treatment of recurrent, not amenable to curative approaches, or metastatic NPC, although – as common in pivotal oncology studies – only patients with a good clinical condition such as ECOG PS of 0 or 1, adequate organ function and a life expectancy of ≥ 12 weeks were enrolled. Patients with uncontrolled brain metastases or leptomeningeal disease were excluded from the study.

Treatments

Tislelizumab was administered at a dose of 200 mg Q3W, which corresponds to the dose that is currently approved for tislelizumab in combination with chemotherapy in other advanced or metastatic tumours. Treatment with tislelizumab was continued until disease progression or unacceptable toxicity. Tislelizumab or placebo were combined with gemcitabine and cisplatin (administered for 4 – 6 cycles) as chemotherapy backbone, which was standard of care worldwide in the 1L treatment of recurrent, not amenable to curative approaches, or metastatic NPC at the time of study initiation. The comparator arm can thus be considered acceptable from a regulatory perspective.

Patients in the placebo plus GC arm were allowed to crossover to tislelizumab monotherapy after IRC-confirmed disease progression, which finally applied to 69 patients (52.3%) in the comparator arm up to the end of the study.

Endpoints

The primary endpoint of Study 309 was PFS assessed by IRC in the ITT population. The independent review of PFS as primary endpoint of the study is endorsed. Secondary endpoints were OS, PFS assessed by investigator, ORR and DOR assessed by IRC, PFS2, and HRQoL. ORR and DOR assessed by investigator, DCR, TTR, the impact of PD-L1 expression level on efficacy outcomes, and the distribution of EBV DNA levels were analysed as exploratory endpoints. All these endpoints were already planned in the original study protocol and remained unchanged in the two subsequent protocol amendments. Overall, the primary and secondary objectives and endpoints are in line with the relevant EMA guidelines (EMA/CHMP/205/95 Rev.6, EMA/CHMP/27994/2008/Rev.) and are deemed appropriate.

Sample size

It was planned that 256 patients were to be enrolled over a 14.3-month period, and that the final analysis would then occur approximately 21.5 months after the first patient was randomised when a total of 181 events would have been observed. The sample size calculation was reproducible and is acceptable. At the end, 263 patients were then included in the study, so there was a slight over-recruitment.

Statistical analysis

The primary endpoint PFS assessed by IRC per RECIST v1.1 was compared between tislelizumab with gemcitabine + cisplatin (Arm A) and placebo + gemcitabine + cisplatin (Arm B), using stratified log-rank test in the ITT analysis set and the HR for PFS was estimated using a stratified Cox regression model. No primary estimand was defined in the protocol, however the estimand that is mostly aligned with the primary analysis is a treatment policy estimand. In case of new anti-cancer treatment, patients got censored at date of last adequate tumour assessment before date of new anticancer treatment as well as patients with a PFS event after 2 missed tumour assessment visit got censored at date of last adequate tumour assessment prior to the missed assessments. However, two sensitivity analyses demonstrated the robustness of the results, which is due to the small number of patients with these two censoring events.

Overall survival was considered as secondary endpoint. No primary estimand was defined, but also here, the estimand that is mostly aligned with the main analysis of OS is a treatment policy estimand. The fact that patients had the opportunity to switch to the experimental arm after progression hampers the interpretation of the results. The Applicant therefore conducted two supplementary analyses, a RPSFT model (Robins and Tsiatis 1991) and the two-stage method (Latimer et al 2014). Both methods are appropriate methods to account for treatment switching. However, both applied methods have their weaknesses and are subject to assumptions that ultimately cannot be verified. For the two-stage model, a limited number of patients from the control arm who progressed per IRC but did not crossover to receive tislelizumab (37 patients) were included in this estimation process, indicating that

these results are subject to some extent of variability. The key assumption of the two-stage model is "no unmeasured confounder", which cannot get verified. For the RPSFTM, patients in the control arm crossed over to receive tislelizumab monotherapy while patients randomised to the experimental arm started tislelizumab in combination with chemotherapy, which might violate the assumption that treatment effects at the time of randomisation and after crossover are expected to be the same. Additionally, the supportive analyses were not pre-specified in the protocol and are hence post-hoc. The results of the two analyses are supportive, but should be interpreted with caution due to the limitations described above.

Furthermore, an interim analysis was planned after approximately 127 PFS would have been observed which was finally conducted after 152 PFS events have been observed. Since a spending function approach was used, this does not lead to problems regarding control of type I error, provided this decision was not data-driven. The Applicant declared that the data cut-off for the interim analysis was selected based on event prediction but that subject enrolment had a sudden acceleration near the end of the enrolment period, which led to an accumulation of events close to the already planned DCO time in March 2021. The IRC assessment made the prediction of the time point for the interim analysis more difficult. Furthermore, the Applicant stated that the decision for IA DCO was independent of any treatment effect observed in this trial.

Conduct of the study

At the data cut-off date of the prespecified IA (26 March 2021), approx. half of the patients in the tislelizumab plus GC arm (51.9%) and 72% in the placebo plus GC arm had discontinued study treatment. Treatment discontinuations were more frequent in the placebo plus GC as compared to the tislelizumab plus GC arm, which could be mainly attributed to higher rates of progressive disease in the placebo plus GC arm.

A rather high rate of treatment discontinuations due to "withdrawal by subject" was noted up to the study end date (49 patients; 18.6%). Among these patients, the specific reasons for withdrawal were not captured in the study database for 32 patients, but were assessed as "patient decision". However, 23 of these 32 patients (71.9%) agreed to provide further survival information after permanent treatment discontinuation. Taking this and the generally balanced rate of treatment discontinuations due to "withdrawal by subject" between the treatment arms (19.8% in the tislelizumab plus GC arm vs. 17.4% in the placebo plus GC arm) into account, a relevant impact on study results may be excluded.

The median study follow-up time at the IA was 10 months and was comparable between the two treatment arms. At that time, 78.7% of patients still remained on study. At the study end date (LPLV, DCO: 8 December 2023), the median study follow-up time was 33 months in the tislelizumab plus GC arm and 25 months in the placebo plus GC arm, indicative of a higher rate of earlier study discontinuations (e.g. due to death/inferior efficacy) in the placebo plus GC arm.

The original protocol for Study 309 (dated 28 November 2018) was amended twice. No changes were made to the planned analyses and none of the changes implemented in the two protocol amendments were assessed as substantial.

The occurrence of important protocol deviations was equally distributed between both treatment arms. Critical protocol deviations with potential impact on efficacy were solely reported in 6 patients (2.3%). Since the study was conducted during the time of the global COVID-19 pandemic, deviations occurred regarding originally planned protocol-defined scheduled visits and assessments. However, major protocol deviations related to COVID-19 were solely identified in 2 patients (0.8%), with 1 patient in each arm reporting a deviation concerning laboratory (missing tumour assessments at Weeks 12 and 18, and missing tumour assessment at Week 24). In general, the number of patients with protocol

deviations was low and no relevant differences were observed in their frequency 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 309 was predominantly male (78.3%) and had a median age of 50.0 years. The majority of patients had non-keratinised tumour histology (86.3%) and was EBV positive (75%). These characteristics are typical for an endemic NPC population, but are somewhat distinct from disease characteristics of NPC patients in lower incidence areas such as Europe (with bimodal age peak, higher proportion of NPC patients with keratinising histology).

Most patients had metastatic disease (95.1%) and were PD-L1 expression positive (72.6% of patients had PD-L1 expression status ≥1%, 9.1% of patients was not evaluable for PD-L1 expression). Overall, demographics and baseline characteristics were balanced between the tislelizumab + GC and the placebo + GC arm. Slight imbalances were nevertheless observed in ECOG PS (score of 1 in 61.1% in Arm A and 65.2% in Arm B), smoking status (56.5% vs. 50.0% of never smokers in Arm A vs. Arm B and correspondingly less former smokers in Arm A), EBV positivity (80.2% vs. 72.0% in Arm A vs. Arm B with EBV DNA level ≥500 IU/mL), and PD-L1 expression status (PD-L1 <10% in 32.1% of patients in Arm A vs. 25.0% of patients in Arm B). However, referring to the PFS results presented by subgroups, these imbalances are not considered to have meaningfully impacted the overall efficacy outcome, since comparable benefit was shown in subgroups by ECOG PS, smoking status, EBV positivity, and PD-L1 status in the subgroups < 10% and ≥ 10%.

Efficacy data and additional analyses

Efficacy data provided for Study 309 are based on the pre-planned interim analysis with a data cut-off date of 26 March 2021. Additionally, updated efficacy information with approximately 17 additional months of median study follow-up as of the study end date of 8 December 2023 was provided.

The study met its primary objective. The primary analysis of PFS assessed by IRC in the ITT population demonstrated a statistically significant benefit of tislelizumab plus GC over placebo plus GC with an event rate of 49.6% and 65.9%, respectively (stratified HR = 0.52 [95% CI: 0.38 – 0.73], p < 0.0001, median PFS 9.2 months for tislelizumab plus GC vs. 7.4 months for placebo plus GC). The majority of PFS events were due to disease progression. At the time of the IA, most patients were censored due to being ongoing on study without events. With longer follow-up, censoring rate was decreased to 27.5% in Arm A and 19.7% in Arm B. The updated efficacy outcome at closeout was consistent with the primary analysis results, showing a sustained PFS benefit for the tislelizumab plus GC over the placebo plus GC arm (stratified HR = 0.53 [95% CI: 0.39 – 0.71], median PFS 9.6 months for tislelizumab plus GC vs. 7.4 months for placebo plus GC). Furthermore, sensitivity analyses of the primary endpoint PFS (considering progression as PFS event irrespective of start of a subsequent anticancer therapy or missing of 2 or more consecutive tumour assessments) confirmed the robustness of the primary analysis.

PFS assessed by the investigator, which was analysed as secondary endpoint, was also consistent with the primary PFS analysis per IRC assessment (stratified HR = 0.54 [95% CI: 0.38 – 0.76], p = 0.0002, median PFS 9.8 months for tislelizumab plus GC vs. 7.6 months for placebo plus GC).

No statistical testing aiming at demonstration of OS superiority was conducted due to the allowance of crossover to tislelizumab monotherapy in the placebo + GC arm, which was considered a potential confounder of the OS effect. OS data at the time of the IA were immature and are therefore not further discussed. The OS analysis at the study end date revealed an improvement in OS of patients treated

with tislelizumab plus GC as compared to patients treated with placebo plus GC (stratified HR = 0.73 [95% CI: 0.51 - 1.05], median OS 45.3 months for tislelizumab plus GC vs. 31.8 months for placebo plus GC), despite 52.3% of patients in the control arm that switched to tislelizumab monotherapy after confirmed disease progression. Still, it should be noted that Kaplan-Meier OS curves separated in favour of the tislelizumab plus GC arm not until 12 months after start of treatment, but a clinically relevant OS benefit was maintained thereafter. It should be kept in mind that the possibility to crossover to tislelizumab monotherapy after progression hampers the interpretation of the results.

Two supportive OS analyses were conducted to adjust for the effect of crossover and to estimate benefit of tislelizumab + GC on OS assuming no control arm patients had crossed over to receive tislelizumab monotherapy after disease progression. OS analyses based on both Rank-Preserving Structural Failure Time (RPSFT) Method and the Two Stage Method revealed that HR estimates were numerically slightly better than in the primary OS analysis, indicating that the crossover effect could have impacted the magnitude of the treatment effect measured. However, both applied methods have their weaknesses and are subject to assumptions that ultimately cannot be verified. For more details regarding potential weaknesses of the methods see the discussion on statistical methods above. The results of the two analyses are therefore supportive, but should be interpreted with caution.

The analysis of confirmed ORR assessed by IRC (at IA; DCO 26 March 2021) indicated higher tumour response rates in the tislelizumab plus GC arm than in the placebo plus GC arm (69.5% vs. 55.3%, ORR difference = 14.2%) and the analysis of DOR assessed by IRC (at IA; DCO 26 March 2021) revealed a trend towards more durable tumour response in the tislelizumab plus GC arm than in the placebo plus GC arm (median DOR 8.5 months vs. 6.1 months), both supporting the positive primary endpoint outcome.

Of note, treatment with tislelizumab plus GC also prolonged the time to disease progression or death after the next line of treatment: HR of PFS2 at study closeout was 0.51 (95% CI: 0.34 to 0.75) and median PFS2 was 45.3 months in the tislelizumab plus GC arm vs. 20.5 months in the placebo plus GC arm.

No clinically meaningful differences in HRQoL endpoints (as analysed by EORTC QLQ-C30 and its NPC module QLQ-H&N35) were observed between patients in the tislelizumab plus GC arm vs. patients in the placebo plus GC arm.

Efficacy by subgroups and applicability to EU population

Subgroup analyses of PFS assessed by IRC were provided for the data cutoff date of the IA and end of study. There were no considerable changes in subgroup results between the two timepoints of analysis. Subgroup analyses of OS were presented for the data cutoff of the end of study and overall confirmed the PFS subgroup results.

In general, PFS benefit in favour of the tislelizumab plus GC arm is evident across all subgroups, except for the subgroup of patients aged ≥65 years. The HR of PFS assessed by IRC in this subgroup of patients indicates that there may be a lack of benefit or even a detrimental treatment effect (PFS HR = 1.89 [95% CI: 074, 4.83]), although the low sample size needs to be taken into account (only 8.4% [N=22] of patients were ≥65 years old). To further elaborate on this, the Applicant explored potential reasons leading to inconsistencies in efficacy outcomes of patients aged ≥65 years compared to the overall population. Differences in metastatic burden were noted, i.e. more patients in Arm Tisle+GC had metastatic disease compared to Arm Placebo+GC including metastases in bone (90% vs 50%), lung (60% vs 33.3%), brain (10% vs 0%), and lymph nodes (90% vs 16.7%), while the proportion of patients with liver metastasis was slightly higher in the control arm (30% in Arm Tisle+GC vs 41.7% in Arm Placebo+GC). Overall, it is indicated that an underlying greater tumour burden in the tislelizumab + GC arm may have confounded efficacy results in the subgroup of patients aged 65 years and older.

In addition, there is no clinical or scientific rationale to anticipate a lack of benefit of treatment with tislelizumab in elderly patients.

Still, considering that there is data from literature describing that the age distribution differs between low-risk and high-risk populations[15] and/or between geographic areas[16], a higher proportion of patients in Europe would be anticipated to be ≥65 years old. In this regard, the lack of conclusive data for this subgroup of patients in Study 309 is deemed an uncertainty, which has now been reflected in section 5.1 of the SmPC ("Data from NPC patients aged 65 years or older are too limited to draw conclusions in this population").

Similarly, the sample size of the subgroup of patients with keratinising NPC histology in Study 309 was extremely small, resulting in PFS HR with large variability. Results must therefore be interpreted with caution and no reliable conclusions may be drawn from these data. Although the non-keratinising NPC subtype is the most prevalent subtype in both endemic and non-endemic regions, the percentage of the keratinising subtype of NPC is reported to be higher in the EU patient population (up to 25%) as compared to endemic patient populations (including Study 309 with 6.5% of patients with keratinising histology). Unfortunately, the samples size of patients with keratinising NPC was also highly limited (≤1%) in studies conducted with other immune checkpoint inhibitors in the same indication (camrelizumab[17], toripalimab[18,19]). The aforementioned regional differences in distribution of NPC subtype, combined with the limited clinical data available in the subgroup of patients with keratinising NPC histology, raise uncertainty regarding clinical efficacy of tislelizumab in this subgroup of patients. However, those data that have so far been reported for the subgroup of patients with keratinising NPC (Study 309 for tislelizumab with PFS HR of 0.52 [95% CI: 0.16, 1.67] and ORR of 55.6% versus 37.5% in favour of tislelizumab + GC vs. placebo + GC; and Study POLARIS-02 for toripalimab with ORR of 62.5% in 2L+ RM-NPC patients vs. 20.5% in the overall ITT population) do not indicate a lack of benefit of anti-PD-1 therapy in this subgroup of patients. In light of this and considering that the low number of patients with keratinizing NPC histology is adequately reflected in the SmPC, this uncertainty will not be further pursued.

In order to provide further evidence of the applicability of Study 309 data to the EU patient population, the Applicant conducted literature reviews and statistical analysis to extrapolate treatment effects observed in Study 309 relative to the EU NPC population. In an initial analysis of scientific and medical literature on European NPC patients' baseline and disease characteristics, it was found that baseline and disease characteristics overall appeared comparable, except for a higher rate of Stage I/II/III disease than Stage IV disease, a higher rate of keratinising disease histology (as already discussed above), and a lower rate of NPC patients being EBV-positive in the EU population as compared to Study 309 patients.

Differences in NPC clinical stage between the two populations can be explained by the fact that Study 309 excluded patients with early stage or local recurrence suitable for curative surgery or radiotherapy, resulting in a high percentage of Stage IV patients on study.

Differences identified in EBV status are considered to be of minor concern, given that subgroup analysis results from Study 309 did not indicate a differential treatment effect of tislelizumab plus GC in either EBV-positive (EBV DNA level ≥500 IU/mL) or EBV-negative (EBV DNA level <500 IU/mL) NPC

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[16] Bossi et al. Nasopharyngeal carcinoma: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. ESMO Annals of Oncology. 2010
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[18] Wang et al. Efficacy, safety, and correlative biomarkers of toripalimab in previously treated recurrent or metastatic nasopharyngeal carcinoma: a phase II clinical trial (POLARIS-02). J Clin Oncol. 2021
[19] EPAR Loqtorzi. EMA/CHMP/372271/2024, published: 24/09/2024

patients (PFS HR [95% CI] of 0.52 [0.36, 0.75] vs. 0.45 [0.21, 0.94]). In addition, current treatment recommendations are identical for non-EBV-associated and EBV-associated recurrent or metastatic NPC. It is further noted that 25% of the reviewed EU population had an unknown EBV status, which might have contributed to the detected differences in EBV status between the Study 309 and the EU patient population.

In the statistical analysis of the applicability of Study 309 results to the EU population, an outcome regression approach was used to predict the treatment effect (PFS and OS) in the target population (the population observed in the RWE studies) using its published aggregated characteristics as inputs in the predictive equation. Several methodological weaknesses are associated with this analysis. The regression model for the base case only included adjustment for age and EBV as effect modifiers, as well as disease stage and liver metastases (for PFS only) as prognostic factor. Histological subtype for example was not included. Study 309, whose data were used to initially fit the regression model, contains very few older patients over 65 and patients over 75 were excluded. Unlike propensity score weighting, outcome regression models are not limited by the lack of overlap in population characteristics; however, it is essential to exercise caution when employing predictive equations to extrapolate beyond the range of observed data. The validity of such extrapolations cannot be assured or verified through testing. In the presence of randomised treatments, the resulting estimator would be unbiased if the outcome regression model was correctly specified and there were no unmeasured effect modifiers that were not balanced between the populations, which cannot get verified and thus represents a major weakness of these predictions. In addition, and in particular, this prediction model cannot take into account genetic differences with potential treatment modifying effects between populations by design since the model was fitted on Asian patients only. The results of the statistical analysis should hence be interpreted with caution.

In Study 309, PD-L1 expression status in NPC patients was determined on tumour cells, with a prespecified cut-off of 10% (<10% vs. ≥10%). Additional subgroup analyses based on PD-L1 expression status <1% and ≥1% were provided as requested in the Pre-submission phase.

Referring to the forest plots presented for the subgroups by PD-L1 status, an improvement of PFS with tislelizumab plus GC was observed regardless of PD-L1 expression levels in tumour cells (PD-L1 < 1%, ≥ 1%, < 10%, and ≥ 10%). However, in the exploratory analysis of the impact of baseline tumour cell PD-L1 expression levels on PFS, it is noted that the PFS event rate in patients with PD-L1 expression <1% was higher in the tislelizumab plus GC arm (81.5%) than in the placebo plus GC arm (72.7%) at study closeout. This likely resulted from a higher rate of late events occurring in the tislelizumab plus GC arm. Still, PFS HR and median PFS in patients with PD-L1 expression <1% indicate a benefit of treatment with tislelizumab plus GC over placebo plus GC (PFS HR = 0.53, median PFS 7.7 months vs. 4.3 months). The impact of baseline PD-L1 expression levels was further evaluated with regard to OS outcomes at study end date. This analysis revealed comparable OS event rates in the subgroup of patients with PD-L1 expression <1% (63.0% in the tislelizumab plus GC arm vs. 63.6% in the placebo plus GC arm) with an OS HR of 0.92 (95% CI: 0.45 to 1.87). Conclusively, the data do not suggest an apparent OS benefit in PD-L1 negative NPC patients, although of course the limitations of such exploratory subgroup analyses, together with the small sample size of the subgroup of patients with PD-L1 expression <1% (N=27 in Arm A, N=22 in Arm B; corresponding to 18.6% of the study population), must be taken into account. In the remaining subgroups by PD-L1 expression levels, OS event rates and HRs suggested an improvement in OS with tislelizumab plus GC treatment (PD-L1 ≥ 1%: OS HR = 0.59 [95% CI: 0.38, 0.91]; PD-L1 < 10%: OS HR = 0.68 [95% CI: 0.36, 1.27]; PD-L1 ≥ 10%: OS HR = 0.66 [95% CI: 0.41, 1.05]). Overall, the efficacy data presented for subgroups by PD-L1 expression are too limited to draw any reliable conclusions.

In summary, some uncertainty remains regarding the extent of the treatment effect of tislelizumab in PD-L1 negative (PD-L1 <1%) patients. However, the available clinical data do currently not warrant a restriction of the indication based on PD-L1 status. This is also supported by external evidence from other studies with PD-(L)1 inhibitors in recurrent or metastatic NPC.

2.4.4. Conclusions on the clinical efficacy

Study 309 demonstrated a statistically significant and clinically relevant PFS benefit favouring tislelizumab in combination with chemotherapy over placebo in combination with chemotherapy in patients with NPC. Descriptive OS results and additional secondary endpoint analyses overall supported the primary PFS outcome.

2.5. Clinical safety

Introduction

The safety analysis is primarily based on the Phase 3 Study BGB-A317-309, which compared the efficacy and safety of tislelizumab in combination with gemcitabine and cisplatin with that of placebo in combination with gemcitabine and cisplatin as first-line treatment in patients with recurrent or metastatic NPC. Safety data from the use of tislelizumab from other clinical studies in multiple tumour types are provided as supportive information. All analyses are based on the Study 309 Safety Analysis Set as of the study end date (data cutoff date of 08 December 2023). The safety data at the time of the primary analysis (data cutoff 26 March 2021) were consistent with the safety outcomes reported at the study end date. The Study 309 data, pooled monotherapy and combination therapy safety data Table 42 are presented side by-side in all sections, including Section 2.8 for characterization of the ADR profile of tislelizumab.

- **Study 309** Tislelizumab + Chemotherapy Arm (**Arm Tisle+GC**; N = 133) includes all randomised patients who received any dose of tislelizumab based on the actual treatment regimen received. Two patients who were randomised to Arm P+GC but were erroneously dosed with tislelizumab were included in Arm Tisle+GC (Section 10.2 in Study 309 final CSR).

- **Study 309** Placebo + Chemotherapy Arm (**Arm P+GC**; N = 130) includes all patients from Study 309 who received any dose of placebo based on the actual treatment regimen received. Only AEs reported prior to patients crossing over to receive tislelizumab monotherapy are included in the safety analyses.

- **Tislelizumab Monotherapy Pool (N = 1952)** includes all patients who received tislelizumab 200 mg once every 3 weeks from 9 studies.

- **Tislelizumab Combination Therapy Pool (N = 1950)** includes all patients from 9 studies who received tislelizumab 200 mg once every 3 weeks in combination with various chemotherapies

Table 42- *Safety Analysis Populations*

Analysis set	N	Definition	Purpose
Study 309 (see below)	263	All randomised patients from Study 309 who received ≥ 1 dose of study treatment	Primary source of safety data for the intended indication
Tislelizumab mono-therapy pool	1952	Patients with various tumour types who received tislelizumab monotherapy at 200 mg Q3W in Studies **001, 102, 203, 204, 208, 209, 301, 302, and 303**	Reference population for the known safety profile of **tislelizumab monotherapy**
Tislelizumab combination therapy pool	1950	Patients with various tumour types who received tislelizumab 200 mg Q3W plus chemotherapy in Studies **205, 206, 304, 305, 306, 307, 309, 312, and 315**	For ADR determination and presentation

Data from these Tislelizumab monotherapy pool and combination therapy pools are considered as supportive and will only be discussed in individual instances. This is due to the fact that differences in the included studies' design, patient populations, tumour types, previous therapy (first- or second-line) etc. are substantial, precluding a direct comparison of data from Study 309 and the tislelizumab monotherapy pool, respectively.

Primary Study Providing Safety Data						
309	Recurrent or metastatic NPC	• Phase 3 • Randomised, double-blind, placebo-controlled, multicentre	China, Taiwan, Thailand	Tisle 200 mg IV Q3W or matched placebo in combination with gemcitabine [a] and cisplatin [b]	Safety Analysis Set: 263 Tisle+GC: 133 P+GC: 130	Completed/ 08 December 2023
Tislelizumab Monotherapy Pool Providing Supportive Safety Data						
001	ST (CRC, NSCLC, MM, cuSCC, UM, GC, PC, OC, UC, HNSCC, RCC, TNBC, HCC, ESCC, MCC, CC, GIST, sarcoma, or other tumours with known MSI-H or dMMR)	• Phase 1 [c] • Open-label, multiple-dose, dose-escalation and expansion study investigating the safety, tolerability, PK, and antitumour activity of tislelizumab	Australia; New Zealand; USA; South Korea; China, Taiwan	Tisle 200 mg Q3W [d]	13	Completed/ 12 August 2020
102	ST (NSCLC, MM, GC, ESCC, OC, UC, HNSCC, RCC, TNBC, CRC,	• Phase 1/2 • Open-label, multicentre study •	China	Tisle 200mg Q3W, 200mg W1D1,	300	Completed/ 31 May 2020

	SCNEC or other tumours with known MSIH or dMMR, NPC, Child-Pugh Class A HCC)			W5+D1 Q3W [e] (PK sub-study)		
203	R/R cHL	• Phase 2 • Open-label, multicentre, single-arm study to evaluate tislelizumab therapy	China	Tisle 200 mg Q3W	70	Completed/ 02 November 2020
204	UC	• Phase 2 • Single-arm, multicentre study to evaluate the efficacy and safety of tislelizumab	China, South Korea	Tisle 200 mg Q3W	113	Completed/ 11 March 2021
208	Previously treated, unresectable HCC	• Phase 2 • Open-label, multicentre study investigating the efficacy, safety, and PK of tislelizumab	China, Taiwan; Germany, Spain, France, UK, Italy, and Poland	Tisle 200 mg Q3W	249	Completed/ 06 July 2022
209	ST (tumours with known MSIH or dMMR)	• Phase 2 • Open-label, multicentre, single-arm study	China	Tisle 200 mg Q3W	80	Ongoing/ 08 July 2021
301	Unresectable HCC	• Phase 3 • Randomised, open-label, controlled, multicentre study tislelizumab vs.sorafenib	China, Taiwan, Czech Republic, France, Germany, Italy, Poland, Spain, UK, USA, Japan	Tisle 200 mg Q3W	338 in Tisle arm	Completed/ 14 December 2023
302	Advanced unresectable/ metastatic ESCC	• Phase 3 • Randomised, open-label, controlled, multicentre study tislelizumab vs chemotherapy	China,Taiwan, Belgium, Spain, France, UK, Italy, Japan, Korea, USA, Germany	Tisle 200 mg Q3W	255 in Tisle arm	Completed/ 28 December 2022
303	Locally advanced unresectable or metastatic NSCLC (squamous or nonsquamous)	• Phase 3 • Randomised, open-label, multicentre study tislelizumab vs. docetaxel	China, Bulgaria, Brazil, Lithuania Mexico, New Zealand, Poland,	Tisle 200 mg Q3W	534 in Tisle arm	Completed/ 18 January 2024

			Russia, Slovakia, Turkey			
Tislelizumab Combination Therapy Pool Providing Supportive Safety Data						
205	ESCC, GC/GEJ adenocarcinoma	• Phase 2 • Open-label, multicentre, 2 cohorts	China	Tisle 200 mg Q3W Platinum-containing chemotherapy doublet (cisplatin or oxaliplatin) with fluoropyrimidine (capecitabine or 5-FU) [f].	30	Completed / 31-Mar-2019
206	Advanced or metastatic NSCLC or SCLC	• Phase 2 • Open-label, multicentre, 4 cohorts	China	Tisle 200 mg Q3W Platinum-containing doublet chemotherapy as per histology [g]	54	Completed / 31-Dec-2019
304	Stage IIIB or IV nonsquamous NSCLC	• Phase 3 • Randomised, open-label, multicentre	China	Tisle 200 mg Q3W Cisplatin [h] or carboplatin [h] and pemetrexed [h]	222	Completed / 26-Apr-2023
305	Locally advanced unresectable or metastatic GC/GEJ	• Phase 3 • Randomised, double-blind, placebo-controlled, multicentre	China, Taiwan, Japan, South Korea, the UK, Russia, France, Italy, Poland, Puerto Rico, Spain, Turkey, and USA	Tisle 200 mg Q3W Fluoropyrimidine- (capecitabine [i] or 5-FU [j]) and platinum- (oxaliplatin [k] or cisplatin [l]) based chemotherapy	498	Ongoing/ 28-Feb-2023
306	Unresectable, locally advanced recurrent or metastatic ESCC	• Phase 3 • Randomised, double-blind, placebo-controlled, multicentre	China, Taiwan, Japan, Korea, Belgium, Czech Republic, France, Germany, Italy, Poland, Romania, Russia, Spain, the	Tisle 200 mg Q3W Platinum-containing chemotherapy doublet (cisplatin or oxaliplatin) with fluoropyrimidine (capecitabine or 5-FU) [f] or paclitaxel [w]	324	Ongoing/ 28-Feb-2022

			UK, USA, and Australia			
307	Stage IIIB or IV squamous NSCLC	• Phase 3 • Randomised, open-label, multicentre	China	Tisle 200 mg Q3W T+PC [m]: Paclitaxel and carboplatin; T+nPC [m]: Nab-paclitaxel and carboplatin [m]	238	Completed / 28-Apr-2023
309	Recurrent or metastatic NPC	• Phase 3 • Randomised, double-blind, placebo-controlled, multicentre	China, Taiwan and Thailand	Tisle 200 mg Q3W Gemcitabine [n] and cisplatin [o]	131 [p]	Completed / 08-Dec-2023
312	Untreated extensive-stage SCLC	• Phase 3 • Randomised, double-blind, placebo-controlled, multicentre	China	Tisle 200 mg Q3W Cisplatin [q] or carboplatin [r] and etoposide [s]	227	Completed / 29-Dec-2023
315	Resectable Stage II or IIIA NSCLC	• Phase 3 • Randomised, double-blind, placebo-controlled, multicentre	China	Tisle 200 mg Q3W (neoadjuvant phase) and 400 mg Q6W (adjuvant phase) Cisplatin [t]/carboplatin [u] plus pemetrexed [v] (for nonsquamous) or paclitaxel [w] (for squamous)	226	Ongoing/ 21-Aug-2023

Patient exposure

Study 309: The median duration of exposure to tislelizumab was 10.51 months, with 45.1% of patients receiving tislelizumab for ≥ 12 months. The median Relative Dose Intensity (RDI) was 95.71%.

Tislelizumab monotherapy and combination therapy pools: The median duration of exposure to tislelizumab was lower in both pools (4.14 months in the monotherapy pool and 7.20 months in the combination therapy pool) than the exposure to tislelizumab in Arm Tisle+GC of Study 309, with 24.7% and 31.9% of patients receiving tislelizumab for ≥ 12 months, respectively. The median RDI was 100% and 95.45%, respectively.

Table 43- Summary of Treatment Exposure to Tislelizumab (Safety Analysis Set)

	Study 309		
	Tislelizumab + Chemotherapy (N = 133)	**Tislelizumab Monotherapy (N = 1952)**	**Tislelizumab Combination Therapy (N = 1950)**
Duration of Exposure (Months) [a]			
Mean (SD)	15.45 (13.939)	9.78 (12.386)	11.09 (11.011)
Median	10.51	4.14	7.20
Min, Max	0.3, 53.1	0.2, 63.2	0.1, 53.9
Duration of Exposure (Months), n (%)			
< 3	22 (16.5)	789 (40.4)	402 (20.6)
3 to < 6	15 (11.3)	368 (18.9)	447 (22.9)
6 to < 9	26 (19.5)	222 (11.4)	296 (15.2)
9 to < 12	10 (7.5)	90 (4.6)	182 (9.3)
12 to < 18	21 (15.8)	127 (6.5)	290 (14.9)
18 to < 24	9 (6.8)	87 (4.5)	90 (4.6)
>= 24	30 (22.6)	269 (13.8)	243 (12.5)
Number of Cycles Received [b]			
Mean (SD)	20.8 (18.86)	13.5 (16.96)	14.1 (14.61)
Median	14.0	6.0	9.0
Min, Max	1, 69	1, 88	1, 77
Cumulative Dose Administered (mg)			
Mean (SD)	4163.9 (3773.88)	2706.1 (3389.94)	2944.6 (2922.88)
Median	2800.0	1200.0	2000.0
Min, Max	100, 13800	200, 17600	200, 15400
Actual Dose Intensity (mg/week) [c]			
Mean (SD)	61.68 (6.911)	64.57 (4.439)	61.72 (6.018)
Median	63.81	66.67	63.64
Min, Max	30.6, 68.5	30.8, 71.8	23.1, 71.8
Relative Dose Intensity (%) [d]			
Mean (SD)	92.52 (10.366)	96.94 (6.549)	92.57 (9.026)
Median	95.71	100.00	95.45
Min, Max	45.9, 102.8	46.2, 107.7	34.7, 107.7
(Source: SCS Table 3)			

Table 44-Summary of Treatment Exposure to Chemotherapy (Safety Analysis Set)

	Study 309		
	Tislelizumab + Chemotherapy (N = 133)	**Placebo + Chemotherapy (N = 130)**	**Tislelizumab Combination Therapy (N = 1950)**
Duration of Exposure (Months) [a]			
n	131	130	1950
Mean (SD)	3.76 (1.189)	3.68 (1.071)	6.01 (7.054)
Median	4.14	4.14	4.01
Q1, Q3	2.96, 4.47	2.99, 4.37	2.76, 5.78
Min, Max	0.3, 6.2	0.6, 5.8	0.1, 52.6
Number of Cycles Received			
n	131	130	1950
Mean (SD)	5.0 (1.48)	4.9 (1.40)	8.0 (9.39)
Median	6.0	6.0	5.0
Q1, Q3	4.0, 6.0	4.0, 6.0	4.0, 8.0
Min, Max	1, 6	1, 6	1, 69

Adverse events

Adverse events summary

Since different tislelizumab studies used different TEAE definitions, to ensure a more meaningful assessment, a harmonised TEAE definition was used for analysis of safety parameters for the safety pools as well as the pivotal Study 309

- A TEAE was defined as an AE that had an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose of study treatment up to 30 days after the last dose of study treatment or surgery (whichever comes later, only applicable to Study 315), or initiation of new anticancer therapy, whichever occurred first.

In view of this harmonization procedure, safety data presented in this Assessment Report were principally extracted from the Summary of Clinical Safety.

A summary of TEAEs (including related TEAEs) is presented.

Table 45- Overview of Treatment-Emergent Adverse Events (Safety Analysis Set)

	Study 309			
	Tislelizumab + Chemotherapy (N = 133) n (%)	**Placebo + Chemotherapy (N = 130) n (%)**	**Tislelizumab Monotherapy (N = 1952) n (%)**	**Tislelizumab Combination Therapy (N = 1950) n (%)**
Patients With Any TEAE	133 (100.0)	129 (99.2)	1886 (96.6)	1943 (99.6)
Treatment-Related	133 (100.0)	129 (99.2)	1472 (75.4)	1918 (98.4)
Related to Tislelizumab/Placebo	104 (78.2)	97 (74.6)	1472 (75.4)	1446 (74.2)
Related to Any Component of Chemotherapies	133 (100.0)	129 (99.2)	NA	1908 (97.8)
>= Grade 3	113 (85.0)	111 (85.4)	916 (46.9)	1531 (78.5)
Treatment-Related	102 (76.7)	109 (83.8)	364 (18.6)	1352 (69.3)
Related to Tislelizumab/Placebo	32 (24.1)	29 (22.3)	364 (18.6)	594 (30.5)
Related to Any Component of Chemotherapies	101 (75.9)	109 (83.8)	NA	1276 (65.4)
Serious	47 (35.3)	46 (35.4)	683 (35.0)	822 (42.2)
Treatment-Related	31 (23.3)	39 (30.0)	241 (12.3)	502 (25.7)
Related to Tislelizumab/Placebo	13 (9.8)	15 (11.5)	241 (12.3)	351 (18.0)
Related to Any Component of Chemotherapies	25 (18.8)	38 (29.2)	NA	342 (17.5)
Leading to Death	6 (4.5)	2 (1.5)	150 (7.7)	128 (6.6)
Treatment-Related	2 (1.5)	2 (1.5)	21 (1.1)	42 (2.2)
Related to Tislelizumab/Placebo	1 (0.8)	1 (0.8)	21 (1.1)	37 (1.9)
Related to Any Component of Chemotherapies	2 (1.5)	2 (1.5)	NA	29 (1.5)
Leading to Treatment Discontinuation	22 (16.5)	14 (10.8)	253 (13.0)	478 (24.5)
Treatment-Related	17 (12.8)	12 (9.2)	118 (6.0)	400 (20.5)
Leading to Tislelizumab/Placebo Discontinuation	12 (9.0)	6 (4.6)	253 (13.0)	281 (14.4)
Leading to Any Component of Chemotherapies Discontinuation	12 (9.0)	11 (8.5)	NA	374 (19.2)
Leading to Treatment Modification	97 (72.9)	93 (71.5)	582 (29.8)	1386 (71.1)
Treatment-Related	90 (67.7)	92 (70.8)	350 (17.9)	1295 (66.4)
Leading to Treatment Modification of Tislelizumab/Placebo	66 (49.6)	53 (40.8)	582 (29.8)	1006 (51.6)

	Study 309			
	Tislelizumab + Chemotherapy (N = 133) n (%)	Placebo + Chemotherapy (N = 130) n (%)	Tislelizumab Monotherapy (N = 1952) n (%)	Tislelizumab Combination Therapy (N = 1950) n (%)
Leading to Treatment Modification of Any Component of Chemotherapies	84 (63.2)	90 (69.2)	NA	1270 (65.1)
Immune-Mediated AE	71 (53.4)	49 (37.7)	659 (33.8)	778 (39.9)
Immune-Mediated AE >= Grade 3	6 (4.5)	1 (0.8)	105 (5.4)	173 (8.9)
Infusion-Related Reaction	7 (5.3)	9 (6.9)	58 (3.0)	123 (6.3)
Infusion-Related Reaction >= Grade 3	0 (0.0)	0 (0.0)	2 (0.1)	12 (0.6)

Most common adverse events

Table 46-Treatment-Emergent Adverse Events With Incidence >= 15% by Preferred Term (Safety Analysis Set)

	Study 309			
Preferred Term	Tislelizumab + Chemotherapy (N = 133) n (%)	Placebo + Chemotherapy (N = 130) n (%)	Tislelizumab Monotherapy (N = 1952) n (%)	Tislelizumab Combination Therapy (N = 1950) n (%)
Patients With Any TEAE	133 (100.0)	129 (99.2)	1886 (96.6)	1943 (99.6)
Anaemia	116 (87.2)	118 (90.8)	511 (26.2)	1291 (66.2)
Neutrophil count decreased	82 (61.7)	77 (59.2)	113 (5.8)	988 (50.7)
White blood cell count decreased	82 (61.7)	82 (63.1)	160 (8.2)	961 (49.3)
Nausea	78 (58.6)	94 (72.3)	196 (10.0)	844 (43.3)
Platelet count decreased	72 (54.1)	80 (61.5)	157 (8.0)	651 (33.4)
Decreased appetite	64 (48.1)	65 (50.0)	290 (14.9)	782 (40.1)
Vomiting	55 (41.4)	69 (53.1)	166 (8.5)	533 (27.3)
Neutropenia	47 (35.3)	38 (29.2)	31 (1.6)	533 (27.3)
Constipation	46 (34.6)	60 (46.2)	227 (11.6)	511 (26.2)
Hyponatraemia	41 (30.8)	37 (28.5)	172 (8.8)	353 (18.1)
Hypothyroidism	41 (30.8)	20 (15.4)	251 (12.9)	277 (14.2)
Aspartate aminotransferase increased	39 (29.3)	31 (23.8)	482 (24.7)	590 (30.3)
Alanine aminotransferase increased	38 (28.6)	27 (20.8)	430 (22.0)	597 (30.6)
Pyrexia	35 (26.3)	13 (10.0)	311 (15.9)	360 (18.5)
Pruritus	29 (21.8)	18 (13.8)	215 (11.0)	198 (10.2)
Rash	34 (25.6)	29 (22.3)	201 (10.3)	287 (14.7)
Hypokalaemia	30 (22.6)	30 (23.1)	153 (7.8)	326 (16.7)
Malaise	29 (21.8)	31 (23.8)	113 (5.8)	251 (12.9)
Hypocalcaemia	25 (18.8)	17 (13.1)	59 (3.0)	142 (7.3)
Hyperuricaemia	24 (18.0)	25 (19.2)	88 (4.5)	156 (8.0)
Back pain	23 (17.3)	18 (13.1)	154 (7.9)	167 (8.6)
Dizziness	23 (17.3)	19 (14.6)	76 (3.9)	177 (9.1)
Upper respiratory tract infection	22 (16.5)	12 (9.2)	180 (9.2)	165 (8.5)
Hypoalbuminaemia	22 (16.5)	29 (22.3)	244 (12.5)	395 (20.3)
Hypomagnesaemia	22 (16.5)	16 (12.3)	36 (1.8)	102 (5.2)

	Study 309			
Preferred Term	**Tislelizumab + Chemotherapy (N = 133) n (%)**	**Placebo + Chemotherapy (N = 130) n (%)**	**Tislelizumab Monotherapy (N = 1952) n (%)**	**Tislelizumab Combination Therapy (N = 1950) n (%)**
Hypoaesthesia	20 (15.0)	20 (15.4)	26 (1.3)	240 (12.3)
Diarrhoea	21 (15.8)	14 (10.8)	196 (10.0	394 (20.2)

Notably, Hypothyroidism was reported at a higher frequency in Arm Tisle+GC than in the monotherapy and combination therapy pools (30.8% versus 12.9% versus 14.2%). This refers also to Pyrexia (26.3% vs. 15.9% vs. 18.5%); Pruritus (21.8% vs. 13.8% vs. 11.0%).

TEAEs Related to Tislelizumab/Placebo

Table 47-Treatment-Emergent Adverse Events Related to Tislelizumab/Placebo With Incidence >= 10% by Preferred Term (Safety Analysis Set)

	Study 309			
Preferred Term	**Tislelizumab + Chemotherapy (N = 133) n (%)**	**Placebo + Chemotherapy (N = 130) n (%)**	**Tislelizumab Monotherapy (N = 1952) n (%)**	**Tislelizumab Combination Therapy (N = 1950) n (%)**
Patients With Any TEAE Related to Tislelizumab/Placebo	104 (78.2)	97 (74.6)	1472 (75.4)	1446 (74.2)
Hypothyroidism	34 (25.6)	16 (12.3)	235 (12.0)	258 (13.2)
Rash	31 (23.3)	20 (15.4)	163 (8.4)	223 (11.4)
Alanine aminotransferase increased	28 (21.1)	13 (10.0)	304 (15.6)	313 (16.1)
Aspartate aminotransferase increased	28 (21.1)	12 (9.2)	334 (17.1)	303 (15.5)
Anaemia	25 (18.8)	22 (16.9)	204 (10.5)	323 (16.6)
Pruritus	24 (18.0)	14 (10.8)	159 (8.1)	128 (6.6)
White blood cell count decreased	20 (15.0)	16 (12.3)	117 (6.0)	241 (12.4)
Neutrophil count decreased	17 (12.8)	17 (13.1)	77 (3.9)	247 (12.7)
Platelet count decreased	9 (6.8)	18 (13.8)	84 (4.3)	185 (9.5)
Nausea	7 (5.3)	13 (10.0)	85 (4.4)	164 (8.4)
Source: SCS Table 8				

TEAEs of ≥ Grade 3

Table 48-Treatment-Emergent Adverse Events >= Grade 3 With Incidence >= 5% by Preferred Term (Safety Analysis Set)

	Study 309			
Preferred Term	**Tislelizumab + Chemotherapy (N = 133) n (%)**	**Placebo + Chemotherapy (N = 130) n (%)**	**Tislelizumab Monotherapy (N = 1952) n (%)**	**Tislelizumab Combination Therapy (N = 1950) n (%)**
Patients With Any TEAE >= Grade 3	113 (85.0)	111 (85.4)	916 (46.9)	1531 (78.5)
Anaemia	41 (30.8)	43 (33.1)	92 (4.7)	278 (14.3)
White blood cell count decreased	40 (30.1)	51 (39.2)	10 (0.5)	282 (14.5)
Neutrophil count decreased	39 (29.3)	49 (37.7)	18 (0.9)	572 (29.3)
Neutropenia	30 (22.6)	23 (17.7)	10 (0.5)	344 (17.6)

	Study 309			
Preferred Term	**Tislelizumab + Chemotherapy (N = 133) n (%)**	**Placebo + Chemotherapy (N = 130) n (%)**	**Tislelizumab Monotherapy (N = 1952) n (%)**	**Tislelizumab Combination Therapy (N = 1950) n (%)**
Leukopenia	29 (21.8)	20 (15.4)	4 (0.2)	147 (7.5)
Platelet count decreased	27 (20.3)	33 (25.4)	16 (0.8)	158 (8.1)
Lymphocyte count decreased	14 (10.5)	18 (13.8)	21 (1.1)	53 (2.7)
Hypokalaemia	7 (5.3)	8 (6.2)	36 (1.8)	86 (4.4)
Thrombocytopenia	6 (4.5)	10 (7.7)	6 (0.3)	126 (6.5)

Table 49-Treatment-Emergent Adverse Events ≥ Grade 3 by System Organ Class (Safety Analysis Set)

	Study 309			
	Tislelizumab + Chemotherapy (N = 133) n (%)	**Placebo + Chemotherapy (N = 130) n (%)**	**Tislelizumab Monotherapy (N = 1952) n (%)**	**Tislelizumab Combination Therapy (N = 1950) n (%)**
Primary System Organ Class				
Patients With Any TEAE	113 (85.0)	111 (85.4)	916 (46.9)	1531 (78.5)
Blood and lymphatic system disorders	63 (47.4)	63 (48.5)	125 (6.4)	645 (33.1)
Investigations	69 (51.9)	75 (57.7)	282 (14.4)	847 (43.4)
Metabolism and nutrition disorders	22 (16.5)	14 (10.8)	178 (9.1)	290 (14.9)
Infections and infestations	15 (11.3)	9 (6.9)	156 (8.0)	184 (9.4)
General disorders and administration site conditions	8 (6.0)	4 (3.1)	99 (5.1)	134 (6.9)
Nervous system disorders	7 (5.3)	5(3.8)	53 (2.7)	71 (3.6)
Skin and subcutaneous tissue disorders	6 (4.5)	0 (0.0)	31 (1.6)	76 (3.9)
Hepatobiliary disorders	4 (3.0)	1 (0.8)	75 (3.8)	55 (2.8)
Respiratory, thoracic and mediastinal disorders	3 (2.3)	1 (0.8)	113 (5.8)	117 (6.0)
Gastrointestinal disorders	2 (1.5)	6 (4.6)	165 (8.5)	217 (11.1)
Musculoskeletal and connective tissue disorders	2 (1.5)	1 (0.8)	39 (2.0)	32 (1.6)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	2 (1.5)	1 (0.8)	37 (1.9)	19 (1.0)
Renal and urinary disorders	2 (1.5)	0 (0.0)	24 (1.2)	29 (1.5)
Ear and labyrinth disorders	1 (0.8)	1 (0.8)	3 (0.2)	3 (0.2)
Eye disorders	1 (0.8)	0 (0.0)	9 (0.5)	11(0.6)
Immune system disorders	0 (0.0)	1 (0.8)	2 (0.1)	9 (0.5)
Product issues	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)

Table 50-Treatment-Emergent Adverse Events Related to Tislelizumab/Placebo of >= Grade 3 With Incidence >= 1% by Preferred Term (Safety Analysis Set)

	Study 309			
Preferred Term	**Tislelizumab + Chemotherapy (N = 133) n (%)**	**Placebo + Chemotherapy (N = 130) n (%)**	**Tislelizumab Monotherapy (N = 1952) n (%)**	**Tislelizumab Combination Therapy (N = 1950) n (%)**
Patients With Any TEAE Related to Tislelizumab/Placebo of >= Grade 3	32 (24.1)	29 (22.3)	364 (18.6)	594 (30.5)
White blood cell count decreased	8 (6.0)	8 (6.2)	4 (0.2)	66 (3.4)
Anaemia	5 (3.8)	8 (6.2)	27 (1.4)	60 (3.1)
Neutrophil count decreased	5 (3.8)	8 (6.2)	9 (0.5)	121 (6.2)
Rash	5 (3.8)	0 (0.0)	10 (0.5)	31 (1.6)
Blood creatine phosphokinase increased	3 (2.3)	1 (0.8)	15 (0.8)	9 (0.5)
Neutropenia	3 (2.3)	5 (3.8)	7 (0.4)	65 (3.3)
Leukopenia	2 (1.5)	5 (3.8)	3 (0.2)	38 (1.9)
Lymphocyte count decreased	2 (1.5)	3 (2.3)	10 (0.5)	12 (0.6)
Platelet count decreased	2 (1.5)	6 (4.6)	5 (0.3)	40 (2.1)
Alanine aminotransferase increased	1 (0.8)	0 (0.0)	26 (1.3)	26 (1.3)
Aspartate aminotransferase increased	1 (0.8)	0 (0.0)	39 (2.0)	26 (1.3)
Gamma-glutamyltransferase increased	1 (0.8)	0 (0.0)	22 (1.1)	15 (0.8)
Hyponatraemia	1 (0.8)	1 (0.8)	9 (0.5)	20 (1.0)
Thrombocytopenia	1 (0.8)	4 (3.1)	3 (0.2)	32 (1.6)
Pneumonia	0 (0.0)	3 (2.3)	14 (0.7)	22 (1.1)
Pneumonitis	0 (0.0)	0 (0.0)	17 (0.9)	32 (1.6)

Serious adverse event/deaths/other significant events

Table 51-Serious Treatment-Emergent Adverse Events With Incidence >= 1% by Preferred Term (Safety Analysis Set)

	Study 309			
Preferred Term	**Tislelizumab + Chemotherapy (N = 133) n (%)**	**Placebo + Chemotherapy (N = 130) n (%)**	**Tislelizumab Monotherapy (N = 1952) n (%)**	**Tislelizumab Combination Therapy (N = 1950) n (%)**
Patients With Any Serious TEAE	47 (35.3)	46 (35.4)	683 (35.0)	822 (42.2)
Platelet count decreased	9 (6.8)	14 (10.8)	4 (0.2)	42 (2.2)
Sepsis	4 (3.0)	0 (0.0)	7 (0.4)	14 (0.7)
Thrombocytopenia	4 (3.0)	3 (2.3)	2 (0.1)	34 (1.7)
Anaemia	3 (2.3)	5 (3.8)	6 (0.3)	23 (1.2)
Neutrophil count decreased	3 (2.3)	6 (4.6)	0 (0.0)	26 (1.3)
White blood cell count decreased	3 (2.3)	5 (3.8)	0 (0.0)	14 (0.7)
Febrile neutropenia	2 (1.5)	1 (0.8)	0 (0.0)	20 (1.0)
Myelosuppression	2 (1.5)	1 (0.8)	0 (0.0)	7 (0.4)
Pneumonia	2 (1.5)	4 (3.1)	85 (4.4)	86 (4.4)
Pyrexia	2 (1.5)	1 (0.8)	19 (1.0)	24 (1.2)
Alanine aminotransferase increased	2 (1.5)	1 (0.8)	12 (0.6)	15 (0.8)
Hyponatraemia	2 (1.5)	1 (0.8)	8 (0.4)	15 (0.8)
Acute kidney injury	2 (1.5)	0 (0.0)	5 (0.3)	15 (0.8)
Covid 19	2 (1.5)	0 (0.0)	3(0.2)	6(0.3)
Pneumonitis	1 (0.8)	0 (0.0)	25 (1.3)	58 (3.0)
Leukopenia	0 (0.0)	4 (3.1)	0 (0.0)	9 (0.5)

Table 52-Serious Treatment-Emergent Adverse Events Related to Tislelizumab/Placebo With Incidence >= 2 in study 309 patients by Preferred Term Safety Analysis Set

	Study 309			
Preferred Term	**Tislelizumab + Chemotherapy (N = 133) n (%)**	**Placebo + Chemotherapy (N = 130) n (%)**	**Tislelizumab Monotherapy (N = 1952) n (%)**	**Tislelizumab Combination Therapy (N = 1950) n (%)**
Patients With Any Serious TEAE Related to Tislelizumab/Placebo	13 (9.8)	15 (11.5)	241 (12.3)	351 (18.0)
Alanine aminotransferase increased	2 (1.5)	0 (0.0)	10 (0.5)	15 (0.8)
Aspartate aminotransferase increased	1 (0.8)	0 (0.0)	11 (0.6)	15 (0.8)
Hepatic function abnormal	1 (0.8)	0 (0.0)	4 (0.2)	6 (0.3)
Hyponatraemia	1 (0.8)	1 (0.8)	3 (0.2)	2 (0.1)
Interstitial lung disease	1 (0.8)	0 (0.0)	11 (0.6)	9 (0.5)
Myocarditis	1 (0.8)	0 (0.0)	4 (0.2)	7 (0.4)
Myositis	1 (0.8)	0 (0.0)	4 (0.2)	5 (0.3)
Pneumonitis	1 (0.8)	0 (0.0)	24 (1.2)	54 (2.8)
Pyrexia	1 (0.8)	0 (0.0)	4 (0.2)	8 (0.4)
Rash	1 (0.8)	0 (0.0)	3 (0.2)	6 (0.3)
Acute kidney injury	0 (0.0)	0 (0.0)	1 (0.1)	6 (0.3)
Adrenal insufficiency	0 (0.0)	0 (0.0)	1 (0.1)	9 (0.5)

Deaths

The incidence of deaths was 42.9% in Arm Tisle+GC and 23.8% in Arm P+GC. It should be noted that Table 53 does not include all patients in Arm P+GC after crossover; when including deaths reported after crossover in Arm P+GC, the incidence of deaths was lower in Arm Tisle+GC than in Arm P+GC (42.9% versus 50.8%).

A summary of all deaths is presented in Table 53, differentiating between deaths within 30 days ("on-treatment" deaths) and deaths more than 30 days after the last dose of study treatment.

Table 53-Summary of All Deaths (Safety Analysis Set)

	Study 309			
Category	**Tislelizumab + Chemotherapy (N = 133) n (%)**	**Placebo + Chemotherapy (N = 130) n (%)**	**Tislelizumab Monotherapy (N = 1952) n (%)**	**Tislelizumab Combination Therapy (N = 1950) n (%)**
Total Number of Deaths	57 (42.9)	31 (23.8)	1412 (72.3)	1171 (60.1)
Cause of Death				
Disease Under Study	37 (27.8)	18 (13.8)	1181 (60.5)	914 (46.9)
Adverse Event	7 (5.3)	2 (1.5)	87 (4.5)	85 (4.4)
Concurrent Illness	0 (0.0)	0 (0.0)	9 (0.5)	0 (0.0)
Indeterminate	0 (0.0)	0 (0.0)	49 (2.5)	97 (5.0)
Unknown	0 (0.0)	0 (0.0)	13 (0.7)	0 (0.0)
Other	13 (9.8)	11 (8.5)	73 (3.7)	75 (3.8)
Death Within 30 Days After Last Dose of Study Drug	4 (3.0)	2 (1.5)	140 (7.2)	98 (5.0)
Cause of Death				
Adverse Event	3 (2.3)	2 (1.5)	58 (3.0)	54 (2.8)
Disease Under Study	1 (0.8)	0 (0.0)	78 (4.0)	43 (2.2)
Concurrent Illness	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Indeterminate	0 (0.0)	0 (0.0)	2 (0.1)	1 (0.1)
Other	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Death > 30 Days After Last Dose of Study Drug	52 (39.1)	28 (21.5)	1272 (65.2)	1072 (55.0)
Cause of Death				
Disease Under Study	36 (27.1)	18 (13.8)	1103 (56.5)	871 (44.7)
Adverse Event	4 (3.0)	0 (0.0)	29 (1.5)	31 (1.6)
Concurrent Illness	0 (0.0)	0 (0.0)	8 (0.4)	0 (0.0)
Indeterminate	0 (0.0)	0 (0.0)	47 (2.4)	96 (4.9)
Unknown	0 (0.0)	0 (0.0)	13 (0.7)	0 (0.0)
Other	12 (9.0)	10 (7.7)	72 (3.7)	74 (3.8)

Table 54-Treatment-Emergent Adverse Events Leading to Death With Incidence >= 0.5% by Preferred Term (Safety Analysis Set)

	Study 309			
Preferred Term	**Tislelizumab + Chemotherapy (N = 133) n (%)**	**Placebo + Chemotherapy (N = 130) n (%)**	**Tislelizumab Monotherapy (N = 1952) n (%)**	**Tislelizumab Combination Therapy (N = 1950) n (%)**
Patients With Any TEAE Leading to Death	6 (4.5)	2 (1.5)	150 (7.7)	128 (6.6)
Accidental death	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.1)
Death	1 (0.8)	1 (0.8)	18 (0.9)	21 (1.1)
Depressed level of consciousness	1 (0.8)	0 (0.0)	1 (0.1)	4 (0.2)
Hypoxia	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.1)
Myelodysplastic syndrome	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.1)
Pharyngeal haemorrhage	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.1)

	Study 309			
Preferred Term	**Tislelizumab + Chemotherapy (N = 133) n (%)**	**Placebo + Chemotherapy (N = 130) n (%)**	**Tislelizumab Monotherapy (N = 1952) n (%)**	**Tislelizumab Combination Therapy (N = 1950) n (%)**
Pneumonia aspiration	1 (0.8)	0 (0.0)	0 (0.0)	2 (0.1)
Arrhythmia	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)
General physical health deterioration	0 (0.0)	0 (0.0)	10 (0.5)	8 (0.4)
Hepatic failure	0 (0.0)	0 (0.0)	12 (0.6)	2 (0.1)
Hypernatraemia	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)
Multiple organ dysfunction syndrome	0 (0.0)	0 (0.0)	11 (0.6)	3 (0.2)
Pneumonia	0 (0.0)	0 (0.0)	12 (0.6)	8 (0.4)
Respiratory failure	0 (0.0)	0 (0.0)	10 (0.5)	7 (0.4)
Upper gastrointestinal haemorrhage	0 (0.0)	0 (0.0)	9 (0.5)	1 (0.1)

Other significant adverse events

There was a higher incidence of patients with **imAEs** (53.4% versus 37.7%) and ≥ Grade 3 imAEs (4.5% versus 0.8%) in Arm Tisle+GC than in Arm P+GC, respectively. A total of 5 patients (3.8%) in Arm Tisle+GC and 1 patient (0.8%) in Arm P+GC had serious imAEs. None of the patients in either arm experienced imAEs leading to death. The most frequently reported imAEs (≥ 5% incidence) were *immune-mediated skin adverse reaction* and *immune-mediated endocrinopathies (hypothyroidism)*.

Tislelizumab monotherapy and combination therapy pools: The incidence of imAEs in Arm Tisle+GC of Study 309 was higher than in the monotherapy and combination therapy pools (53.4% versus 33.8% versus 39.9%). Similar to Arm Tisle+GC of Study 309, immune mediated skin adverse reaction and immune-mediated endocrinopathies (hypothyroidism) were the most frequently reported imAEs (≥ 10% incidence) in both pools. In contrast, the incidences of ≥ Grade 3 imAEs, serious imAEs, and imAEs leading to treatment discontinuation or modification in Arm Tisle+GC were comparable to the monotherapy pool and lower than the combination therapy pool.

Table 55-Overview of Immune-Mediated Adverse Events (Safety Analysis Set)

	Study 309			
	Tislelizumab + Chemotherapy (N = 133) n (%)	**Placebo + Chemotherapy (N = 130) n (%)**	**Tislelizumab Monotherapy (N = 1952) n (%)**	**Tislelizumab Combination Therapy (N = 1950) n (%)**
Patients With Any Immune-Mediated Adverse Event	71 (53.4)	49 (37.7)	659 (33.8)	778 (39.9)
>= Grade 3	6 (4.5)	1 (0.8)	105 (5.4)	173 (8.9)
Leading to Death	0 (0.0)	0 (0.0)	2 (0.1)	11 (0.6)
Serious	5 (3.8)	1 (0.8)	113 (5.8)	177 (9.1)
Leading to Treatment Discontinuation	4 (3.0)	0 (0.0)	66 (3.4)	121 (6.2)
Leading to Treatment Discontinuation of Tislelizumab/Placebo	4 (3.0)	0 (0.0)	66 (3.4)	113 (5.8)
Leading to Treatment Modification	8 (6.0)	3 (2.3)	144 (7.4)	242 (12.4)
Leading to Treatment Modification of Tislelizumab/Placebo	7 (5.3)	1 (0.8)	144 (7.4)	215 (11.0)
Treated With Systemic Corticosteroids	8 (6.0)	7 (5.4)	183 (9.4)	242 (12.4)
Treated With Other Immunosuppressant	0 (0.0)	0 (0.0)	11 (0.6)	18 (0.9)
Treated With Hormone Therapy	30 (22.6)	12 (9.2)	199 (10.2)	232 (11.9)

Table 56- Immune-Mediated Adverse Events by Category (Safety Analysis Set)

	Study 309			
Category	**Tislelizumab + Chemotherapy (N = 133) n (%)**	**Placebo + Chemotherapy (N = 130) n (%)**	**Tislelizumab Monotherapy (N = 1952) n (%)**	**Tislelizumab Combination Therapy (N = 1950) n (%)**
Patients With Any Immune-Mediated AE	71 (53.4)	49 (37.7)	659 (33.8)	778 (39.9)
Immune-mediated endocrinopathies (hypothyroidism)	39 (29.3)	19 (14.6)	269 (13.8)	296 (15.2)
Immune-mediated skin adverse reaction	39 (29.3)	32 (24.6)	247 (12.7)	327 (16.8)
Immune-mediated endocrinopathies (hyperthyroidism)	6 (4.5)	1 (0.8)	100 (5.1)	107 (5.5)
Immune-mediated pneumonitis	3 (2.3)	0 (0.0)	101 (5.2)	151 (7.7)
Immune-mediated myocarditis/pericarditis	2 (1.5)	0 (0.0)	15 (0.8)	23 (1.2)
Immune-mediated myositis/rhabdomyolysis	2 (1.5)	2 (1.5)	16 (0.8)	13 (0.7)
Immune-mediated colitis	1 (0.8)	0 (0.0)	11 (0.6)	20 (1.0)
Immune-mediated endocrinopathies (hypophysitis)	1 (0.8)	0 (0.0)	5 (0.3)	11 (0.6)
Immune-mediated hepatitis	1 (0.8)	5 (3.8)	23 (1.2)	29 (1.5)
Other immune-mediated reactions (musculoskeletal)	1 (0.8)	0 (0.0)	17 (0.9)	13 (0.7)
Immune-mediated endocrinopathies (adrenal insufficiency)	0 (0.0)	0 (0.0)	10 (0.5)	15 (0.8)

	Study 309			
Category	**Tislelizumab + Chemotherapy (N = 133) n (%)**	**Placebo + Chemotherapy (N = 130) n (%)**	**Tislelizumab Monotherapy (N = 1952) n (%)**	**Tislelizumab Combination Therapy (N = 1950) n (%)**
Immune-mediated endocrinopathies (diabetes mellitus)	0 (0.0)	0 (0.0)	12 (0.6)	28 (1.4)
Immune-mediated endocrinopathies (thyroiditis)	0 (0.0)	0 (0.0)	21 (1.1)	14 (0.7)
Immune-mediated nephritis and renal dysfunction	0 (0.0)	0 (0.0)	4 (0.2)	8 (0.4)
Other immune-mediated reactions (CNS)	0 (0.0)	0 (0.0)	1 (0.1)	4 (0.2)
Other immune-mediated reactions (blood dyscrasias)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.2)
Other immune-mediated reactions (ocular)	0 (0.0)	0 (0.0)	2 (0.1)	3 (0.2)
Other immune-mediated reactions (other)	0 (0.0)	0 (0.0)	1 (0.1)	10 (0.5)
Other immune-mediated reactions (pancreatitis)	0 (0.0)	0 (0.0)	5 (0.3)	8 (0.4)

Table 57-Summary of Immune-Mediated Adverse Events Occurring in ≥ 1% of Patients in Arm Tisle+GC of Study 309 Safety Analysis Set by Category

imAE Category /Group	Total / ≥ Gr 3, n (%)	Led to Modified Treatment, n (%)	Led to Discontinued Treatment, n (%)	Corticosteroids			Immuno-suppressants, n (%)	Hormone Replacement, n (%)	Patients Recovered, n (%)	Median (months)		
				Treated / High-dose, n (%)	Median					Time to First Onset	Duration of Event	Duration of Resolved Event
					Initial Dose (mg/day)	Duration (months)						
Hypothyroidism												
Tisle+GC	**39 (29.3) / 1 (0.8)**	**1 (0.8)**	**0 (0.0)**	**0 (0.0) / 0 (0.0)**	**--**	**--**	**0 (0.0)**	**29 (74.4)**	**16 (41.0)**	**4.600**	**5.355**	**2.694**
P+GC	19 (14.6) / 0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0) / 0 (0.0)	--	--	0 (0.0)	12 (63.2)	10 (52.6)	4.862	4.140	2.152
Tisle mono	269 (13.8) / 2 (0.1)	12 (0.6)	2 (0.1)	2 (0.7) / 0 (0.0)	10.000	1.938	0 (0.0)	174 (64.7)	98 (36.4)	4.008	7.524	2.070
Tisle Combo	296 (15.2) / 5 (0.3)	38 (1.9)	7 (0.4)	4 (1.4) / 2 (0.7)	50.000	1.183	0 (0.0)	198 (66.9)	100 (33.8)	4.271	5.651	2.070
Skin adverse reaction												
Tisle+GC	**39 (29.3) / 5 (3.8)**	**2 (1.5)**	**0 (0.0)**	**5 (12.8) / 3 (7.7)**	**40.000**	**0.082**	**0 (0.0)**	**--**	**35 (89.7)**	**0.329**	**0.296**	**0.263**
P+GC	32 (24.6) / 0 (0.0)	1 (0.8)	0 (0.0)	6 (18.8) / 2 (6.3)	33.333	0.099	0 (0.0)	--	28 (87.5)	0.263	0.296	0.279
Tisle mono	247 (12.7) / 22 (1.1)	25 (1.3)	2 (0.1)	37 (15.0) / 13 (5.3)	30.000	0.690	1 (0.4)	--	177 (71.7)	1.544	2.004	1.068
Tisle Combo	327 (16.8) / 44 (2.3)	46 (2.4)	11 (0.6)	64 (19.6) / 35 (10.7)	33.333	0.378	5 (1.5)	--	246 (75.2)	1.018	0.953	0.624
Hyperthyroidism												
Tisle+GC	6 (4.5) / 0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0) / 0 (0.0)	--	--	0 (0.0)	1 (16.7)	5 (83.3)	13.175	2.070	1.823
P+GC	1 (0.8) / 0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0) / 0 (0.0)	--	--	0 (0.0)	0 (0.0)	0 (0.0)	33.446	NR	--

imAE Category /Group	Total / ≥ Gr 3, n (%)	Led to Modified Treatment, n (%)	Led to Discontinued Treatment, n (%)	Corticosteroids			Immuno-suppressants, n (%)	Hormone Replacement, n (%)	Patients Recovered, n (%)	Median (months)		
				Treated / High-dose, n (%)	Median					Time to First Onset	Duration of Event	Duration of Resolved Event
					Initial Dose (mg/day)	Duration (months)						
Tisle mono	100 (5.1) / 0 (0.0)	5 (0.3)	1 (0.1)	3 (3.0) / 1 (1.0)	30.000	0.854	0 (0.0)	11 (11.0)	77 (77.0)	2.070	2.070	1.413
Tisle Combo	107 (5.5) / 1 (0.1)	8 (0.4)	2 (0.1)	1 (0.9) / 1 (0.9)	100.000	0.033	0 (0.0)	16 (15.0)	80 (74.8)	3.450	2.201	2.103
Pneumonitis												
Tisle+GC	3 (2.3) / 0 (0.0)	1 (0.8)	1 (0.8)	1 (33.3) / 1 (33.3)	25.000	3.318	0 (0.0)	--	1 (33.3)	9.626	NR	3.220
P+GC	0 (0.0) / 0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0) / 0 (0.0)	--	--	0 (0.0)	--	0 (0.0)	--	--	--
Tisle mono	101 (5.2) / 34 (1.7)	37 (1.9)	36 (1.8)	69 (68.3) / 63 (62.4)	63.750	1.643	2 (2.0)	--	48 (47.5)	4.140	6.275	2.793
Tisle Combo	151 (7.7) / 43 (2.2)	67 (3.4)	50 (2.6)	95 (62.9) / 82 (54.3)	50.000	1.610	8 (5.3)	--	66 (43.7)	5.487	8.345	2.595
Myocarditis/pericarditis												
Tisle+GC	2 (1.5) / 0 (0.0)	1 (0.8)	2 (1.5)	1 (50.0) / 1 (50.0)	75.000	NR	0 (0.0)	--	0 (0.0)	7.162	NR	0.920
P+GC	0 (0.0) / 0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0) / 0 (0.0)	--	--	0 (0.0)	--	0 (0.0)	--	--	--
Tisle mono	15 (0.8) / 4 (0.2)	8 (0.4)	7 (0.4)	10 (66.7) / 9 (60.0)	75.000	0.936	1 (6.7)	--	9 (60.0)	1.577	5.060	1.183
Tisle Combo	23 (1.2) / 9 (0.5)	5 (0.3)	15 (0.8)	18 (78.3) / 16 (69.6)	100.000	1.873	1 (4.3)	--	13 (56.5)	2.957	3.055	1.708
Myositis/rhabdomyolysis												
Tisle+GC	2 (1.5) / 0 (0.0)	1 (0.8)	0 (0.0)	1 (50.0) / 1 (50.0)	60.000	0.230	0 (0.0)	--	1 (50.0)	10.628	1.413	1.150
P+GC	2 (1.5)	1 (0.8)	0 (0.0)	1 (50.0)	95.000	NR	0 (0.0)	--	1 (50.0)	3.253	1.216	0.263

imAE Category /Group	Total / ≥ Gr 3, n (%)	Led to Modified Treatment, n (%)	Led to Discontinued Treatment, n (%)	Corticosteroids			Immuno-suppressants, n (%)	Hormone Replacement, n (%)	Patients Recovered, n (%)	Median (months)		
				Treated / High-dose, n (%)	Median					Time to First Onset	Duration of Event	Duration of Resolved Event
					Initial Dose (mg/day)	Duration (months)						
	/ 0 (0.0)			/ 1 (50.0)								
Tisle mono	16 (0.8) / 5 (0.3)	9 (0.5)	4 (0.2)	9 (56.3) / 8 (50.0)	75.000	1.478	1 (6.3)	--	12 (75.0)	1.511	1.413	1.248
Tisle Combo	13 (0.7) / 5 (0.3)	4 (0.2)	4 (0.2)	9 (69.2) / 9 (69.2)	90.000	1.051	1 (7.7)	--	9 (69.2)	2.825	1.478	1.281

Laboratory findings

Study 309: Haematology abnormalities that deteriorated by ≥ 2 CTCAE toxicity grades from baseline were comparable between the 2 arms.

Table 58-Summary of Laboratory Abnormalities Worsened from Baseline: Hematology (Safety Analysis Set)

		Study 309							
		Tislelizumab + Chemotherapy (N = 133)		Placebo + Chemotherapy (N = 130)		Tislelizumab Monotherapy (N = 1952)		Tislelizumab Combination Therapy (N = 1950)	
Parameter	Directionality	All Grades n/M (%)	Grade 3 - 4 n/M (%)	All Grades n/M (%)	Grade 3 - 4 n/M (%)	All Grades n/M (%)	Grade 3 - 4 n/M (%)	All Grades n/M (%)	Grade 3 - 4 n/M (%)
Hemoglobin (g/L)	High	5/131 (3.8)	0/131 (0.0)	1/128 (0.8)	0/128 (0.0)	86/1914 (4.5)	2/1914 (0.1)	39/1901 (2.1)	0/1901 (0.0)
Hemoglobin (g/L)	Low	130/131 (99.2)	43/131 (32.8)	125/128 (97.7)	47/128 (36.7)	752/1914 (39.3)	85/1914 (4.4)	1559/1901 (82.0)	269/1901 (14.2)
Leukocytes (10^9/L)	Low	123/131 (93.9)	69/131 (52.7)	121/128 (94.5)	73/128 (57.0)	321/1914 (16.8)	18/1914 (0.9)	1454/1901 (76.5)	443/1901 (23.3)
Lymphocytes (10^9/L)	High	8/131 (6.1)	1/131 (0.8)	4/126 (3.2)	0/126 (0.0)	40/1890 (2.1)	3/1890 (0.2)	38/1161 (3.3)	1/1161 (0.1)
Lymphocytes (10^9/L)	Low	111/131 (84.7)	76/131 (58.0)	119/126 (94.4)	72/126 (57.1)	776/1890 (41.1)	169/1890 (8.9)	714/1161 (61.5)	208/1161 (17.9)
Neutrophils (10^9/L)	Low	118/131 (90.1)	66/131 (50.4)	116/126 (92.1)	77/126 (61.1)	258/1891 (13.6)	39/1891 (2.1)	1499/1881 (79.7)	887/1881 (47.2)
Platelets (10^9/L)	Low	90/131 (68.7)	34/131 (26.0)	99/128 (77.3)	41/128 (32.0)	315/1914 (16.5)	24/1914 (1.3)	1148/1900 (60.4)	267/1900 (14.1)

Study 309: Clinical chemistry abnormalities that deteriorated by ≥ 2 CTCAE toxicity grades from baseline were comparable between the 2 arms for the majority of the parameters with differences (≥ 2%) noted only for creatine kinase increased and glucose decreased.

- More frequent (incidence ≥ 5%) clinical chemistry abnormalities (all grades) in Arm Tisle+GC: aspartate aminotransferase increased, creatine kinase increased, and potassium decreased
- More frequent (incidence ≥ 5%) in Arm P+GC: albumin decreased

Table 59-Summary of Laboratory Abnormalities Worsened from Baseline: Serum Chemistry (Safety Analysis Set)

		Study 309							
		Tislelizumab + Chemotherapy (N = 133)		Placebo + Chemotherapy (N = 130)		Tislelizumab Monotherapy (N = 1952)		Tislelizumab Combination Therapy (N = 1950)	
Parameter	Directionality	All Grades n/M (%)	Grade 3 - 4 n/M (%)	All Grades n/M (%)	Grade 3 - 4 n/M (%)	All Grades n/M (%)	Grade 3 - 4 n/M (%)	All Grades n/M (%)	Grade 3 - 4 n/M (%)
Alanine Aminotransferase (IU/L)	High	53/130 (40.8)	3/130 (2.3)	46/127 (36.2)	2/127 (1.6)	628/1911 (32.9)	49/1911 (2.6)	794/1898 (41.8)	66/1898 (3.5)
Albumin (g/L)	Low	51/130 (39.2)	1/130 (0.8)	62/127 (48.8)	0/127 (0.0)	639/1911 (33.4)	6/1911 (0.3)	887/1898 (46.7)	9/1898 (0.5)
Alkaline Phosphatase (IU/L)	High	34/130 (26.2)	0/130 (0.0)	31/126 (24.6)	0/126 (0.0)	610/1910 (31.9)	52/1910 (2.7)	593/1896 (31.3)	15/1896 (0.8)
Aspartate Aminotransferase (U/L)	High	53/131 (40.5)	1/131 (0.8)	45/127 (35.4)	2/127 (1.6)	708/1911 (37.0)	92/1911 (4.8)	883/1899 (46.5)	58/1899 (3.1)
Bilirubin (umol/L)	High	18/130 (13.8)	3/130 (2.3)	12/127 (9.4)	1/127 (0.8)	452/1910 (23.7)	54/1910 (2.8)	500/1898 (26.3)	38/1898 (2.0)
Creatine Kinase (ukat/L)	High	42/129 (32.6)	5/129 (3.9)	21/127 (16.5)	2/127 (1.6)	259/1254 (20.7)	24/1254 (1.9)	433/1808 (23.9)	41/1808 (2.3)
Creatinine (umol/L)	High	49/130 (37.7)	0/130 (0.0)	42/127 (33.1)	0/127 (0.0)	253/1911 (13.2)	23/1911 (1.2)	420/1898 (22.1)	35/1898 (1.8)
Glucose (mmol/L)	High	57/130 (43.8)	0/130 (0.0)	51/126 (40.5)	0/126 (0.0)	865/1905 (45.4)	83/1905 (4.4)	926/1894 (48.9)	23/1894 (1.2)
Glucose (mmol/L)	Low	30/130 (23.1)	1/130 (0.8)	23/126 (18.3)	1/126 (0.8)	208/1905 (10.9)	9/1905 (0.5)	252/1894 (13.3)	9/1894 (0.5)
Potassium (mmol/L)	High	11/131 (8.4)	1/131 (0.8)	10/128 (7.8)	0/128 (0.0)	191/1906 (10.0)	17/1906 (0.9)	263/1901 (13.8)	24/1901 (1.3)
Potassium (mmol/L)	Low	50/131 (38.2)	12/131 (9.2)	38/128 (29.7)	11/128 (8.6)	296/1906 (15.5)	55/1906 (2.9)	571/1901 (30.0)	144/1901 (7.6)
Sodium (mmol/L)	High	4/131 (3.1)	0/131 (0.0)	1/128 (0.8)	1/128 (0.8)	131/1906 (6.9)	2/1906 (0.1)	127/1901 (6.7)	5/1901 (0.3)
Sodium (mmol/L)	Low	78/131 (59.5)	16/131 (12.2)	80/128 (62.5)	16/128 (12.5)	662/1906 (34.7)	123/1906 (6.5)	1025/1901 (53.9)	219/1901 (11.5)

Safety in special populations

Table 60-Overview of Treatment-Emergent Adverse Events by Intrinsic Factors (Study 309 Safety Analysis Set)

Subgroup Category	Study 309			
	Tislelizumab + Chemotherapy		Placebo + Chemotherapy	
Age	< 65 years (N=123) n (%)	65 -< 75 years (N=10) n (%)	< 65 years (N=118) n (%)	≥ 65 to < 75 years (N=12) n (%)
Patients With Any TEAE	123 (100.0)	10 (100.0)	118 (100.0)	11 (91.7)
>= Grade 3	**103 (83.7)**	**10 (100.0)**	100 (84.7)	11 (91.7)
Serious	**41 (33.3)**	**6 (60.0)**	**42 (35.6)**	**4 (33.3)**

Leading to Death	5 (4.1)	1 (10.0)	2 (1.7)	0 (0.0)
Leading to Treatment Discontinuation	**19 (15.4)**	**3 (30.0)**	12 (10.2)	2 (16.7)
Leading to Treatment Modification	89 (72.4)	8 (80.0)	83 (70.3)	10 (83.3)
Immune-Mediated AE	65 (52.8)	6 (60.0)	45 (38.1)	4 (33.3)
Infusion-Related Reaction	6 (4.9)	1 (10.0)	9 (7.6)	0 (0.0)
Age Group 2	**< 50 years (N=65) n (%)**	**≥ 50 years (N=68) n (%)**	**< 50 years (N=62) n (%)**	**≥ 50 years (N=68) n (%)**
Patients With Any TEAE	65 (100.0)	68 (100.0)	62 (100.0)	67 (98.5)
>= Grade 3	56 (86.2)	57 (83.8)	55 (88.7)	56 (82.4)
Serious	22 (33.8)	25 (36.8)	23 (37.1)	23 (33.8)
Leading to Death	5 (7.7)	1 (1.5)	1 (1.6)	1 (1.5)
Leading to Treatment Discontinuation	13 (20.0)	9 (13.2)	7 (11.3)	7 (10.3)
Leading to Treatment Modification	43 (66.2)	54 (79.4)	46 (74.2)	47 (69.1)
Immune-Mediated AE	39 (60.0)	32 (47.1)	27 (43.5)	22 (32.4)
Infusion-Related Reaction	3 (4.6)	4 (5.9)	6 (9.7)	3 (4.4)
Sex	**Female (N=29) n (%)**	**Male (N=104) n (%)**	**Female (N=28) n (%)**	**Male (N=102) n (%)**
Patients With Any TEAE	29 (100.0)	104 (100.0)	27 (96.4)	102 (100.0)
>= Grade 3	25 (86.2)	88 (84.6)	26 (92.9)	85 (83.3)
Serious	9 (31.0)	38 (36.5)	11 (39.3)	35 (34.3)
Leading to Death	1 (3.4)	5 (4.8)	1 (3.6)	1 (1.0)
Leading to Treatment Discontinuation	4 (13.8)	18 (17.3)	4 (14.3)	10 (9.8)
Leading to Treatment Modification	24 (82.8)	73 (70.2)	23 (82.1)	70 (68.6)
Sex	**Female (N=29) n (%)**	**Male (N=104) n (%)**	**Female (N=28) n (%)**	**Male (N=102) n (%)**
Immune-Mediated AE	19 (65.5)	52 (50.0)	11 (39.3)	38 (37.3)
Infusion-Related Reaction	3 (10.3)	4 (3.8)	1 (3.6)	8 (7.8)
Hepatic Function	**Normal (N=112) n (%)**	**Impairment (N=21) n (%)**	**Normal (N=114) n (%)**	**Impairment (N=16) n (%)**
Patients With Any TEAE	112 (100.0)	21 (100.0)	114 (100.0)	15 (93.8)
>= Grade 3	95 (84.8)	18 (85.7)	99 (86.8)	12 (75.0)
Serious	38 (33.9)	9 (42.9)	40 (35.1)	6 (37.5)
Leading to Death	5 (4.5)	1 (4.8)	2 (1.8)	0 (0.0)
Leading to Treatment Discontinuation	17 (15.2)	5 (23.8)	12 (10.5)	2 (12.5)
Leading to Treatment Modification	80 (71.4)	17 (81.0)	81 (71.1)	12 (75.0)
Immune-Mediated AE	62 (55.4)	9 (42.9)	44 (38.6)	5 (31.3)
Infusion-Related Reaction	7 (6.3)	0 (0.0)	8 (7.0)	1 (6.3)
Renal Function	**Normal (N=113) n (%)**	**Impairment (N=20) n (%)**	**Normal (N=105) n (%)**	**Impairment (N=25) n (%)**
Patients With Any TEAE	113 (100.0)	20 (100.0)	105 (100.0)	24 (96.0)
>= Grade 3	98 (86.7)	15 (75.0)	91 (86.7)	20 (80.0)
Serious	41 (36.3)	6 (30.0)	37 (35.2)	9 (36.0)
Leading to Death	6 (5.3)	0 (0.0)	2 (1.9)	0 (0.0)
Leading to Treatment Discontinuation	21 (18.6)	1 (5.0)	10 (9.5)	4 (16.0)
Leading to Treatment Modification	82 (72.6)	15 (75.0)	75 (71.4)	18 (72.0)
Immune-Mediated AE	65 (57.5)	6 (30.0)	38 (36.2)	11 (44.0)
Infusion-Related Reaction	7 (6.2)	0 (0.0)	6 (5.7)	3 (12.0)
ECOG PS	**0 (N=51) n (%)**	**1 (N=82) n (%)**	**0 (N=46) n (%)**	**1 (N=84) n (%)**

Patients With Any TEAE	51 (100.0)	82 (100.0)	46 (100.0)	83 (98.8)
>= Grade 3	45 (88.2)	68 (82.9)	40 (87.0)	71 (84.5)
Serious	18 (35.3)	29 (35.4)	14 (30.4)	32 (38.1)
Leading to Death	1 (2.0)	5 (6.1)	0 (0.0)	2 (2.4)
Leading to Treatment Discontinuation	9 (17.6)	13 (15.9)	2 (4.3)	12 (14.3)
ECOG PS	**0 (N=51) n (%)**	**1 (N=82) n (%)**	**0 (N=46) n (%)**	**1 (N=84) n (%)**
Leading to Treatment Modification	36 (70.6)	61 (74.4)	32 (69.6)	61 (72.6)
Immune-Mediated AE	24 (47.1)	47 (57.3)	21 (45.7)	28 (33.3)
Infusion-Related Reaction	2 (3.9)	5 (6.1)	2 (4.3)	7 (8.3)

Abbreviations: AE, adverse event; TEAE, treatment-emergent adverse event.

In Study 309, the majority of patients (123 patients, 92.5%) in Arm Tisle+GC were < 65 years old.

Adverse drug reactions

Adverse Drug Reactions by System Organ Class, Group Term and Frequency Category are presented in Table 61.The safety of tislelizumab as monotherapy in section 4.8 of the SmPC is based on the pooled data of 1,952 patients across multiple tumour types.

The presentation of the safety of tislelizumab given in combination with chemotherapy, is based on the combination therapy pool (N=1,950) including safety data from Studies 309, 312 and 315.

Table 61- Adverse Drug Reactions with Tislelizumab by System Organ Class, Group Term and Frequency Category (Safety Analysis Set)

	Study 309											
	Tislelizumab + Chemotherapy (N = 133)			Placebo + Chemotherapy (N = 130)			Tislelizumab Monotherapy (N = 1952)			Tislelizumab Combination Therapy (N = 1950)		
System Organ Class Group Term	All Grades n (%)	Grade 3-4 n (%)	Frequency Category (All Grades)	All Grades n (%)	Grade 3-4 n (%)	Frequency Category (All Grades)	All Grades n (%)	Grade 3-4 n (%)	Frequency Category (All Grades)	All Grades n (%)	Grade 3-4 n (%)	Frequency Category (All Grades)
Infections and infestations												
Pneumonia[1]	12 (9.0)	3 (2.3)	Common	7 (5.4)	4 (3.1)	Common	186 (9.5) *	70 (3.6)	Common	227 (11.6) *	78 (4.0)	Very Common
Blood and lymphatic system disorders												
Anaemia[2]	119 (89.5)	42 (31.6)	Very Common	119 (91.5)	44 (33.8)	Very Common	541 (27.7)	94 (4.8)	Very Common	1311 (67.2)	282 (14.5)	Very Common
Thrombocytopenia[3]	84 (63.2)	33 (24.8)	Very Common	94 (72.3)	43 (33.1)	Very Common	212 (10.9) *	21 (1.1)	Very Common	949 (48.7) *	275 (14.1)	Very Common
Neutropenia[4]	115 (86.5)	64 (48.1)	Very Common	110 (84.6)	71 (54.6)	Very Common	136 (7.0)	28 (1.4)	Common	1397 (71.6)	882 (45.2)	Very Common
Lymphopenia[5]	21 (15.8)	15 (11.3)	Very Common	25 (19.2)	19 (14.6)	Very Common	88 (4.5)	25 (1.3)	Common	200 (10.3)	61 (3.1)	Very Common
Immune system disorders												
Sjogren's syndrome	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-	2 (0.1)	0 (0.0)	Uncommon
Endocrine disorders												
Hypothyroidism[6]	43 (32.3)	1 (0.8)	Very Common	22 (16.9)	0 (0.0)	Very Common	276 (14.1)	2 (0.1)	Very Common	311 (15.9)	5 (0.3)	Very Common
Hyperthyroidism[7]	8 (6.0)	0 (0.0)	Common	2 (1.5)	0 (0.0)	Common	128 (6.6)	0 (0.0)	Common	152 (7.8)	1 (0.1)	Common
Thyroiditis[8]	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-	21 (1.1)	0 (0.0)	Common	14 (0.7)	1 (0.1)	Uncommon

	Study 309											
	Tislelizumab + Chemotherapy (N = 133)			Placebo + Chemotherapy (N = 130)			Tislelizumab Monotherapy (N = 1952)			Tislelizumab Combination Therapy (N = 1950)		
System Organ Class Group Term	All Grades n (%)	Grade 3-4 n (%)	Frequency Category (All Grades)	All Grades n (%)	Grade 3-4 n (%)	Frequency Category (All Grades)	All Grades n (%)	Grade 3-4 n (%)	Frequency Category (All Grades)	All Grades n (%)	Grade 3-4 n (%)	Frequency Category (All Grades)
Adrenal insufficiency[9]	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-	11 (0.6)	5 (0.3)	Uncommon	17 (0.9)	9 (0.5)	Uncommon
Hypophysitis[10]	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-	3 (0.2)	0 (0.0)	Uncommon	9 (0.5)	1 (0.1)	Uncommon
Metabolism and nutrition disorders												
Hyperglycaemia[11]	8 (6.0)	0 (0.0)	Common	5 (3.8)	0 (0.0)	Common	186 (9.5)	30 (1.5)	Common	204 (10.5)	18 (0.9)	Very Common
Hyponatraemia[12]	44 (33.1)	5 (3.8)	Very Common	37 (28.5)	1 (0.8)	Very Common	182 (9.3)	56 (2.9)	Common	364 (18.7)	90 (4.6)	Very Common
Hypokalaemia[13]	30 (22.6)	7 (5.3)	Very Common	32 (24.6)	9 (6.9)	Very Common	158 (8.1)	36 (1.8)	Common	334 (17.1) *	88 (4.5)	Very Common
Diabetes mellitus[14]	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		19 (1.0)	7 (0.4)	Uncommon	32 (1.6)	20 (1.0)	Common
Nervous system disorders												
Guillain-Barre syndrome	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-	1 (0.1)	1 (0.1)	Rare	1 (0.1)	1 (0.1)	Rare
Encephalitis[15]	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-	1 (0.1)	1 (0.1)	Rare
Myasthenia Gravis	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-	1 (0.1)	1 (0.1)	Rare
Eye disorders												
Uveitis[16]	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-	5 (0.3)	0 (0.0)	Uncommon	3 (0.2)	1 (0.1)	Uncommon
Cardiac disorders												
Myocarditis[17]	2 (1.5)	0 (0.0)	Common	0 (0.0)	0 (0.0)	-	14 (0.7)	4 (0.2)	Uncommon	23 (1.2) *	4 (0.2)	Common
Pericarditis	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-	2 (0.1)	0 (0.0)	Uncommon	1 (0.1)	1 (0.1)	Rare
Vascular disorders												

	Study 309											
	Tislelizumab + Chemotherapy (N = 133)			Placebo + Chemotherapy (N = 130)			Tislelizumab Monotherapy (N = 1952)			Tislelizumab Combination Therapy (N = 1950)		
System Organ Class Group Term	All Grades n (%)	Grade 3-4 n (%)	Frequency Category (All Grades)	All Grades n (%)	Grade 3-4 n (%)	Frequency Category (All Grades)	All Grades n (%)	Grade 3-4 n (%)	Frequency Category (All Grades)	All Grades n (%)	Grade 3-4 n (%)	Frequency Category (All Grades)
Hypertension[18]	7 (5.3)	1 (0.8)	Common	7 (5.4)	4 (3.1)	Common	117 (6.0)	47 (2.4)	Common	115 (5.9)	37 (1.9)	Common
Respiratory, thoracic and mediastinal disorders												
Cough	29 (21.8)	0 (0.0)	Very Common	13 (10.0)	0 (0.0)	Very Common	298 (15.3)	5 (0.3)	Very Common	293 (15.0)	5 (0.3)	Very Common
Dyspnoea	5 (3.8)	0 (0.0)	Common	3 (2.3)	0 (0.0)	Common	136 (7.0) *	21 (1.1)	Common	180 (9.2) *	13 (0.7)	Common
Pneumonitis[19]	3 (2.3)	0 (0.0)	Common	0 (0.0)	0 (0.0)	-	101 (5.2) *	33 (1.7)	Common	151 (7.7) *	37 (1.9)	Common
Gastrointestinal disorders												
Diarrhoea[20]	21 (15.8)	0 (0.0)	Very Common	14 (10.8)	1 (0.8)	Very Common	197 (10.1)	13 (0.7)	Very Common	395 (20.3)	35 (1.8)	Very Common
Nausea	78 (58.6)	0 (0.0)	Very Common	94 (72.3)	2 (1.5)	Very Common	196 (10.0)	4 (0.2)	Very Common	844 (43.3)	28 (1.4)	Very Common
Stomatitis[21]	13 (9.8)	0 (0.0)	Common	11 (8.5)	1 (0.8)	Common	64 (3.3)	6 (0.3)	Common	181 (9.3)	22 (1.1)	Common
Pancreatitis[22]	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-	18 (0.9)	13 (0.7)	Uncommon	54 (2.8)	19 (1.0)	Common
Colitis[23]	1 (0.8)	0 (0.0)	Uncommon	0 (0.0)	0 (0.0)	-	14 (0.7)	4 (0.2)	Uncommon	20 (1.0) *	8 (0.4)	Common
Hepatobiliary disorders												
Hepatitis[24]	8 (6.0)	1 (0.8)	Common	11 (8.5)	1 (0.8)	Common	54 (2.8) *	28 (1.4)	Common	73 (3.7) *	33 (1.7)	Common

	Study 309											
	Tislelizumab + Chemotherapy (N = 133)			Placebo + Chemotherapy (N = 130)			Tislelizumab Monotherapy (N = 1952)			Tislelizumab Combination Therapy (N = 1950)		
System Organ Class Group Term	All Grades n (%)	Grade 3-4 n (%)	Frequency Category (All Grades)	All Grades n (%)	Grade 3-4 n (%)	Frequency Category (All Grades)	All Grades n (%)	Grade 3-4 n (%)	Frequency Category (All Grades)	All Grades n (%)	Grade 3-4 n (%)	Frequency Category (All Grades)
Skin and subcutaneous tissue disorders												
Rash[25]	41 (30.8)	6 (4.5)	Very Common	41 (31.5)	0 (0.0)	Very Common	319 (16.3)	26 (1.3)	Very Common	418 (21.4)	57 (2.9)	Very Common
Pruritus	29 (21.8)	0 (0.0)	Very Common	18 (13.8)	0 (0.0)	Very Common	215 (11.0)	1 (0.1)	Very Common	198 (10.2)	3 (0.2)	Very Common
Vitiligo[26]	1 (0.8)	0 (0.0)	Uncommon	0 (0.0)	0 (0.0)	-	13 (0.7)	0 (0.0)	Uncommon	6 (0.3)	0 (0.0)	Uncommon
Erythema multiforme	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-	3 (0.2)	1 (0.1)	Uncommon	1 (0.1)	0 (0.0)	Rare
Stevens-Johnson syndrome	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-	1 (0.1)	1 (0.1)	Rare	0 (0.0)	0 (0.0)	-
Musculoskeletal and connective tissue disorders												
Arthralgia	18 (13.5)	1 (0.8)	Very Common	17 (13.1)	0 (0.0)	Very Common	180 (9.2)	4 (0.2)	Common	227 (11.6)	3 (0.2)	Very Common
Myalgia	2 (1.5)	0 (0.0)	Common	0 (0.0)	0 (0.0)	-	35 (1.8)	0 (0.0)	Common	80 (4.1)	3 (0.2)	Common
Arthritis[27]	1 (0.8)	0 (0.0)	Uncommon	1 (0.8)	0 (0.0)	Uncommon	18 (0.9)	2 (0.1)	Uncommon	21 (1.1)	4 (0.2)	Common
Myositis[28]	2 (1.5)	0 (0.0)	Common	2 (1.5)	0 (0.0)	Common	16 (0.8)	5 (0.3)	Uncommon	14 (0.7)*	4 (0.2)	Uncommon
Renal and urinary disorders												
Nephritis[29]	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-	4 (0.2)	1 (0.1)	Uncommon	8 (0.4)	4 (0.2)	Uncommon
General disorders and administration site conditions												

	Study 309											
	Tislelizumab + Chemotherapy (N = 133)			Placebo + Chemotherapy (N = 130)			Tislelizumab Monotherapy (N = 1952)			Tislelizumab Combination Therapy (N = 1950)		
System Organ Class Group Term	All Grades n (%)	Grade 3-4 n (%)	Frequency Category (All Grades)	All Grades n (%)	Grade 3-4 n (%)	Frequency Category (All Grades)	All Grades n (%)	Grade 3-4 n (%)	Frequency Category (All Grades)	All Grades n (%)	Grade 3-4 n (%)	Frequency Category (All Grades)
Fatigue[30]	57 (42.9)	2 (1.5)	Very Common	54 (41.5)	2 (1.5)	Very Common	481 (24.6)	41 (2.1)	Very Common	796 (40.8)	81 (4.2)	Very Common
Pyrexia[31]	35 (26.3)	2 (1.5)	Very Common	13 (10.0)	0 (0.0)	Very Common	314 (16.1)	7 (0.4)	Very Common	360 (18.5)	11 (0.6)	Very Common
Decreased appetite	64 (48.1)	1 (0.8)	Very Common	65 (50.0)	1 (0.8)	Very Common	290 (14.9) *	16 (0.8)	Very Common	782 (40.1)	51 (2.6)	Very Common
Investigations												
Aspartate aminotransferase increased	39 (29.3)	1 (0.8)	Very Common	31 (23.8)	1 (0.8)	Very Common	482 (24.7)	72 (3.7)	Very Common	590 (30.3)	42 (2.2)	Very Common
Alanine aminotransferase increased	38 (28.6)	2 (1.5)	Very Common	27 (20.8)	1 (0.8)	Very Common	430 (22.0)	37 (1.9)	Very Common	597 (30.6)	41 (2.1)	Very Common
Blood bilirubin increased[32]	8 (6.0)	0 (0.0)	Common	10 (7.7)	0 (0.0)	Common	303 (15.5)	54 (2.8)	Very Common	271 (13.9)	18 (0.9)	Very Common
Blood alkaline phosphatase increased	8 (6.0)	0 (0.0)	Common	4 (3.1)	0 (0.0)	Common	165 (8.5)	26 (1.3)	Common	132 (6.8)	5 (0.3)	Common
Blood creatinine increased	32 (24.1)	0 (0.0)	Very Common	23 (17.7)	0 (0.0)	Very Common	104 (5.3)	4 (0.2)	Common	214 (11.0)	7 (0.4)	Very Common
Injury, poisoning and procedural complications												
Infusion related reaction[33]	7 (5.3)	0 (0.0)	Common	9 (6.9)	0 (0.0)	Common	58 (3.0)	2 (0.1)	Common	123 (6.3)	12 (0.6)	Common

Source: ADSL, ADADR.
Patients with multiple events for a given Group Term and System Organ Class were counted only once at the worst grade for the Group Term and System Organ Class, respectively.

Frequency category was based on the following convention: 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 26.1.
Adverse events were graded for severity using CTCAE (v5.0 for studies 309, 209, 304, 305, 307, 312, and 315, v4.03 for studies 001, 102, 203, 204, 205, 206, 208, 301, 302, 303, and 306).
System Organ Classes were sorted by Internationally Agreed Order.
Within each System Organ Class, events were ranked by the decreasing frequency of Group Term in the 'All Grades' of monotherapy.
New PTs (identified in CCDS 3.0, a combined ADR for studies 309, 312, and 315) compared to 305 submission reflecting already established ADR group term are highlighted bold in the following footnotes.
1. Pneumonia included reports of **bronchopulmonary aspergillosis**, **candida pneumonia**, lower respiratory tract infection, lower respiratory tract infection bacterial, pneumocystis jirovecii pneumonia, pneumonia, pneumonia bacterial, pneumonia fungal, **pneumonia mycoplasmal**, pneumonia staphylococcal and pneumonia viral.
2. Anaemia included reports of anaemia and haemoglobin decreased.
3. Thrombocytopenia included reports of immune thrombocytopenia, platelet count decreased and thrombocytopenia.
4. Neutropenia included reports of neutropenia and neutrophil count decreased.
5. Lymphopenia included reports of lymphocyte count decreased, lymphocyte percentage decreased and lymphopenia.
6. Hypothyroidism included reports of **anti-thyroid antibody increased**, central hypothyroidism, hypothyroidism, **immune-mediated hypothyroidism**, primary hypothyroidism, **thyroid hormones decreased**, thyroxine decreased, thyroxine free decreased, tri-iodothyronine decreased and tri-iodothyronine free decreased.
7. Hyperthyroidism included reports of blood thyroid stimulating hormone decreased, hyperthyroidism, **immune-mediated hyperthyroidism**, thyroxine free increased, thyroxine increased, tri-iodothyronine free increased and tri-iodothyronine increased.
8. Thyroiditis included reports of autoimmune thyroiditis, **immune-mediated thyroiditis**, **silent thyroiditis**, thyroiditis and thyroiditis subacute.
9. Adrenal insufficiency included reports of **Addison's disease**, adrenal insufficiency, glucocorticoid deficiency, immune-mediated adrenal insufficiency, **primary adrenal insufficiency** and secondary adrenocortical insufficiency.
10. Hypophysitis included reports of hypophysitis and hypopituitarism.
11. Hyperglycaemia included reports of blood glucose increased and hyperglycaemia.
12. Hyponatraemia included reports of blood sodium decreased and hyponatraemia.
13. Hypokalaemia included reports of blood potassium decreased and hypokalaemia.
14. Diabetes mellitus included reports of diabetes mellitus, diabetic ketoacidosis, **diabetic ketosis**, **ketoacidosis**, latent autoimmune diabetes in adults and type 1 diabetes mellitus.
15. Encephalitis included reports of immune-mediated encephalitis.
16. Uveitis included reports of chorioretinitis, iridocyclitis, iritis and uveitis.
17. Myocarditis included reports of autoimmune myocarditis, immune-mediated myocarditis and myocarditis.
18. Hypertension included reports of blood pressure increased, essential hypertension and hypertension.
19. Pneumonitis included reports of immune-mediated lung disease, interstitial lung disease, organising pneumonia and pneumonitis.
20. Diarrhoea included reports of diarrhoea and frequent bowel movements.
21. Stomatitis included reports of aphthous ulcer, mouth ulceration, oral mucosa erosion and stomatitis.
22. Pancreatitis included reports of amylase increased, lipase increased, pancreatitis and pancreatitis acute.
23. Colitis included reports of **autoimmune colitis**, colitis, **colitis ulcerative** and immune-mediated enterocolitis.
24. Hepatitis included reports of autoimmune hepatitis, drug-induced liver injury, hepatic function abnormal, hepatitis, hepatotoxicity, immune-mediated hepatitis and liver injury.
25. Rash included reports of acute febrile neutrophilic dermatosis, **autoimmune dermatitis**, dermatitis, dermatitis acneiform, dermatitis allergic, **dermatitis exfoliative**, 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 and urticaria.
26. Vitiligo included reports of leukoderma, skin depigmentation, skin hypopigmentation and vitiligo.
27. Arthritis included reports of arthritis, immune-mediated arthritis and polyarthritis.
28. Myositis included reports of immune-mediated myositis, myositis and rhabdomyolysis.
29. Nephritis included reports of focal segmental glomerulosclerosis, **glomerulonephritis membranous**, immune-mediated nephritis, **immune-mediated renal disorder**, nephritis and

tubulointerstitial nephritis.
30. Fatigue included reports of asthenia, fatigue, lethargy, malaise and **physical deconditioning**.
31. Pyrexia included reports of body temperature increased and pyrexia.
32. Blood bilirubin increased included reports of bilirubin conjugated increased, blood bilirubin increased, blood bilirubin unconjugated increased and hyperbilirubinaemia.
33. Infusion related reaction included reports of anaphylactic reaction, chills, corneal oedema, dermatitis allergic, drug eruption, drug hypersensitivity, face oedema, gingival swelling, **hypersensitivity**, infusion related reaction, **laryngeal obstruction**, laryngeal oedema, lip oedema, lip swelling, mouth swelling, pruritus allergic, rash, rash erythematous, **rash macular**, rash pruritic, rhinitis allergic, swelling face, tongue oedema, type I hypersensitivity and urticaria.
* Including fatal outcomes.

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 and no new information on drug interactions for tislelizumab has been generated in support of the current application(s). As monoclonal antibodies are not metabolised by cytochrome P450 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 incidence of TEAEs leading to discontinuation of any component of study treatment was higher in Arm Tisle+GC than in Arm P+GC (16.5% versus 10.8%, respectively) in Study 309.

In general, TEAEs leading to discontinuation of any study treatment component were diverse and were not driven by specific PTs; no individual PTs were reported in > 2 patients in either arm.

Compared to both arms of Study 309, an overall lower incidence of haematological events was reported in the Tislelizumab monotherapy pool. The incidence of the TEAEs leading to discontinuation was generally lower in both arms of Study 309 than in the combination therapy pool.

Table 62- Treatment-Emergent Adverse Events Leading to Treatment Discontinuation With Incidence >= 1% by Preferred Term (Safety Analysis Set)

	Study 309			
Preferred Term	Tislelizumab + Chemotherapy (N = 133) n (%)	Placebo + Chemotherapy (N = 130) n (%)	Tislelizumab Monotherapy (N = 1952) n (%)	Tislelizumab Combination Therapy (N = 1950) n (%)
Patients With Any TEAE Leading to Treatment Discontinuation	22 (16.5)	14 (10.8)	253 (13.0)	478 (24.5)
Leukopenia	2 (1.5)	1 (0.8)	0 (0.0)	4 (0.2)
Myocarditis	2 (1.5)	0 (0.0)	4 (0.2)	9 (0.5)
Neutrophil count decreased	2 (1.5)	1 (0.8)	0 (0.0)	17 (0.9)
Platelet count decreased	2 (1.5)	2 (1.5)	3 (0.2)	16 (0.8)
Thrombocytopenia	2 (1.5)	1 (0.8)	1 (0.1)	23 (1.2)
White blood cell count decreased	2 (1.5)	1 (0.8)	0 (0.0)	11 (0.6)
Blood creatinine increased	1 (0.8)	1 (0.8)	1 (0.1)	27 (1.4)
Pneumonia	1 (0.8)	1 (0.8)	19 (1.0)	16 (0.8)
Anaemia	0 (0.0)	1 (0.8)	1 (0.1)	37 (1.9)
Peripheral sensory neuropathy	0 (0.0)	0 (0.0)	0 (0.0)	29 (1.5)
Pneumonitis	0 (0.0)	0 (0.0)	16 (0.8)	39 (2.0)

Post marketing experience

Tislelizumab has received marketing authorization in several countries/regions, mainly including China, the United States, EU, United Kingdom, Switzerland, and Australia for various indications. The first marketing authorization for tislelizumab was granted in China on 26-Dec-2019. The first approval in the EU was for tislelizumab as monotherapy for the treatment of adult patients with unresectable,

locally advanced or metastatic esophageal squamous cell carcinoma (ESCC) after prior platinum-based chemotherapy on 13-Sep-2023.

As of 25 June 2024, there is a cumulative total exposure of approximately 266,073 person-years (3,192,876 person-months) based on the treatment cycle of Q3W.

The safety profile of tislelizumab including post-marketing safety data is summarized in the PBRER. During the reporting interval of the first 6-month PBRER (26 December 2023 through 25 June 2024), Immune-mediated cystitis was identified as safety signal and confirmed as an ADR. In addition, two actions were taken for safety reasons in the post-marketing setting during the reporting interval:

- "Stevens-Johnson syndrome (SJS)" and "Toxic epidermal necrolysis (TEN)" were included as ADRs in the sections "Adverse drug reactions" and "Warnings and precautions" of the SmPC (approval of Type II variation on 21 March 2024).
- The signals "Coeliac disease" and "Pancreatic failure" were implemented in the SmPC (approval of grouped Type IA variation on 16 May 2024).

Overall, these safety updates have not resulted in significant changes of the benefit/risk profile of tislelizumab.

2.5.1. Discussion on clinical safety

The safety profile of tislelizumab in combination with gemcitabine and cisplatin for the indication of first-line recurrent or metastatic NPC was assessed primarily based on the data from the all-treated population of the pivotal study 309 n=133 in the tislelizumab plus chemotherapy group and n=130 in the placebo plus chemotherapy group. The primary safety data presented here are based on the end-of-study analysis (with a data cut-off date of 8 December 2023), providing a median study follow-up time of 27.50 months.

Safety data from the tislelizumab monotherapy pool and the tislelizumab combination therapy pool are considered as supportive and are only discussed in individual instances, as patient populations are different (here specially in terms of age).

Similar exposures to chemotherapy were observed in both treatment arms of Study 309 (median duration of exposure 4.14 months in Arm Tisle+GC and Arm P+GC; median number of cycles received 6.0 in both treatment arms). The addition of tislelizumab to a standard chemotherapy regimen did not negatively affect the study participants' ability to receive chemotherapy.

The **adverse event summary** demonstrated a comparable safety profile for treatment with tislelizumab plus chemotherapy compared to placebo+chemotherapy (gemcitabine and cisplatin). All patients in both treatment arms of Study 309 (≥ 99%) experienced ≥ 1 TEAE. The most commonly reported events were (incidence rate ≥ 30% in either arm): Anaemia (87.2% in Arm Tisle+GC versus 90.8% in Arm P+GC), Neutrophil count decreased (61.7% versus 59.2%), White blood cell count decreased (61.7% versus 63.1%), Nausea (58.6% versus 72.3%), Platelet count decreased (54.1% versus 61.5%), Decreased Appetite (48.1% versus 50.0%), Neutropenia (35.3% versus 29.8 %), Cough /Productive cough, (37.3%versus 17.7%) Constipation (34.6% versus 46.2%), Hyponatraemia (30.8% versus 28.5%) and Hypothyroidism (30.8% versus 15.4%). Hypothyroidism was the TEAEs considered to be significantly more frequent compared to the P+GC arm and compared to the tislelizumab monotherapy pool and the tislelizumab combination therapy pool. Except for Immune-Mediated AEs proportions of AE categories for the Tisle+GC group were largely comparable to the proportions of the P+GC group.

The overall incidence rates of **severe TEAEs (CTCAE ≥ Grade 3)** in both treatment arms of Study 309 were similar (85.0% in Arm Tisle+GC versus 85.3% in Arm P+GC). The incidence rates of the most common severe TEAEs by Preferred Term were generally comparable in both treatment arms; the most commonly reported severe events were (incidence rate ≥ 5% in either arm): Anaemia (30.8% versus 33.1%), White blood cell count decreased (30.1% versus 39.2%), Neutrophil count decreased (29.3% versus 37.7%), Neutropenia (22.6% versus 17.7%), Leukopenia (21.8% versus 15.4%), Leukopenia (21.8% versus 15.4%), Platelet count decreased (20.3% versus 25.4%), Lymphocyte count decreased (10.5% versus 13.8%), Hypokalaemia (5.3% versus 6.2%) and Thrombocytopenia (4.5% versus 7.7%). Severe TEAEs by Preferred Term with a higher incidence rate in Arm Tisle+GC than in Arm P+GC (difference ≥ 2%) were Neutropenia and Leukopenia.

The overall incidence rate of **serious** TEAEs was comparable in both arms. The most common serious TEAEs by Preferred Term in Arms Tisle+GC and P+GC were (incidence rate ≥ 2% in either arm): Platelet count decreased (6.8% versus 10.8%), Sepsis (3.0% versus 0%), Thrombocytopenia (3.0% versus 2.3%), Anaemia (2.3% versus 3.8%), Neutrophil count decreased (2.3% versus 3.1%), White blood cell count decreased (2.3% versus 3.8%), Pneumonia (1.5% versus 3.1%). 2 cases of Febrile neutropenia were detected in the Tisle+GC arm.

Most **deaths** occurred > 30 days after the patients' last dose of study treatment. Here, disease under study was the primary cause in both treatment arms (27.1% versus 13.8%). The incidence rates of any TEAEs leading to death were 4.5% (6 patients) in Arm Tisle+GC and 1.5% (2 patients) in Arm P+GC. TEAEs leading to death were Accidental death, Depressed level of consciousness, Hypoxia and Pneumonia aspiration, Myelodysplastic syndrome, Pharyngeal haemorrhage and Death (death of unknown cause) in the Tisle+GC arm. The events leading to death were consistent with the known safety profiles of the study treatment and / or the underlying disease, and / or comorbidities.

TEAEs assessed as causally related to tislelizumab / placebo were experienced by 78.2% of patients in Arm Tisle+GC and by 74.6% of patients in Arm P+GC of Study 309. The incidences of TEAEs Grade ≥ 3 and serious TEAES related to tislelizumab / placebo were comparable in Arm Tisle+GC and Arm P+GC (24.1% in Arm Tisle+GC versus 22.3% in Arm P+GC / 9.8% in Arm Tisle+GC versus 11.5% in Arm P+GC (SAE)). TEAEs leading to death assessed as causally related to tislelizumab / placebo occurred at higher incidence rates in Arm Tisle+GC than in Arm P+GC (3.1% versus 0.0%).

A higher proportion of subjects **discontinued treatment due to an AE** in the Tisle+GC (16.5%) compared to Arm P+GC (10.8%). The most frequently reported AEs resulting in treatment discontinuation in the Tisle+GC group were leukopenia, myocarditis, neutrophil count decreased, platelet count decreased, thrombocytopenia and white blood cell count decreased (1.5% each).

The adverse event profile of both study arms reflects the well-known safety profile of the individual components that is related to the different mode of actions of tislelizumab and chemotherapeutic agents.

The overall incidence of adverse events of **imAEs** was higher in the Tisle+GC group and the P+GC group (53.4% versus 37.7%). imAEs were reported for 10 categories in the Tisle+GC group, hypothyroidism (29.3%), skin adverse reactions (29.3%), hyperthyroidism (4.5%), pneumonitis (2.3%), myocarditis (1.5%), myositis (1.5%), colitis (0.8%), and hepatitis (0.8%).

Safety in special populations

There were generally higher frequencies of AEs with higher age (≥65 years) in the two treatment arms in study 309 in the Tisle+GC arm. All patients older than 65 years experienced severe AEs. No patient older than 75 were included in the study. The rate of SAEs was doubled in this patient population (33% (<=65 years) versus 60% (≥65 years)). A trend to higher incidence rates of all TEAE

categories were observed for patients older than 65 years. However, no firm conclusions can be drawn regarding subjects ≥65 years due to the limited dataset (n=10). Any numerical differences observed were not considered to be clinically meaningful given the limited sample sizes of some of the subgroups and the small number of events that led to these differences.

Only Asian patients were enrolled in Study 309. It is acknowledged that no clinically meaningful differences attributable to ethnic background were identified in other global studies with tislelizumab across various indications so far. Considering the limited data in the elderly population from study 309, indicating a probably worse safety profile in patients older than 65 years, the Applicant was requested to provide an Overview of Treatment-Emergent Adverse Events by age (≥65Y /<65Y) of the tislelizumab combination therapy pool across indications (N=1950)**.** Grade 3 AEs and SAEs were higher in the elderly (ca. 6% and 9% respectively). Nevertheless, less tolerability is expected in elderly and so far the really limited data do not indicate particularly poor tolerability of tislelizumab compared to other PD-1 inhibitors.

The safety profile of patients < 50 years and ≥ 50 years could be regarded as comparable besides the increased incidences of immune mediated AEs (60% versus 47.1%) in the younger age group. It should however be noted that 5 of the 6 patients who died due to a TEAE were younger than 50 years.

Comparison of Tisle+GC arm with the tislelizumab monotherapy pool and the tislelizumab combination therapy pool

In NPC, Median duration of exposure tislelizumab was longer in the tislelizumab plus chemotherapy group (10.51 months) compared with the tislelizumab monotherapy pool (4.14 months) and the tislelizumab combination therapy pool (7.2 months). This may reflect the prognosis of disease and the age of in subjects treated first line for NPC.

Proportions of SAEs were lower in the Tisle+GC arm than in the tislelizumab plus chemotherapy (combination therapy pool) group (35.3% versus 42.2%), but comparable to the tislelizumab monotherapy pool (35.0%), whereas proportions of Grade 3 to 5 adverse events were higher in subjects in the NPC population (85%), compared to both the tislelizumab monotherapy pool and tislelizumab combination therapy pool (46.9% and 78.5%, respectively).

Proportions of deaths were lower in the indication NPC (4.5%), when compared to the tislelizumab monotherapy (7.7%) and the tislelizumab combination therapy pool (6.6%).

With the exception of hypothyroidism (29.3% versus 13.8% and 15.2%) and immune mediated skin reactions (29.3% versus 12.7% and 16.8%) frequency, severity and types of imAEs were generally consistent.

The SmPC section 4.8 reflects the safety data from the tislelizumab combination therapy pool, including study 309 (N=1950) which was already updated in the context of variation EMEA/H/C/005919/II/0016.

2.5.1. Conclusions on clinical safety

Overall, the safety profile observed for tislelizumab in combination with gemcitabine and cisplatin in adult patients with NPC in the first-line setting was consistent with the known safety profiles of the chemotherapy components (mainly haematologic toxicity) and the PD-1 inhibitor tislelizumab (mainly imTEAEs), and the expected additive toxicity when given in combination with chemotherapy. There are no new safety signals for tislelizumab when used in this combination regimen.

2.5.2. PSUR cycle

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

2.6. Risk management plan

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

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

The PRAC considered that the risk management plan version 5.0 is acceptable.
The CHMP endorsed the Risk Management Plan version 5.0 with the following content:

Safety concerns

Table 63: 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

Routine pharmacovigilance activities remain sufficient to further characterise the safety concerns of tislelizumab in all approved indications.

Risk minimisation measures

Table 64: 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.	Routine Pharmacovigilance Activities Beyond Adverse Reactions Reporting and Signal Detection: None Additional Pharmacovigilance Activities: None

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	PL Section 2 and PL Section 4 where guidance on how to early identify signs and symptoms and seek medical attention is included. Additional Risk Minimisation Measures: Patient card Legal Status: Restricted medical prescription	
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		

2.7. Update of the Product information

As a result of this variation, the sections 2, 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC as well as the Annex II are updated. The Package Leaflet (PL) is updated accordingly. In addition, the MAH took the opportunity to introduce editorial and administrative changes to the PI as well as to update the PI in line with the Annex of the Excipients Guideline.

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

2.7.1. User consultation

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

The full user testing of the package leaflet with the active substance tislelizumab was performed under the previous invented name Tizveni as part of the initial marketing authorisation for the treatment of Non-Small Cell Lung Cancer (NSCLC). In addition, a bridging report was carried out with the same active substance in the context of the extension procedure to add the second-line treatment Oesophageal Squamous Cell Carcinoma (OSCC) under Tevimbra.

With regard to the current procedure: "Extension of indication to include, in combination with gemcitabine and cisplatin, the first-line treatment of adult patients with recurrent or metastatic nasopharyngeal carcinoma (NPC) for TEVIMBRA based on final results from study BGB-A317-309 (study 309)" the amendments included in the package leaflet are minor.

In section 1 "What Tevimbra is and what it is used for" a revised wording was included to add the new indication in patient-friendly terms. In addition, section 2 "What you need to know before you are given Tevimbra" was amended in order to implement the warning statement in the context of the excipient polysorbate 20 according to the statement published in the annex of the excipients guideline together with the inclusion of a statement for the dilution step (sodium chloride) of the concentration and the resulting higher daily intake of sodium. Section 4 'Possible side effects' contains an update of new side effects and frequencies observed with Tevimbra alone or in combination. The sections 3, 5 and 6 remain the same.

There are no further proposed changes to the content of the package leaflet. In particular, the key messages for the safe use of the medicinal product are not impacted. Furthermore, the design, layout and format of the package leaflet will be maintained and the readability will not be affected negatively.

Therefore, the justification for not performing a consultation with target patient groups is considered acceptable.

2.7.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Tevimbra (tislelizumab) is included in the additional monitoring list. Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

The approved indication is:

Tevimbra, in combination with gemcitabine and cisplatin, is indicated for the first-line treatment of adult patients with recurrent, not amenable to curative surgery or radiotherapy, or metastatic nasopharyngeal carcinoma.

3.1.1. Disease or condition

NPC is a type of head and neck cancer and represents the most common cancer originating in the nasopharynx. Referring to Globocan, 120,434 new cases of NPC and 73,482 deaths were observed in 2022 worldwide.

NPC is rare throughout most of the Western world, but it is endemic in a few areas including Southern China, Southeast Asia, and North Africa. Several features of the disease differ according to geographic area (e.g. age distribution, pathogenesis and disease histology). The primary risk factors of NPC include genetic predisposition, EBV infection, tobacco and alcohol use, older age, male sex, and dietary factors.

There are 3 major histological subtypes of NPC: keratinising, non-keratinising (differentiated or undifferentiated), and basaloid cell carcinoma. The non-keratinising NPC is the most common subtype in both high- and low-incidence areas, while the prevalence of keratinising NPC is higher in low-incidence areas (including Europe) as compared to endemic areas.

More than 80% of NPC patients present with advanced-stage disease and approximately 7% present with metastatic disease at diagnosis. The outcome for patients with recurrent or newly diagnosed metastatic NPC is very poor, with a median OS of about 20 to 22 months.

3.1.2. Available therapies and unmet medical need

In the past, cytotoxic chemotherapy (gemcitabine plus cisplatin, according to ESMO 2021 and NCCN 2021 guidelines) was the standard of care for 1L treatment of patients with recurrent or metastatic NPC.

Recently, three Phase 3 studies that assessed effects of the anti-PD-1 antibodies tislelizumab (BGB-A317-309), toripalimab (JUPITER-02) and camrelizumab (CAPTAIN-1st), in combination with gemcitabine plus cisplatin, have reported positive outcomes in the 1L setting of recurrent or metastatic NPC. Based on the results of JUPITER-02, toripalimab, in combination with gemcitabine and cisplatin, was subsequently approved for the 1L treatment of adult patients with recurrent, not amenable to surgery or radiotherapy, or metastatic NPC in the EU (LOQTORZI). International clinical guidelines have been updated to recommend treatment with anti-PD-1 antibodies plus chemotherapy as the preferred 1L treatment option for patients with recurrent or metastatic NPC (ESMO 2023; CSCO 2023; NCCN 2024).

3.1.3. Main clinical studies

Study 309 was an Asia-only Phase 3, randomised, multicentre, double-blind, placebo-controlled study that randomised 263 patients with recurrent or metastatic NPC in a 1:1 ratio to receive a 1L treatment of tislelizumab plus gemcitabine and cisplatin (GC) vs. placebo plus GC. Randomisation was stratified by gender and presence of liver metastases (yes vs. no). The primary endpoint was PFS assessed by IRC. Efficacy results were provided from the pre-planned interim analysis with data cut-off date 26 March 2021, as well as from the study end date (closeout) with data cut-off date 08 December 2023.

3.2. Favourable effects

Study 309 demonstrated a statistically significant improvement in PFS with tislelizumab plus GC over placebo plus GC (stratified HR = 0.52 [95% CI: 0.38 – 0.73], p < 0.0001, median PFS 9.2 months for tislelizumab plus GC vs. 7.4 months for placebo plus GC) at the IA (median study follow-up time of 10.02 months). The updated efficacy results at study end date (with 17 additional months of median study follow-up) showed a consistent and sustained PFS benefit for tislelizumab plus GC (stratified HR = 0.53 [95% CI: 0.39 – 0.71], median PFS 9.6 months for tislelizumab + GC vs. 7.4 months for placebo plus GC).

The descriptive OS analysis at the study end date supported the primary PFS outcome and revealed a clinically relevant improvement in OS of patients treated with tislelizumab plus GC (stratified HR = 0.73 [95% CI: 0.51 - 1.05], median OS 45.3 months for tislelizumab plus GC vs. 31.8 months for placebo plus GC).

3.3. Uncertainties and limitations about favourable effects

Study 309 solely recruited patients from the Asia-Pacific region, which is an endemic area of NPC. In contrast, NPC constitutes a rare malignancy in Europe, with several disease features differing between low-incidence and high-incidence populations. In this regard, there is uncertainty about the treatment effect of tislelizumab plus GC in

a. the subgroup of patients aged ≥65 years, and

b. the subgroup of patients with keratinising NPC histology.

Based on literature, the percentage of patients ≥65 years of age and with keratinising disease is expected to be higher in Europe as compared to Asia and the Study 309 population, respectively. The efficacy outcome in the subgroup of patients aged ≥65 years indicated a potential detrimental effect, while the limited clinical data available so far for patients with keratinising NPC do not suggest a lack of benefit of anti-PD-1 therapy in this subgroup. Overall, the sample size of the aforementioned subgroups of patients in Study 309 was too low draw reliable conclusions.

The study generally excluded NPC patients aged ≥ 75 years. No data are available.

3.4. Unfavourable effects

The overall incidence rate of serious TEAEs was comparable in Arm Tisle+GC compared to Arm P+GC of Study 309 (55.3% versus 35.4%). The incidence rates of the most common serious TEAEs by Preferred Term in Arms Tisle+GC and P+GC were mostly comparable in both treatment arms (incidence rate ≥ 2% in either arm): Platelet count decreased; Sepsis, Thrombocytopenia, Anaemia, Neutrophil count decreased, White blood cell count decreased, Pneumonia. Sepsis was the only

serious TEAEs by Preferred Term with a difference ≥ 2% in incidence rates in Arm Tisle+GC compared to Arm P+GC.

Immune-mediated TEAEs were reported more commonly in Arm Tisle+GC than in Arm P+GC of Study 309 (53.4% versus 37.7%). The same applies for all other categories of imTEAEs (imTEAEs Grade ≥ 3, serious imTEAEs, imTEAEs leading to dose modification / discontinuation of treatment / death). imAEs were reported for 10 categories in the T+C group, hypothyroidism (29.3%), skin adverse reactions (29.3%), hyperthyroidism (4.5%), pneumonitis (2.3%), myocarditis (1.5%), myositis (1.5%), colitis (0.8%), and hepatitis (0.8%).

In Study 309, the incidence rate of TEAEs leading to discontinuation of any component of study treatment was higher in Arm Tisle+GC than in Arm P+GC (16.5% versus 10.8%). Generally, this shift was not driven by specific Preferred Terms; notwithstanding, several TEAEs leading to treatment discontinuation were immune-mediated.

The incidence rates of death due to TEAEs was numerically higher in Arm Tisle+GC compared with Arm P+GC (4.5% versus 1.5%). However, there were no new safety signals identified.

3.5. Uncertainties and limitations about unfavourable effects

Uncertainty is associated with the low proportions of elderly patients aged ≥ 65 years (n=10 in Arm Tisle+GC) in Study 309, and this is reflected in section 5.1 of the SmPC. The extrapolation of the safety data observed in the Asian patient population enrolled in Study 309 to a European patient population is restricted, as a higher proportion of patients in Europe would be anticipated to be ≥65 years old.

3.6. Effects Table

Table 65-Effects Table for Tevimbra in combination with gemcitabine and cisplatin for the first-line treatment of recurrent or metastatic NPC (primary analysis based on IA with data cut-off: 26 March 2021, analysis at study end date with data cut-off: 08 December 2023)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects (primary analysis, DCO: 26 March 2021)						
PFS	based on IRC per RECIST v1.1	Months [95% CI]	9.2 [7.6, 10.1]	7.4 [5.6, 7.5]	Double-blind study; consistent and sustained benefit with updated analysis	SCE
		HR [95% CI]	0.52 [0.38, 0.73]			
Favourable Effects (study end date, DCO: 08 December 2023)						
PFS	based on IRC per RECIST v1.1	Months [95% CI]	9.6 [7.6, 11.6]	7.4 [5.6, 7.6]	Asia-only study with uncertain treatment effect in patients aged ≥65 years and patients with keratinising NPC Generally consistent results across subgroups; however, PD-L1 subgroup analyses non-reliable No data for patients ≥75 years	SCE
		HR [95% CI]	0.53 [0.39, 0.71]			
OS	Time from randomisation until death	Months [95% CI]	45.3 [33.4, NE]	31.8 [25.0, NE]		
		HR	0.73			

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
		[95% CI]	[0.51, 1.05]		OS not statistically tested	
Unfavourable Effects						
Serious TEAEs	All causality	%	35.3	35.3		
	related	%	23.3	30.0		
Deaths	Due to TEAEs	%	4.5	1.5		
TEAEs leading to DC	All causality	%	16.5	10.8		
	related	%	12.8	9.2		
im TEAEs	All causality	%	53.4	37.7		
	≥ Grade 3	%	4.5	0.8		

Abbreviations: DCO=Data cut-off, HR=Hazard ratio, IRC=Independent Review Committee, SCE=Summary of Clinical Efficacy

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

In Study BGB-A317-309, a statistically significant improvement of PFS was demonstrated for treatment with tislelizumab in combination with gemcitabine and cisplatin compared with chemotherapy alone in the ITT population. Descriptive OS analysis at the end of study generally supported the primary PFS analysis, although OS KM curves indicated a delayed treatment effect with curves crossing in favour of the treatment arm at 12 months. However, a clinically relevant OS difference was maintained thereafter.

Higher incidence rates of imTEAEs, and TEAEs leading to discontinuation have been observed for tislelizumab in combination with gemcitabine and cisplatin as compared to placebo in combination with gemcitabine and cisplatin. However, additional toxicity would be expected for immunochemotherapy, and no new safety signals were identified for tislelizumab when used in this combination.

3.7.2. Balance of benefits and risks

The improvement in PFS demonstrated in patients with recurrent or metastatic NPC overall outweighs the additional toxicity of tislelizumab in the combination with standard chemotherapy.

3.7.3. Additional considerations on the benefit-risk balance

None.

3.8. Conclusions

The overall B/R of Tevimbra is considered 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, II and IIIB

Extension of indication to include, in combination with gemcitabine and cisplatin, the first-line treatment of adult patients with recurrent, not amenable to curative surgery or radiotherapy or metastatic nasopharyngeal carcinoma (NPC) for TEVIMBRA based on final results from study BGB-A317-309 (study 309). Study 309 was a Phase 3 randomised, double-blind, placebo-controlled, Asia-only study that compared the efficacy and safety of tislelizumab combined with gemcitabine plus cisplatin (GC) versus placebo combined with GC as 1L treatment for recurrent or metastatic NPC. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 5.0 of the RMP has also been agreed. In addition, the MAH took the opportunity to introduce editorial and administrative changes to the PI as well as to update the PI in line with the Excipients Guideline.

The variation leads to amendments to the Summary of Product Characteristics, Annex II 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, II and IIIB and to the Risk Management Plan are recommended.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.