24 July 2025
EMA/CHMP/212902/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tevimbra

International non-proprietary name: Tislelizumab

Procedure No. EMEA/H/C/005919/II/0018

Note

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

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List of abbreviations

1L	first-line
ADA	antidrug antibody
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BICR	blinded independent central review
BIPR	blinded independent pathology review
CDE	Centre for Drug Evaluation
CSCO	Chinese Society of Clinical Oncology
CSR	clinical study report
DFS	disease-free survival
ECG	electrocardiogram
EFS	event-free survival
EGFR	epidermal growth factor receptor
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EORTC QLQ-LC13	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Lung Cancer
EQ-5D-5L	European Quality of Life 5-Dimension 5-Level Questionnaire
ER	exposure-response
EU	European Union
FDA	Federal Drug Administration
G/GEJ	gastric/gastroesophageal junction
GI	gastrointestinal
HR	hazard ratio
HRQoL	health-related quality of life
ICH	International Council for Harmonisation
ICI	immune checkpoint inhibitor
IDMC	Independent Data Monitoring Committee
IgG4	Immunoglobulin G4
imAE	immune-mediated adverse event
IRR	infusion-related reaction
ITT	Intent-to-Treat (analysis set)
LLN	lower limit of normal
MPR	major pathological response
NAb	neutralizing antibodies
NCCN	National Comprehensive Cancer Network
NMPA	National Medical Products Administration
NSCLC	non-small-cell lung cancer
ORR	objective response rate
OS	overall survival
OSCC	oesophageal squamous cell carcinoma
PBRER	Periodic Benefit Risk Evaluation Report
pCR	pathological complete response
PD-1	programmed death protein-1
PD-L1	programmed death protein ligand-1
PK	pharmacokinetic
PopPK	population PK
PT	Preferred Term
RWE	real world evidence
SCE	Summary of Clinical Efficacy
SCP	Summary of Clinical Pharmacology
SCS	Summary of Clinical Safety
T4	thyroxine
TEAE	treatment-emergent adverse event
TLR	targeted literature review
TSH	thyroid stimulating hormone
ULN	upper limit of normal

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Beone Medicines Ireland Limited submitted to the European Medicines Agency on 28 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 and IIIB

Extension of indication for Tevimbra in combination with platinum-containing chemotherapy as neoadjuvant treatment and then continued as monotherapy as adjuvant treatment, for the treatment of adult patients with resectable NSCLC based on interim results from study BGB-A317-315. Study BGB-A317-315 is a phase 3 randomized, placebo-controlled, double-blind study to compare the efficacy and safety of neoadjuvant treatment with tislelizumab plus platinum-based doublet chemotherapy followed by adjuvant tislelizumab versus neoadjuvant treatment with placebo plus platinum-based doublet chemotherapy followed by adjuvant placebo in patients with resectable Stage II or IIIA NSCLC. 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 2.7 of the RMP has also been submitted.

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

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0142/2019 on the granting of a product-specific waiver for tislelizumab for the treatment of all conditions included in the category of malignant neoplasms (except central nervous system, haematopoietic and lymphoid tissue).

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The MAH 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	28 November 2024
Start of procedure:	28 December 2024
CHMP Rapporteur Assessment Report	21 February 2025
PRAC Rapporteur Assessment Report	3 March 2025
PRAC Outcome	13 March 2025
CHMP members comments	17 March 2025
Updated CHMP Rapporteur(s) (Joint) Assessment Report	20 March 2025
Request for supplementary information (RSI)	27 March 2025
CHMP Rapporteur Assessment Report	24 June 2025
PRAC Rapporteur Assessment Report	26 June 2025
PRAC members comments	n/a
Updated PRAC Rapporteur Assessment Report	n/a
PRAC Outcome	10 July 2025
CHMP members comments	14 July 2025
Updated CHMP Rapporteur Assessment Report	17 July 2025
Opinion	24 July 2025

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Resectable (Stage IIA-IIIA) NSCLC (staged per the AJCC staging system for lung cancer 8th Edition).

State the claimed therapeutic indication

Tevimbra, in combination with platinum-containing chemotherapy as neoadjuvant treatment and then continued as monotherapy as adjuvant treatment, is indicated for the treatment of adult patients with resectable (tumours ≥4 cm or node positive) NSCLC.

Epidemiology and risk factors

Lung cancer is the second most common cause of cancer morbidity and the most common cause of cancer-related death worldwide, with 2.2 million new cases and 1.8 million deaths observed in 2020. In Europe, an estimated 477,534 new cases of lung cancer were diagnosed with approximately 384,176 deaths related to lung cancer.

NSCLC is the predominant subtype of lung cancer, accounting for approximately 85% of all cases (Howlader et al 2015). NSCLC can be divided into 2 major histologic types: adenocarcinoma and squamous cell carcinoma (Travis et al 2011). The incidence of adenocarcinoma has risen globally and represents 40% of all subtypes and all stages of NSCLC, followed by squamous cell carcinoma (25%) (Leiter et al 2023). About one-third of NSCLC cases present with surgically resectable disease, including most Stage I to IIIA cases and a small proportion of Stage IIIB cases (Chansky et al 2017).

Clinical presentation, diagnosis and stage/prognosis

Approximately 20% to 25% of NSCLC patients present with resectable lung cancer (Liang et al 2013) and this is expected to increase with the implementation of lung cancer screening in high-risk populations (Passiglia et al 2021). For early-stage NSCLC, the 5-year survival rate remains low at 56% to 65% for patients with Stage II, and 24% to 41% for patients with Stage III disease (Goldstraw et al 2016). The overall 5-year relative survival rate for Stage I-IIIA NSCLC was 49.5% in Central and Eastern Europe (Sheikh et al 2023).

Management

In the adjuvant treatment setting randomized studies of platinum-based chemotherapy demonstrated an improvement in OS in patients with resected NSCLC. The Lung Adjuvant Cisplatin Evaluation meta-analysis of pooled data from the five largest trials of cisplatin-based chemotherapy after NSCLC complete resection indicated a 5.4% absolute benefit in 5-year survival for chemotherapy vs no chemotherapy. The benefit of adjuvant chemotherapy was different depending on stage, with higher stage correlating with an increased magnitude of benefit (HR 1.4 [95%CI: 0.95 to 2.06] for Stage IA disease; HR = 0.93 for Stage IB disease [95%CI: 0.78 to 1.10]; HR 0.83 for Stage II disease [95%CI: 0.73 to 0.95]; and HR 0.83 for Stage III disease [95%CI: 0.72 to 0.94]) (Pignon et al 2008). However, the recurrence rate remains high, ranging from 62% in patients with Stage II and 76% of patients with Stage III disease (Pignon et al 2008), which in turn is associated with poor survival rates in this patient population (Goldstraw et al 2016). Multiple trials have demonstrated comparable outcomes between neoadjuvant and adjuvant therapy. However, due to its simpler implementation as well as earlier availability of survival data from clinical trials, adjuvant chemotherapy was more widely adopted than neoadjuvant chemotherapy (Kalvapudi et al 2023).

Reported long-term benefit of ICIs in patients with metastatic disease provided the rationale to evaluate PD-(L)1 inhibitors in the early disease setting to reduce the risk of recurrence and improve survival (Garon et al 2019; Herbst et al 2021; Novello et al 2023; de Castro et al 2022).

With the successful development of cancer immunotherapy in advanced NSCLC, several PD-(L)1 inhibitors have been approved by the European Commission as neoadjuvant or adjuvant treatment for adult patients with resectable NSCLC (see below). In addition, pembrolizumab has been approved in the adjuvant setting (Keytruda II-121) and nivolumab has been approved in the perioperative setting for patients whose tumors have PD-L1 expression ≥1% (Opdivo II-140).

Table 1: Overview of treatments approved as neoadjuvant and/or adjuvant treatment for adult patients with resectable NSCLC in Europe

Study	KEYNOTE-671		AEGEAN		CheckMate 77T		IMpower010	
Treatment	Pembrolizumab		Durvalumab		Nivolumab		Atezolizumab	
Indication	In combination with platinum -containing chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment, is indicated for the treatment of resectable non-small cell lung carcinoma at high risk of recurrence in adults (		IMFINZI in combination with platinum-based chemotherapy as neoadjuvant treatment, followed by IMFINZI as monotherapy after surgery, is indicated for the treatment of adults with resectable (tumors ≥ 4 cm and/or node positive) NSCLC and no known EGFR mutations or ALK rearrangements		In combination with platinum-based chemotherapy is indicated for the neoadjuvant treatment of resectable NSCLC at high risk of recurrence in adult patients whose tumors have PD-L1 expression ≥ 1%		As adjuvant monotherapy following complete resection and platinum-based chemotherapy for adult patients with NSCLC with a high risk of recurrence whose tumors have PD-L1 expression on ≥ 50% of TCs and who do not have EGFR mutant or ALK-positive NSCLC	
Patient Population	Resectable Stage II to IIIB NSCLC(AJCC 8.Edition)		Resectable Stage II to IIIB NSCLC(AJCC 8.Edition)		Resectable Stage II to IIIB NSCLC (AJCC 8.Edition)		Resectable Stage IB to IIIA NSCLC PD-L1 ≥ 50% TC (AJCC 7.Edition)	
Dosing Regimen	<u>Neoadjuvant:</u> pembrolizumab/placebo 200 mg, Q3W + cisplatin-doublet chemotherapy, up to 4 cycles <u>Adjuvant:</u> pembrolizumab/placebo 200 mg (Q3W, up to 13 cycles)		<u>Neoadjuvant:</u> durvalumab/placebo 1500 mg + platinum-doublet chemotherapy (Q3W for 4 cycles) <u>Adjuvant:</u> durvalumab/placebo 1500 mg (Q4W, up to 12 cycles)		<u>Neoadjuvant:</u> nivolumab/placebo 360 mg + platinum-doublet chemotherapy (Q3W for 4 cycles) <u>Adjuvant:</u> nivolumab/placebo 480 mg (Q4W for 1 year)		<u>Adjuvant:</u> Cisplatin-based chemotherapy (up to four cycles) Followed by atezolizumab 1 200 mg (Q3W up to 16 cycles) or BSC	
Country/Region	Global		Global		Global		Global	
ITT [a]	397 vs 400		(Modified ITT population) 366 vs 374		229 vs 232		106 vs 103	
Median EFS (months) [a]	47.2 months	18.3 months	NR (95% CI: 42.3 months-NR)	30.0 months (95% CI: 20.6 months-NR)	40.1 months (95% CI: 33.7 months-NR)	17.0 months (95% CI: 13.6-28.1 months)	(DFS) NE (95% CI: NE)	(DFS) NE (95% CI: 32.0 months-NE)
EFS HR	0.59 (95% CI: 0.48-0.72)		0.69 (95% CI: 0.55-0.88)		0.59 (95% CI: 0.45-0.79)		DFS HR: 0.52 (0.33, 0.80)	
pCR Rate [a]	18.1% vs 4.0% Difference: 14.2% (95% CI: 10.1%-18.7%); p < 0.0001		17.2% vs 4.3% Difference: 13.0% (95% CI: 8.7%-17.6%); p < 0.0001		25.3% vs 4.7% Difference: 20.5% (95% CI: 14.3%-26.6%)			

Study	KEYNOTE-671	AEGEAN	CheckMate 77T	IMpower010
OS [a]	NR (95% CI: NR-NR) vs 52.4 months (95% CI: 45.7-NR) HR = 0.72 (95% CI: 0.56-0.93); p = 0.00517	NR (95% CI: NR-NR) vs 53.2 months (95% CI: 44.3 months-NR) HR = 0.89 (95% CI: 0.70-1.14)	N/A	NE vs 87.1 (95% CI: 72.0 months-NE) HR = 0.47 (95% CI: 0.28-0.80)

2.1.2. About the product

Tislelizumab is an Fc-engineered humanized monoclonal IgG4 kappa antibody with an approximate molecular weight of 147 kDa. Tislelizumab binds 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 of T cells 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.

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 for the first-line treatment of adult patients with extensive-stage SCLC.

The applied indication:

Tevimbra, in combination with platinum-containing chemotherapy as neoadjuvant treatment and then continued as monotherapy as adjuvant treatment, is indicated for the treatment of adult patients with resectable (tumours ≥4 cm or node positive) NSCLC.

The adopted indication:

Tevimbra, in combination with platinum-containing chemotherapy as neoadjuvant treatment and then continued as monotherapy as adjuvant treatment, is indicated for the treatment of adult patients with resectable NSCLC at high risk of recurrence (for selection criteria, see section 5.1).

The approved dosing regimen of tislelizumab in the adjuvant treatment phase is 400 mg administered by intravenous infusion once every 6 weeks.

The approved dosing regimen in the neoadjuvant phase is 200 mg administered by intravenous infusion once every 3 weeks, in combination with chemotherapy for 3 or 4 cycles or until disease progression that precludes definitive surgery or unacceptable toxicity.

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

The MAH did not seek CHMP scientific advice regarding the clinical development for 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 2: Overview of clinical studies

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Participants or Diagnosis of Patients	End of Treatment [a]	Study Status; Type of Report
Efficacy and Safety	BGB-A317-315	Module 5.3.5.1	Efficacy assessed by MPR rate by BIPR, EFS by BICR, pCR rate by BIPR, OS, ORR, DFS by BICR, EFS by investigator, HRQoL; the safety and tolerability; PK and immunogenicity	Phase 3, randomised, double-blind, placebo-controlled	• Tislelizumab 200 mg, D1, Q3W, IV • Matched placebo, D1, Q3W, IV • Cisplatin 75 mg/m² (or carboplatin AUC of 5 mg/mL/min), D1, Q3W, IV • Pemetrexed 500 mg/m², D1, Q3W, IV • Paclitaxel 175 mg/m², D1, Q3W, IV • Tislelizumab 400 mg, D1, Q6W, IV • Matched placebo, D1, Q6W, IV *Arm A:* tislelizumab (200 mg Q3W) + cisplatin or carboplatin + pemetrexed (nonsq) or paclitaxel (sq), followed by surgery, and then tislelizumab (400 mg Q6W); *Arm B:* placebo (Q3W) + cisplatin or carboplatin + pemetrexed (nonsq) or paclitaxel (sq), followed by surgery, and then placebo (Q6W)	**453 patients randomised:** *Arm A* (N = 226) *Arm B* (N = 227) **Treated with tislelizumab:** N = 226	Chinese adult patients with resectable Stage II or IIIA NSCLC without *EGFR* mutation or *ALK* gene translocation	Adjuvant treatment complete, disease recurrence/progression, intolerable toxicity, or other treatment discontinuation criteria were met.	Ongoing; Full (DCO 20 Feb 2023 [FA of MPR and pCR]; DCO 21 Aug 2023 [IA of EFS]); CSR erratum (the same DCO)

The clinical pharmacology and safety of tislelizumab in the proposed patient population are further supported by several other studies in the development program.

2.3.2. Pharmacokinetics

The recommended dose of tislelizumab for the neoadjuvant treatment is the same as the previously approved posology in several indications (200 mg IV Q3W).

The recommended dose of tislelizumab for the adjuvant treatment is 400 mg once every 6 weeks for maximum of 8 cycles after surgery or until disease recurrence, or metastasis, or unacceptable toxicity. The adjuvant phase dose of 400 mg administered intravenously once every 6 weeks was selected by matching dose and exposure (the AUC) with the exposure of the 200 mg once-every-3-weeks regimen.

Pharmacokinetics of tislelizumab have been adequately characterized throughout the initial marketing authorization procedure (EMEA/H/C/005919/0000). Therefore, in this assessment report, only summarized data on tislelizumab ADME, dose proportionality, special populations and interaction studies are presented.

13 clinical studies (Phase 1, 2, and 3 studies) in multiple indications were used to characterize the clinical pharmacology of tislelizumab. The PK profile of tislelizumab was characterized using noncompartmental analysis and PopPK analysis.

In the pivotal Study 315, only sparse PK samples were collected and thus no formal noncompartmental analysis was conducted. The sparse PK samples were collected at the following time-points:

During the neoadjuvant phase, predose (within 60 minutes before starting infusion of tislelizumab or placebo) samples were collected at Day 1 of Cycles 1 and 2; a postdose (within 30 minutes after completing infusion of tislelizumab or placebo) sample was collected at Day 1 of Cycle 1.

An additional PK sample was collected before surgery.

During the adjuvant phase, predose (within 60 minutes before starting infusion) samples were collected at Day 1 of Cycles 1, 3 and 5; a postdose (within 30 minutes after completing infusion) sample was collected at Day 1 of Cycles 1 and 3.

An additional PK sample was collected at the safety follow-up visit.

The PK data from pivotal Study 315 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 315. ER analyses explored the relationships between PK and efficacy as well as PK and safety parameters; an integrated analysis of immunogenicity was done.

Table 3: Clinical and Pharmacometric Studies Supporting the Assessment of Tislelizumab Clinical Pharmacology

Analysis	Studies Included in the Analysis
NCA PK	Study 001, Study 102
PopPK analysis	Full PK analysis set: including Studies 001, 102, 203, 204, 205, 206, 208, 209, 303, 304, 307, and 302 (as previously included in the 2L OSCC submission) External validation for Study 315 data
ER analysis on efficacy	Pivotal study dataset for ER efficacy: based upon the pivotal Study 315
ER analysis on safety	Pivotal studies dataset for ER safety: based upon the pivotal Study 315
ADA summary in the study CSRs	ADA analysis set of the studies
Overview of immunogenicity	Based on the pivotal study (Study 315), as well as the supportive studies from tislelizumab monotherapy studies 001, 102, 203, 204, 208, 302, and 303 and combo studies 206, 304, 305, 306, 307, 309, and 312

Abbreviations: ADA, antidrug antibodies; CSR, clinical study report; ER, exposure-response; NCA, noncompartmental analysis; OSCC, oesophageal squamous cell carcinoma; PK, pharmacokinetic; PopPK, population PK.

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). The 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. There are no changes since the original submission in the formulation and composition of tislelizumab drug substance and drug product. No new information is provided with the current dossier, as there are no changes in the bioanalytical methods and assays.

Population PK model

The previously final PopPK model was developed from the pooled PK analysis dataset, that included 14,473 measurable tislelizumab concentrations from 2596 patients across 12 studies (Studies 001, 102, 203, 204, 205, 206, 208, 209, 302, 303, 304, and 307), to quantitatively describe the PK properties of tislelizumab and identify sources of interindividual variability.

A nonlinear mixed-effects modeling approach with the first-order conditional estimation with interaction (FOCEI) method in NONMEM 7, Version 7.4.3 (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. No time-varying CL was identified following tislelizumab treatment.

The impact of potential covariates such as baseline age, body weight, sex, race (Asian/White/Other), eGFR, bilirubin, ALT, AST, albumin, tumor type, tumor size, LDH, ECOG Performance Status score, and ADA on the PK of tislelizumab was investigated.

Baseline body weight, age, sex, albumin (ALB), tumor size at baseline (TUMSZ for solid tumors, SUMPPD for cHL), tumor type, and treatment-emergent ADA were identified as statistically significant covariates on the PK of tislelizumab.

For the external validation of the Study 315 data, model parameter estimation and model evaluation were implemented with NONMEM 7, version 7.5 (ICON Development Solutions. Ellicott City, Maryland, USA) [11] with GNU Fortran 95 Compiler (Version 4.6), Perl-Speaks-NONMEM (PsN) version 4.2 (Uppsala University, Sweden) [12][13] and R 4.2.3 or above. PopPK estimation was performed using the first-order conditional estimation with interaction (FOCEI) method in NONMEM.

Absorption

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

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

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

Distribution

Based on Population PK analysis:

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.

Based on Population PK analysis:

The geometric mean elimination half-life at steady state 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-A317-315 (Study 315)

Study 315 is a double-blind, randomized, multicenter, Phase 3 study of neoadjuvant treatment with tislelizumab in combination plus platinum-based doublet chemotherapy followed by adjuvant tislelizumab in patients with resectable Stage II or IIIA NSCLC.

A total of 453 patients were enrolled in the study, 226 of whom received at least one dose of tislelizumab-containing treatment (200 mg Q3W in neoadjuvant phase and 400 mg Q6W in adjuvant phase).

Pharmacokinetic results and conclusions:

The geometric mean (GCV%) predose and postdose serum concentrations after the IV administration of tislelizumab 200 mg once every 3 weeks as neoadjuvant therapy on Cycles 1 and 2 along with serum concentrations after IV administration of tislelizumab 400 mg once every 6 weeks as adjuvant therapy on Cycles 1, 3, and 5 are presented in the below table.

Table 4: Summary of Tislelizumab Serum Concentrations – Geometric Means (GCV%) in Study 315

	Tislelizumab Concentrations (µg/mL) (N = 226)			
	Predose		**Postdose**	
Visit	n	Geometric Mean (GCV%)	n	Geometric Mean (GCV%)
Neoadj Cycle 1 Day 1	221	NC	223	66.25 (20.2%)
Neoadj Cycle 2 Day 1	212	16.60 (31.5%)	NA	NA
Adj Cycle 1 Day 1	166	5.37 (88.6%)	166	142.84 (40.9%)
Adj Cycle 3 Day 1	147	29.25 (43.8%)	147	180.25 (22.9%)
Adj Cycle 5 Day 1	125	34.72 (41.2%)	NA	NA

Data cutoff: 30APR2023. Data extraction:18Sep2023.
Abbreviations: GCV, geometric coefficient of variation; NA, not available; NC, not calculated.
Tislelizumab was given IV 200 mg Q3W during neoadjuvant phase and 400 mg Q6W during adjuvant phase.
Population: 226 patients; Sex (M/F): 205/21; Age: 61.6 (30 to 80) years; Body weight: 66.3 (45 to 116) kg. 1.5% (21/1428) of sample were excluded from the summary due to aberrant sample collection information.

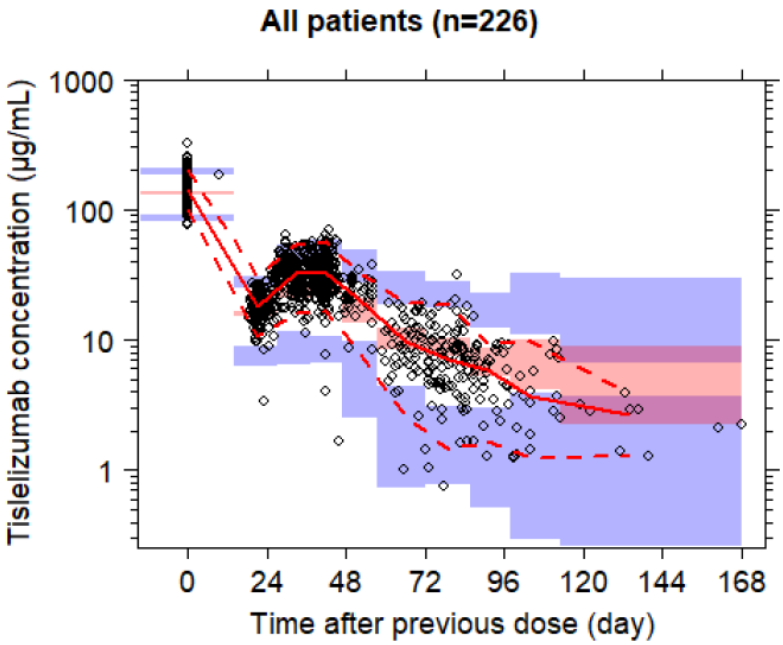
External validation of the previously developed final PopPK model (original PopPK model) for Study 315

Since Study 315 was not incorporated in the original PopPK model development and only sparse samples were collected in this study, an external validation was performed to verify the predictive performance of the previously developed final PopPK model using Study 315 data.

The final external model validation (EMV) dataset was comprised of 226 patients contributing a total of 1488 tislelizumab concentrations.

The ability of the existing PopPK model to reproduce the distribution of tislelizumab concentration data (2.5th to 97.5th percentile) over time was evaluated using prediction-corrected visual predictive check (pcVPC) based on 1000 simulated replicates of the Study 315 dataset.

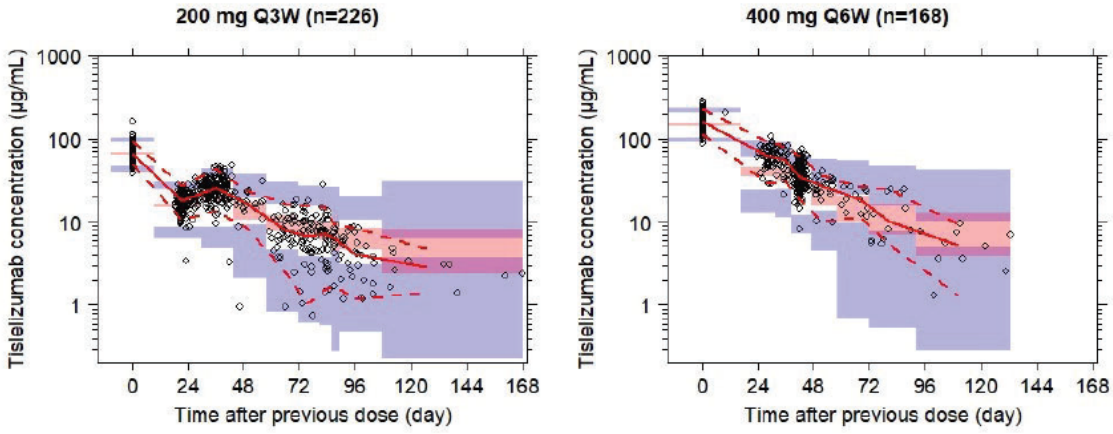
Figure 1: pcVPC of Tislelizumab Concentration-Time Profiles for Validation Patients in Study 315



Circles are observed tislelizumab serum concentrations, solid red lines represent the median observed value, and dashed red lines represent the 2.5th percentile and 97.5th 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 2.5th percentile and 97.5th percentile of the predicted concentrations.

The pcVPC plots showed that the observed median, 2.5th and 97.5th %tiles of the concentration-time profiles were generally contained within the simulation-based 95% confidence intervals for the corresponding model predicted median and 2.5th and 97.5th %tiles in all validation patients.

Figure 2: pcVPC of tislelizumab concentration-time profiles stratified by dose regimen for validation patients in study BGB-A317-315



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.

Table 5: Simulated Steady State PK Parameters of Tislelizumab for Study 315 (Pharmacokinetic Analysis Set)

Treatment	Phase	Summary	$C_{max,ss}$ (µg/mL)	$C_{min,ss}$ (µg/mL)	AUC_{ss} (day.µg/mL)	$C_{avg,ss}$ (µg/mL)
Arm A (N = 226)	Neoadjuvant Phase	n	58	58	58	58
		Geometric Mean (Geometric CV%)	112.22 (17.06)	44.56 (22.83)	1342.74 (18.64)	63.94 (18.64)
Arm A (N = 226)	Overall Phase	n	226	226	226	226
		Geometric Mean (Geometric CV%)	116.64 (17.35)	47.56 (25.52)	1414.41 (20.29)	67.35 (20.29)

Abbreviations: $C_{max, ss}$, Peak Concentration at Steady State; $C_{min,ss}$, Minimum Concentration at Steady State; AUC_{ss}, Area Under the Curve at Steady State; $C_{avg,ss}$, Average Concentration at Steady State; Arm A, tisle (200 mg Q3W) + chemo → surgery → tisle (400 mg Q6W); 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(S^2) - 1) * 100, where S^2 was the sample variance for concentrations of study drug in the logarithmic scale.

$C_{avg,ss}$ (µg/mL) is equal to AUC_{ss} (day.µg/mL) /21 days.

Neoadjuvant phase included patients who did not enter adjuvant phase; overall phase included patients who received at least one dose of tislelizumab.

Special populations

Information on PK in special populations can be found in the Tevimbra public assessment report (EPAR) for the initial marketing authorisation.

Pharmacokinetic interaction studies

No formal drug-drug interaction studies have been conducted with tislelizumab. Information on pharmacokinetic interaction studies can be found in the Tevimbra public assessment report (EPAR) for the initial marketing authorisation.

Pharmacokinetics using human biomaterials

Not applicable.

2.3.3. Pharmacodynamics

No specific pharmacodynamic endpoint were investigated in Study 315.

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 315.

Immunogenicity of tislelizumab was assessed as exploratory objective in Study 315.

Mechanism of action

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

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

Primary and secondary pharmacology

Immunogenicity

Immunogenicity in Study 315

In the pivotal Study 315, ADA samples were collected at the following time-points:

During the neoadjuvant phase, anti-tislelizumab antibodies were collected predose (within 60 minutes before infusion of tislelizumab or placebo) at Day 1 on Cycles 1 and 2. An additional ADA sample was collected at the presurgical visit. During the adjuvant phase, predose (within 60 minutes before starting infusion of tislelizumab or placebo) ADA samples were collected at Day 1 of Cycles 1, 3 and 5. An additional ADA sample was collected at the Safety Follow-up Visit.

A total of 1186 serum samples from the 226 tislelizumab-treated patients were tested for the presence of ADA to tislelizumab, and 219 patients were determined to be evaluable for ADA (ADA Evaluable Analysis Set).

Treatment-emergent ADA positivity occurred in 105 out of 219 evaluable patients (47.9%), with 6 patients (2.7%) positive for NAb. Of these 105 patients, 47 patients (21.5%) had a transient ADA response, 56 patients (25.6%) had a persistent ADA response, and 2 (0.9%) patients were ADA-positive at baseline and were treatment boosted.

Table 6: Summary of Immunogenicity Results for Study 315 (ADA Analysis Set)

	Tislelizumab (N = 219) N(%)
Treatment-Emergent ADA	105 (47.9)
Treatment-Boosted ADA	2 (0.9)
Treatment-Induced ADA	103 (47.0)
Persistent ADA	56 (25.6)
Transient ADA	47 (21.5)
NAb Positive	6 (2.7)

Abbreviations: ADA, anti-drug antibodies; NAb, neutralizing antibodies.

The total median ADA onset time was 23.0 days, and the total median duration was 182 days after treatment with tislelizumab.

Onset of NAb positivity occurred over the range of 122 to 273 days post start of treatment with tislelizumab.

Table 7: ADA Incidence Overall and by Subgroups (ADA Evaluable Analysis Set)

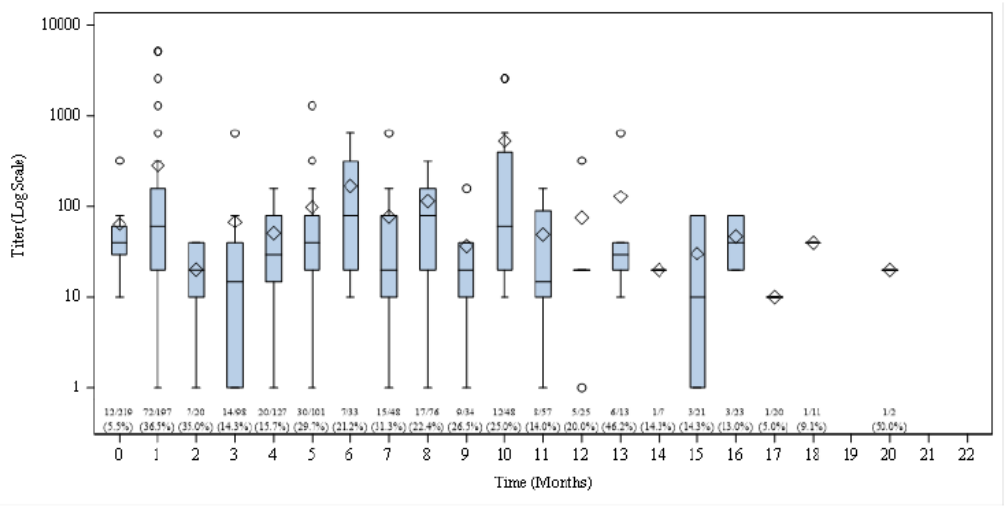
Subgroup	Evaluable Patients: n	ADA Prevalence [a] n	ADA Negative [b]: n (%)	Treatment-emergent ADA Positive [c]: n (%)	Treatment-boosted [d] ADA: n (%)	Treatment induced [e] ADA: n (%)	Persistent [f] ADA: n (%)	Transient [g] ADA: n (%)	NAb Positive [h]: n (%)
Overall	219	115	114 (52.1)	105 (47.9)	2 (0.9)	103 (47.0)	56 (25.6)	47 (21.5)	6 (2.7)
Age									
< 65 years	139	67	77 (55.4)	62 (44.6)	1 (0.7)	61 (43.9)	32 (23.0)	29 (20.9)	2 (1.4)
>= 65 years	80	48	37 (46.3)	43 (53.8)	1 (1.3)	42 (52.5)	24 (30.0)	18 (22.5)	4 (5.0)
Sex									
Female	20	9	12 (60.0)	8 (40.0)	0	8 (40.0)	4 (20.0)	4 (20.0)	0
Male	199	106	102 (51.3)	97 (48.7)	2 (1.0)	95 (47.7)	52 (26.1)	43 (21.6)	6 (3.0)
ECOG PS									
0	137	69	75 (54.7)	62 (45.3)	2 (1.5)	60 (43.8)	33 (24.1)	27 (19.7)	5 (3.6)
1	81	45	39 (48.1)	42 (51.9)	0	42 (51.9)	23 (28.4)	19 (23.5)	1 (1.2)
Disease Stage									
II	87	34	56 (64.4)	31 (35.6)	1 (1.1)	30 (34.5)	20 (23.0)	10 (11.5)	0
IIIA	132	81	58 (43.9)	74 (56.1)	1 (0.8)	73 (55.3)	36 (27.3)	37 (28.0)	6 (4.5)
Histology Type of Tumor									
Squamous	171	91	87 (50.9)	84 (49.1)	2 (1.2)	82 (48.0)	47 (27.5)	35 (20.5)	5 (2.9)
Non-Squamous	48	24	27 (56.3)	21 (43.8)	0	21 (43.8)	9 (18.8)	12 (25.0)	1 (2.1)
PD-L1 Status									
< 1%	88	47	45 (51.1)	43 (48.9)	1 (1.1)	42 (47.7)	24 (27.3)	18 (20.5)	2 (2.3)
≥ 1%	124	64	66 (53.2)	58 (46.8)	1 (0.8)	57 (46.0)	30 (24.2)	27 (21.8)	4 (3.2)
Not Evaluable/ Indeterminate	7	4	3 (42.9)	4 (57.1)	0	4 (57.1)	2 (28.6)	2 (28.6)	0
Smoking Status									
Current	43	19	26 (60.5)	17 (39.5)	0	17 (39.5)	9 (20.9)	8 (18.6)	1 (2.3)
Former	145	85	67 (46.2)	78 (53.8)	2 (1.4)	76 (52.4)	42 (29.0)	34 (23.4)	5 (3.4)
Never	31	11	21 (67.7)	10 (32.3)	0	10 (32.3)	5 (16.1)	5 (16.1)	0

Source: Appendix Table 1

ADA, anti-drug antibody; ECOG PS, Eastern Cooperative Oncology Group Performance Status; n, number; NAb, neutralizing antibody; PD-L1, programmed cell death protein ligand-1.

[a] ADA Prevalence: ADA positive, including pre-existing ADA, at any time point.
[b] ADA negative: The sum of ADA negative and nontreatment-boosted ADA.
[c] Treatment-emergent ADA: Sum of both treatment-induced ADA and treatment-boosted ADA, synonymous with "ADA Incidence".
[d] Treatment-boosted ADA: ADA positive at baseline that was boosted to a 4-fold or higher-level following drug administration.
[e] Treatment-induced ADA: ADA negative at baseline and ADA positive post-baseline following drug administration.
[f] 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 incidence only in the last sampling time point of the treatment study period.
[g] Transient ADA: Treatment-induced ADA detected only at one sampling time point during the treatment or follow-up observation period, or two or more time points during the treatment, where the first and last ADA-positive samples are separated by a period of less than 16 weeks, and the patient's last sampling time point is ADA-negative.
[h] NAb positive: Treatment-emergent ADA that were confirmed NAb positive.

Figure 3: Median and Range of ADA titers in patients treated with Tislelizumab (ADA evaluable analysis set)



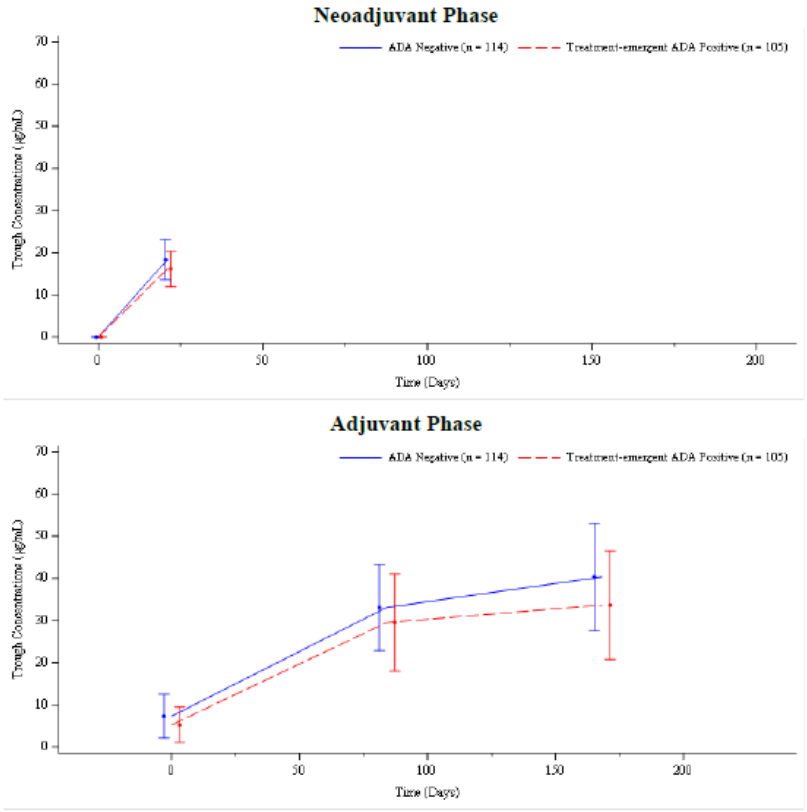
Source: Appendix Figure 3
ADA, anti-drug antibody
Note: The boxes indicate the first and third quartile. Text in the figure shows [n ADA positive samples/n total samples (% of the ADA positive samples)]. The blue horizontal bar within the box illustrates the median (or second quartile). The whiskers are the minimum and maximum observation within the 1.5 inter-quartile range of the first and third quartiles, respectively. Circles = Outliers; Diamonds = Mean.

The median titer levels fluctuated between approximately 10 and 100, over 20 months. The percentage of samples with ADA present by month from 1 to 20 months ranged from 5% to 50.0%. Over the time course of the study, titer values for most patients did not show an increasing trend.

Impact of ADA on PK (Study 315)

The summary of trough concentrations over time is stratified by neoadjuvant and adjuvant phases to examine any variation resulting from the dose difference in each phase. Comparisons of treatment-emergent ADA-positive and ADA-negative patients during neoadjuvant and adjuvant phases are depicted in the following Figure.

Figure 4: ADA Impact on Mean (± Standard Deviation) Trough Tislelizumab Serum Concentrations (ADA Evaluable Analysis Set)



Source: Appendix Figure 6
ADA, anti-drug antibody; BLQ, below the limit of quantification; n, number; StD, standard deviation
For presentation purposes only, all BLQ values were set to 0 (BLQ < 0.4 µg/mL). ADA positive consists of patients classified as "Treatment-emergent ADA". The x-axis for the figures was offset for visibility purpose.

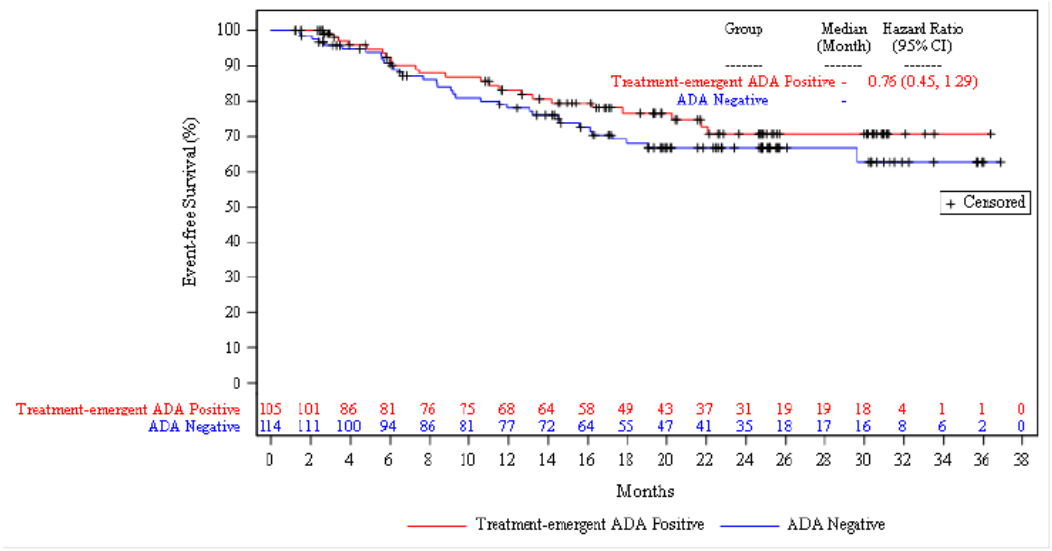
Impact of ADA on efficacy (Study 315)

Table 8: Analysis of Clinical Responses after Tislelizumab Treatment by ADA Status (ADA Evaluable Analysis Set)

	Clinical Responses			
	MPR		pCR	
Treatment-emergent ADA	Yes % (n/N)	No % (n/N)	Yes % (n/N)	No % (n/N)
Yes	59.0 (62/105)	41.0 (43/105)	43.8 (46/105)	56.2 (59/105)
No	57.0 (65/114)	43.0 (49/114)	40.4 (46/114)	59.6 (68/114)
Total	58.0 (127/219)	42.0 (92/219)	42.0 (92/219)	58.0 (127/219)

Source: Appendix Table 8
ADA, anti-drug antibody; MPR, major pathological response; N, total number of patients in the subgroups (Yes, Treatment Emergent Yes, No, Treatment Emergent No, Total, ADA Evaluable Patients); n, number of patients with observed endpoints; pCR, pathological complete response.

Figure 5: Event-Free Survival by Blinded Independent Central Review by ADA Status after Tislelizumab Treatment (ADA Evaluable Analysis Set)



Source: Appendix Figure 8
ADA, anti-drug antibody; CI, confidence interval; RECIST, response evaluation criteria in solid tumors.
Event-free survival values were assessed by Blinded Independent Central Review per RECIST v1.1.

Table 9: Analyses of Event-free Survival by Blinded Independent Central Review Using the Principal Stratum Strategy in Patients (Intent-To-Treat Analysis Set)

Landmark[a,b]	Variable Selection[c]	Baseline Covariates Selected[d]	Treatment-emergent ADA Positive HR (95% CI)	ADA Negative HR (95% CI)
No	No	All covariates	0.46 (0.27, 0.77)	0.67 (0.43, 1.05)
No	Yes	Smoking status, Disease stage, Lactate dehydrogenase	0.46 (0.28, 0.77)	0.67 (0.42, 1.04)
Yes	No	All covariates	0.56 (0.30, 1.04)	0.57 (0.38, 0.85)
Yes	Yes	ECOG PS, Disease stage, Albumin	0.56 (0.30, 1.04)	0.57 (0.38, 0.85)

Source: Appendix Table 9
ADA, anti-drug antibody; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EFS, event-free survival; HR, hazard ratio; PD-L1, programmed cell death protein ligand-1.
Baseline covariates include: Age group, Sex, Weight, ECOG PS, Disease Stage, Histologic Type, PD-L1 expression, Smoking status, Sum of target lesion diameters, Albumin, Lactate dehydrogenase.
[a] The landmark time point of 4 weeks was chosen to reflect the approximate median time to ADA onset, and a small proportion of patients who experienced EFS event/censored prior to the landmark time point were excluded.
[b] No: ADA status was not defined by landmark; Yes: ADA status was defined by landmark.
[c] No: no variable selection, used all the baseline covariates in the logistic regression; Yes: implemented stepwise variable selection.
[d] All the baseline covariates listed are applied to the variable selection "Yes" models.

Impact of ADA on safety (Study 315)

Table 10: Adverse Events After Tislelizumab Treatment by ADA Status (ADA Evaluable Analysis Set)

Treatment-emergent Adverse Events	Treatment-emergent ADA	Study Phase % (n/N)		
		Neoadjuvant	Adjuvant	Overall
imAE	Yes	26.7 (28/105)	21.5 (17/79)	44.8 (47/105)
	No	21.1 (24/114)	21.3 (19/89)	36.8 (42/114)
	Total	23.7 (52/219)	21.4 (36/168)	40.6 (89/219)
IRR	Yes	2.9 (3/105)	0	2.9 (3/105)
	No	2.6 (3/114)	3.4 (3/89)	4.4 (5/114)
	Total	2.7 (6/219)	1.8 (3/168)	3.7 (8/219)
AESI	Yes	29.5 (31/105)	21.5 (17/79)	45.7 (48/105)
	No	23.7 (27/114)	23.6 (21/89)	40.4 (46/114)
	Total	26.5 (58/219)	22.6 (38/168)	42.9 (94/219)
AE Grade>=3	Yes	71.4 (75/105)	17.7 (14/79)	80.0 (84/105)
	No	69.3 (79/114)	16.9 (15/89)	77.2 (88/114)
	Total	70.3 (154/219)	17.3 (29/168)	78.5 (172/219)
SAE	Yes	13.3 (14/105)	17.7 (14/79)	31.4 (33/105)
	No	9.6 (11/114)	21.3 (19/89)	31.6 (36/114)
	Total	11.4 (25/219)	19.6 (33/168)	31.5 (69/219)
AE Discontinue	Yes	1.9 (2/105)	7.6 (6/79)	8.6 (9/105)
	No	2.6 (3/114)	5.6 (5/89)	10.5 (12/114)
	Total	2.3 (5/219)	6.5 (11/168)	9.6 (21/219)
AE Modification	Yes	16.2 (17/105)	24.1 (19/79)	35.2 (37/105)
	No	16.7 (19/114)	23.6 (21/89)	36.0 (41/114)
	Total	16.4 (36/219)	23.8 (40/168)	35.6 (78/219)

Source: Appendix Table 10, Appendix Table 11, Appendix Table 12

ADA, anti-drug antibody; AE, adverse event; AE Discontinue, TEAE leading to tislelizumab discontinuation; AE Grade >= 3, TEAE greater than or equal to grade 3; AE Modification, TEAE leading to tislelizumab treatment modification; AESI, adverse event of special interest (IRR+imAE); imAE, immune-mediated TEAE; IRR, infusion-related reaction; N, total number of patients in the subgroups (Yes, Treatment Emergent Yes, No, Treatment Emergent No, Total, ADA Evaluable Patients); n, number of patients with one or more the same type of adverse events; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events v 5.0; SAE, serious TEAE; TEAE, treatment-emergent adverse events.

Toxicity grades apply event-specific NCI CTCAE grading criteria: Grade 1, mild; Grade 2, moderate; Grade 3, severe; Grade 4, very severe; Grade 5, death related to adverse event.

Only AEs which were treatment-emergent AEs were included.

Table 11: Toxicity Grade 3 Adverse Events After Tislelizumab Treatment by ADA Status (ADA Evaluable Analysis Set)

Summary of All Treatment Emergent Grade ≥ 3 Adverse Events				
Treatment-emergent Adverse Events	Treatment-emergent ADA	Study Phase n (%)		
		Neoadjuvant [a]	Adjuvant [b]	Overall [c]
TEAE Grade ≥ 3	ADA-Positive	75 (71.4)	14 (17.7)	84 (80.0)
	ADA Negative	79 (69.3)	15 (16.9)	88 (77.2)
TEAE Grade ≥ 3 and started after the first detection of ADA+	ADA-Positive	47 (44.8)	12 (15.2)	60 (57.1)
	ADA Negative	--	--	--
Summary of All Treatment Emergent Grade 3 Adverse Events				
TEAE Grade 3	ADA-Positive	69 (65.7)	14 (17.7)	80 (76.2)
	ADA Negative	68 (59.6)	15 (16.9)	78 (68.4)
Treatment-related TEAE Grade 3	ADA-Positive	19 (18.1)	9 (11.4)	31 (29.5)
	ADA Negative	17 (14.9)	7 (7.9)	23 (20.2)
Summary of Patients with TEAE of Grade 3 the Highest TEAE Experienced[d]				
TEAE Grade 3	ADA-Positive	40 (38.1)	13 (16.5)	49 (46.7)
	ADA Negative	43 (37.7)	15 (16.9)	50 (43.9)
Treatment-related TEAE Grade 3	ADA-Positive	10 (9.5)	8 (10.1)	19 (18.1)
	ADA Negative	8 (7.0)	7 (7.9)	11 (9.6)

Source: Appendix Table 13, Appendix Table 14, Appendix Table 15, Appendix Table 16, Appendix Table 17, Appendix Table 18

ADA, anti-drug antibody; N, total number of patients in the subgroup; n, number of patients with at least one event in each category; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events v 5.0; TEAE, treatment emergent adverse event; Treatment-related TEAE are tislelizumab treatment related TEAEs.

Toxicity grades apply event-specific NCI CTCAE grading criteria: Grade 1, mild; Grade 2, moderate; Grade 3, severe; Grade 4, very severe; Grade 5, death related to adverse event.

[a] During the neoadjuvant phase there were N=105 ADA-positive patients and N=114 ADA-negative patients.

[b] During the adjuvant phase there were N=79 ADA-positive patients and N=89 ADA-negative patients.

Table 12: Treatment-emergent Adverse Events by ADA Status and Highest Toxicity Grade (ADA Evaluable Analysis Set) (Overall Phase)

Treatment-emergent Adverse Events	Treatment-emergent ADA	Study Phase n (%)		
		Neoadjuvant [a]	Adjuvant [b]	Overall [c]
Summary of All Treatment Emergent Grade ≥ 3 Adverse Events				
TEAE Grade ≥ 3	ADA-Positive	75 (71.4)	14 (17.7)	84 (80.0)
	ADA Negative	79 (69.3)	15 (16.9)	88 (77.2)
TEAE Grade ≥ 3 and started after the first detection of ADA+	ADA-Positive	47 (44.8)	12 (15.2)	60 (57.1)
	ADA Negative	--	--	--
Summary of All Treatment Emergent Grade 3 Adverse Events				
TEAE Grade 3	ADA-Positive	69 (65.7)	14 (17.7)	80 (76.2)
	ADA Negative	68 (59.6)	15 (16.9)	78 (68.4)
Treatment-related TEAE Grade 3	ADA-Positive	19 (18.1)	9 (11.4)	31 (29.5)
	ADA Negative	17 (14.9)	7 (7.9)	23 (20.2)
Summary of Patients with TEAE of Grade 3 the Highest TEAE Experienced[d]				
TEAE Grade 3	ADA-Positive	40 (38.1)	13 (16.5)	49 (46.7)
	ADA Negative	43 (37.7)	15 (16.9)	50 (43.9)
Treatment-related TEAE Grade 3	ADA-Positive	10 (9.5)	8 (10.1)	19 (18.1)
	ADA Negative	8 (7.0)	7 (7.9)	11 (9.6)

Source: Appendix Table 13, Appendix Table 14, Appendix Table 15, Appendix Table 16, Appendix Table 17, Appendix Table 18

ADA, anti-drug antibody; N, total number of patients in the subgroup; n, number of patients with at least one event in each category; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events v 5.0; TEAE, treatment emergent adverse event; Treatment-related TEAE are tislelizumab treatment related TEAEs.

Toxicity grades apply event-specific NCI CTCAE grading criteria: Grade 1, mild; Grade 2, moderate; Grade 3, severe; Grade 4, very severe; Grade 5, death related to adverse event.

[a] During the neoadjuvant phase there were N=105 ADA-positive patients and N=114 ADA-negative patients.

[b] During the adjuvant phase there were N=79 ADA-positive patients and N=89 ADA-negative patients.

	Treatment-emergent ADA Positive N = 105 n (%)	ADA Negative N = 114 n (%)
TEAE Grade ≥ 3	84 (80.0)	88 (77.2)
TEAE Grade ≥ 3 and started after the first detection of ADA+	60 (57.1)	0
TEAE Grade 3	49 (46.7)	50 (43.9)
Treatment-related TEAE Grade 3	19 (18.1)	11 (9.6)
TEAE Grade 4	34 (32.4)	34 (29.8)
Treatment-related TEAE Grade 4	10 (9.5)	10 (8.8)
TEAE leading to death (Grade 5)	1 (1.0)	4 (3.5)
Treatment-related TEAE leading to death (Grade 5)	1 (1.0)	3 (2.6)

Source: Appendix Listing 2, Appendix Listing 6, Appendix Listing 7, Appendix Listing 8.

ADA, anti-drug antibody; N, total number of patients in the subgroup; n, number of patients with at least one event in each category; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events v 5.0; TEAE, treatment emergent adverse event; Treatment-related TEAE are tislelizumab treatment related TEAEs.

Toxicity grades apply event-specific NCI CTCAE grading criteria: Grade 1, mild; Grade 2, moderate; Grade 3, severe; Grade 4, very severe; Grade 5, death related to adverse event.

The highest TEAE grade observed for each patient was selected for the analysis.

Neutralizing Antibodies(Study 315)

Table 13: NAb positive Patients with key Endpoints (ADA Evaluable Analysis Set)

Patient ID	*	*	*	*		
Treatment-emergent ADA	Yes	Yes	Yes	Yes	Yes	Yes
Sex	Male	Male	Male	Male	Male	Male
Age (Year)	65 ≤75	65 ≤75	65 ≤75	<65	65 ≤75	<65
ECOG PS	0	0	0	0	0	1
Disease Stage	Stage IIIA	Stage IIIA	Stage IIIA	Stage IIIA	Stage IIIA	Stage IIIA
Histologic Type	Squamous	Squamous	Squamous	Squamous	Non-Squamous	Squamous
PD-L1 Status	< 1%	>= 1%	>= 1%	>= 1%	>= 1%	< 1%
Smoking Status	Current	Former	Former	Former	Former	Former
ADA Positive Titer	160, 2560	5120, 160, 160, 160, 10	10, 80, 80, 320, 20	40, 640, 2560, 640	1280, 640, 160	160, 320
ADA Positive Day	25, 273	24, 91, 143, 296, 383	43, 97, 134, 216, 305	84, 188, 272, 363	122, 164, 268	23, 156
NAb Positive Onset Day	273	143	216	188	122	156
MPR	Yes	Yes	Yes	Yes	Yes	--
EFS by BICR (Months)	14.49	19.78	30.85	30.42	15.21	5.62
pCR	Yes	Yes	No	Yes	Yes	--
OS (Months)	15.11	21.32	35.15	33.41	17.51	6.24
imAE (Day)	--	Hypothyroidism (142)	Pneumonitis (18), Hypothyroidism (19)	Thyroiditis (42)	Immune-mediated lung disease (323)	--
AESI (Day)	--	Hypothyroidism (142)	Pneumonitis (18), Hypothyroidism (19)	Thyroiditis (42)	Immune-mediated lung disease (323)	--
AE Grade >= 3 (Day)	Neutrophil count decreased (34), White blood cell count decreased (34), Neutrophil count decreased (82)	Blood creatine phosphokinase increased (242)	Neutrophil count decreased (8), White blood cell count decreased (8), Anaemia (10), Febrile neutropenia (10), Hypokalaemia (10), Neutrophil count decreased (50)	--	Neutrophil count decreased (8), Immune-mediated lung disease (323)	White blood cell count decreased (8), Neutrophil count decreased (12), Neutrophil count decreased (29), White blood cell count decreased (29), Pneumonia (37)
SAE (Day)	--	Hypothyroidism (142)	Febrile neutropenia (10)	--	Immune-mediated lung disease (323)	--
AE Modification (Day)	White blood cell count decreased (34)	Hypothyroidism (142)	Neutrophil count decreased (8), Pneumonitis (18)	Thyroiditis (42)	Immune-mediated lung disease (323)	White blood cell count decreased (8), Neutrophil count decreased (12), Pneumonia (37)

Source: Appendix Table 4, Appendix Table 5, Appendix Table 6
--, missing; ADA, anti-drug antibody; AE, adverse event; AE Discontinue, TEAE leading to tislelizumab discontinuation; AE Grade >= 3, TEAE greater than or equal to grade 3; AE Modification, TEAE leading to tislelizumab treatment modification; AESI, adverse event of special interest (IRR+imAE); imAE, immune-mediated TEAE; IRR, infusion-related reaction; NAb, neutralizing antibodies; RECIST, response evaluation criteria in solid tumors; SAE, serious TEAE; TEAE, treatment emergent adverse event. EFS, Event-free survival; MPR, major pathological response; OS, overall survival; pCR, pathological complete response.
Treatment-related TEAE are tislelizumab treatment related TEAEs.
Values in parenthesis represent the actual day of observation. Only AEs which were treatment-emergent AEs were included.
Day represents the actual day of ADA titer or event.
Patients with * on their Patient ID had their NAb onset occur after starting 400 mg Q6W dosing regimen in the adjuvant phase.

Integrated Immunogenicity Analysis

The immunogenicity profile of tislelizumab has been characterized in clinical studies using validated assays. Serum samples from tislelizumab-treated patients in 15 Phase 1 to 3 clinical studies were assessed for treatment-emergent ADA and NAb. Analyses of ADA and its potential impact on PK, efficacy, and safety were performed for 3563 evaluable patients.

ADA Incidence

Overall, across all tislelizumab doses and tumor types, the incidence of treatment-emergent ADA was 21.1% (761/3614 ADA-evaluable patients). The incidence of treatment-emergent ADA was 16.5% (236/1427) among evaluable patients in the monotherapy studies (200 mg once-every-3-weeks dose regimen); a slightly higher incidence of 25.3% (462/1826) among evaluable patients was observed in the combination therapy studies (including 200 mg once every 3 weeks in the neoadjuvant phase and 400 mg once every 6 weeks in the adjuvant phase for study 315). 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 once-every-3-weeks regimen. NAb

were detected in 33 patients (0.9% of 3614 evaluable patients), with a low incidence (< 2%) across most studies that tested the fixed dose of 200 mg once every 3 weeks.

Table 14: Summary of ADA Incidence by Dose Regimen (ADA Evaluable Analysis Set)

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)
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)

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	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)

Abbreviations: ADA, Antidrug antibody; Q2W, every 2 weeks; Q3W, every 3 weeks; Q6W, every 6 weeks.
N is the total number of patients in the ADA Evaluable Analysis sets of the overall phase of 315 and other studies; n is the number of patients in relevant category from the ADA Evaluable Analysis sets. Percentages were based on N.

[a] Includes patients who received tislelizumab at 200 mg Q3W in neoadjuvant phase of study 315 regardless of whether received tislelizumab at 400 mg Q6W in adjuvant phase.

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.

Table 15 : 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 001 - Solid Tumors		
Objective Response	11/66 (16.7)	48/306 (15.7)
Disease Control	34/66 (51.5)	159/306 (52.0)
Clinical Benefit	20/66 (30.3)	93/306 (30.4)
Study 102 - Solid Tumors		
Objective Response	5/43 (11.6)	46/237 (19.4)
Disease Control	14/43 (32.6)	120/237 (50.6)
Clinical Benefit	8/43 (18.6)	88/237 (37.1)
Study 203 - cHL		
Objective Response	5/6 (83.3)	56/64 (87.5)
Disease Control	5/6 (83.3)	58/64 (90.6)
Study 204 - UC		
Objective Response	4/18 (22.2)	21/86 (24.4)
Disease Control	8/18 (44.4)	35/86 (40.7)
Clinical Benefit	6/18 (33.3)	27/86 (31.4)
Study 208 – HCC		
Objective Response	12/51 (23.5)	20/180 (11.1)
Disease Control	33/51 (64.7)	96/180 (53.3)
Clinical Benefit	16/51 (31.4)	40/180 (22.2)
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		
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)

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

Abbreviations: ADA, Antidrug antibody; BOR, Best Overall Response; BIPR, Blinded Independent Pathology Review; cHL, classic Hodgkin Lymphoma; CR, Complete Response; IRC, Independent Review Committee; MPR, Major Pathological Response; pCR, pathological Complete Response; PR, Partial Response; SD, Stable Disease; HCC, Hepatocellular Carcinoma; ESCC, Esophageal Squamous Cell Carcinoma; G/GEJC, Gastric cancer/Gastroesophageal Junction cancer; NPC, Nasopharyngeal Cancer; NSCLC, Non-small cell lung cancer; SCLC, Small cell lung cancer; UC, Urethral Cancer; T+PC, tislelizumab + paclitaxel + carboplatin; T+nPC, tislelizumab + nab-paclitaxel + carboplatin.
The response results of study 203 were assessed by IRC per the Lugano classification. MPR and pCR of study 315 were assessed by BIPR. Disease response with confirmation by IRC (for studies 204, 208, 304, 307, 309) or by investigator (for the rest studies) per RECIST 1.1 were presented in the table.
MPR rate is defined as the proportion of patients with <= 10% residual viable tumor in the resected primary tumor and all resected lymph nodes after completion of neoadjuvant therapy. The pCR rate is defined as the proportion of patients with absence of residual tumor in the resected primary tumor and all resected lymph nodes after completion of neoadjuvant therapy as assessed.
Objective response includes BOR of CR or PR. Disease control is defined as BOR of CR, PR, or SD. Clinical benefit is defined as BOR of CR, PR, or durable SD (SD >= 24 weeks).

Impact of ADA on safety (Integrated ADA Analysis)

Table 16: Summary of Treatment-Emergent ADA by Treatment-Emergent Adverse Event for Patients Treated With Tislelizumab 200 mg Once Every 3 Weeks (ADA Evaluable Analysis Set)

	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)
Study 304 - NSCLC, N	48	165
Immune-Mediated Adverse Events, n (%)	23 (47.9)	79 (47.9)
Infusion-Related Reactions, n (%)	1 (2.1)	4 (2.4)
TEAEs >= Grade 3, n (%)	39 (81.3)	117 (70.9)
Serious TEAEs, n (%)	23 (47.9)	69 (41.8)

	Treatment-Emergent ADA Positive	Treatment-Emergent ADA Negative
TEAEs Leading to Tislelizumab Discontinuation, n (%)	7 (14.6)	33 (20.0)
TEAEs Leading to Treatment Modification of Tislelizumab, n (%)	34 (70.8)	110 (66.7)
Study 305 - G/GEJC, N	107	363
Immune-Mediated Adverse Events, n (%)	35 (32.7)	115 (31.7)
Infusion-Related Reactions, n (%)	8 (7.5)	24 (6.6)
TEAEs >= Grade 3, n (%)	75 (70.1)	248 (68.3)
Serious TEAEs, n (%)	41 (38.3)	151 (41.6)
TEAEs Leading to Tislelizumab Discontinuation, n (%)	18 (16.8)	51 (14.0)
TEAEs Leading to Treatment Modification of Tislelizumab, n (%)	55 (51.4)	182 (50.1)
Study 306 - ESCC, N	66	234
Immune-Mediated Adverse Events, n (%)	23 (34.8)	87 (37.2)
Infusion-Related Reactions, n (%)	8 (12.1)	17 (7.3)
TEAEs >= Grade 3, n (%)	53 (80.3)	185 (79.1)
Serious TEAEs, n (%)	35 (53.0)	110 (47.0)
TEAEs Leading to Tislelizumab Discontinuation, n (%)	8 (12.1)	33 (14.1)
TEAEs Leading to Treatment Modification of Tislelizumab, n (%)	34 (51.5)	124 (53.0)
Study 307 - NSCLC, N	63	165
Immune-Mediated Adverse Events, n (%)	35 (55.6)	81 (49.1)
Infusion-Related Reactions, n (%)	5 (7.9)	15 (9.1)
TEAEs >= Grade 3, n (%)	56 (88.9)	151 (91.5)
Serious TEAEs, n (%)	32 (50.8)	74 (44.8)
TEAEs Leading to Tislelizumab Discontinuation, n (%)	10 (15.9)	23 (13.9)
TEAEs Leading to Treatment Modification of Tislelizumab, n (%)	36 (57.1)	116 (70.3)
Study 309 - NPC, N	11	114
Immune-Mediated Adverse Events, n (%)	5 (45.5)	63 (55.3)
Infusion-Related Reactions, n (%)	2 (18.2)	5 (4.4)
TEAEs >= Grade 3, n (%)	9 (81.8)	98 (86.0)
Serious TEAEs, n (%)	7 (63.6)	35 (30.7)
TEAEs Leading to Tislelizumab Discontinuation, n (%)	1 (9.1)	9 (7.9)
TEAEs Leading to Treatment Modification of Tislelizumab, n (%)	3 (27.3)	61 (53.5)
Study 312 - SCLC, N	55	165
Immune-Mediated Adverse Events, n (%)	23 (41.8)	68 (41.2)
Infusion-Related Reactions, n (%)	8 (14.5)	7 (4.2)
TEAEs >= Grade 3, n (%)	48 (87.3)	150 (90.9)
Serious TEAEs, n (%)	26 (47.3)	66 (40.0)
TEAEs Leading to Tislelizumab Discontinuation, n (%)	9 (16.4)	17 (10.3)
TEAEs Leading to Treatment Modification of Tislelizumab, n (%)	26 (47.3)	83 (50.3)
Study 315 - NSCLC, N	105	114
Immune-Mediated Adverse Events, n (%)	47 (44.8)	42 (36.8)
Infusion-Related Reactions, n (%)	3 (2.9)	5 (4.4)
TEAEs >= Grade 3, n (%)	84 (80.0)	88 (77.2)
Serious TEAEs, n (%)	33 (31.4)	36 (31.6)
TEAEs Leading to Tislelizumab Discontinuation, n (%)	9 (8.6)	12 (10.5)
TEAEs Leading to Treatment Modification of Tislelizumab, n (%)	37 (35.2)	41 (36.0)

Abbreviations: ADA, Antidrug Antibody; ESCC, Esophageal Squamous Cell Carcinoma; G/GEJC, Gastric Cancer/Gastroesophageal

Junction Cancer; NPC, Nasopharyngeal Cancer; NSCLC, Non-Small Cell Lung Cancer; SCLC, Small Cell Lung Cancer; TEAE, Treatment-Emergent Adverse Event.

Patients in Study 001 with weight-based dosing Q2W/Q3W were excluded from this table.

Immune-mediated AEs were identified based on BeiGene standard process as defined in Immune-Mediated Adverse Event Identification Charter v1.2, imAE CCQ v2.4.

Dose modification for Tislelizumab includes dose interruption, dose delay, dose temporary discontinuation and infusion rate decrease.

Adverse events were graded for severity using CTCAE (v5.0 for studies 304, 305, 307, 309, 312, and 315, v4.03 for studies 001, 102, 203, 204, 208, 302, 303, and 306).

2.3.4. PK/PD modelling

The tislelizumab time-course PK profile was simulated using the Bayesian post-hoc PK parameters for each subject in study 315. The following exposure metrics were calculated: average concentration after the first dose (Cavg,dose1) and peak concentration after the first dose (Cmax,dose1). Cavg,dose1 was calculated as AUCdose1/tau, where tau is 21 days for every 3 weeks (Q3W). AUCdose1 is the area under the time-concentration curve of the first dose interval and is calculated with the linear up/log down variant of the trapezoidal rule using R software. 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,dose1 was used as the primary exposure endpoint in this E-R efficacy analysis, while the model predicted Cmax,dose1 was used as the primary exposure endpoint in this E-R safety analysis.

Exposure-efficacy analysis:

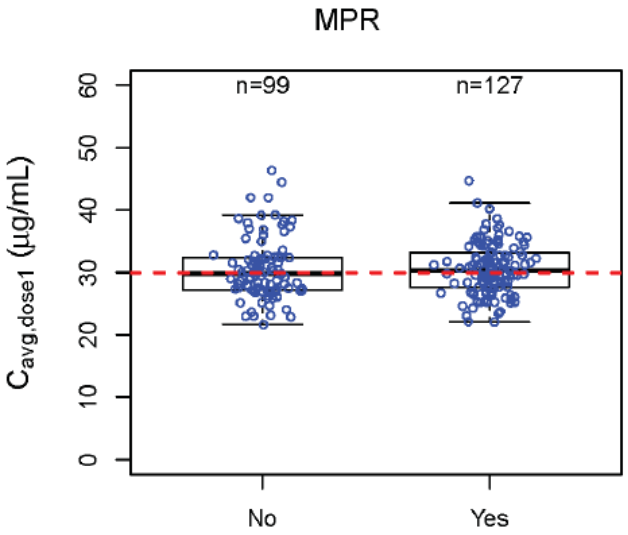
Exposure-efficacy analyses in Study 315 were based on efficacy endpoints MPR by BIPR, pCR by BIPR, EFS by BICR and OS. EFS and OS were reported in terms of months.

The exposure-efficacy relationship for tislelizumab was explored using an efficacy dataset containing data from 226 patients who received at least 1 dose of tislelizumab and had PopPK model-predicted Cavg,dose1 for exposure-efficacy.

The E-R relationships for the time-to-event variable of OS and EFS were explored separately by Kaplan-Meier estimates and were analyzed by Cox proportional-hazards models if an E-R trend was observed.

Exposure Versus MPR

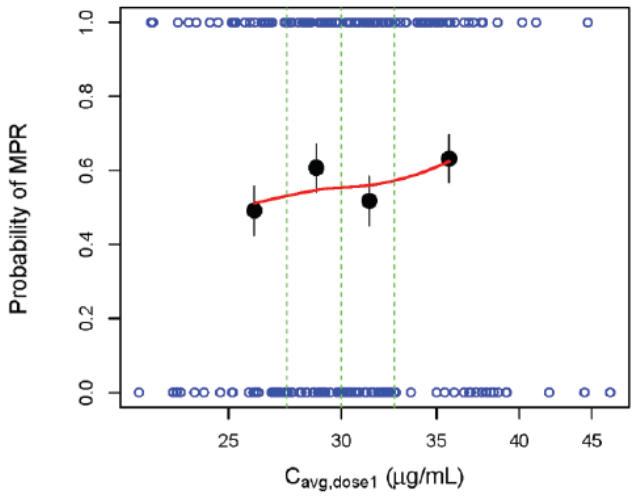
Figure 6: The relationship between tislelizumab exposure and MPR



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-A317-315.

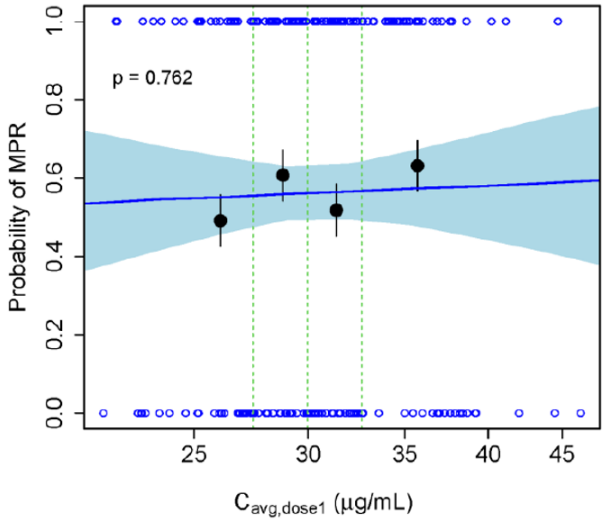
The probability estimates of major pathologic response versus PopPK predicted Cavg,dose1 were evaluated across four quartiles of Cavg,dose1. Logistic regression was further used to evaluate the relationship between exposure and response.

Figure 7: Probability of major pathologic response versus tislelizumab exposure



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.

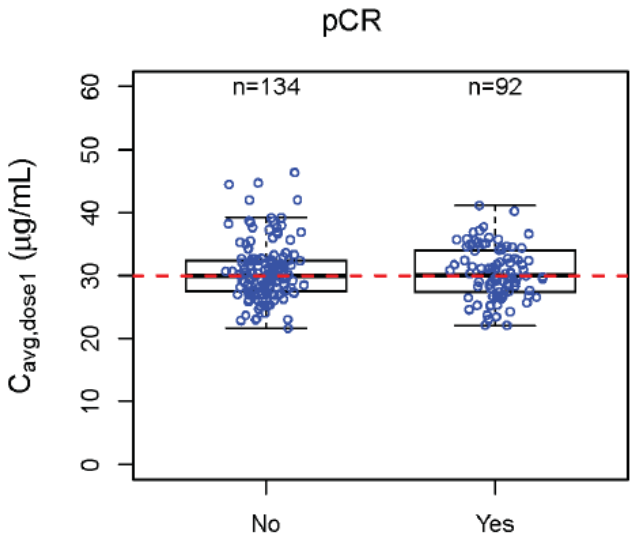
Figure 8: Logistic Regression of Probability of Major Pathologic Response Versus Exposure



Source: Section 5.2.1 Study 315 PopPK-ER Report
Abbreviations: $C_{avg,dose1}$, average concentration after the first dose; MPR, mean pathologic response.
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) of exposures (plotted at the median value within each quantile). The blue line is the model-predicted probability. The blue line and light blue shaded area are the median and 95% prediction interval based on the 1000 bootstrap samples of the model.

Exposure versus pCR

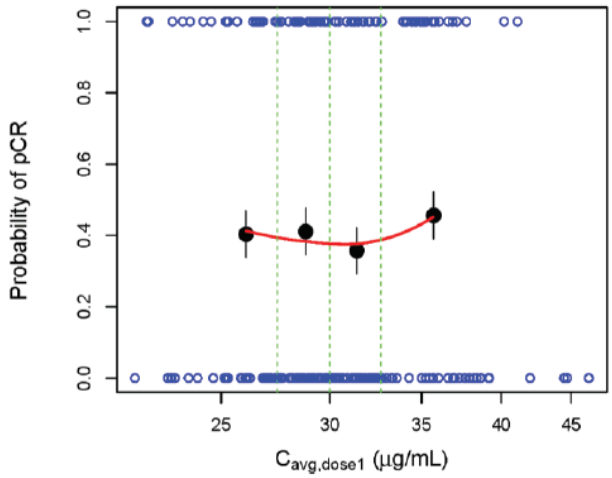
Figure 9: The relationship between tislelizumab exposure and pCR



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-A317-315.

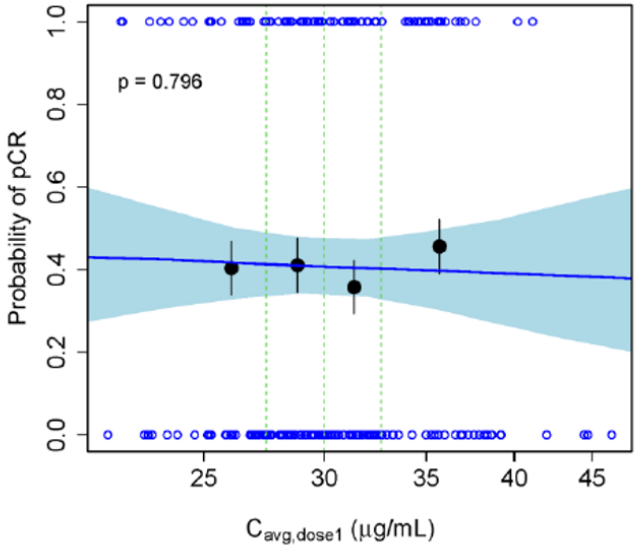
The probability estimates of pCR versus PopPK predicted Cavg,dose1 were evaluated across four quartiles of Cavg,dose1. Logistic regression was further used to evaluate the relationship between exposure and response.

Figure 10: Probability of pathologic complete response versus tislelizumab exposure



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.

Figure 11: Logistic Regression of Probability of Pathologic Complete Response Versus Exposure

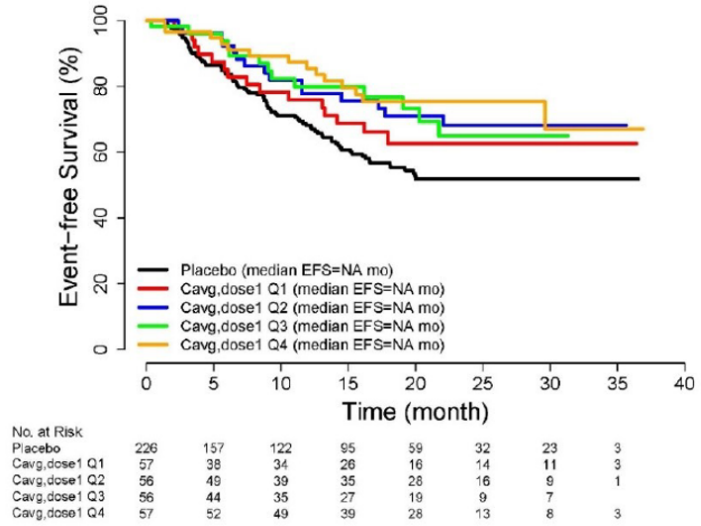


Source: Study 315 PopPK-ER Report Section 5.2.2
Abbreviations: $C_{avg,dose1}$, average concentration after the first dose; pCR, pathological complete response. Open blue circles reflect the observed events. The filled black symbols are the observed probability of events and the error bars are SE [sqrt (P*(1-P)/N)] for quantiles (at 100x(1/4)th percentiles) of exposures (plotted at the median value within each quantile). The blue line is the model-predicted probability. The blue line and light blue shaded area are the median and 95% prediction interval based on the 1000 bootstrap samples of the model.

Exposure Versus EFS

The Kaplan-Meier plot of EFS by quartiles of model-predicted Cavg,dose1 for patients receiving tislelizumab (N = 226) are shown in the following Figure.

Figure 12: Kaplan-Meier EFS Curves Stratified by Tislelizumab Cavg,dose1 Quartiles



Source: Study 315 PopPK-ER Report Section 5.2.4
Abbreviations: $C_{avg,dose1}$, average concentration after the first dose; EFS, event free survival; NA, not available.

To further investigate the effect of prognostic factors on EFS, 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 EFS using a two step forward-addition and backward-elimination method based on the significance level of $p<0.05$.

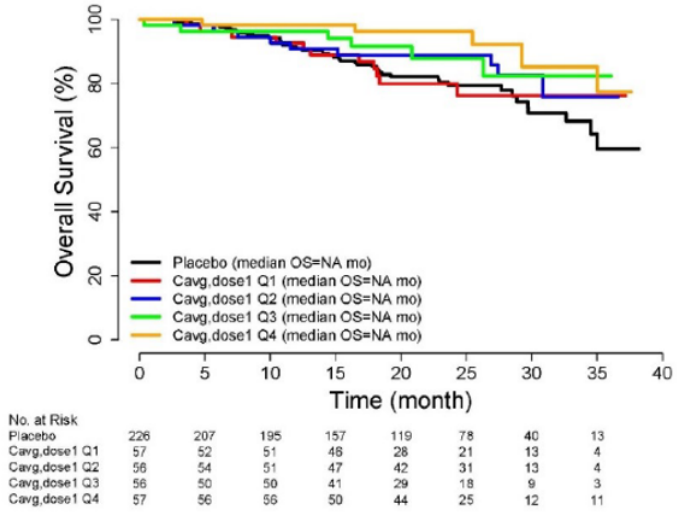
Table 17: Summary of Cox model parameters for EFS

Run	Predictor	Parameter Estimates		Wald p-value	95% CI for β	
		β	exp(β)		Lower	Upper
18	$Log(C_{avg,dose1})$	-0.9906	0.3714	0.2895	-2.8237	0.8425

Exposure Versus OS

The Kaplan-Meier plot of OS by quartiles of model-predicted Cavg,dose1 for patients receiving tislelizumab (N = 226) are shown in the following figure below.

Figure 13: Kaplan-Meier OS Curves Stratified by Tislelizumab Cavg,dose1 Quartiles



Source: Study 315 PopPK-ER Report Section 5.2.3
Abbreviations: $C_{avg,dose1}$, average concentration after the first dose; OS, overall survival; NA, not available.

To further investigate the effect of prognostic factors on 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 OS using a twostep forward-addition and backward-elimination method based on the significance level of $p<0.05$.

Table 18: Summary of Cox model parameters for OS

Run	Predictor	Parameter Estimates		Wald p-value	95% CI for β	
		β	exp(β)		Lower	Upper
18	$Log(C_{avg,dose1})$	-2.4646	0.0850	0.0592	-5.0248	0.0956

Exposure-safety analysis

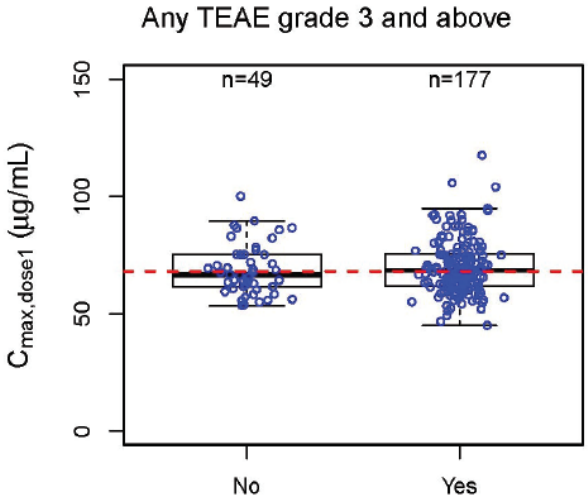
Exposure-safety analyses explored the relationship between model-predicted tislelizumab exposure and clinically relevant safety endpoints in Study 315: CTCAE ≥ Grade 3 TEAEs, TEAEs leading to tislelizumab discontinuation, TEAEs leading to tislelizumab dose modification (ie, dose interruption, dose delay, and infusion rate decrease), AESIs (AESI safety endpoints were imAEs and IRRs), and serious TEAEs. These endpoints are characterized by incidence only. Box-plots display PopPK-predicted Cmax,dose1 for patients with and without the safety event of interest.

Table 19: Summary of safety endpoints for tislelizumab treated patients [% (Yes/All)]

Clinical response	BGB-A317-315 (N=226)
Any TEAE Grade ≥ 3	78.3% (177/226)
Immune-mediated TEAEs	39.8% (90/226)
TEAEs leading to treatment discontinuation	10.6% (24/226)
Infusion related reactions	4.40% (10/226)
TEAEs leading to dose modification	35.0% (79/226)
Special interest TEAEs	42.9% (97/226)
Serious TEAEs	31.0% (70/226)

Any TEAE with CTCAE grade ≥ 3

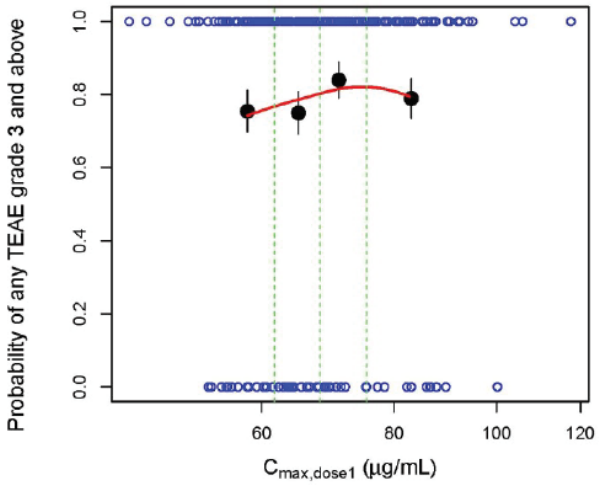
Figure 14: The relationship between exposure and any TEAE grade ≥ 3 for tislelizumab treated patients



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-A317-315.

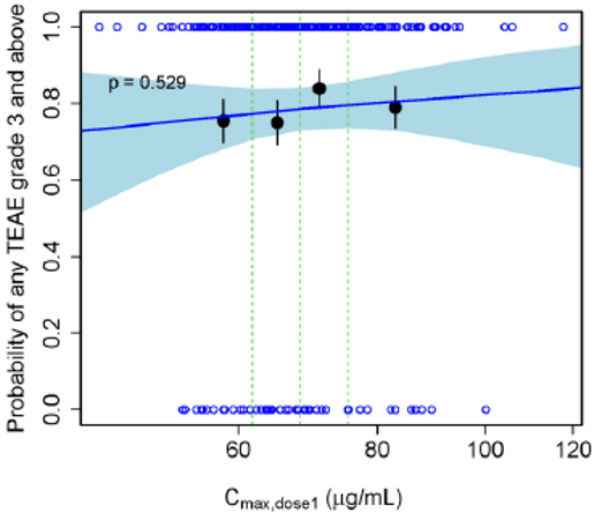
The probability estimates of any TEAE grade ≥ versus PopPK predicted Cmax,dose1 were evaluated across four quartiles of Cmax,dose1. Logistic regression was further used to evaluate the relationship between exposure and response.

Figure 15: Probability of any TEAE grade ≥ 3 versus exposure for tislelizumab treated patients



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.

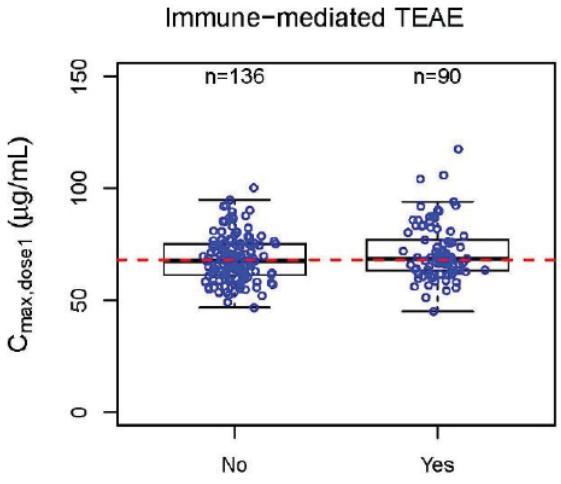
Figure 16: Logistic regression of probability of any TEAE Grade ≥ 3 versus exposure for Tislelizumab treated patients



Source: Study 315 PopPK-ER Report Figure 16
Abbreviations: $C_{max,dose1}$, maximum concentration after the first dose; TEAE, treatment-emergent adverse event.
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) of exposures (plotted at the median value within each quantile). The blue line is the model-predicted probability. The blue line and light blue shaded area are the median and 95% prediction interval based on the 1000 bootstrap samples of the model.

Immune-mediated TEAEs

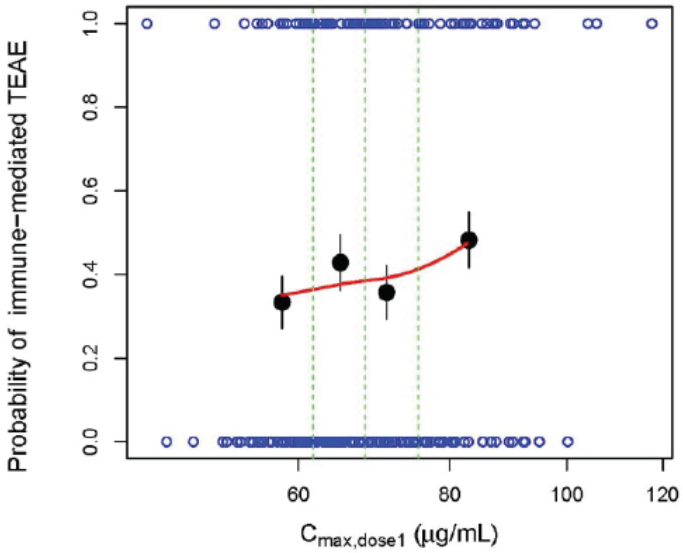
Figure 17: The relationship between exposure and immune-mediated TEAEs for tislelizumab treated patients



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-A317-315.

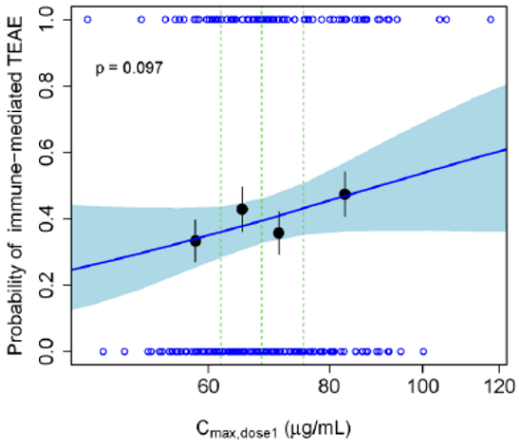
The probability estimates of immune-mediated TEAEs versus PopPK predicted Cmax,dose1 were evaluated across four quartiles of Cmax,dose1. Logistic regression was further used to evaluate the relationship between exposure and response.

Figure 18: Probability of immune-mediated TEAEs versus exposure for tislelizumab treated patients



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.

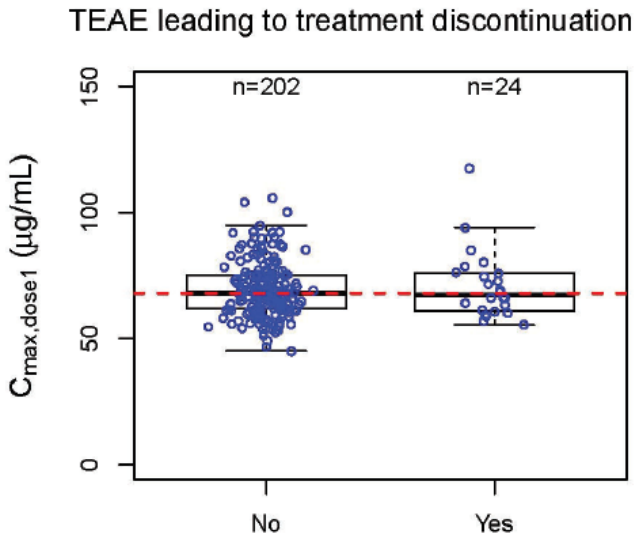
Figure 19: Logistic Regression of Probability of imAEs Versus Exposure for Tislelizumab Treated Patients



Source: Study 315 PopPK-ER Report Figure 19
Abbreviations: $C_{max,dose1}$, maximum concentration after the first dose; TEAE, treatment-emergent adverse event.
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) of exposures (plotted at the median value within each quantile). The blue line is the model-predicted probability. The blue line and light blue shaded area are the median and 95% prediction interval based on the 1000 bootstrap samples of the model.

TEAEs leading to treatment discontinuation

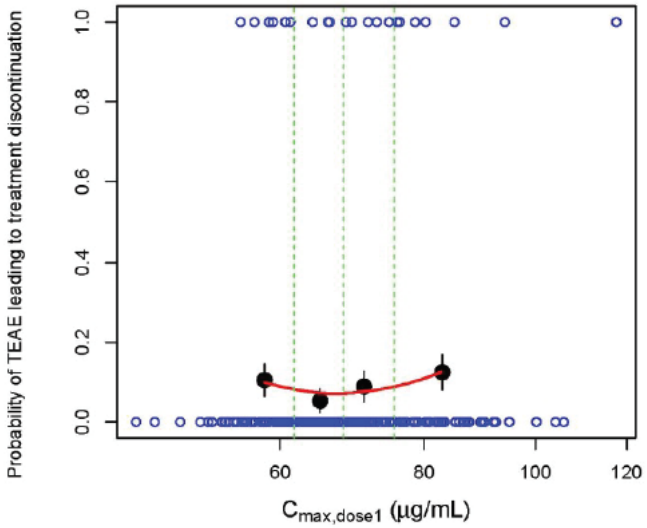
Figure 20: The relationship between exposure and TEAEs leading to treatment discontinuation



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-A317-315.

The probability estimates of TEAEs leading to treatment discontinuation versus PopPK predicted Cmax,dose1 were evaluated across four quartiles of Cmax,dose1.

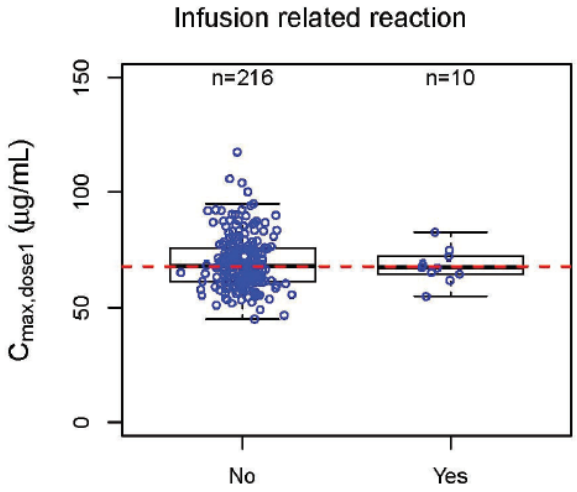
Figure 21: Probability of TEAEs leading to treatment discontinuation versus tislelizumab exposure



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

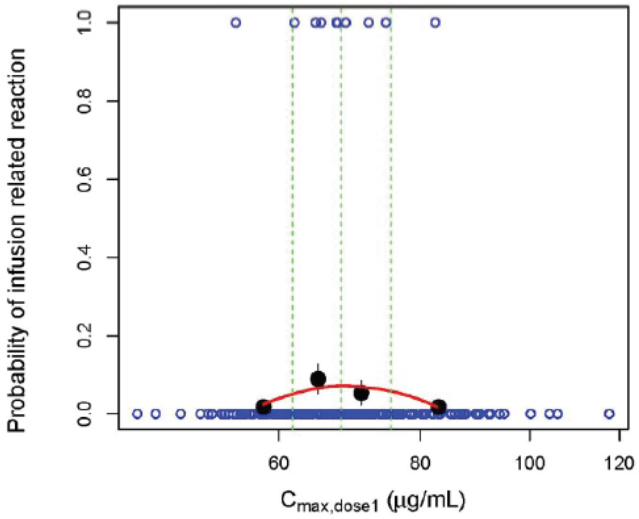
Figure 22: The relationship between exposure and infusion related reactions



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-A317-315.

The probability estimates of infusion-related reactions versus PopPK predicted Cmax,dose1 were evaluated across four quartiles of Cmax,dose1.

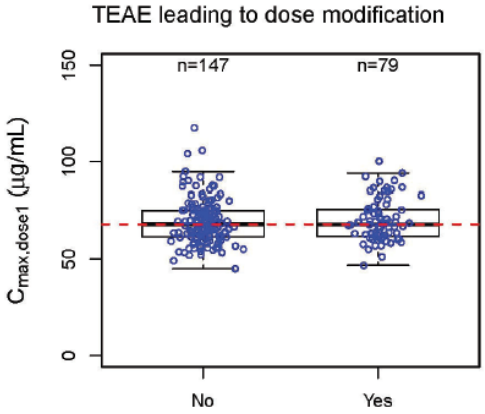
Figure 23: Probability of infusion related reactions versus tislelizumab exposure



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.

TEAEs Leading to Dose Modification

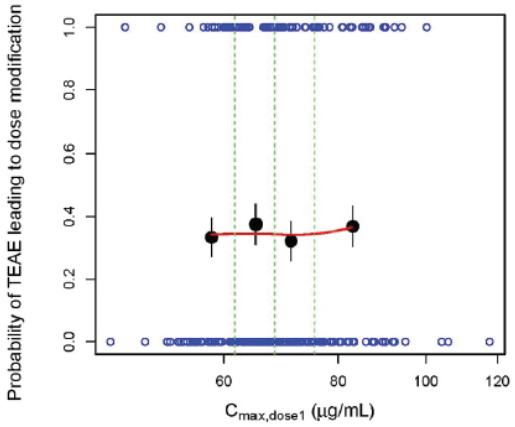
Figure 24: The relationship between exposure and TEAEs leading to dose modification



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-A317-315.

The probability estimates of TEAEs leading to dose modification versus PopPK predicted Cmax,dose1 were evaluated across four quartiles of Cmax,dose1.

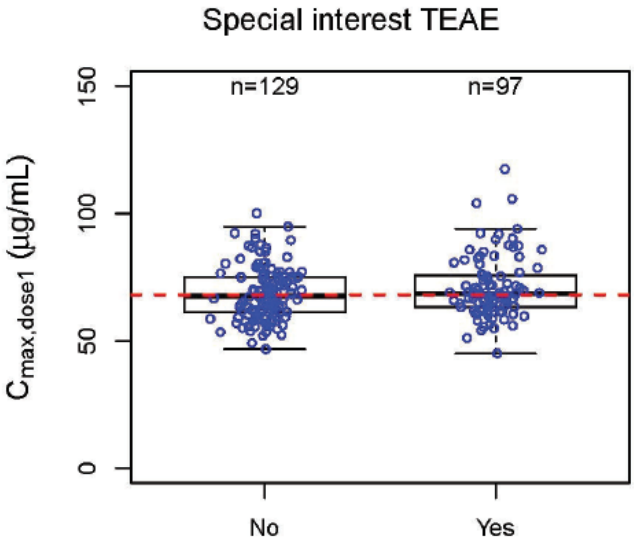
Figure 25: Probability of TEAEs leading to dose modification



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.

TEAEs of Special Interest of Tislelizumab

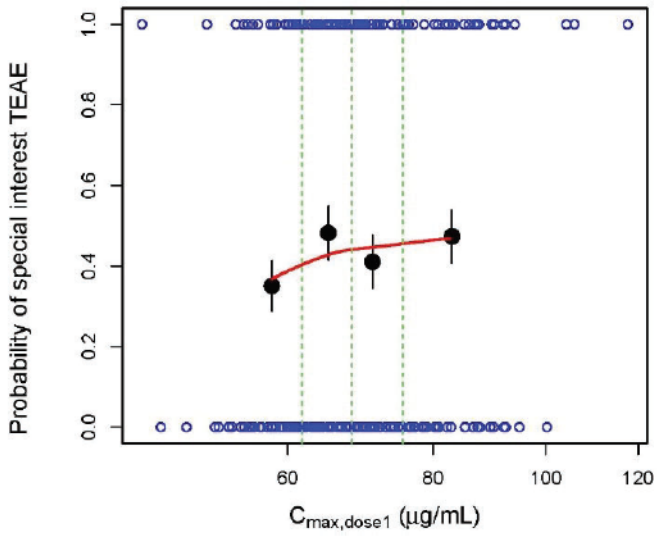
Figure 26: The relationship between exposure and special interest TEAEs



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-A317-315.

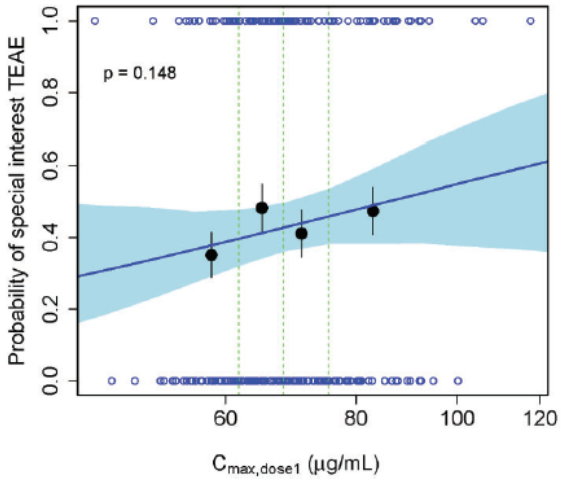
The probability estimates of special interest TEAEs versus PopPK predicted Cmax,dose1 were evaluated across four quartiles of Cmax,dose1. Logistic regression was further used to evaluate the relationship between exposure and response.

Figure 27: Probability of special interest TEAEs



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.

Figure 28: Logistic Regression of Probability of Special Interest TEAEs Versus Tislelizumab Exposure

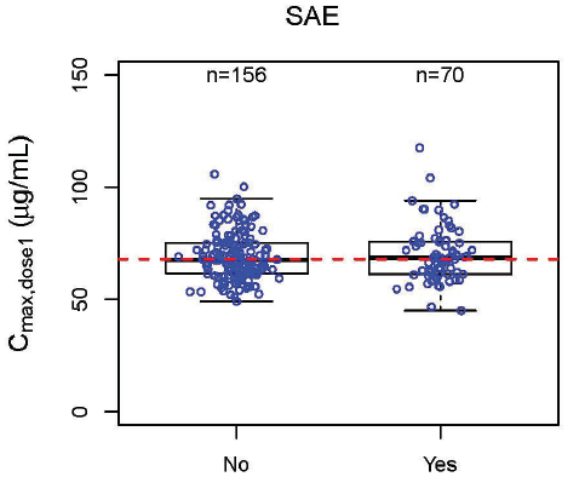


Open blue circles reflect the observed events. The filled black symbols are the observed probability of events and the error bars are SE [sqrt (P*(1-P)/N)] for quantiles (at 100x(1/4)th percentiles) of exposures (plotted at the median value within each quantile). The blue line is the model-predicted probability. The blue line and light blue shaded area are the median and 95% prediction interval based on the 1000 bootstrap samples of the model.

Serious TEAEs of Tislelizumab

The box plot for the relationship between exposure and serious TEAEs for tislelizumab treated patients shows that the median Cmax,dose1 values of tislelizumab were slightly higher in between patients with serious TEAEs (N=70) than in patients without serious TEAEs(N=156).

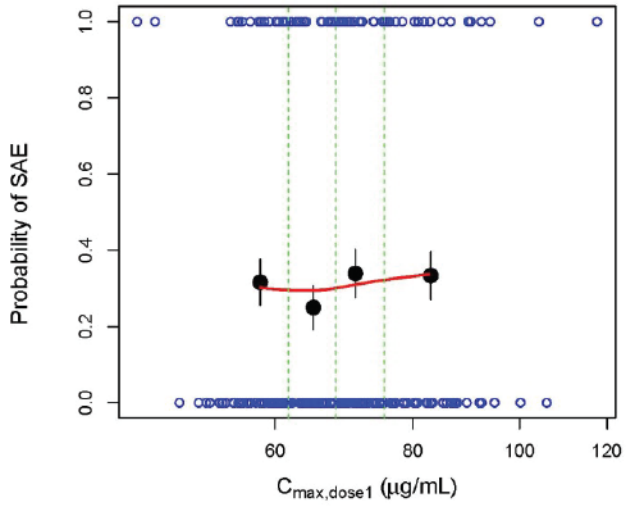
Figure 29: The relationship between exposure and serious TEAEs



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-A317-315.

The probability estimates of serious TEAEs versus PopPK predicted Cmax,dose1 were evaluated across four quartiles of Cmax,dose1.

Figure 30: Probability of serious TEAEs versus tislelizumab exposure



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 Analyses for Adjuvant Phase

The relationship between tislelizumab exposure and clinical safety endpoints was also explored based on data in the adjuvant phase when patients received tislelizumab 400 mg once every 6 weeks.

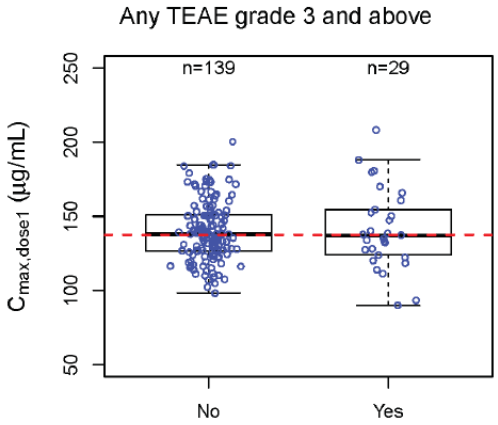
Table 20: Summary of safety endpoints for tislelizumab treated patients in the adjuvant phase [%(Yes/All)]

Clinical response	BGB-A317-315 (N=168)
Any TEAE grade ⩾ 3	17.3% (29/168)
Immune-mediated TEAEs	21.4% (36/168)
TEAEs leading to treatment discontinuation	6.50% (11/168)
Infusion related reactions	1.80% (3/168)
TEAEs leading to dose modification	23.8% (40/168)
Special interest TEAEs	22.6% (38/168)
Serious TEAEs	19.6% (33/168)

Any TEAE Grade ≥ 3 (adjuvant phase)

The box plot for the relationship between exposure and any TEAE grade ≥ 3 for tislelizumab treated patients in the adjuvant phase shows that the median Cmax,dose1 values of tislelizumab were more or less comparable between patients with (N=29) and without (N=139) any TEAE grade ≥ 3.

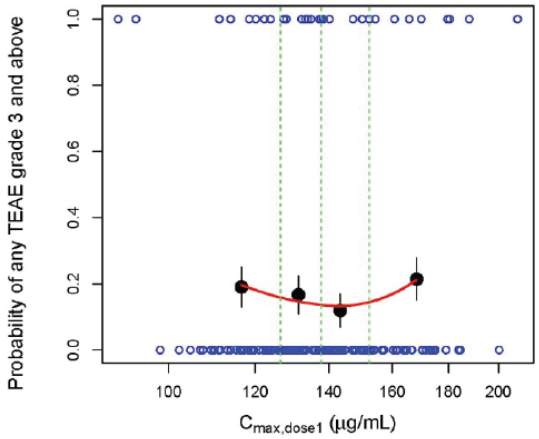
Figure 31: The relationship between tislelizumab exposure and any TEAE grade ≥ 3 in the adjuvant phase



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-A317-315.

The probability estimates of any TEAE grade ≥ 3 versus PopPK predicted Cmax,dose1 were evaluated across four quartiles of Cmax,dose1.

Figure 32: Probability of any TEAE grade ≥ 3 versus tislelizumab exposure in the adjuvant phase

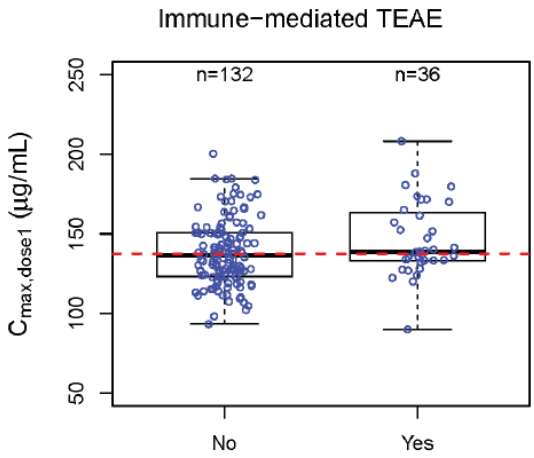


Open blue circles reflect the observed events. The filled black symbols are the observed probability of events and the error bars are SE [sqrt (P*(1-P)/N)] for quantiles (at 100x(1/4)th percentiles, vertical dotted lines) of exposures (plotted at the median value within each quantile), where P is the 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.

Immune-mediated TEAEs (adjuvant phase)

The boxplot for the relationship between exposure and immune-mediated TEAEs for tislelizumab treated patients in the adjuvant phase showed that the median Cmax,dose1 values and the upper quartile of tislelizumab were higher in patients with immune-mediated TEAEs (N=36) compared to patients without immune-mediated TEAEs (N=132).

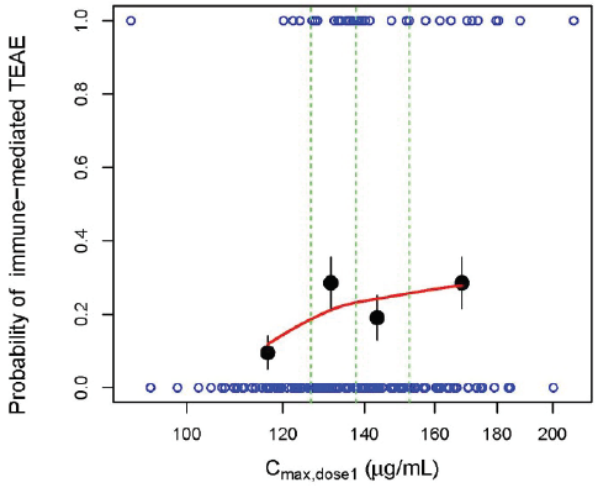
Figure 33: The relationship between tislelizumab exposure and immune-mediated TEAEs in the adjuvant phase



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-A317-315.

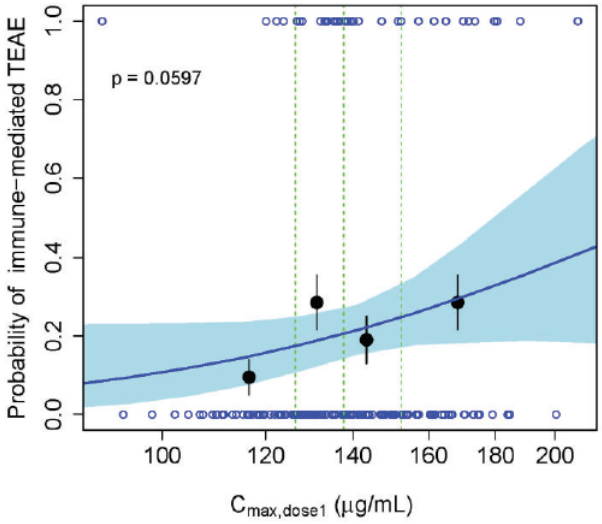
The probability estimates of immune-mediated TEAEs versus PopPK predicted Cmax,dose1 were evaluated across four quartiles of Cmax,dose1. Logistic regression was further used to evaluate the relationship between exposure and response.

Figure 34: Probability of immune-mediated TEAEs versus tislelizumab exposure in the adjuvant phase



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.

Figure 35: Logistic regression of probability of immune-mediated TEAEs versus tislelizumab exposure in the adjuvant phase

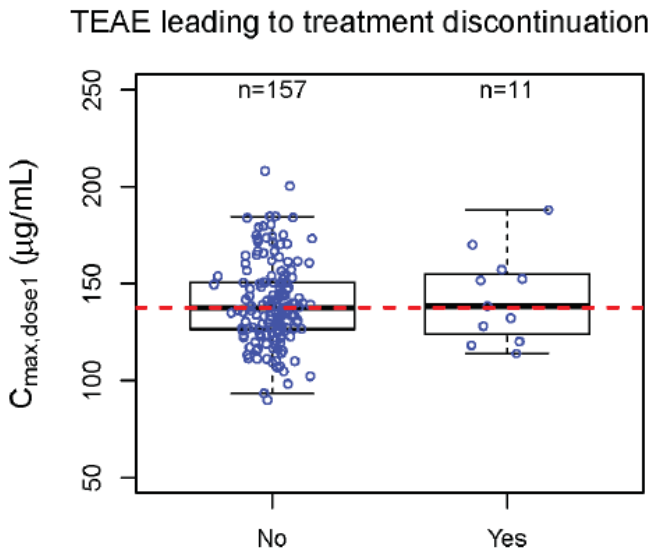


Open blue circles reflect the observed events. The filled black symbols are the observed probability of events and the error bars are SE [sqrt (P*(1-P)/N)] for quantiles (at 100x(1/4)th percentiles) of exposures (plotted at the median value within each quantile). The blue line is the model-predicted probability. The blue line and light blue shaded area are the median and 95% prediction interval based on the 1000 bootstrap samples of the model.

TEAEs Leading to Treatment Discontinuation (adjuvant phase)

The boxplot for the relationship between exposure and TEAEs leading to treatment discontinuation for tislelizumab treated patients in the adjuvant phase showed that the median Cmax,dose1 values of tislelizumab were more or less comparable between patients with (N=11) and without (N=157) TEAEs leading to treatment discontinuation.

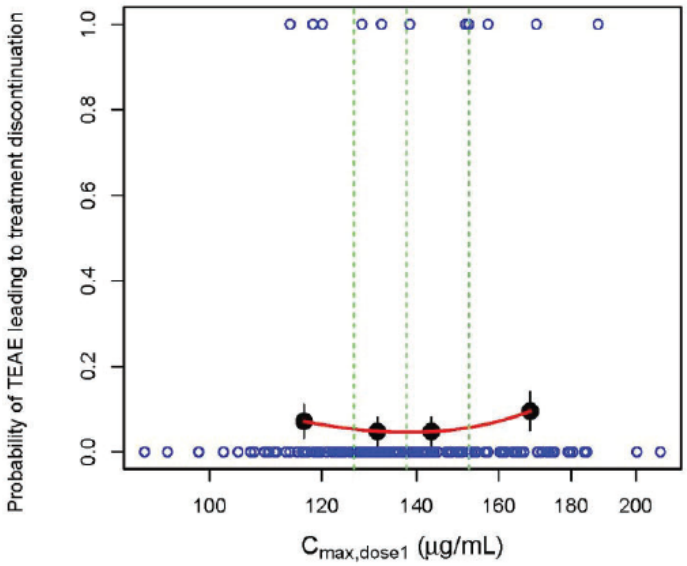
Figure 36: The relationship between exposure and TEAEs leading to treatment discontinuation in the adjuvant phase



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-A317-315.

The probability estimates of TEAEs leading to treatment discontinuation versus PopPK predicted Cmax,dose1 were evaluated across four quartiles of Cmax,dose1.

Figure 37: Probability of TEAEs leading to treatment discontinuation versus tislelizumab exposure in the adjuvant phase

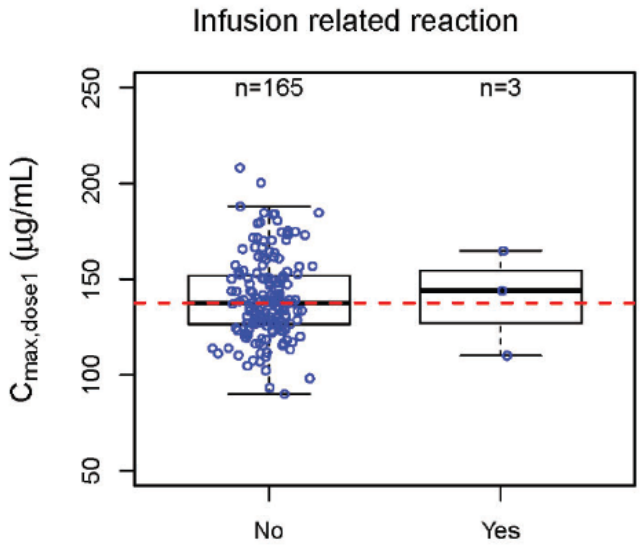


Open blue circles reflect the observed events. The filled black symbols are the observed probability of events and the error bars are SE [sqrt (P*(1-P)/N)] for quantiles (at 100x(1/4)th percentiles, vertical dotted lines) of exposures (plotted at the median value within each quantile), where P is the 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 (adjuvant phase)

The boxplot for the relationship between exposure and infusion-related reactions for tislelizumab treated patients in the adjuvant phase showed that the median Cmax,dose1 values of tislelizumab were higher in patients with infusion-related reactions (N=3) than in patients without (N=165) infusion-related reactions.

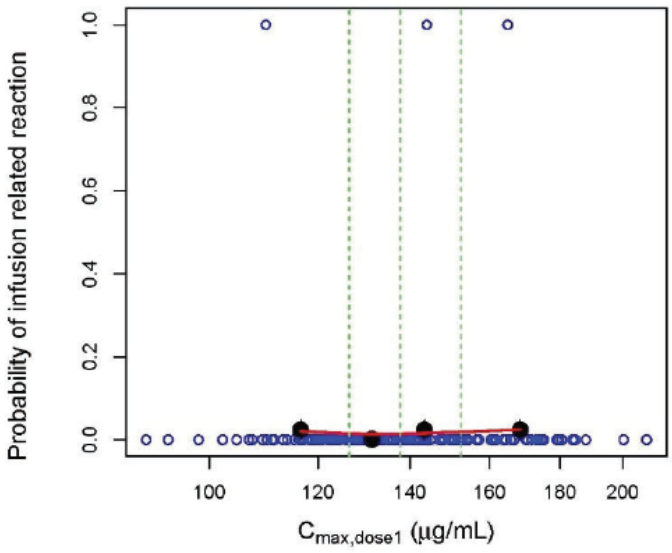
Figure 38: The relationship between exposure and infusion related reactions in the adjuvant phase



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-A317-315.

The probability estimates of infusion-related reactions versus PopPK predicted Cmax,dose1 were evaluated across four quartiles of Cmax,dose1.

Figure 39: Probability of TEAE leading to infusion related reactions in the adjuvant phase

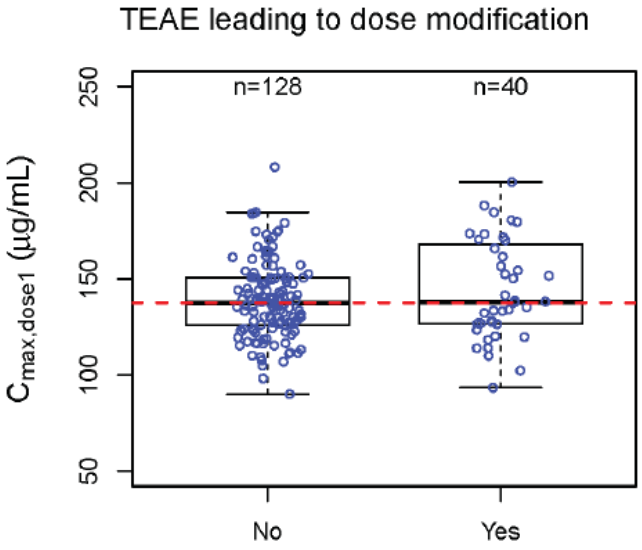


Open blue circles reflect the observed events. The filled black symbols are the observed probability of events and the error bars are SE [sqrt (P*(1-P)/N)] for quantiles (at 100x(1/4)th percentiles, vertical dotted lines) of exposures (plotted at the median value within each quantile), where P is the 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.

TEAEs Leading to Dose Modification (adjuvant phase)

The boxplot for the relationship between exposure and TEAEs leading to dose modification for tislelizumab treated patients in the adjuvant phase showed that the median Cmax,dose1 values were comparable between patients with (N=40) and without TEAEs leading to dose modification (N=128). The upper quartile of tislelizumab were larger in patients with TEAEs leading to dose modification (N=40) compared to patients without TEAEs leading to dose modification (N=128).

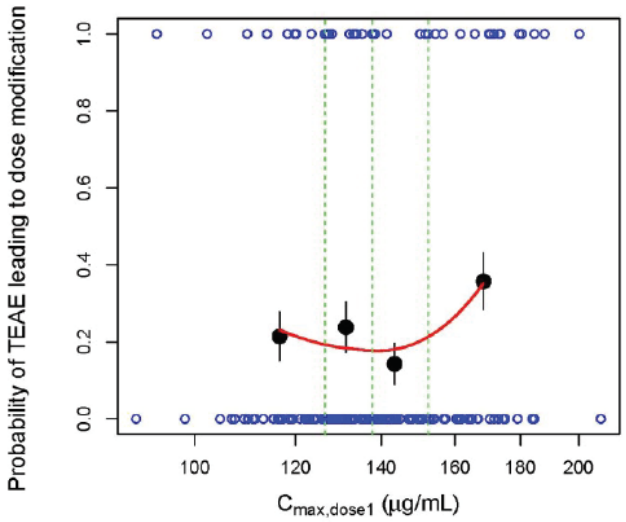
Figure 40: The relationship between exposure and TEAEs leading to dose modification in the adjuvant phase



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-A317-315.

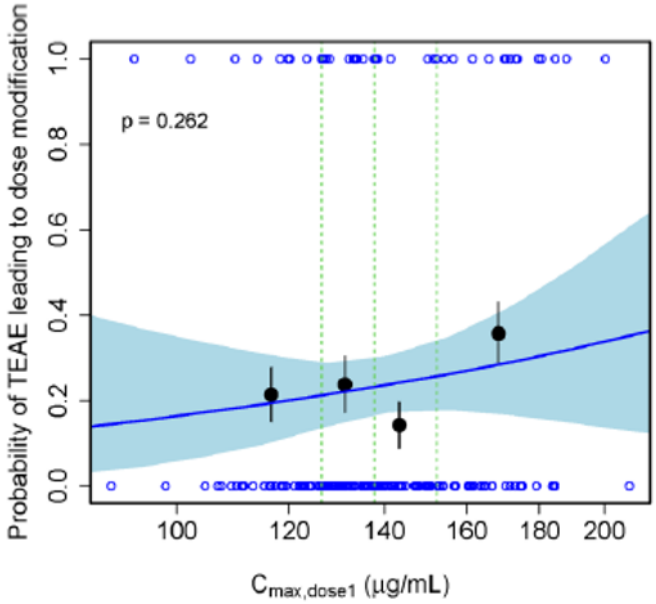
The probability estimates of TEAEs leading to dose modification versus PopPK predicted Cmax,dose1 were evaluated across four quartiles of Cmax,dose1. Logistic regression was further used to evaluate the relationship between exposure and response.

Figure 41: Probability of TEAE leading to TEAEs leading to dose modification in the adjuvant phase



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.

Figure 42: Logistic Regression of Probability of TEAEs Leading to Dose Modification Versus Tislelizumab Exposure in the Adjuvant Phase



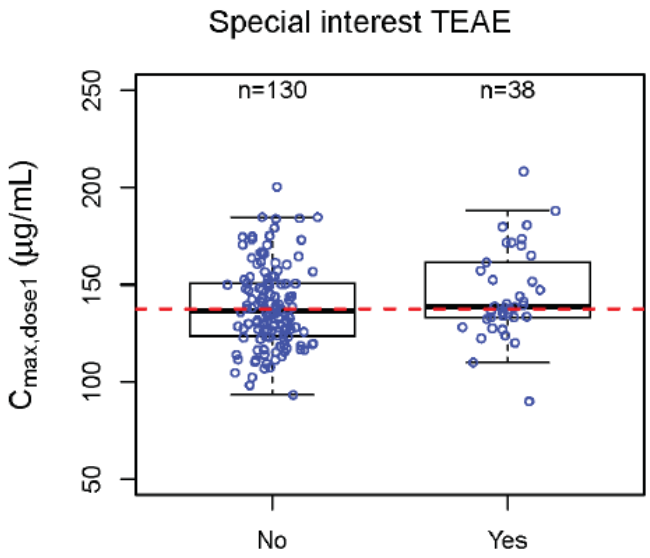
Source: Study 315 PopPK-ER Report Figure 42
Abbreviations: $C_{max,dose1}$, maximum concentration after the first dose; TEAE, treatment-emergent adverse event.
Open blue circles reflect the observed events. The filled black symbols are the observed probability of events and the error bars are SE [sqrt (P*(1-P)/N)] for quantiles (at 100x(1/4)th percentiles) of exposures (plotted at the median value within each quantile). The blue line is the model-predicted probability. The blue line and light blue shaded area are the median and 95% prediction interval based on the 1000 bootstrap samples of the model.

Special Interest TEAEs

The boxplot for the relationship between exposure and TEAEs of special interest for tislelizumab treated patients in the adjuvant phase showed that the median Cmax,dose1 values were slightly higher in

patients with (N=38) TEAEs of special interest compared to patients without TEAEs of special interest (N=130). In addition, the upper quartile of tislelizumab were larger and the lower quartile smaller in patients with TEAEs of special interest (N=38) compared to patients without TEAEs of special interest (N=130).

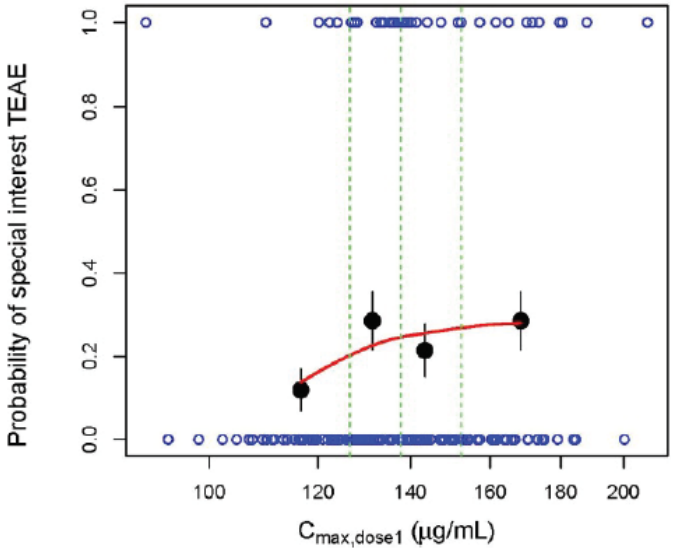
Figure 43: The relationship between exposure and special interest TEAEs in the adjuvant phase



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-A317-315.

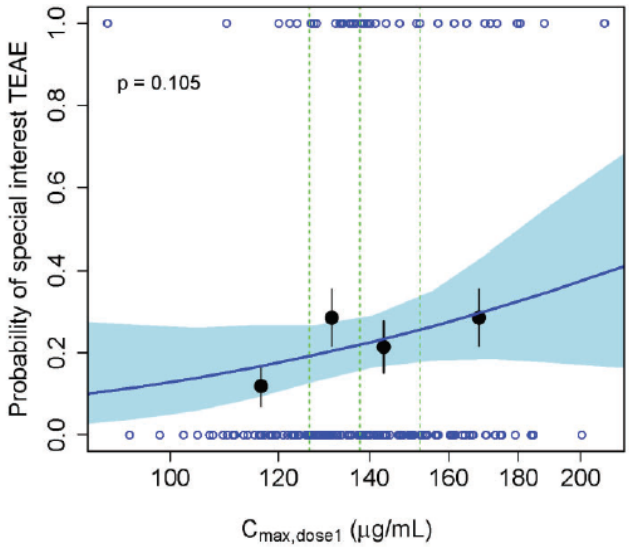
The probability estimates of special interest TEAEs versus PopPK predicted Cmax,dose1 were evaluated across four quartiles of Cmax,dose1. Logistic regression was further used to evaluate the relationship between exposure and response.

Figure 44: Probability of TEAE leading to special interest TEAEs in the adjuvant phase



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.

Figure 45: Logistic regression of probability of special interest TEAEs versus tislelizumab exposure in the adjuvant phase

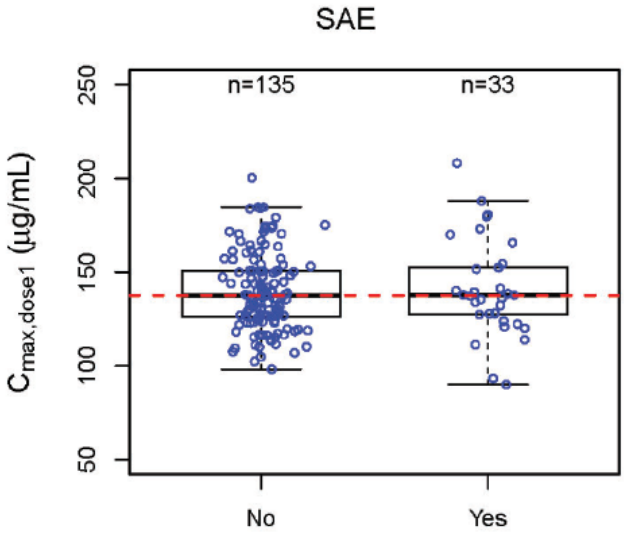


Open blue circles reflect the observed events. The filled black symbols are the observed probability of events and the error bars are SE [sqrt (P*(1-P)/N)] for quantiles (at 100x(1/4)th percentiles) of exposures (plotted at the median value within each quantile). The blue line is the model-predicted probability. The blue line and light blue shaded area are the median and 95% prediction interval based on the 1000 bootstrap samples of the model.

Serious TEAEs (adjuvant phase)

The boxplot for the relationship between exposure and serious TEAEs for tislelizumab treated patients in the adjuvant phase showed that the median Cmax,dose1 values were comparable between patients with (N=33) and without (N=135) serious TEAEs.

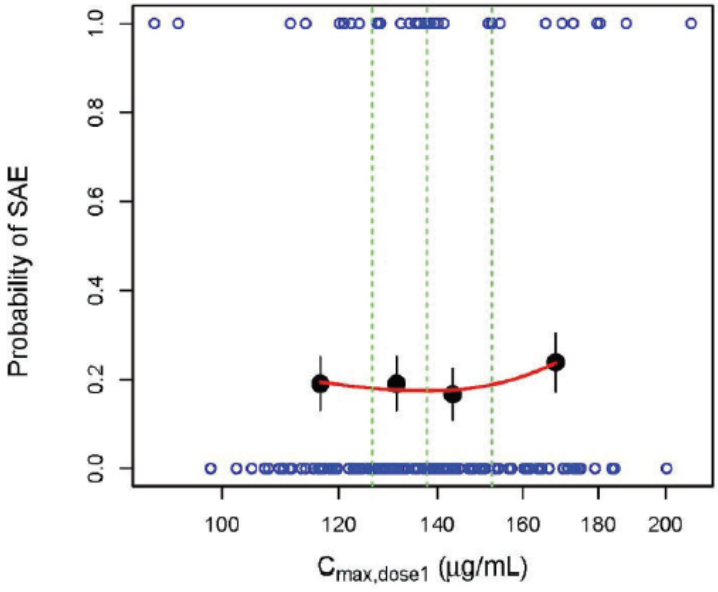
Figure 46: The relationship between exposure and serious TEAEs in the adjuvant phase



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-A317-315.

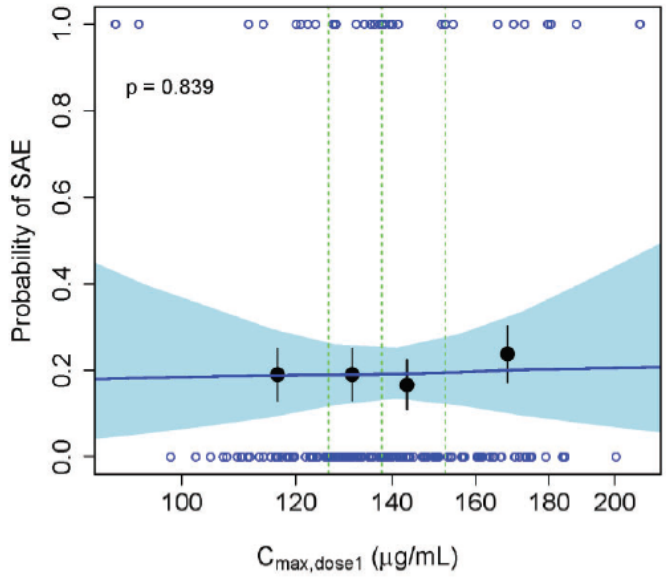
The probability estimates of serious TEAEs versus PopPK predicted Cmax,dose1 were evaluated across four quartiles of Cmax,dose1. Logistic regression was further used to evaluate the relationship between exposure and response.

Figure 47: Probability of serious TEAEs versus tislelizumab exposure in the adjuvant phase



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.

Figure 48: Logistic regression of probability of serious TEAEs versus exposure in the adjuvant phase



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) of exposures (plotted at the median value within each quantile). The blue line is the model-predicted probability. The blue line and light blue shaded area are the median and 95% prediction interval based on the 1000 bootstrap samples of the model.

Treatment-Emergent Adverse Events by Weight Quartile (Adjuvant Phase)

Table 21: Incidence of Treatment-Emergent Adverse Events by Weight Quartile for Tislelizumab and Placebo Treatment Groups in Adjuvant Phase (Safety Analysis Set)

Weight Category	imAEs n (%)	AESI n (%)	TEAEs Leading to Dose Modification n (%)
Tislelizumab Arm – Adjuvant Phase			
<= Q1 (n=46)	14 (30.4%)	14 (30.4%)	13 (28.3%)
(Q1, Q2] (n=43)	10 (23.3%)	11 (25.6%)	12 (27.9%)
(Q2, Q3] (n=35)	9 (25.7%)	10 (28.6%)	7 (20%)
> Q3 (n=42)	3 (7.14%)	3 (7.14%)	8 (19%)
Overall (n=166)	36 (21.7%)	38 (22.9%)	40 (24.1%)
Placebo Arm - Adjuvant Phase			
<= Q1 (n=38)	3 (7.89%)	3 (7.89%)	7 (18.4%)
(Q1, Q2] (n=36)	2 (5.56%)	2 (5.56%)	3 (8.33%)
(Q2, Q3] (n=39)	5 (12.8%)	5 (12.8%)	10 (25.6%)
> Q3 (n=34)	2 (5.88%)	2 (5.88%)	4 (11.8%)
Overall (n=147)	12 (8.16%)	12 (8.16%)	24 (16.3%)

Abbreviations: TEAE, treatment-emergent adverse event; imAE, immune-mediated adverse event; AESI, adverse event of special interest which included imAE and infusion related reaction; Q1, 1st quartile; Q2, 2nd quartile; Q3, 3rd quartile. n is the number of patients with non-missing baseline weight and fall into the corresponding weight category. Two patients have been excluded from this table due to no body weight data availability. Percent values are calculated based on n from each corresponding row.
A TEAE during 'adjuvant phase' is an AE that happened from the first dose of study treatment in adjuvant phase to 30 days after the last dose of adjuvant study treatment, data cutoff date, death date, end of study date, or new-anticancer therapy start date, whichever comes first. TEAEs also include all imAEs occurring from the date of first adjuvant dose to 90 days after the last dose of study drug in adjuvant phase.

2.3.5. Discussion on clinical pharmacology

Pharmacokinetics

In the pivotal study 315, the recommended dose of tislelizumab for the neoadjuvant treatment is 200 mg Q3W, and for the adjuvant treatment is 400 mg Q6W for maximum of 8 cycles, after surgery or until disease recurrence, or metastasis, or unacceptable toxicity.

The pharmacokinetics of tislelizumab for the proposed dosing regimen of 200 mg Q3W had already been extensively characterized in previous applications.

The adjuvant phase dose of 400 mg administered intravenously once every 6 weeks was selected by matching dose and exposure (the AUC) with the exposure of the 200 mg once-every-3-weeks regimen.

In the pivotal study 315 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 315.

In Study 315, the sparse pre- (Ctrough) and post-dose (Cmax) concentrations of tislelizumab during the neoadjuvant phase (200 mg once every 3 weeks) and the pre-dose (Ctrough) concentration during the adjuvant phase (400 mg once every 6 weeks) were similar to the concentrations reported in previous studies in which tislelizumab (200 mg once every 3 weeks) was administered in combination with chemotherapy. The post-dose concentration (Cmax) during the adjuvant phase (400 mg once every 6 weeks) was higher in study 315 compared to the concentrations reported in previous studies in which tislelizumab (200 mg once every 3 weeks) was administered in combination with chemotherapy. However, the time points for the PK sample collection were few in study 315 and differed slightly between the study 315 and the previous tislelizumab studies.

The external validation using the data from Study 315 indicate that the final PopPK model was able to adequately describe the observed PK data from Study 315. Simulated steady state exposure of tislelizumab (Cmaxss, Cminss, AUCss) for Study 315 was comparable between the neoadjuvant phase and the overall phase. In addition, the simulated steady state exposure for the neoadjuvant and for the overall phase in Study 315 appears also comparable to the simulated steady state exposure of tislelizumab in previous studies of Tislelizumab. The use of the final PopPK model is considered adequate to generate exposure metrics for subsequent ER analyses.

Overall, the PK-data (albeit limited) from the pivotal Study 315 and the PopPK-predicted exposure of tislelizumab in Study 315 support the proposed tislelizumab neoadjuvant dose of 200 mg administered intravenously once every 3 weeks and the adjuvant dose of 400 mg administered intravenously once every 6 weeks for the Stage II and IIIA NSCLC population.

Immunogenicity

The immunogenicity profile of tislelizumab has been characterized in clinical studies using validated assays. Serum samples from tislelizumab-treated patients in 15 clinical studies (Phase 1 to 3) were assessed for treatment-emergent ADA and NAb. Analyses of ADA and its potential impact on PK, efficacy, and safety were performed for 3563 evaluable patients.

In study 315, 219 patients were determined to be evaluable for ADA. 105 (47.9%) out of 219 evaluable patients had treatment-emergent ADAs, of which 47 patients (21.5%) had a transient ADA response, 56 patients (25.6%) had a persistent ADA response, and 2 (0.9%) patients were ADA-positive at baseline and were treatment boosted. Neutralizing antibodies (NAb) were detected in 6 patients (2.7%).

The overall incidence of treatment-emergent ADA patients with Stage II or IIIA NSCLC treated with neoadjuvant tislelizumab 200 mg once every 3 weeks in combination with chemotherapy and adjuvant

tislelizumab 400 mg once every 6 weeks was approximately 2-fold higher in study 315 than that observed in previous tislelizumab studies (Phase 3 monotherapy studies 302 and 303 [14.3% and 16.3%, respectively] and Phase 3 combination therapy studies 304, 305, 306, 307, 309, and 312 [8.8% to 27.6%]). Although the reason for this 2-fold higher ADA incidence is not entirely clear at present, patients in Study 315 are at relatively earlier stages and lines of therapy compared to the patient populations from other tislelizumab studies, which may be a contributing factor for the higher ADA incidence. The totality of data currently presented do not allow firm conclusions on the clinically relevance of these 2-fold higher ADA rate. However, the results of study 315 regarding the treatment-emergent ADA do not seem to have a major negative impact on PK, efficacy or safety of tislelizumab in patients with NSCLC and no consistent clinically relevant exposure-response relationship was observed between tislelizumab exposure and efficacy and safety endpoints.

Impact of ADAs on PK

In the ADA evaluable analysis set for both the neoadjuvant and adjuvant treatment phase in study 315, the median and geometric mean serum concentrations of tislelizumab were numerically slightly lower in treatment-emergent ADA positive patients compared to ADA-negative patients until adjuvant Cycle 5. Although the standard deviations were overlapping, it seems that in the adjuvant phase the numerical difference in the trough concentration between the ADA-positive and ADA negative patients increase over time. Although, it is acknowledged that ADA positivity could be associated with other negative prognostic factors, a similar trend towards reduced exposure of tislelizumab in ADA-positive patients has also been observed in other tislelizumab combination therapy studies (e.g. Study 302, 304 and Study 307). Thus, based on the data provided and the potential trend observed, an impact of positive ADAs on the PK of tislelizumab, specifically in the adjuvant treatment phase of this patient population (Stage II or IIIA NSCLC), can currently not entirely be excluded. However, the totality of data currently presented do not allow firm conclusions on the clinically relevance of the potential impact of positive ADAs on PK.

Impact of ADAs on Efficacy

The impact of ADAs on the efficacy endpoints MPR, pCR, and EFS were investigated in study 315, whereas in the studies 302, 303, 305, 306, and 312 the impact of the ADA status was applied to the primary endpoint of OS and PFS in Studies 304 and 307. Thus, the results of study 315 are not directly comparable with the other studies.

Based on the data provided in study 315, the clinical response does not appear to be affected by the ADA status. The results for the major pathological response (MPR) and for the pathological complete response were similar between ADA-positive and ADA-negative patients. The results of the clinical response for the ADA positive patients appear numerically even slightly better than for the ADA negative patients.

The EFS results by ADA status showed slightly higher EFS for treatment emergent ADA-positive compared to ADA-negative patients based on the descriptive subgroup analysis (Hazard Ratio [95% CI]: 0.76). The EFS results using the principal stratum strategy indicated similar treatment benefits in treatment-emergent ADA-positive and ADA-negative groups compared to their corresponding controls.

Impact of ADAs on Safety

The results on the impact of the ADA status on the safety endpoints **in the overall phase** in study 315 showed a slight trend of higher rates for imAEs, AESIs and AEs grade ≥3 for treatment-emergent ADA positive patients compared to ADA-negative patients. The incidence of IRR was in general low in both ADA-positive (2.9%) and ADA-negative (4.4%) patient groups.

Considering the incidence of adverse events by ADA status only in the **neoadjuvant phase**, slightly more imAEs, IRRs, AESI, SAEs were reported for ADA positive patients compared to ADA negative patients.

In the **adjuvant phase** slightly more imAEs, AEs grade ≥3, AEs leading to discontinuation and AEs leading to modification were reported for ADA positive patients compared to ADA negative patients.

Overall, the results on the impact of the ADA status on the safety endpoints **across all phases** showed a trend of slightly higher rates for imAEs of treatment-emergent ADA positive patients (ADA positive: 44.8% vs. ADA negative: 36.8%), AESIs (ADA positive: 45.7% vs. ADA negative: 40.4%) and AEs grade ≥3 (ADA positive: 80.0% vs. ADA negative: 77.2%), and thus an impact of positive ADAs on the safety of tislelizumab can currently not entirely be excluded. Especially, for treatment-related adverse events of grade 3, which occurred more frequently in ADA-positive patients compared with ADA-negative patients in the study overall (76.2% versus 68.4%) and during the neoadjuvant phase (65.7% versus 59.6%). However, such a trend was not as prevalent for treatment-related adverse events of Grade 4 and Grade 5 and only a small numerical difference in the incidence of treatment-related TEAEs grade 4 and 5 were observed between ADA-positive and ADA-negative patients. It must be highlighted, that the ADA titers in patients treated with tislelizumab fluctuate over time and the standard deviations of the titers were quite large. In conclusion, no general trend or direct correlation between higher event grades and patient ADA status was observed.

Overall, the results of Study 315 on the impact of ADAs on safety appear to be consistent with the results from both monotherapy and combination tislelizumab studies, except the results of imAEs. The incidence of immune-mediated adverse events by ADA positive patients in study 315 was higher than in ADA negative patients (ADA positive: 44.8% vs. ADA negative: 36.8%) and such a difference of immune-mediated AEs between ADA positive and ADA negative patients (~8%) was neither observed in the monotherapy Studies (001, 102, 203, 204, 208, 302, and 303) nor in the combination therapy studies (304, 305, 306, 307 and 312). However, the currently available data do not allow firm conclusions to be drawn.

Neutralizing antibodies

In total of the 105 reported treatment-emergent ADA positive patients, 6 patients (2.7%) were positive for **NAb** with an ADA titer ≥160. It was noticed that all of these patients were male, had a disease stage IIIA and were current or former smokers. Therefore, a trend appears that ADA/Nab positivity could be associated with specific baseline characteristics/negative prognostic factors. However, the presence of NAb does not appear to have an impact on the efficacy or safety. Nevertheless, the number of NAbs is quite small and the results should therefore be interpreted with caution.

Overall, the number of positive detected NAbs across the studies was generally low, and frequency of positive detected NAbs in the phase 3 studies (monotherapy studies 302 and 303 and combination therapy studies 304, 305, 306, 307, 309, and 312) ranged between 0.0%-2.2%.

Exposure-response analyses

The original PopPK model was used as basis for analyses of the exposure-efficacy and exposure-safety relationship for tislelizumab. Data from 226 patients who had at least one adequately documented tislelizumab administration and a corresponding efficacy or safety measurement after the dose received were utilized for the exposure response analysis in study 315.

Exposure-Efficacy-Relationship

MPR, pCR, OS and EFS were investigated as efficacy parameters. In the exposure-efficacy analysis of Study 315, MPR (by BIPR) and pCR (by BIPR) explored by tislelizumab exposure boxplots by PopPK predicted Cavg,dose1 and the probability of response plots for patients with resectable stage II or IIIA

NSCLC. The mean exposure values between responder and non-responder for both, MPR (by BIPR) and pCR (by BIPR), were similar. The probability of response plots showed a slight trend between tislelizumab Cavg,dose1 and MPR/pCR. However, subsequent Cox proportional-hazards model analyses showed that Cavg.dose1 ($p > 0.05$) was not a significant predictor of MPR (by BIPR) or pCR (by BIPR).

Kaplan-Meier plots for OS and EFS stratified by PopPK predicted Cavg,dose1 quartiles revealed longer EFS 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 of EFS or OS.

Exposure-Safety-Relationship

IRRs, imAEs, TEAEs with CTCAE grade ≥ 3, TEAEs leading to tislelizumab treatment discontinuation, TEAEs leading to tislelizumab treatment dose modification and serious TEAEs were investigated as safety parameters. These safety endpoints were characterized by incidence only.

For each safety endpoint in the overall phase, the PopPK-predicted exposures (Cmax,dose1) of patients who experience the event and patients who did not experience the event were comparatively similar. Although there was a trend towards slightly higher tislelizumab exposure in patients with ≥ Grade 3 TEAEs, imAEs and AESI, the exposure-response logistic regression models indicated that Cmax,dose1 was not associated with the probability of ≥ Grade 3 TEAEs, imAEs, and AESI in tislelizumab-treated patients ($p > 0.05$). No clinically meaningful relationship between tislelizumab Cmax,dose1 and the probability of serious TEAEs, TEAEs leading to tislelizumab treatment discontinuation, TEAEs leading to tislelizumab treatment dose modification and IRR was observed.

The relationship between tislelizumab exposure and clinical safety endpoints was also explored based on data in the adjuvant phase (n=168) when patients received tislelizumab 400 mg once every 6 weeks. The PopPK-predicted exposures (Cmax,dose1) of patients who experience the event and patients who did not experience the event were also comparatively similar in the adjuvant phase. A trend towards slightly higher tislelizumab exposure in patients with imAEs, AESI, TEAEs leading to dose modification and serious TEAES was observed in the adjuvant phase. However, the exposure-response logistic regression models indicated that Cmax,dose1 was not associated with the probability of imAEs, AESI, TEAEs leading to dose modification and serious TEAEs in tislelizumab-treated patients ($p > 0.05$). Overall, no clinically meaningful relationship between tislelizumab Cmax,dose1 and the probability of ≥ Grade 3 TEAEs, TEAEs leading to tislelizumab treatment discontinuation and IRR was identified for the average individual in the adjuvant phase. In addition, no clear clinically meaningful relationship between patient weight and the incidence of AEs including imAEs, AESIs and TEAEs leading to dose modification was observed.

In conclusion, based on the data provided, no consistent clinically relevant exposure-response relationship 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 was identified in study 315, neither in the overall phase nor in the adjuvant phase.

2.3.6. Conclusions on clinical pharmacology

The pharmacokinetics and pharmacodynamics of tislelizumab have been sufficiently characterized. The results from the pivotal study 315 supporting this application for extension of indication are overall consistent with the analyses provided in previous applications.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

Not applicable.

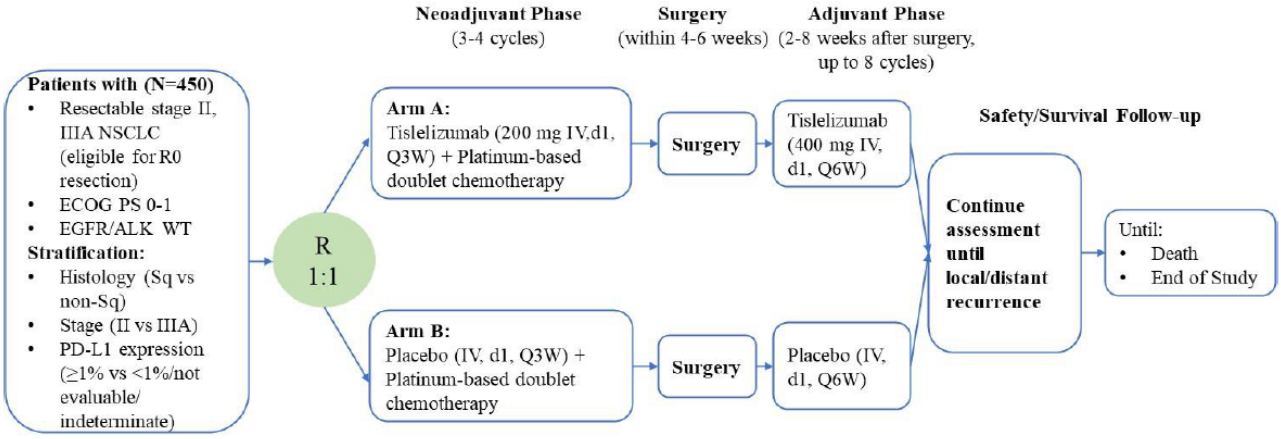
2.4.2. Main study

Neoadjuvant and adjuvant treatment of resectable NSCLC: BGB-A317-315 Study 315

A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study to Compare the Efficacy and Safety of Neoadjuvant Treatment With Tislelizumab or Placebo Plus Platinum-Based Doublet Chemotherapy Followed By Adjuvant Tislelizumab or Placebo in Resectable Stage II or IIIA Non-Small Cell Lung Cancer

Study design

Figure 49*: Schema Study 315*



Abbreviation: IV, intravenously; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death ligand-1; Q3W, once every 3 weeks; Q6W, once every 6 weeks; R, randomisation; Sq, squamous; non-Sq, nonsquamous; WT, wild-type.
Note: Platinum-based chemotherapy options permitted for Study 315: 1) For nonsquamous NSCLC: cisplatin/carboplatin + pemetrexed; 2) For squamous NSCLC, cisplatin/carboplatin + paclitaxel. The choice of platinum-based chemotherapy was decided by the investigator.

The study consisted of the following phases: screening phase, treatment phase (neoadjuvant phase, surgery, adjuvant phase), a safety follow-up phase and a survival follow-up phase.

Stratification factors included: disease stage (II vs. IIIA), histology (squamous vs. nonsquamous), and PD-L1 expression (≥ 1% vs. < 1% / not evaluable or indeterminate).

Patients were randomized in a 1:1 ratio to Arm A (tislelizumab 200 mg once every 3 weeks + platinum-based doublet chemotherapy for 3 to 4 cycles, followed by surgical resection and then adjuvant tislelizumab 400 mg once every 6 weeks for up to 8 cycles) or Arm B (placebo + platinum-based doublet chemotherapy for 3 to 4 cycles, followed by surgical resection and then placebo on a 6-week cycle for up to 8 cycles).

Treatment beyond initial investigator-assessed progression was permitted if the patient was expected to benefit from continued treatment in the investigator's judgment and with agreement by the medical monitor. Crossover between the 2 arms was not allowed.

Methods

Study participants

Key inclusion criteria

- Age ≥ 18 years on the day of signing the informed consent form
- Histologically confirmed Stage II or IIIA NSCLC (per the Eighth American Joint Committee on Cancer/Union International Contre le Cancer NSCLC staging system)
    - T4 primary NSCLC only allowed on the basis of size (tumors > 7 cm). Invasion of the diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, and separate tumor nodules in a different ipsilateral lobe is not permitted.
- Eligible for R0 resection with curative intent
- Adequate cardiopulmonary function to be eligible for surgical resection with curative intent
- ECOG Performance Status 0 or 1
- Measurable disease as assessed by the investigator per RECIST v1.1
- Evaluation by an attending thoracic surgeon to confirm eligibility for an R0 resection with curative intent
- Adequate cardiopulmonary function to be eligible for surgical resection with curative intent
- Eligibility to receive a platinum-based doublet chemotherapy regimen
- Adequate organ function as indicated by the following laboratory values obtained ≤ 14 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
    - Calculated creatinine clearance (CrCl) (Cockcroft-Gault formula) for patients intended to receive cisplatin: creatinine clearance ≥ 60mL/min; for patients intended to receive carboplatin: creatinine clearance ≥ 45mL/min
- Willing to use highly effective method of birth control through ≥ 120 days after the last dose of study treatment

Key exclusion criteria

- Any prior therapy for current lung cancer, including chemotherapy, or radiotherapy.
- Prior treatment with an immune checkpoint inhibitor (anti-CTLA-4, anti-PD(L)-1)
- Patients with large cell neuroendocrine carcinoma (LCNEC).
- Known EGFR mutation or ALK gene translocation.

  - For non-squamous patients, a documentation of wild type EGFR reported by a tissue-based test is required. For non-squamous patients without documented EGFR status, EGFR mutation testing locally or at a central laboratory before enrollment is mandatory.
  - Patients with squamous NSCLC and unknown EGFR mutation status will not be required to be tested at screening.
  - Patients (non-squamous or squamous histology) with unknown ALK fusion oncogene status will not be required to be tested.
- Presence of locally advanced unresectable regardless of stage or metastatic disease (Stage IV). Mediastinal lymph node samples are required for clinical staging to assess nodal involvement in patients with mediastinal adenopathy on CT scan to rule out Stage IIIB/C disease.
- Active autoimmune diseases or history of autoimmune diseases that may relapse.
- Any condition that required systemic treatment with either corticosteroids (> 10 mg daily of prednisone or equivalent) or other immunosuppressive medication ≤ 14 days before randomization.
- With history of interstitial lung disease, non-infectious pneumonitis or uncontrolled lung diseases including pulmonary fibrosis, acute lung diseases, etc.
- Severe chronic or active infections requiring systemic antibacterial, antifungal or antiviral therapy, including tuberculosis infection, etc.
- Prior allogeneic stem cell transplantation or organ transplantation.

Treatments

Dosing schedules for study treatment are provided in the table below.

Table 22: Selection and Timing of Dose for Each Patient

Study drug	Dose	Frequency of administration	Route of administration	Duration of treatment
Tislelizumab or placebo	200 mg	Day 1 of every 3 weeks	Intravenous infusion	3 to 4 cycles during the neoadjuvant phase
Cisplatin	75 mg/m^2			
Carboplatin	AUC of 5 mg/mL/min			
Pemetrexed	500 mg/m^2	Day 1 of every 3 weeks for nonsquamous		
Paclitaxel	175 mg/m^2	Day 1 of every 3 weeks for squamous		
Tislelizumab or placebo	400 mg	Day 1 of every 6 weeks		Up to 8 cycles during the adjuvant phase

Source: Section 5.2 of Study 315 Protocol Amendment Version 3.0 (Appendix 16.1.1).
Abbreviation: AUC, area under the concentration-time curve.

Administration of tislelizumab and chemotherapy continued until treatment completion, disease progression, unacceptable AE, death, or patient and/or investigator's decision to discontinue study treatment.

Tislelizumab

Tislelizumab 200 mg (or placebo) was administered on Day 1 of each 21-day cycle (once every 3 weeks) in the neoadjuvant phase, while in the adjuvant phase, tislelizumab 400 mg (or placebo) was administered on Day 1 of each 42-day cycle (once every 6 weeks).

The infusion of the initial dose of tislelizumab 200 mg in the neoadjuvant phase was delivered over 60 minutes; if this was well tolerated, then the subsequent neoadjuvant infusions could be administered over 30 minutes.

The infusion of the initial dose of tislelizumab 400 mg in the adjuvant phase was delivered over a period of 90 minutes; if this was well tolerated, the second infusion could be administered over 60 minutes. If the second infusion was well tolerated, subsequent infusions could be administered over 30 minutes.

Matched Placebo

The matched placebo contained the same composition as the solution for the active drug (tislelizumab), except that no active drug (tislelizumab) was present in the formulation.

Chemotherapy Agents

Patients received treatment with platinum-based doublet chemotherapy during the neoadjuvant phase. The choice of platinum (cisplatin or carboplatin) was at the investigator's discretion.

Cisplatin 75 mg/m² (administered intravenously over 2 hours) or **carboplatin** AUC of 5 mg/mL/min (administered intravenously over 1 hour) was administered as an intravenous infusion on Day 1 of each 3-week cycle for 3 to 4 cycles. **Pemetrexed** 500 mg/m^2 (administered intravenously over 10 minutes for non-squamous) or **paclitaxel** 175 mg/m^2 (administered intravenously over 3 hours for squamous) was administered as an intravenous infusion on Day 1 of each 3-week cycle for 3 to 4 cycles.

Postoperative Radiotherapy

Although PORT cannot be recommended as the standard of care in all patients with completely resected Stage IIIA-N2 NSCLC, it is optional for patients with pathological N2+ disease after surgery at the investigator's discretion. Either PORT or another surgical procedure could be performed for patients with positive tumor margins before starting adjuvant treatment per standard of care. R0 resection should be confirmed by pathological evaluation after the other surgical procedure. PORT should be administered before adjuvant treatment. PORT should begin between 30 and 60 days after surgery and be in accordance with the American Society for Radiation Oncology recommended guidelines (Rodrigues et al 2015) or local guidelines. Adjuvant treatment should be administered between 7 and 30 days after the last scheduled PORT treatment, and patients should have recovered from any radiation-associated toxicities.

Objectives

Primary objectives

• To evaluate and compare **MPR rate assessed by Blinded Independent Pathology Review (BIPR)** in patients receiving tislelizumab plus platinum-based doublet chemotherapy versus patients receiving placebo plus platinum-based doublet chemotherapy as neoadjuvant treatment

• To evaluate and compare **EFS assessed by Blinded Independent Central Review (BICR)** in patients receiving tislelizumab plus platinum-based doublet chemotherapy as neoadjuvant treatment followed by tislelizumab as adjuvant treatment versus patients receiving placebo plus platinum-based doublet chemotherapy as neoadjuvant treatment followed by placebo as adjuvant treatment

Secondary objectives

Key secondary objective:

• To evaluate and compare **BIPR-assessed pCR rate** of neoadjuvant treatment with tislelizumab versus placebo plus platinum-based doublet chemotherapy

Other secondary objectives:

• To evaluate and compare **OS** of neoadjuvant treatment with tislelizumab plus platinum-based doublet chemotherapy followed by adjuvant tislelizumab versus neoadjuvant treatment with placebo plus platinum-based doublet chemotherapy followed by placebo

• To evaluate and compare **objective response rate (ORR)** of neoadjuvant treatment with tislelizumab versus placebo plus platinum-based doublet chemotherapy before surgery assessed by BICR and by investigator, respectively

• To evaluate and compare **BICR-assessed DFS** of adjuvant tislelizumab treatment versus placebo after R0 resection

• To evaluate and compare **investigator-assessed EFS** of neoadjuvant treatment with tislelizumab plus platinum-based doublet chemotherapy followed by adjuvant tislelizumab versus neoadjuvant treatment with placebo plus platinum-based doublet chemotherapy followed by adjuvant placebo

• To evaluate and compare the **safety and tolerability** of neoadjuvant treatment with tislelizumab plus platinum-based doublet chemotherapy followed by adjuvant tislelizumab versus neoadjuvant treatment with placebo plus platinum-based doublet chemotherapy followed by placebo by treatment-emergent adverse events

• To evaluate and compare **health-related quality of life (HRQoL)** of neoadjuvant treatment with tislelizumab plus platinum-based doublet chemotherapy followed by adjuvant tislelizumab versus neoadjuvant treatment with placebo plus platinum-based doublet chemotherapy followed by placebo

Exploratory Objectives

• To assess the **outcome of surgery**, including feasibility and rate of peri- and postoperative complications

• To characterize **pharmacokinetics (PK)** of tislelizumab in patients with resectable Stage II or IIIA NSCLC

• To evaluate host **immunogenicity** to tislelizumab by assessing antidrug antibodies (ADAs) against tislelizumab

• To evaluate correlations of PD-L1 expression and clinical efficacy

• To evaluate the association of potential tissue and blood-based biomarkers of tislelizumab with clinical efficacy, functional and resistance mechanisms, and patient prognosis

Outcomes/endpoints

Table 23: Definitions of endpoints in Study 315

Endpoints	Definitions in Study 315
MPR rate by BIPR	The proportion of patients with ≤ 10% residual viable tumour in the resected primary tumour and all resected lymph nodes after completion of neoadjuvant therapy
EFS by BICR	The time from randomisation until any of the following events, whichever occurs first: disease progression precluding surgery, local or distant recurrence assessed by BICR, or death due to any cause
pCR rate by BIPR	The proportion of patients with absence of residual tumour in the resected primary tumour and all resected lymph nodes after completion of neoadjuvant therapy as assessed by BIPR
OS	The time from the date of randomisation to the date of death due to any cause
ORR by BICR and by investigator	**The proportion of patients who had CR or PR before surgery as assessed by** BICR and by investigator per RECIST v1.1 in all randomised patients with measurable disease at baseline
DFS by BICR	The time from the start date of surgery with outcome R0 resection to local or distant recurrence (by BICR) or death due to any cause, whichever occurs first after surgery
EFS by the investigator	The time from randomisation until any of the following events, whichever occurs first: disease progression precluding surgery, local or distant recurrence assessed by investigator, or death due to any cause
HRQoL	Measured using 3 validated patient-reported outcome questionnaires: EORTC QLQ-LC13, EORTC QLQ-C30, and EQ-5D-5L, defined as changes in most relevant lung cancer symptoms (dyspnoea, dysphagia, coughing, chest pain, pain in the arm and shoulders, haemoptysis, peripheral neuropathy, and fatigue), global health status, and physical function

Biomarker

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

Sample size

Number of Patients: 453

The sample size calculation is driven by the number of events required to demonstrate the EFS superiority of Arm A to Arm B. Exponential distribution is assumed for EFS. The key assumptions of EFS, MPR, and pCR are as following, respectively:

Event-free survival (EFS):

- Median EFS of 30 months in Arm B.
- At a 1-sided α of 0.02, **80% power** to detect an **HR of 0.65**, corresponding to an improvement in median progression-free survival from 30 months to 46.2 months, in the EFS of Arm A versus Arm B comparison.
- One **EFS interim analysis** is planned when approximately **75% of the targeted EFS events** have occurred, with Lan-DeMets' alpha spending function approximation to the O'Brien Fleming boundary.

- Piecewise **EFS dropout pattern** is assumed, ie, **3.5% monthly for the neoadjuvant phase** that is assumed to last around 4.5 months from randomization and 5% annually for the adjuvant phase.

Major pathological response (MPR):

- At a 1-sided α of 0.005, ≥ 95% power to detect a 20% difference in MPR rate (40% versus 20%).

Pathological complete response (pCR):

- At a 1-sided α of 0.005, ≥ 95% power to detect a 15% difference in pCR rate (19% versus 4%).

In addition, a **randomization ratio of 1:1** was assumed. With these assumptions, a total of **184 EFS events** are required for the ITT Analysis Set for the final EFS analysis.

A total of 3 data cutoffs (DCO) were planned, assuming **450 patients** were to be enrolled over a 27-month period at a steady-state enrollment rate of 18 patients per month, the final analysis of MPR and pCR would occur at approximately 33 months after first patient being randomized, the interim analysis of EFS would occur at approximately 38 months when approximately 138 EFS events have been observed across all treatments, and the final analysis of EFS would occur at approximately 51 months after first patient being randomized when 184 EFS events have occurred.

The study was not sized to power OS, at final analysis of EFS, it was to be formally tested if the EFS, MPR and pCR testing were positive.

Randomisation

Eligible patients were randomised in a 1:1 ratio to 1 of the 2 arms, using the IRT system for this study by permuted block stratified randomization with stratification factors of disease stage (II versus IIIA), histology (squamous versus nonsquamous), and PD-L1 expression (≥ 1% versus < 1%/not evaluable/indeterminate). The choice of platinum (carboplatin versus cisplatin) was determined by the investigator before randomization.

Blinding (masking)

This is a randomized, double-blind, Phase 3 study. Patients were randomized to 1 of the 2 study arms in a double-blind fashion such that neither the investigator, nor the patient, medical or ancillary medical staff, the blinded sponsor staff nor its designees, know which drug (tislelizumab vs placebo) was being administered in addition to chemotherapy.

If MPR/pCR is positive, per sponsor decision, a separate unblinded team was responsible for MPR/pCR publication and heath authority consultation. The unblinded team had access to individual patient treatment assignment and had no interaction with blinded team. The blinded team had no individual patient treatment assignment and was responsible for ongoing clinical trial conduct and strategic oversight. The detail of data access of blinded and unblinded team were specified in MPR/pCR Final Analysis Data Integrity Protection Plan.

An IDMC performed regular safety monitoring and interim efficacy data review as well as ad hoc reviews based on new information, if applicable. The IDMC could recommend continuation, modification, or discontinuation of this study based on reported safety data. The IDMC reviewed

unblinded interim data and informed the sponsor whether the comparison of MPR succeeded and whether interim boundaries of EFS were met.

Analysis sets

The **ITT Analysis Set** includes all randomized patients. Patients were analyzed according to their randomized treatment arms. This was the **primary analysis set for all efficacy analyses**, including analyses of MPR, pCR, and EFS endpoints.

The **Safety Analysis Set** included all randomized patients who received ≥ 1 dose of any component of study drugs; it was the analysis set for the safety analyses. Patients were analyzed according to the actual treatment regimen received.

The **PK Analysis Set** included all patients who receive ≥ 1 dose of tislelizumab per the protocol, for whom any postbaseline PK data are available.

The **Immunogenicity Analysis Set** included all patients who received ≥ 1 dose of tislelizumab and for whom both baseline ADA and ≥ 1 postbaseline ADA results are available.

Statistical methods

Efficacy analyses (incl. censoring)

MPR as assessed by the BIPR (primary efficacy endpoint)

MPR rate assessed by the BIPR is defined as the proportion of patients with ≤ 10% residual viable tumor in the resected primary tumor and all resected lymph nodes after completion of neoadjuvant therapy as assessed by BIPR. Patients who do not receive surgical resection will be considered as nonresponders in analysis.

MPR per BIPR was planned to be compared between tislelizumab combined with platinum-based doublet chemotherapy (Arm A) and placebo combined with platinum-based doublet chemotherapy (Arm B) as follows:

The null hypothesis to be tested was:

$$H0: \text{MPR in Arm A} \leq \text{MPR in Arm B}$$

Against the alternative hypothesis:

$$Ha: \text{MPR in Arm A} > \text{MPR in Arm B}$$

MPR rate per the BIPR was planned to be computed in each arm with the exact 95% CI using Clopper-Pearson method. The odds ratio between Arm A and Arm B stratified by histology, disease stage, and PD-L1 expression was planned to be provided along with the 95% CI using Cochran-Mantel-Haenszel method.

The primary analysis of MPR was planned after last operable patient having valid pathological result.

EFS as assessed by the BICR (primary efficacy endpoint)

EFS assessed by the BICR is defined as the time from randomization until any of the following events, whichever occurs first:

- disease progression precluding surgery,

- local or distant recurrence assessed by BICR, or
- death due to any cause.

The following additional EFS derivation rules were defined:

- A disease progression not reaching the RECIST v1.1 criteria by BICR but still precludes surgery (progressive disease or tumor unresectability assessed by investigator)
- Patients who do not undergo surgery due to reasons other than progressive disease and tumor unresectability will be considered to have an event of RECIST v1.1 defined progression by BICR or death.
- Patients who die without a progression/disease recurrence will be considered to have experienced an event on the date of their death.
- Patients with post-surgery recurrence/progression per RECIST 1.1 by BICR

The following patients were censored:

- A pre-surgical progression (even if reaching the RECIST 1.1 criteria by BICR) which does not preclude surgery is not considered as an event.
- Patients who did not report progression/recurrence of disease or die will be censored on the date of their last evaluable tumor assessment.
- Patients who did not have any on-study tumor assessment and did not die will be censored on the date they were randomized.
- Patients who started any subsequent anticancer therapy outside of the protocol-specified adjuvant therapy without a prior reported progression/recurrence will be censored at the last evaluable tumor assessment before initiation of the subsequent anticancer therapy.

Patient missed more than 1 tumor assessment before disease progression, local or distant recurrence or death, its EFS will be censored at the date of last adequate disease assessment before the missing tumour assessments.

EFS per BICR was planned to be compared between Arm A and Arm B as follows:

The null hypothesis to be tested was:

$$H0: \text{EFS in Arm A} \leq \text{EFS in Arm B}$$

Against the alternative hypothesis:

$$Ha: \text{EFS in Arm A} > \text{EFS in Arm B}$$

The p-values from a stratified log-rank test were to be presented using stratification factors in the IRT at randomization. The HR for EFS for Arm A versus Arm B were to be estimated using a stratified Cox regression model. The 95% CI for the HR were to be provided. Unstratified analysis were also to be presented. Kaplan-Meier methodology was to be used to estimate median EFS for each treatment arm, and a Kaplan-Meier curve was to be constructed to provide a visual description of the difference among arms.

<u>pCR as assessed by BIPR (key secondary endpoint)</u>

The pCR rate by BIPR is defined as the proportion of patients with absence of residual tumor in the resected primary tumor and all resected lymph nodes after completion of neoadjuvant therapy. Patients who do not receive surgical resection will be considered as nonresponders in analysis. After success of MPR testing, pCR per BIPR was to be compared between tislelizumab combined with

platinum-based doublet chemotherapy (Arm A) and placebo combined with platinum-based doublet chemotherapy (Arm B), using Cochran-Mantel-Haenszel chi-square test methodology. Similar methodology used to evaluate MPR per the BIPR was to be applied to analyze pCR per BIPR.

OS (secondary endpoint)

OS is defined as the time from the date of randomization to the date of death due to any cause. Data for patients who are not reported as having died at the time of analysis will be censored at the date last known to be alive. Data for patients who do not have postbaseline information will be censored at the date of randomization. OS distribution was to be estimated using Kaplan-Meier method. Comparison of OS between Arm A versus Arm B was to be tested at the earliest data cutoff when MPR, pCR, and EFS tests are statistically significant using the stratified log-rank test.

The null hypothesis to be tested was:

$$H0 : \text{OS of Arm A} \leq \text{OS of Arm B}$$

against the alternative:

$$Ha : \text{OS of Arm A} > \text{OS of Arm B}$$

After statistical significance of MPR, pCR and EFS testing, the null hypothesis of OS was to be tested using a log-rank test stratified by histology, disease stage, and PD-L1 expression using stratification factors with values as recorded in IRT. The test against H0 was to be controlled at a 1- sided type one error of 0.025. An interim OS analysis was to be performed at the interim EFS analysis with Haybittle-Peto p-value boundary at 0.0001. The final OS analysis was to occur at EFS final analysis.

Multiplicity

The overall type I error was planned to be strongly controlled at a 1-sided α of 0.025. Initially, the significance level was assigned as follows:

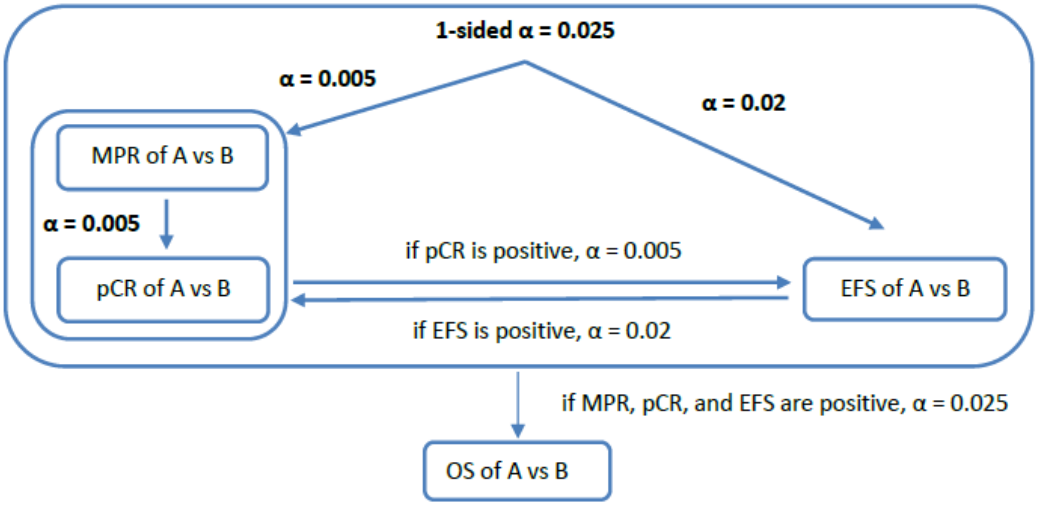
- α of 0.005 was assigned to the primary hypothesis testing of MPR of A versus B
- α of 0.02 was assigned to the primary hypothesis testing of EFS of A versus B.

The following recycling scheme was implemented:

- If MPR in the comparison of A versus B was statistically significant at initial assigned α of 0.005, then the α of 0.005 was to be passed on to the hypothesis test of pCR in the comparison of A versus B;
- if pCR comparison was statistically significant, then the α of 0.005 was to be passed on to the hypothesis test of EFS in the comparison of A versus B, and EFS in that comparison was to be tested at an overall 1-sided α of 0.025.

If the null hypothesis of MPR, pCR, and EFS were rejected, OS in the ITT Analysis Set was to be sequentially tested with a re-cycled α of 0.025. The method of α allocation (Burman et al 2009), including possible α recycling, is in Figure 3 of the protocol as below.

Figure 50: Type I Error Control Scheme



α-recycling: if MPR results positive in A versus B comparison, the alpha = 0.005 can be passed on to hypothesis testing in pCR between A versus B; if pCR results positive in A versus B, the alpha = 0.005 can be passed to hypothesis testing in EFS of A versus B and thus can be tested under alpha = 0.025; the same applies the other way around; if MPR, pCR, and EFS results are positive in A versus B, the alpha = 0.025 can be passed to hypothesis testing in OS of A versus B.

Interim analyses

This study included 2 interim analyses.

The final analysis of MPR and pCR per BIPR as one of the interim analyses of the study was planned after surgery of the last patient receiving operation.

A subsequent interim efficacy analysis of EFS was to be performed after approximately 138 EFS events (75% of the target number of approximately 184 EFS events) were observed, which was expected to occur at approximately 38 months.

An independent statistical review was to be conducted to perform MPR and pCR analysis and to determine if the required number of events have occurred.

The interim boundary was based on Lan-DeMets O'Brien-Fleming approximation spending function. The interim and final analysis and stopping boundaries for EFS are summarized in Tables below for the scenario where alpha is not recycled and where alpha is recycled.

When the comparison of pCR was significant, the EFS hypothesis may be tested at recycled α = 0.025. With recycled α, the study had approximately 58% success rate at interim analysis under approximately HR threshold of 0.671, and 82% success rate at final analysis under approximately HR threshold of 0.743.

Table 24: Analysis timing and stopping boundaries for EFS at 1-Sided α = 0.02 (initial alpha argument)

Type of Analysis	Time (months)	Number of Events	Testing Boundary	
			p-value Boundary	Approximate Hazard Ratio Threshold
Interim Analysis	38	138	0.007	0.659
Final Analysis	51	184	0.018	0.734

Abbreviations: EFS, event-free survival; MPR, major pathological response

Note: The time for interim and final analysis is based on protocol-defined enrolment and EFS assumption. The actual analysis time will depend on when to observed enough EFS events that required for interim and final analysis.

Table 25: Analysis timing and stopping boundaries for EFS at 1-Sided α = 0.025 (alpha recycled after pCR is succeed)

Type of Analysis	Time (months)	Number of Events	Testing Boundary	
			p-value Boundary	Approximate Hazard Ratio Threshold
Interim Analysis	38	138	0.01	0.671
Final Analysis	51	184	0.022	0.743

Abbreviations: EFS, event-free survival; MPR, major pathological response
Note: The time for interim and final analysis is based on protocol-defined enrollment and EFS assumption. The actual analysis time will depend on when to observed enough EFS events that required for interim and final analysis.

Source: Protocol Amendment v.4.0

An interim OS analysis was to be performed at the interim EFS analysis with Haybittle-Peto p-value boundary at 0.0001. The final OS analysis occured at EFS final analysis.

Changes to the statistical methods

- After primary analysis of MPR/pCR, nonsubstantial changes on viable tumor percentage and lymph node assessment were found during data quality monitoring. To assess the impact of the data changes, post hoc analyses were performed for MPR and pCR in the ITT Analysis Set (refer to Appendix 16.1.15 for details).
- Given that patients who had experienced treatment-emergent adverse event assessed as postoperative complication were all included in the Safety Analysis Set (Surgery), the summary of treatment-emergent adverse events assessed as postoperative complication by SOC, PT, and Worst Grade was performed for the overall phase in the Safety Analysis Set (Surgery) but not in the Safety Analysis Set (Overall).

Results

Participant flow

Figure 51: BGB-A317-315 Study Profile

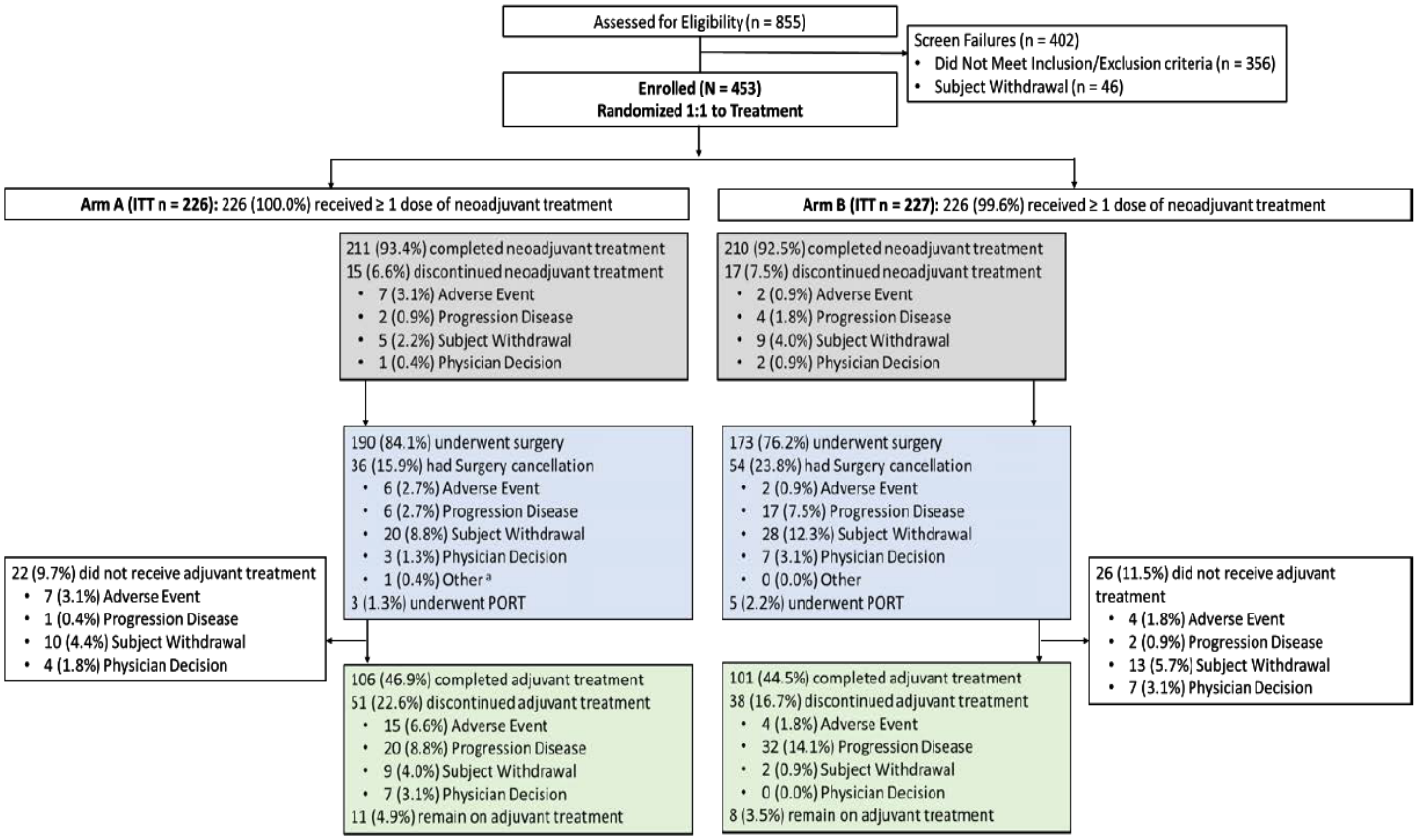


Table 26: Patient Disposition and Reasons for Discontinuation - Overall Phase (ITT Analysis Set)

	Arm A (N = 226)	Arm B (N = 227)	Total (N = 453)
Overall			
Patients Randomized, n (%)	226 (100.0)	227 (100.0)	453 (100.0)
Patients Randomized, but Not Treated, n (%)	0 (0.0)	1 (0.4)	1 (0.2)
Patients Treated, n (%)	226 (100.0)	226 (99.6)	452 (99.8)
Patients Discontinued From Study, n (%)	41 (18.1)	68 (30.0)	109 (24.1)
Reason for Discontinuation			
Subject Withdrawal	8 (3.5)	22 (9.7)	30 (6.6)
Lost to Follow-up	2 (0.9)	0 (0.0)	2 (0.4)
Death	31 (13.7)	46 (20.3)	77 (17.0)
Related to COVID-19 [a]	2 (0.9)	1 (0.4)	3 (0.7)
Patients Remained in Study, n (%)	185 (81.9)	159 (70.0)	344 (75.9)
Phase Status of Neoadjuvant/Surgery/Adjuvant Phase, n (%)			
Treatment Completed [b]	106 (46.9)	101 (44.5)	207 (45.7)
Completed/Completed/Completed	104 (46.0)	101 (44.5)	205 (45.3)
Discontinued/Completed/Completed	2 (0.9)	0 (0.0)	2 (0.4)
Treatment Ongoing	11 (4.9)	8 (3.5)	19 (4.2)
Completed/Completed/Ongoing	11 (4.9)	8 (3.5)	19 (4.2)

	Arm A (N = 226)	Arm B (N = 227)	Total (N = 453)
Adjuvant Treatment Discontinued	73 (32.3)	64 (28.2)	137 (30.2)
Completed/Completed/Discontinued	71 (31.4)	64 (28.2)	135 (29.8)
Discontinued/Completed/Discontinued	2 (0.9)	0 (0.0)	2 (0.4)
Surgery Cancellation	36 (15.9)	54 (23.8)	90 (19.9)
Completed/Cancelled/Not Applicable	25 (11.1)	37 (16.3)	62 (13.7)
Discontinued/Cancelled/Not Applicable	11 (4.9)	17 (7.5)	28 (6.2)
Study Follow-up Time (Months)			
n	226	227	453
Mean (SD)	22.88 (8.749)	20.54 (9.409)	21.71 (9.151)
Median	23.15	20.90	21.98
Minimum Follow-up Time (Months)	11.7	11.7	11.7

Abbreviations: Arm A, tisle (200 mg Q3W) + chemo → surgery → tisle (400 mg Q6W); Arm B, placebo + chemo → surgery → placebo.
Study follow-up time is defined as the time from the randomization date to the death date or end of study date (whichever occurs first) for patients discontinued from the study, or the database cutoff date for ongoing patients.
Minimum follow-up time is defined as a difference between the date of analysis cutoff and the date of last patient randomized.
a Death related to COVID-19 included COVID-19 infection and suspected COVID-19.
b Completion of neoadjuvant treatment is based on whether patients received 3 to 4 cycles of neoadjuvant treatments; completion of adjuvant treatment is based on whether patients received 8 cycles of adjuvant treatments; patients completed overall treatment include patients who completed planned surgery after neoadjuvant treatment and completed adjuvant treatments.

Recruitment

This study is currently being conducted at 50 study centers in China.

The first patient enrolled in Study 315 was randomized on 08 June 2020. The randomisation of the last patient occurred on 31 August 2022.

Study End Date (last patient completed): Ongoing

Conduct of the study

Protocol amendments

The original protocol for this study was dated 09 August 2019. The protocol was amended 3 times before the data cut-off date for this CSR.

Amendment Version 1.0 (10 November 2019)
No patient was randomized at the time of protocol amendment finalization.

- Added PD-L1 expression as one of the stratification factors and adjusted the subgroup analysis accordingly
- Specified analysis of PD-L1 expression as predictive biomarker for efficacy
- Added tumour assessment procedure for patients with EOT before surgery, i.e. tumor assessment every 6 weeks per RECIST v1.1 until any of the following events, whichever occurs first: radiographic disease progression assessed by BICR according to RECIST v1.1, death or begin of another systemic anticancer treatment.
- Rescheduled tumor assessment from every 4 months to every 3 months after surgery in the first two years and the time window accordingly

Amendment Version 2.0 (25 November 2021)
N=319 patients were randomized at the time of protocol amendment finalization.

- Revised to increase the sample size from 380 to 450 based on the updated assumption of dropout pattern:
    - Piecewise EFS dropout pattern is assumed, ie, 3.5% monthly for the neoadjuvant phase that is assumed to last around 4.5 months from randomization and 5% annually for the adjuvant phase.
- Clarification of tumour tissues for PD-L1 test and the definition for PD-L1 positive, negative, and not evaluable/ indeterminate
- Clarification of follow-up actions for patients who discontinue neoadjuvant treatment, i.e. these patients will remain eligible for all on-study treatments; patients who do not proceed to surgery may receive other anticancer treatment and will remain in the study for routine tumour assessment every 6 weeks since last tumour assessment until disease progression
- Added the sequential test for pCR and OS
    - After success of MPR testing, pCR per BIPR will be compared between tislelizumab combined with platinum-based doublet chemotherapy (Arm A) and placebo combined with platinum-based doublet chemotherapy (Arm B), using Cochran-Mantel-Haenszel chi-square test methodology; if pCR testing is statistically significant, the α of 0.005 will be passed on to the hypothesis test of EFS
    - Comparison of OS between Arm A versus Arm B will be tested at the earliest data cutoff when MPR, pCR, and EFS tests are statistically significant using the stratified log-rank test
    - If MPR, pCR, and EFS tests are all statistically significant, the α of 0.025 will be sequentially passed on to the hypothesis test of OS in the comparison of A versus B.

Amendment Version 3.0 (28 December 2022)
N= 453 patients were randomized at the time of protocol amendment finalization.

- Updated EFS definition to clarify that any progression although not reaching RECIST v1.1 criteria, but still precluding surgery is an EFS event (not assessed by BICR)
- Updated EFS definition to clarify that patients who do not undergo surgery due to reasons other than progressive disease and tumour unresectability will be considered to have an event of RECIST v1.1 defined progression by BICR or death
- Clarification of the need to record such patient population that is solely assessed by investigator
- Revised to use stratification factors collected in IRT for primary efficacy analysis per ITT principal

Amendment Version 4.0 (26 Jan 2024)
N= 453 patients were randomized at the time of protocol amendment finalization.

- The primary purpose of Amendment 4.0 is to specify the time of early unblinding to help investigators manage the study patients (eg, know the whole picture of disease condition and make decision of subsequent treatment):
    - The investigators, site personnel, patients, and sponsor will be unblinded to the treatment arms of the study 30 days after the last patient completes or discontinues from the last study treatment. Visits are required to be performed on schedule regardless of whether the patient has been unblinded.

Protocol deviations

Table 27: Summary of Important Protocol Deviations (ITT Analysis Set)

Category Subcategory	Arm A (N = 226) n (%)	Arm B (N = 227) n (%)	Total (N = 453) n (%)
Patients With Any Important Protocol Deviation	65 (28.8)	53 (23.3)	118 (26.0)
Protocol Compliance	59 (26.1)	43 (18.9)	102 (22.5)
Study Assessments & Procedures	25 (11.1)	12 (5.3)	37 (8.2)
Prohibitive Medication or Treatment	19 (8.4)	17 (7.5)	36 (7.9)
Randomization / Stratification	11 (4.9)	8 (3.5)	19 (4.2)
Inclusion / Exclusion	5 (2.2)	6 (2.6)	11 (2.4)
Visit Compliance	4 (1.8)	1 (0.4)	5 (1.1)
Sample Management	0 (0.0)	3 (1.3)	3 (0.7)
Maintaining Study Blind	2 (0.9)	0 (0.0)	2 (0.4)
Safety	5 (2.2)	9 (4.0)	14 (3.1)
Safety Reporting (Sponsor, IRB/IEC)	5 (2.2)	8 (3.5)	13 (2.9)
AE/SAE Follow-up	0 (0.0)	1 (0.4)	1 (0.2)
Investigational Product	6 (2.7)	3 (1.3)	9 (2.0)
Dosing & Administration	3 (1.3)	2 (0.9)	5 (1.1)
Dosing Compliance	2 (0.9)	0 (0.0)	2 (0.4)
Storage & Accountability	1 (0.4)	1 (0.4)	2 (0.4)
Informed Consent	0 (0.0)	2 (0.9)	2 (0.4)
Consenting Process	0 (0.0)	1 (0.4)	1 (0.2)
Timing of Consent	0 (0.0)	1 (0.4)	1 (0.2)
Others	1 (0.4)	0 (0.0)	1 (0.2)
Others	1 (0.4)	0 (0.0)	1 (0.2)

Abbreviations: Arm A, tisle (200 mg Q3W) + chemo → surgery → tisle (400 mg Q6W); Arm B, placebo + chemo → surgery → placebo.
Patients with multiple important protocol deviations in each category/subcategory were counted only once at the category/subcategory level.
Events were sorted by decreasing frequency of category and subcategory in the "Total" column.

Table 28: Summary of Important Protocol Deviations Related to COVID-19 – ITT Analysis Set

Category Subcategory	Arm A (N = 226) n (%)	Arm B (N = 227) n (%)	Total (N = 453) n (%)
Patients with Any Important Protocol Deviation Related to COVID-19	20 (8.8)	9 (4.0)	29 (6.4)
Protocol Compliance	19 (8.4)	9 (4.0)	28 (6.2)
Study Assessments & Procedures	10 (4.4)	4 (1.8)	14 (3.1)
Randomization / Stratification	5 (2.2)	4 (1.8)	9 (2.0)
Visit Compliance	3 (1.3)	0 (0.0)	3 (0.7)
Prohibitive Medication or Treatment	1 (0.4)	0 (0.0)	1 (0.2)
Sample Management	0 (0.0)	1 (0.4)	1 (0.2)
Investigational Product	1 (0.4)	0 (0.0)	1 (0.2)
Dosing & Administration	1 (0.4)	0 (0.0)	1 (0.2)

Baseline data

Table 29: Demographic and Baseline Characteristics (ITT Analysis Set)

Characteristic	Arm A (N = 226)	Arm B (N = 227)	Total (N = 453)
Age (Years)			

Characteristic	Arm A (N = 226)	Arm B (N = 227)	Total (N = 453)
n	226	227	453
Mean (SD)	61.6 (7.61)	61.7 (8.05)	61.6 (7.83)
Median	62.0	63.0	62.0
Age Group, n (%)			
< 65 Years	143 (63.3)	129 (56.8)	272 (60.0)
>= 65 Years	83 (36.7)	98 (43.2)	181 (40.0)
Sex, n (%)			
Male	205 (90.7)	205 (90.3)	410 (90.5)
Female	21 (9.3)	22 (9.7)	43 (9.5)
Weight (kg)			
n	224	227	451
Mean (SD)	66.30 (10.514)	65.48 (10.800)	65.89 (10.655)
Median	65.50	65.00	65.00
BMI (kg/m2)			
n	224	227	451
Mean (SD)	23.63 (3.175)	23.31 (2.815)	23.47 (3.000)
Median	23.44	23.15	23.26
ECOG Performance Status, n (%)			
0	142 (62.8)	154 (67.8)	296 (65.3)
1	83 (36.7)	73 (32.2)	156 (34.4)
Missing	1 (0.4)	0 (0.0)	1 (0.2)
Smoking Status, n (%)			
Current	43 (19.0)	52 (22.9)	95 (21.0)
Former	150 (66.4)	138 (60.8)	288 (63.6)
Never	33 (14.6)	37 (16.3)	70 (15.5)
Histology From CRF, n (%)			
Squamous	179 (79.2)	175 (77.1)	354 (78.1)
Nonsquamous	45 (19.9)	50 (22.0)	95 (21.0)
Other [a]	2 (0.9)	2 (0.9)	4 (0.9)
Disease Stage From CRF, n (%) [b]			
IB	1 (0.4)	0 (0.0)	1 (0.2)
II	92 (40.7)	91 (40.1)	183 (40.4)
IIIA	132 (58.4)	133 (58.6)	265 (58.5)
IIIB	1 (0.4)	3 (1.3)	4 (0.9)
PD-L1 Expression From Central Lab, n (%)			
< 1%	89 (39.4)	84 (37.0)	173 (38.2)
>= 1%	130 (57.5)	132 (58.1)	262 (57.8)
1-49%	59 (26.1)	70 (30.8)	129 (28.5)
>= 50%	71 (31.4)	62 (27.3)	133 (29.4)
Not Evaluable/Indeterminate	7 (3.1)	11 (4.8)	18 (4.0)
EGFR Mutation Status at Randomization, n (%)			
Positive	0 (0.0)	3 (1.3)	3 (0.7)
Negative	62 (27.4)	66 (29.1)	128 (28.3)
Unknown/not done	164 (72.6)	158 (69.6)	322 (71.1)
ALK Rearrangement Status at Randomization, n (%)			
Negative	30 (13.3)	37 (16.3)	67 (14.8)
Unknown/not done	196 (86.7)	190 (83.7)	386 (85.2)

Source: ADSL, ADBASE. Data cutoff: 21AUG2023. Data extraction: 18SEP2023.
Abbreviations: Arm A, tisle (200 mg Q3W) + chemo → surgery → tisle (400 mg Q6W); Arm B, placebo + chemo → surgery → placebo; BMI, body mass index.
[a] Patients with mix histology were categorized into "Other" in CRF.
[b] Patients with stage IB and IIIB were enrolled mistakenly with protocol deviation reported.

Table 30: Summary of Post-Treatment Anticancer Therapy - ITT Analysis Set

	Arm A (N = 226) n (%)	Arm B (N = 227) n (%)	Total (N = 453) n (%)
Patients With Any Post-Treatment Anticancer Therapy	35 (15.5)	56 (24.7)	91 (20.1)
Immunotherapy Regimen	21 (9.3)	30 (13.2)	51 (11.3)
Chemotherapy Regimen	12 (5.3)	14 (6.2)	26 (5.7)
Chemoradiotherapy Regimen	4 (1.8)	8 (3.5)	12 (2.6)
Target Therapy	3 (1.3)	10 (4.4)	13 (2.9)
Other Therapies	0 (0.0)	1 (0.4)	1 (0.2)
First Post-Treatment Systemic Anticancer Therapy			
Immunotherapy Regimen	20 (8.8)	27 (11.9)	47 (10.4)
Chemotherapy Regimen	7 (3.1)	12 (5.3)	19 (4.2)
Chemoradiotherapy Regimen	4 (1.8)	7 (3.1)	11 (2.4)
Target Therapy	2 (0.9)	8 (3.5)	10 (2.2)
Other Therapies	0 (0.0)	1 (0.4)	1 (0.2)
Second Post-Treatment Systemic Anticancer Therapy			
Immunotherapy Regimen	1 (0.4)	4 (1.8)	5 (1.1)
Chemotherapy Regimen	2 (0.9)	3 (1.3)	5 (1.1)
Target Therapy	1 (0.4)	2 (0.9)	3 (0.7)
Third Post-Treatment Systemic Anticancer Therapy			
Immunotherapy Regimen	0 (0.0)	1 (0.4)	1 (0.2)
Chemotherapy Regimen	1 (0.4)	2 (0.9)	3 (0.7)
Fourth Post-Treatment Systemic Anticancer Therapy			
Chemotherapy Regimen	1 (0.4)	0 (0.0)	1 (0.2)

Source: ADSL, ADCM. Data cutoff: 21AUG2023. Data extraction: 18SEP2023.
Abbreviations: Arm A, tisle (200 mg Q3W) + chemo → surgery → tisle (400 mg Q6W); Arm B, placebo + chemo → surgery → placebo.
Medication terms were coded using WHODRUG GLOBAL B3 March 1 2023.

Numbers analysed

Table 31: Analysis Sets (ITT Analysis Set)

Analysis Set	Arm A (N = 226) n (%)	Arm B (N = 227) n (%)	Total (N = 453) n (%)
Intent-to-Treat Analysis Set [a]	226 (100.0)	227 (100.0)	453 (100.0)
Safety Analysis Set (Overall) [b]	226 (100.0)	226 (99.6)	452 (99.8)
Safety Analysis Set (Neoadjuvant) [c]	226 (100.0)	226 (99.6)	452 (99.8)
Safety Analysis Set (Surgery) [d]	190 (84.1)	173 (76.2)	363 (80.1)
Safety Analysis Set (Adjuvant) [e]	168 (74.3)	147 (64.8)	315 (69.5)
Pharmacokinetic Analysis Set [f]	226 (100.0)	0 (0.0)	226 (49.9)
ADA Analysis Set [g]	219 (96.9)	0 (0.0)	219 (48.3)

Source: ADSL. Data cutoff: 21AUG2023. Data extraction: 18SEP2023.
Abbreviations: Arm A, tisle (200 mg Q3W) + chemo → surgery → tisle (400 mg Q6W); Arm B, placebo + chemo → surgery → placebo; ADA, antidrug antibody.
[a] The Intent-to-Treat (ITT) analysis set consists of all the patients who were randomized to a treatment arm.
[b] The safety analysis set (overall) includes all patients who were randomized and received at least one dose of any study drugs.
[c] The safety analysis set (neoadjuvant) includes all patients who received at least 1 dose of any component of study drugs in neoadjuvant phase.
[d] The safety analysis set (surgery) includes all patients who received surgery for curative intent in surgery phase.
[e] The safety analysis set (adjuvant) includes all patients who received at least 1 dose of any component of study drugs in adjuvant phase.
[f] The Pharmacokinetic analysis set consists of all the patients who received any dose of the tislelizumab and for whom any postbaseline PK data are available.
[g] The ADA Analysis Set includes all patients who received at least 1 dose of tislelizumab for whom both baseline ADA and at least 1 post-baseline ADA results are available.

Outcomes and estimation

Primary Efficacy Endpoints

Major Pathological Response (MPR) Rate by Blinded Independent Pathology Review (data cutoff: 20 Feb 2023)

Table 32: Table Analysis of MPR by Blinded Independent Pathology Review (ITT Analysis Set)

Response Category	Arm A (N = 226)	Arm B (N = 227)
MPR, n (%)	127 (56.2)	34 (15.0)
95% CI [a]	(49.5, 62.8)	(10.6, 20.3)
Odds Ratio (95% CI) [b]	7.49 (4.75, 11.82)	--
Difference, % (95% CI) [c]	41.1 (33.2, 49.1)	--
1-Sided p-Value [d]	< 0.0001	--

Data cutoff: 20FEB2023. Data extraction: 24MAR2023
Patients without surgery or pathological results were considered as non-responders.
a The 95% CI was estimated using the Clopper-Pearson method.
b Mantel-Haenszel common odds ratio was estimated along with its 95% CI constructed by a normal approximation of log odds ratio and the Robins, Breslow, and Greenland variance estimate stratified by histology (squamous vs non-squamous), disease stage (stage II vs stage IIIA) and PD-L1 expression (<1%/not evaluable/indeterminate vs >=1%) from Interactive Response Technology.
c Mantel-Haenszel common risk difference was estimated along with its 95% CIs constructed by a normal approximation and Sato's variance estimator stratified by histology (squamous vs non-squamous), disease stage (stage II vs stage IIIA) and PD-L1 expression (<1%/not evaluable/indeterminate vs >=1%) from Interactive Response Technology.
d The p-value was obtained using the Cochran-Mantel-Haenszel method stratified by histology (squamous vs non-squamous), disease stage (stage II vs stage IIIA) and PD-L1 expression (<1%/not evaluable/indeterminate vs >=1%) from Interactive Response Technology.

Event-Free Survival by Blinded Independent Central Review
EFS Interim Analysis (data cutoff: 21 Aug 2023)

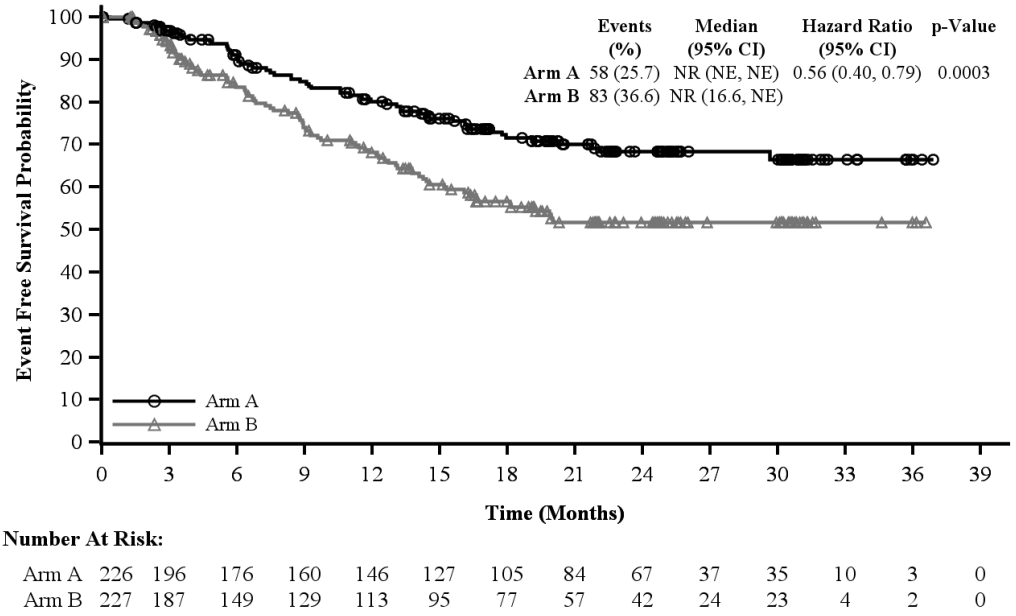
Table 33: Analysis of Event-Free Survival by Blinded Independent Central Review (ITT)

	Arm A (N = 226)	Arm B (N = 227)
Event-Free Survival		
Events, n (%)	58 (25.7)	83 (36.6)
Progressive Disease Precluding Study Surgery [a]	7 (3.1)	20 (8.8)
Progressive Disease [b]	41 (18.1)	56 (24.7)
Death	10 (4.4)	7 (3.1)
Censored, n (%)	168 (74.3)	144 (63.4)
No Baseline Assessment	5 (2.2)	5 (2.2)
No Postbaseline Assessment	0 (0.0)	1 (0.4)
No Post Surgery Assessment	6 (2.7)	13 (5.7)
New Anticancer Therapy Before Progression/Recurrence/Death	13 (5.8)	18 (7.9)
Progression/Recurrence/Death After > 1 Missed Assessment	2 (0.9)	4 (1.8)
Lost to Follow-up	1 (0.4)	0 (0.0)
Subject Withdrawal	3 (1.3)	6 (2.6)
Ongoing Without Events	138 (61.1)	97 (42.7)
Stratified Hazard Ratio (95% CI) [c]	0.56 (0.40, 0.79)	--
1-Sided Stratified p-Value [d]	0.0003	--
Event-Free Survival (Months) [e]		

	Arm A (N = 226)	Arm B (N = 227)
Median (95% CI)	NR (NE, NE)	NR (16.6, NE)
Q1 (95% CI)	16.1 (11.5, 22.1)	8.9 (6.7, 11.6)
Q3 (95% CI)	NR (NE, NE)	NR (NE, NE)
Event-Free Survival Rate at, % (95% CI) [f]		
3 Months	96.7 (93.3, 98.4)	93.8 (89.5, 96.3)
6 Months	91.2 (86.3, 94.3)	83.6 (77.6, 88.1)
9 Months	84.9 (79.0, 89.2)	74.0 (67.0, 79.7)
12 Months	80.0 (73.7, 85.0)	68.1 (60.8, 74.4)
24 Months	68.3 (60.8, 74.8)	51.8 (43.8, 59.2)
36 Months	66.5 (58.2, 73.5)	51.8 (43.8, 59.2)
Follow-up Time (Months) [g]		
Median (95% CI)	22.1 (19.8, 24.6)	19.9 (18.9, 22.0)
Min, Max	0.0, 36.9	0.0, 36.6

Data cutoff: 21AUG2023. Data extraction: 18SEP2023.
Abbreviations: Arm A, tisle (200 mg Q3W) + chemo → surgery → tisle (400 mg Q6W); Arm B, placebo + chemo → surgery → placebo.
a Progressive disease precluding surgery included radiographic disease progression per RECIST 1.1 precluding surgery or a disease progression not reaching the RECIST 1.1 criteria but which still precludes surgery (reason for no surgery is progressive disease or tumor unresectable).
b Progressive disease included patients who did not receive surgery but had disease progression after presurgical visit and patients receiving surgery with local or distant recurrence.
c Hazard ratio and 95% CIs were estimated using a Cox regression model stratified by histology (squamous vs non-squamous), disease stage (stage II vs stage IIIA) and PD-L1 expression (<1%/not evaluable/indeterminate vs >=1%) from Interactive Response Technology.
d The p-value was calculated using a log-rank test stratified by histology (squamous vs non-squamous), disease stage (stage II vs stage IIIA) and PD-L1 expression (<1%/not evaluable/indeterminate vs >=1%) from Interactive Response Technology.
e Medians and other quartiles were estimated by the Kaplan-Meier method with 95% CIs estimated using the Brookmeyer and Crowley method with log-log transformation.
f Event-free rates were estimated using the Kaplan-Meier method with 95% CIs estimated using the Greenwood formula.
g Median was estimated by the reverse Kaplan-Meier method with 95% CIs estimated using the Brookmeyer and Crowley method.

Figure 52: KM Plot for Event-Free Survival by BICR (ITT Analysis Set)



Data cutoff: 21AUG2023. Data extraction: 18SEP2023.
Abbreviations: Arm A, tisle (200 mg Q3W) + chemo → surgery → tisle (400 mg Q6W); Arm B, placebo + chemo → surgery → placebo.
Hazard ratio and 95% CIs were estimated using a Cox regression model stratified by histology (squamous vs non-squamous), disease stage (stage II vs stage IIIA) and PD-L1 expression (<1%/not evaluable/indeterminate vs >=1%) from Interactive Response Technology.
The p-value was calculated using a log-rank test stratified by histology (squamous vs non-squamous), disease stage (stage II vs stage IIIA) and PD-L1 expression (<1%/not evaluable/indeterminate vs >=1%) from Interactive Response Technology.

Final Analysis (data cutoff: 07 Mar 2025)

Table 34: Analysis of Event-Free Survival by Blinded Independent Central Review (ITT)

	Arm A (N = 226)	**Arm B (N = 227)**
Event-Free Survival		
Events, n (%)	72 (31.9)	98 (43.2)
Progressive Disease Precluding Study Surgery [a]	7 (3.1)	20 (8.8)
Progressive Disease [b]	55 (24.3)	71 (31.3)
Death	10 (4.4)	7 (3.1)
Censored, n (%)	154 (68.1)	129 (56.8)
No Baseline Assessment	5 (2.2)	5 (2.2)
No Postbaseline Assessment	0 (0.0)	1 (0.4)
No Post Surgery Assessment	5 (2.2)	13 (5.7)
New Anticancer Therapy Before Progression/Recurrence/Death	13 (5.8)	21 (9.3)
Progression/Recurrence/Death After > 1 Missed Assessment	7 (3.1)	4 (1.8)
Lost to Follow-up	1 (0.4)	0 (0.0)
Subject Withdrawal	4 (1.8)	6 (2.6)
Ongoing Without Events	119 (52.7)	79 (34.8)
Stratified Hazard Ratio (95% CI) [c]	0.58 (0.43, 0.79)	--
Event-Free Survival (Months) [d]		
Median (95% CI)	NR (50.3, NE)	30.6 (16.6, 45.3)
Q1 (95% CI)	16.2 (11.5, 22.1)	8.9 (6.5, 11.2)
Q3 (95% CI)	NR (NE, NE)	NR (NE, NE)

	Arm A (N = 226)	Arm B (N = 227)
Event-Free Survival Rate at, % (95% CI) [e]		
24 Months	67.7 (60.6, 73.9)	52.0 (44.4, 59.0)
36 Months	64.7 (57.4, 71.1)	48.0 (40.4, 55.2)
48 Months	61.2 (53.5, 68.0)	41.1 (32.3, 49.6)
Follow-up Time (Months) [f]		
Median (95% CI)	36.8 (36.3, 41.5)	36.4 (35.7, 41.1)
Min, Max	0.0, 55.4	0.0, 54.0

Abbreviations: Arm A, tisle (200 mg Q3W) + chemo => surgery => tisle (400 mg Q6W); Arm B, placebo + chemo => surge => placebo.

[a] Progressive disease precluding surgery included radiographic disease progression per RECIST v1.1 precluding surgery or a disease progression not reaching the RECIST v1.1 criteria but which still precludes surgery (reason for no surgery is progressive disease or tumor unresectable).

[b] Progressive disease included patients who did not receive surgery but had disease progression after presurgical visit and patients receiving surgery with local or distant recurrence.

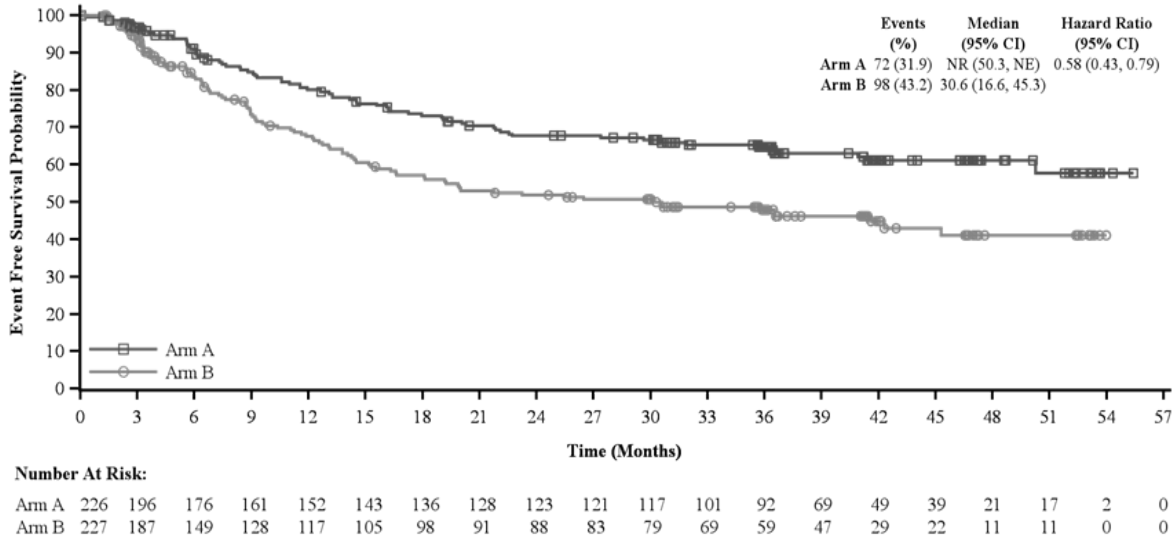
[c] Hazard ratio and 95% CIs were estimated using a Cox regression model stratified by histology (squamous vs nonsquamous), disease stage (stage II vs stage IIIA) and PD-L1 expression (<1%/not evaluable/indeterminate vs >=1%) from IRT.

[d] Medians and other quartiles were estimated by the Kaplan-Meier method with 95% CIs estimated using the Brookmeyer and Crowley method with log-log transformation.

[e] Event-free rates were estimated using the Kaplan-Meier method with 95% CIs estimated using the Greenwood formula.

[f] Median was estimated by the reverse Kaplan-Meier method with 95% CIs estimated using the Brookmeyer and Crowley method.

Figure 53: KM Plot for Event-Free Survival by BICR (ITT Analysis Set)



Data cutoff: 7MAR2025. Data extraction: 28MAR2025.

Secondary Efficacy Endpoints

Pathological Complete Response Rate by Blinded Independent Pathology Review

Table 35: Analysis of Pathological Complete Response by BICR (ITT Analysis Set) DCO 20 Feb 2023

Response Category	Arm A (N = 226)	Arm B (N = 227)
pCR, n (%)	92 (40.7)	13 (5.7)
95% CI [a]	(34.2, 47.4)	(3.1, 9.6)
Odds Ratio (95% CI) [b]	11.54 (6.18, 21.54)	--
Difference, % (95% CI) [c]	35.0 (27.9, 42.1)	--
1-Sided p-Value [d]	< 0.0001	--

Data cutoff: 20FEB2023. Data extraction: 24MAR2023.
Abbreviations: Arm A, tisle (200 mg Q3W) + chemo → surgery → tisle (400 mg Q6W); Arm B, placebo + chemo → surgery → placebo; pCR, complete pathological response.
Patients without surgery or pathological results were considered as non-responders.
a The 95% CI was estimated using the Clopper-Pearson method.
b Mantel-Haenszel common odds ratio was estimated along with its 95% CI constructed by a normal approximation of log odds ratio and the Robins, Breslow, and Greenland variance estimate stratified by histology (squamous vs non-squamous), disease stage (stage II vs stage IIIA) and PD-L1 expression (<1%/not evaluable/indeterminate vs >=1%) from Interactive Response Technology.
c Mantel-Haenszel common risk difference was estimated along with its 95% CIs constructed by a normal approximation and Sato's variance estimator stratified by histology (squamous vs non-squamous), disease stage (stage II vs stage IIIA) and PD-L1 expression (<1%/not evaluable/indeterminate vs >=1%) from Interactive Response Technology.
d The p-value was obtained using the Cochran-Mantel-Haenszel method stratified by histology (squamous vs non-squamous), disease stage (stage II vs stage IIIA) and PD-L1 expression (<1%/not evaluable/indeterminate vs >=1%) from Interactive Response Technology.

Overall Survival

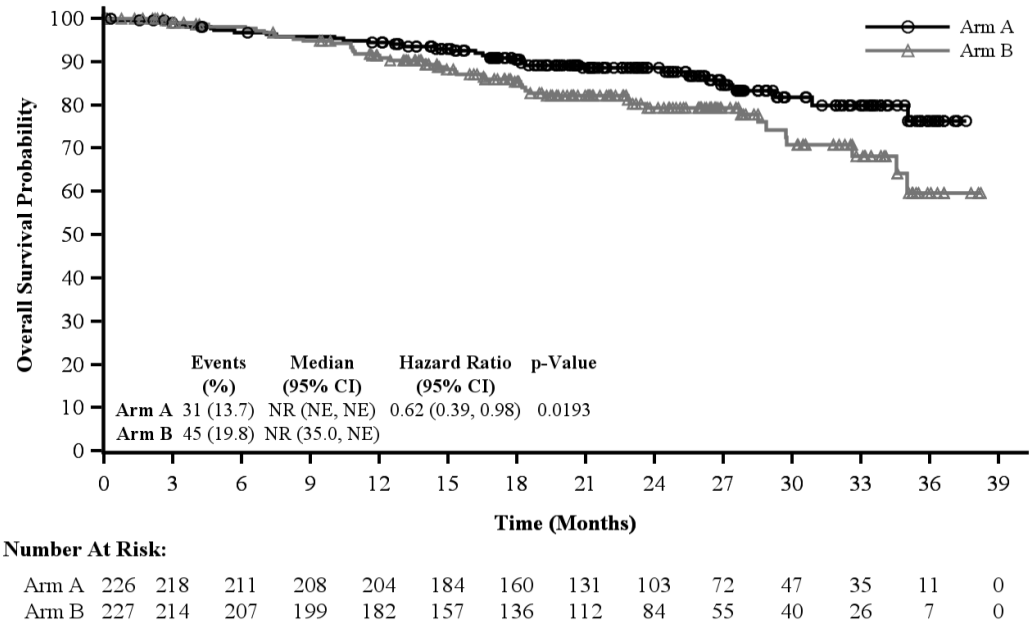
Interim Analysis (data cutoff: 21 Aug 2023)

Table 36: Analysis of Overall Survival (ITT Analysis Set) (DCO 21 Aug 2023)

	Arm A (N = 226)	Arm B (N = 227)
Overall Survival		
Death, n (%)	31 (13.7)	45 (19.8)
Censored, n (%)	195 (86.3)	182 (80.2)
Subject Withdrawal	8 (3.5)	22 (9.7)
Lost to Follow-up	2 (0.9)	0 (0.0)
Ongoing Without Event	185 (81.9)	159 (70.0)
Study Discontinuation Due to Other Reasons	0 (0.0)	1 (0.4)
Stratified Hazard Ratio (95% CI) [a]	0.62 (0.39, 0.98)	--
1-Sided Stratified p-Value [b]	0.0193	--
Overall Survival (Months) [c]		
Median (95% CI)	NR (NE, NE)	NR (35.0, NE)
Q1 (95% CI)	NR (29.2, NE)	28.8 (22.8, 34.5)
Q3 (95% CI)	NR (NE, NE)	NR (NE, NE)
Overall Survival Rate at, % (95% CI) [d]		
3 Months	99.1 (96.5, 99.8)	99.1 (96.4, 99.8)
6 Months	96.8 (93.4, 98.5)	98.1 (95.1, 99.3)
9 Months	95.9 (92.3, 97.8)	94.8 (90.8, 97.1)
12 Months	94.5 (90.5, 96.8)	90.9 (86.1, 94.1)
24 Months	88.6 (83.3, 92.3)	79.4 (72.5, 84.8)
36 Months	76.3 (64.5, 84.7)	59.6 (44.1, 72.2)
Follow-up Time (Months) [e]		
Median (95% CI)	24.6 (22.8, 26.1)	22.7 (21.3, 25.1)
Min, Max	0.1, 37.6	0.0, 38.2

Data cutoff: 21AUG2023. Data extraction: 18SEP2023.
Abbreviations: Arm A, tisle (200 mg Q3W) + chemo → surgery → tisle (400 mg Q6W); Arm B, placebo + chemo → surgery → placebo.
a Hazard ratio and 95% CIs were estimated using a Cox regression model stratified by histology (squamous vs non-squamous), disease stage (stage II vs stage IIIA) and PD-L1 expression (<1%/not evaluable/indeterminate vs >=1%) from Interactive Response Technology.
b The p-value was calculated using a log-rank test stratified by histology (squamous vs non-squamous), disease stage (stage II vs stage IIIA) and PD-L1 expression (<1%/not evaluable/indeterminate vs >=1%) from Interactive Response Technology.
c Medians and other quartiles were estimated by the Kaplan-Meier method with 95% CIs estimated using the Brookmeyer and Crowley method with log-log transformation.
d Overall survival rates were estimated using the Kaplan-Meier method with 95% CIs estimated using the Greenwood formula.
e Median was estimated by the reverse Kaplan-Meier method with 95% CIs estimated using the Brookmeyer and Crowley method.

Figure 54: Kaplan-Meier Plot for Overall Survival (ITT Analysis Set)



Data cutoff: 21AUG2023. Data extraction: 18SEP2023.
Hazard ratio and 95% CIs were estimated using a Cox regression model stratified by histology (squamous vs non-squamous), disease stage (stage II vs stage IIIA) and PD-L1 expression (<1%/not evaluable/indeterminate vs >=1%) from Interactive Response Technology.
The p-value was calculated using a log-rank test stratified by histology (squamous vs non-squamous), disease stage (stage II vs stage IIIA) and PD-L1 expression (<1%/not evaluable/indeterminate vs >=1%) from Interactive Response Technology.

Final Analysis (data cutoff: 07 Mar 2025)

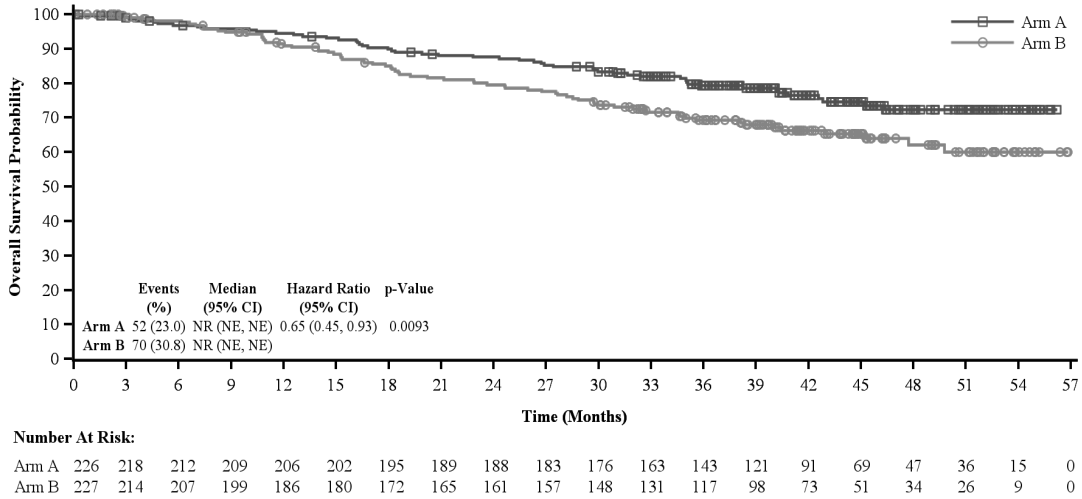
Table 37: Analysis of Overall Survival (ITT)

	Arm A (N = 226)	**Arm B (N = 227)**
Overall Survival		
Death, n (%)	52 (23.0)	70 (30.8)
Censored, n (%)	174 (77.0)	157 (69.2)
Subject Withdrawal	10 (4.4)	22 (9.7)
Lost to Follow-up	3 (1.3)	1 (0.4)
Ongoing Without Event	161 (71.2)	133 (58.6)
Study Discontinuation Due to Other Reasons	0 (0.0)	1 (0.4)
Stratified Hazard Ratio (95% CI) [a]	0.65 (0.45, 0.93)	--
1-Sided Stratified p-Value [b]	0.0093	--
Overall Survival (Months) [c]		
Median (95% CI)	NR (NE, NE)	NR (NE, NE)
Q1 (95% CI)	42.8 (35.0, NE)	29.7 (22.8, 38.1)

	Arm A (N = 226)	Arm B (N = 227)
Q3 (95% CI)	NR (NE, NE)	NR (NE, NE)
Overall Survival Rate at, % (95% CI) [d]		
12 Months	94.5 (90.6, 96.9)	90.9 (86.1, 94.1)
24 Months	87.6 (82.4, 91.3)	79.6 (73.4, 84.5)
36 Months	79.3 (73.1, 84.2)	69.3 (62.3, 75.2)
48 Months	72.3 (64.6, 78.5)	62.2 (53.8, 69.5)
Follow-up Time (Months) [e]		
Median (95% CI)	43.3 (41.2, 44.6)	41.6 (39.9, 43.8)
Min, Max	0.1, 56.2	0.0, 56.8

Data cutoff: 7MAR2025. Data extraction: 28MAR2025.

Figure 55: Kaplan-Meier Plot for Overall Survival (ITT Analysis Set)



Data cutoff: 7MAR2025. Data extraction: 28MAR2025.

Objective Response Rate Before Study Surgery

Table 38*:* Analysis of Disease Response Before Study Surgery by BICR per RECIST 1.1 (ITT)

Response Category	Arm A (N = 226)	Arm B (N = 227)
Best Overall Response, n (%)		
Complete Response	1 (0.4)	3 (1.3)
Partial Response	160 (70.8)	122 (53.7)
Stable Disease	54 (23.9)	94 (41.4)
Progressive Disease	4 (1.8)	2 (0.9)
Could Not Be Determined	7 (3.1)	6 (2.6)
Overall Response Rate, n (%)	161 (71.2)	125 (55.1)
95% CI (%) [a]	(64.9, 77.0)	(48.3, 61.7)
Odds Ratio (95% CI) [b]	2.06 (1.39, 3.08)	--
Risk Difference, % (95% CI) [c]	15.9 (7.3, 24.5)	--
1-Sided p-Value [d]	0.0002	--

Data cutoff: 21AUG2023. Data extraction: 18SEP2023.
Best overall response of could not be determined included patients with no postbaseline response assessment (Not Assessable) or assessment as Not Evaluable per RECIST v1.1.
For patient who received surgery, only tumor assessment on or prior to surgery or the start of new anti-cancer therapy, whichever comes first, will be included. For patient without surgery, tumor assessment on or prior to progressive disease or start of new anti-cancer therapy, whichever comes first, will be included.
a The 95% CI was estimated using the Clopper-Pearson method.

b Mantel-Haenszel common odds ratio was estimated along with its 95% CI constructed by a normal approximation of log odds ratio and the Robins, Breslow, and Greenland variance estimate stratified by histology (squamous vs non-squamous), disease stage (stage II vs stage IIIA) and PD-L1 expression (<1%/not evaluable/indeterminate vs >=1%)) from Interactive Response Technology.
c Mantel-Haenszel common risk difference was estimated along with its 95% CIs constructed by a normal approximation and Sato's variance estimator stratified by histology (squamous vs non-squamous), disease stage (stage II vs stage IIIA) and PD-L1 expression (<1%/not evaluable/indeterminate vs >=1%) from Interactive Response Technology.
d The descriptive p-value was obtained using the Cochran-Mantel-Haenszel method stratified by histology (squamous vs non-squamous), disease stage (stage II vs stage IIIA) and PD-L1 expression (<1%/not evaluable/indeterminate vs >=1%) from Interactive Response Technology.

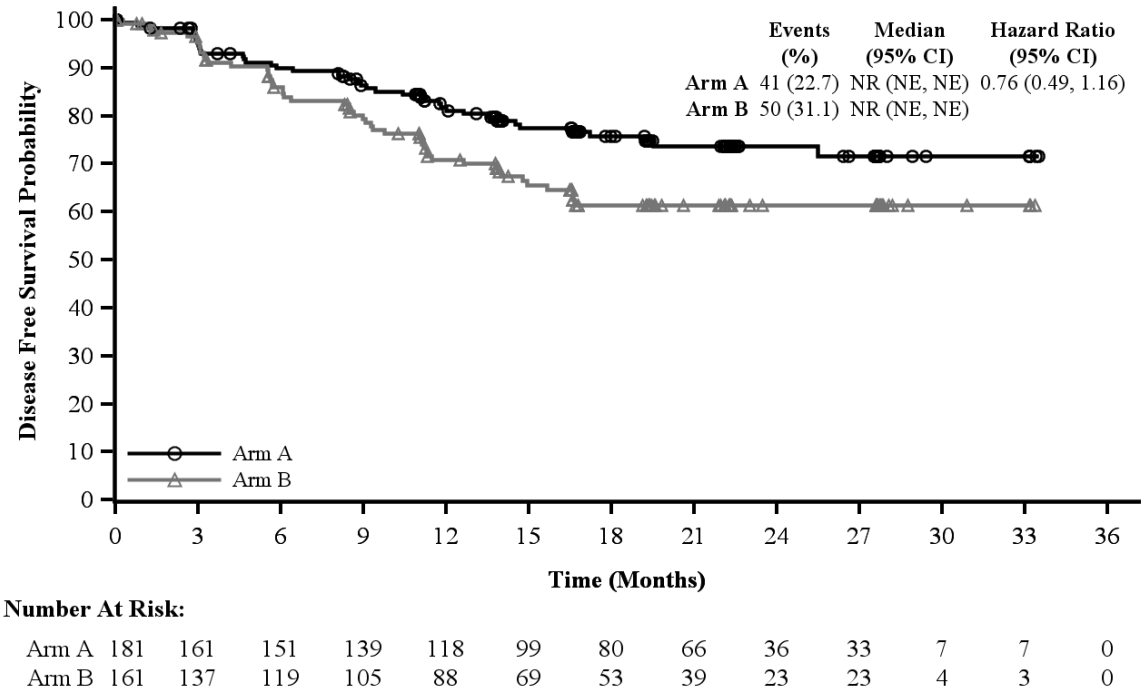
Disease-Free Survival by Blinded Independent Central Review

Table 39: Analysis of Disease-Free Survival by Blinded Independent Central Review (ITT Analysis Set)

	Arm A (N = 226)	Arm B (N = 227)
Number of Patients with R0 Resection	181	161
Disease-Free Survival		
Events, n (%)	41 (22.7)	50 (31.1)
Local or Distant Recurrence	33 (18.2)	44 (27.3)
Death	8 (4.4)	6 (3.7)
Censored, n (%)	140 (77.3)	111 (68.9)
No Tumor Assessment After Surgery	7 (3.9)	12 (7.5)
New Anticancer Therapy Initiated Before Recurrence/Death	3 (1.7)	7 (4.3)
Recurrence/Death After > 1 Missed Assessment	0 (0.0)	2 (1.2)
Ongoing Without Events	130 (71.8)	90 (55.9)
Stratified Hazard Ratio (95% CI) [a]	0.76 (0.49, 1.16)	--
1-Sided Stratified p-Value [b]	0.0986	--
Disease-Free Survival (Months) [c]		
Median (95% CI)	NR (NE, NE)	NR (NE, NE)
Q1 (95% CI)	19.2 (12.0, NE)	11.1 (8.5, 14.0)
Q3 (95% CI)	NR (NE, NE)	NR (NE, NE)
Disease-Free Survival Rate at, % (95% CI) [d]		
3 Months	94.7 (90.1, 97.2)	95.2 (90.2, 97.7)
6 Months	90.0 (84.4, 93.7)	86.0 (79.2, 90.8)
9 Months	86.4 (80.2, 90.7)	79.4 (71.7, 85.2)
12 Months	81.1 (74.2, 86.4)	70.9 (62.4, 77.7)
24 Months	73.6 (65.6, 80.1)	61.3 (52.1, 69.3)
36 Months	NE (NE, NE)	NE (NE, NE)

Source: ADSL,ADBASE,ADTTE. Data cutoff: 21AUG2023. Data extraction: 18SEP2023.
Abbreviations: Arm A, tisle (200 mg Q3W) + chemo → surgery → tisle (400 mg Q6W); Arm B, placebo + chemo → surgery → placebo.
This analysis includes all the patients who had surgery and with R0 as surgery outcome. The percentage of patients who had events and were censored is based on this patient population.
a Hazard ratio and 95% CIs were estimated using a Cox regression model stratified by histology (squamous vs non-squamous), PD-L1 expression (<1%/not evaluable/indeterminate vs >=1%) from Interactive Response Technology, and pathological disease stage (0/1 vs II vs III) from EDC.
b The descriptive p-value was calculated using a log-rank test stratified by histology (squamous vs non-squamous), PD-L1 expression (<1%/not evaluable/indeterminate vs >=1%) from Interactive Response Technology, and pathological disease stage (0/1 vs II vs III) from EDC.
c Medians and other quartiles were estimated by the Kaplan-Meier method with 95% CIs estimated using the Brookmeyer and Crowley method with log-log transformation.
d Disease-free survival rates were estimated using the Kaplan-Meier method with 95% CIs estimated using the Greenwood formula.

Figure 56: Kaplan-Meier Plot for Disease Free Survival by BICR (ITT Analysis Set)



Number At Risk:

Arm A	181	161	151	139	118	99	80	66	36	33	7	7	0
Arm B	161	137	119	105	88	69	53	39	23	23	4	3	0

Source: ADSL, ADTTE. Data cutoff: 21AUG2023. Data extraction: 18SEP2023.
Abbreviations: Arm A, tisle (200 mg Q3W) + chemo → surgery → tisle (400 mg Q6W); Arm B, placebo + chemo → surgery → placebo.
This analysis includes all the patients who had surgery and with R0 as surgery outcome.
Hazard ratio and 95% CIs were estimated using a Cox regression model stratified by histology (squamous vs non-squamous), PD-L1 expression (<1%/not evaluable/indeterminate vs >=1%) from Interactive Response Technology, and pathological disease stage (0/1 vs II vs III) from EDC.

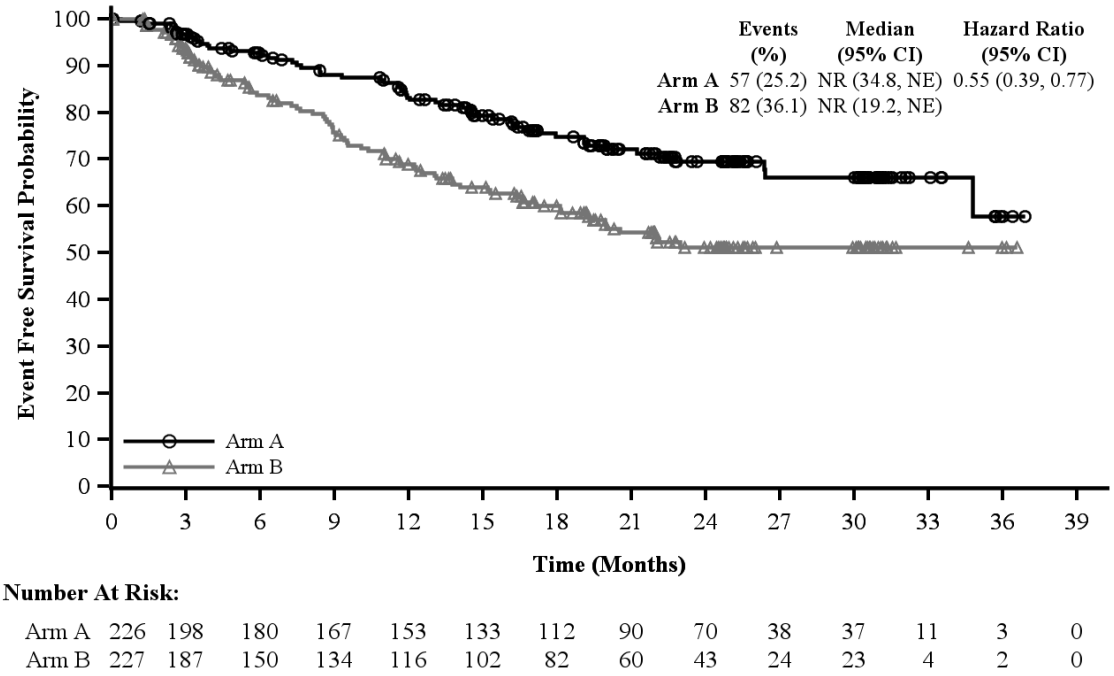
Event-Free Survival by the Investigator

Table 40: Analysis of Event-Free Survival by Investigator (ITT Analysis Set)

	Arm A (N = 226)	Arm B (N = 227)
Event-Free Survival		
Events, n (%)	57 (25.2)	82 (36.1)
Progressive Disease Precluding Study Surgery [a]	7 (3.1)	19 (8.4)
Progressive Disease [b]	40 (17.7)	56 (24.7)
Death	10 (4.4)	7 (3.1)
Censored, n (%)	169 (74.8)	145 (63.9)
No Postbaseline Assessment	5 (2.2)	6 (2.6)
No Post Surgery Assessment	6 (2.7)	12 (5.3)
New Anticancer Therapy Before Progression/Recurrence/Death	11 (4.9)	19 (8.4)
Progression/Recurrence/Death After > 1 Missed Assessment	1 (0.4)	2 (0.9)
Lost to Follow-up	1 (0.4)	0 (0.0)
Subject Withdrawal	4 (1.8)	7 (3.1)
Ongoing Without Events	141 (62.4)	99 (43.6)
Stratified Hazard Ratio (95% CI) [c]	0.55 (0.39, 0.77)	--
1-Sided Stratified p-Value [d]	0.0002	--
Event-Free Survival (Months) [e]		
Median (95% CI)	NR (34.8, NE)	NR (19.2, NE)
Q1 (95% CI)	17.9 (14.2, 26.3)	9.3 (7.5, 12.2)
Q3 (95% CI)	NR (NE, NE)	NR (NE, NE)
Event-Free Survival Rate at, % (95% CI) [f]		
3 Months	96.7 (93.3, 98.4)	93.8 (89.6, 96.4)
6 Months	92.8 (88.3, 95.6)	83.7 (77.6, 88.2)
9 Months	88.0 (82.7, 91.8)	75.8 (68.9, 81.3)
12 Months	83.2 (77.2, 87.8)	68.9 (61.6, 75.0)
24 Months	69.5 (61.9, 75.9)	51.1 (42.8, 58.9)
36 Months	57.8 (39.5, 72.3)	51.1 (42.8, 58.9)

Data cutoff: 21AUG2023. Data extraction: 18SEP2023.
Abbreviations: Arm A, tisle (200 mg Q3W) + chemo → surgery → tisle (400 mg Q6W); Arm B, placebo + chemo → surgery → placebo.
a Progressive disease precluding surgery included radiographic disease progression per RECIST 1.1 precluding surgery or a disease progression not reaching the RECIST 1.1 criteria but which still precludes surgery (reason for no surgery is progressive disease or tumor unresectable).
b Progressive disease included patients who did not receive surgery but had disease progression after presurgical visit and patients receiving surgery with local or distant recurrence.
c Hazard ratio and 95% CIs were estimated using a Cox regression model stratified by histology (squamous vs non-squamous), disease stage (stage II vs stage IIIA) and PD-L1 expression (<1%/not evaluable/indeterminate vs >=1%) from Interactive Response Technology.
d The descriptive p-value was calculated using a log-rank test stratified by histology (squamous vs non-squamous), disease stage (stage II vs stage IIIA) and PD-L1 expression (<1%/not evaluable/indeterminate vs >=1%) from Interactive Response Technology.
e Medians and other quartiles were estimated by the Kaplan-Meier method with 95% CIs estimated using the Brookmeyer and Crowley method with log-log transformation.
f Event-free rates were estimated using the Kaplan-Meier method with 95% CIs estimated using the Greenwood formula.
(Source: Report Body Table 20)

Figure 57: Kaplan-Meier Plot for Event-Free Survival by Investigator (ITT Analysis Set)



PRO (Patient-Reported Outcomes)

In Study 315, Health-Related Quality of Life (HRQoL) outcomes were assessed based on descriptive analyses using the EORTC QLQ C30, EORTC QLQ LC13, and EQ 5D 5L.

- Compliance

The compliance rates (ie, adjusted completion rates: the percentages of patients who completed the questionnaire at each visit divided by the number of patients still in treatment) for the EORTC QLQ C30, EORTC QLQ LC13, and EQ-5D-5L questionnaires were 100% at baseline, at Cycle 3 of the neoadjuvant phase, and at each cycle of the adjuvant phase for both arms.

- Score Change from Baseline by Visit

Table 41: Summary of the mean changes in scores from baseline (assessor's table):

Questionnaire/ Parameter - Mean change (standard deviation)	**Tislelizumab + Chemotherapy**	**Placebo + Chemotherapy**	**Tislelizumab**	**Placebo**
	At cycle 3 in neoadjuvant phase		**At cycle 7 in adjuvant phase**	
EORTC QLQ-C30 in the overall phase				
GHS (Global Health Status)/QoL	-3.1 (19.28)	-1.1 (16.07)	3.1 (18.84)	1.7 (17.17)
Physical functioning	-2.3 (9.65)	-1.9 (8.48)	-1.8 (9.81)	-2.5 (9.89)
Fatigue	4.5 (16.02)	5.6 (14.77)	0.9 (15.75)	2.5 (16.25)
EORTC QLQ-LC13 in the overall phase				
Index score	2.0 (7.78)	2.2 (6.71)	-0.9 (7.79)	0.2 (7.11)

Coughing	-10.0 (24.02)	-11.5 (20.76)	-11.7 (24.88)	-8.3 (25.65)
Chest pain	-3.5 (16.62)	-1.1 (16.67)	-1.1 (19.04)	3.2 (18.21)
Dyspnoea	0.7 (14.50)	0.2 (11.21)	1.8 (14.59)	4.9 (17.56)

- **Least Squares Mean Change** (based on the mixed-effects model analysis)

Table 42: Summary of Least Square (LS) Mean Changes from Baseline (95% CI) (assessor's table):

Questionnaire/ Parameter – LS Mean change difference (95% CI)	**Tislelizumab + Chemotherapy**	**Placebo + Chemotherapy**	**Tislelizumab**	**Placebo**
	At cycle 3 in neoadjuvant phase		**At cycle 7 in adjuvant phase**	
EORTC QLQ-C30 in the overall phase				
GHS (Global Health Status)/QoL	-4.56 (-6.78, -2.34)	-2.21 (-4.40, -0.03)	1.09 (-1.34, 3.53)	1.90 (-0.66, 4.46)
Physical functioning	-3.11 (-4.34, -1.88)	-2.17 (-3.37, -0.96)	-2.60 (-4.20, -1.00)	-2.23 (-3.92, -0.54)
Fatigue	5.70 (3.62, 7.78)	5.99 (3.95, 8.04)	2.54 (0.09, 4.99)	2.87 (0.30, 5.45)
EORTC QLQ-LC13 in the overall phase				
Coughing	-1.053 (11.8671)	-0.769 (10.7698)	-10.93 (-14.36, -7.49)	-6.26 (-9.88, -2.63)
Chest pain	-1.053 (11.8671)	-0.769 (10.7698)	-6.44 (-9.15, -3.72)	-7.00 (-9.86, -4.14)
Dyspnoea	1.87 (0.27, 3.47)	-0.18 (-1.75, 1.39)	3.18 (0.82, 5.55)	4.56 (2.07, 7.06)

- Time to Deterioration

The time to deterioration analysis measured by EORTC QLQ LC13 showed that the TIS Arm was at lower risk of worsening of

- Chest pain HR = 0.59, 95% CI: 0.38 to 0.91).

The risk of worsening was similar in all other PRO endpoints between the 2 arms:

- Dyspnea: HR of 0.87 (95% CI: 0.66, 1.14)],
- Coughing: HR of 1.14 (95% CI 0.72, 1.81).

Outcome of surgery

The outcome of surgery, including feasibility and rate of peri- and postoperative complications was assessed as exploratory objective (please see also Tables 5.5. 1 – 5.5. 2 for an overview of TEAEs leading to surgery cancellation, surgery delay and postoperative complications).

A total of 80.1% patients had curative surgery performed and more patients having underwent surgery in Arm A compared with Arm B (190 patients [84.1%] versus 173 patients [76.2%], respectively).

Table 43: Patient Disposition and Reasons for Surgery Cancellation - Surgery Phase

	Arm A (N = 226)	Arm B (N = 227)	Total (N = 453)
Surgery Phase			
Patients Having Performed Surgery, n (%)	190 (84.1)	173 (76.2)	363 (80.1)
Patients With Surgery Cancellation, n (%)	36 (15.9)	54 (23.8)	90 (19.9)
Surgery Cancellation Reason			
Adverse Event	6 (2.7)	2 (0.9)	8 (1.8)
Progressive Disease	6 (2.7)	17 (7.5)	23 (5.1)
Radiographic Progressive Disease	5 (2.2)	12 (5.3)	17 (3.8)
Physician Decision-Tumor Unresectable	1 (0.4)	5 (2.2)	6 (1.3)
Subject Withdrawal	20 (8.8)	28 (12.3)	48 (10.6)
Physician Decision	3 (1.3)	7 (3.1)	10 (2.2)
Other	1 (0.4)	0 (0.0)	1 (0.2)
Exploratory Thoracotomy	1 (0.4)	2 (0.9)	3 (0.7)

Table 44: Summary of Surgical Procedures and Outcomes (Safety Analysis Set [Surgery])

	Arm A (N = 190)	Arm B (N = 173)
Type of Surgery, n (%)		
Lobectomy	135 (71.1)	106 (61.3)
Pneumonectomy	16 (8.4)	21 (12.1)
Sleeve lobectomy	20 (10.5)	16 (9.2)
Bilobectomy	18 (9.5)	29 (16.8)
Segmentectomy	1 (0.5)	1 (0.6)
Approach of Surgery, n (%)		
Open	65 (34.2)	70 (40.5)
Minimally Invasive	114 (60.0)	87 (50.3)
Minimally invasive to thoracotomy	11 (5.8)	16 (9.2)
Completeness of Resection, n (%)		
R0 (no residual tumor)	181 (95.3)	161 (93.1)
R1 (microscopic residual tumor)	1 (0.5)	6 (3.5)
R2 (macroscopic residual tumor)	4 (2.1)	5 (2.9)
R(un) (uncertain)	3 (1.6)	1 (0.6)
Missing	1 (0.5)	0 (0.0)
Number of Lymph Node Dissected		
N	190	173
Mean (SD)	18.42 (9.870)	18.65 (12.062)
Median	18.00	16.00
Q1, Q3	11.00, 24.00	10.00, 23.00
Min, Max	0.0, 55.0	0.0, 84.0
Time From Last Neoadjuvant Dose to Surgery [a] (Weeks)		
N	190	173
Mean (SD)	5.72 (1.636)	5.51 (0.983)
Median	5.50	5.29
Q1, Q3	5.00, 6.00	5.00, 5.86
Min, Max	3.7, 19.9	4.0, 10.3

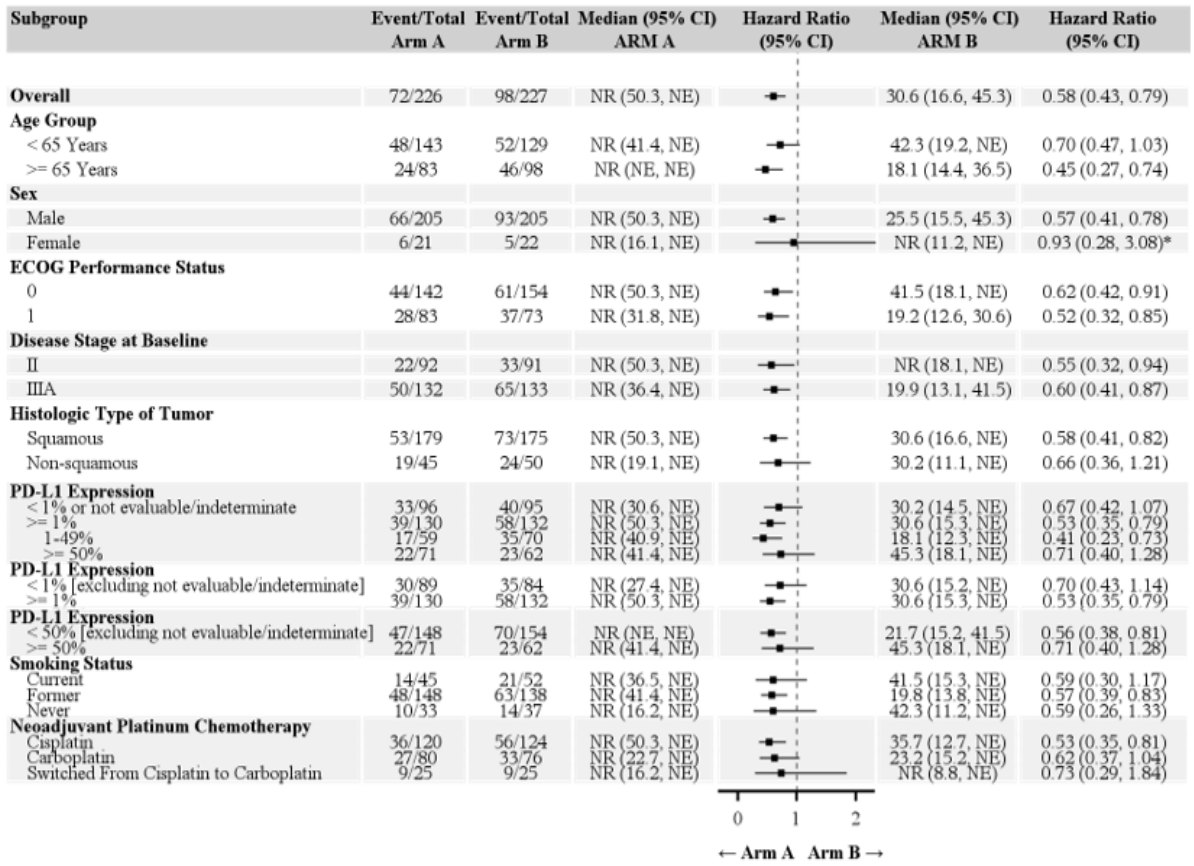
Duration of Surgery [b] (Hours)		
N	188	173
Mean (SD)	3.03 (1.362)	3.12 (1.316)
Median	2.66	2.83
Q1, Q3	2.17, 3.56	2.17, 3.75
Min, Max	1.0, 8.4	1.0, 9.7
Length of Hospital Stay (Days)		
N	190	173
Mean (SD)	8.03 (3.987)	8.08 (3.862)
Median	7.00	7.00
Q1, Q3	5.00, 9.00	6.00, 9.00
Min, Max	4.0, 24.0	2.0, 25.0
Patients Having Surgery Delayed, n (%)	31 (16.3)	22 (12.7)
Adverse Events	12 (6.3)	6 (3.5)
Other	19 (10.0)	16 (9.2)
Related to COVID-19	8 (4.2)	7 (4.0)
Length of Surgery Delay [c], n (%)		
<= 2 Weeks	22 (11.6)	18 (10.4)
> 2 - <= 4 Weeks	5 (2.6)	3 (1.7)
> 4 - <= 6 Weeks	1 (0.5)	1 (0.6)
> 6 Weeks	2 (1.1)	0 (0.0)
Patients Received Postoperative Radiotherapy, n (%)	3 (1.6)	5 (2.9)

a (Surgery start date - last neoadjuvant treatment date + 1) / 7.
b (Surgery end date and time - surgery start date and time)/3600.
c Length of surgery delay is defined as (surgery start date - last neoadjuvant treatment date - 6 weeks*7)/7 for patients having surgery delayed.

Ancillary analyses

- **Subgroup Analyses including PD-L1 subgroups**

Figure 58: Forest Plot for Event-Free Survival by BICR (ITT) – at FA (DCO 07 Mar 2025)

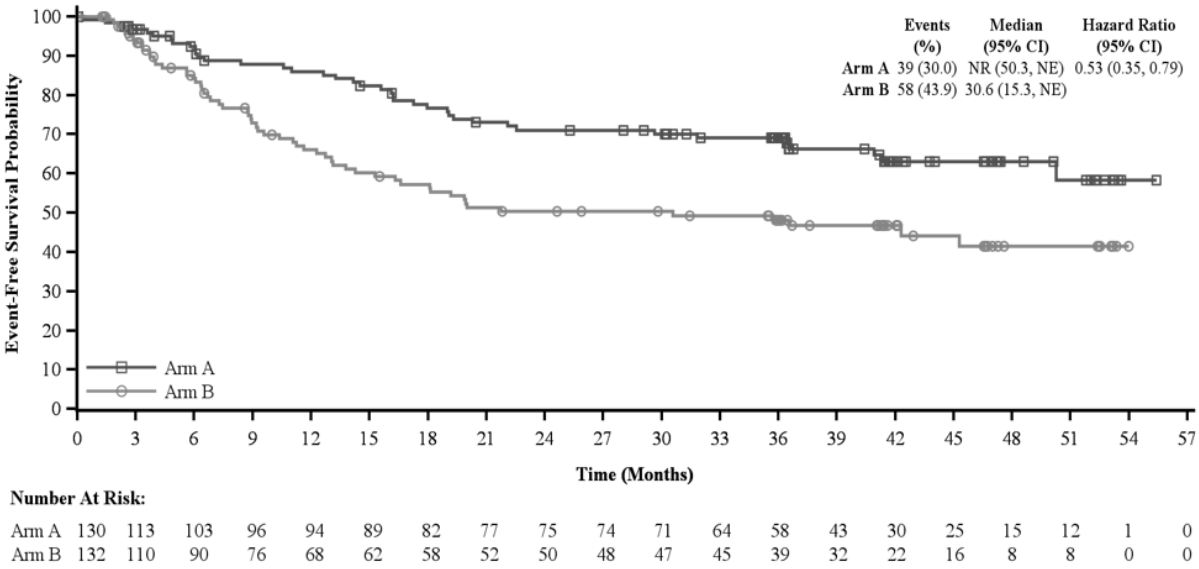


Subgroup	Event/Total Arm A	Event/Total Arm B	Median (95% CI) ARM A	Hazard Ratio (95% CI)	Median (95% CI) ARM B	Hazard Ratio (95% CI)
Overall	72/226	98/227	NR (50.3, NE)		30.6 (16.6, 45.3)	0.58 (0.43, 0.79)
Age Group						
< 65 Years	48/143	52/129	NR (41.4, NE)		42.3 (19.2, NE)	0.70 (0.47, 1.03)
>= 65 Years	24/83	46/98	NR (NE, NE)		18.1 (14.4, 36.5)	0.45 (0.27, 0.74)
Sex						
Male	66/205	93/205	NR (50.3, NE)		25.5 (15.5, 45.3)	0.57 (0.41, 0.78)
Female	6/21	5/22	NR (16.1, NE)		NR (11.2, NE)	0.93 (0.28, 3.08)*
ECOG Performance Status						
0	44/142	61/154	NR (50.3, NE)		41.5 (18.1, NE)	0.62 (0.42, 0.91)
1	28/83	37/73	NR (31.8, NE)		19.2 (12.6, 30.6)	0.52 (0.32, 0.85)
Disease Stage at Baseline						
II	22/92	33/91	NR (50.3, NE)		NR (18.1, NE)	0.55 (0.32, 0.94)
IIIA	50/132	65/133	NR (36.4, NE)		19.9 (13.1, 41.5)	0.60 (0.41, 0.87)
Histologic Type of Tumor						
Squamous	53/179	73/175	NR (50.3, NE)		30.6 (16.6, NE)	0.58 (0.41, 0.82)
Non-squamous	19/45	24/50	NR (19.1, NE)		30.2 (11.1, NE)	0.66 (0.36, 1.21)
PD-L1 Expression						
< 1% or not evaluable/indeterminate	33/96	40/95	NR (30.6, NE)		30.2 (14.5, NE)	0.67 (0.42, 1.07)
>= 1%	39/130	58/132	NR (50.3, NE)		30.6 (15.3, NE)	0.53 (0.35, 0.79)
1-49%	17/59	35/70	NR (40.9, NE)		18.1 (12.3, NE)	0.41 (0.23, 0.73)
>= 50%	22/71	23/62	NR (41.4, NE)		45.3 (18.1, NE)	0.71 (0.40, 1.28)
PD-L1 Expression						
< 1% [excluding not evaluable/indeterminate]	30/89	35/84	NR (27.4, NE)		30.6 (15.2, NE)	0.70 (0.43, 1.14)
>= 1%	39/130	58/132	NR (50.3, NE)		30.6 (15.3, NE)	0.53 (0.35, 0.79)
PD-L1 Expression						
< 50% [excluding not evaluable/indeterminate]	47/148	70/154	NR (NE, NE)		21.7 (15.2, 41.5)	0.56 (0.38, 0.81)
>= 50%	22/71	23/62	NR (41.4, NE)		45.3 (18.1, NE)	0.71 (0.40, 1.28)
Smoking Status						
Current	14/45	21/52	NR (36.5, NE)		41.5 (15.3, NE)	0.59 (0.30, 1.17)
Former	48/148	63/138	NR (41.4, NE)		19.8 (13.8, NE)	0.57 (0.39, 0.83)
Never	10/33	14/37	NR (16.2, NE)		42.3 (11.2, NE)	0.59 (0.26, 1.33)
Neoadjuvant Platinum Chemotherapy						
Cisplatin	36/120	56/124	NR (50.3, NE)		35.7 (12.7, NE)	0.53 (0.35, 0.81)
Carboplatin	27/80	33/76	NR (22.7, NE)		23.2 (15.2, NE)	0.62 (0.37, 1.04)
Switched From Cisplatin to Carboplatin	9/25	9/25	NR (16.2, NE)		NR (8.8, NE)	0.73 (0.29, 1.84)

Data cutoff: 7 Mar 2025. Data extraction: 28 Mar 2025.
Unstratified hazard ratio and its 95% CIs were estimated using a Cox regression model.
* The confidence interval of this subgroup is not shown completely due to space limit.

Figure 59: KM Plots for EFS by BICR Review by PD-L1 Status - 1% Threshold (ITT Analysis Set)

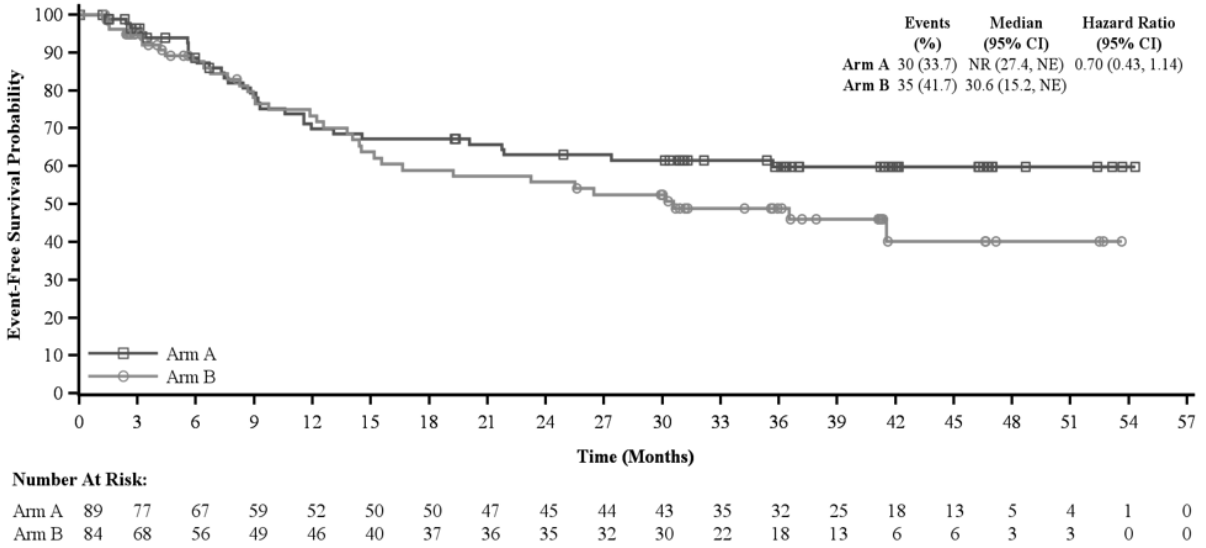
PD-L1 ≥ 1%



Number At Risk:

Arm A	130	113	103	96	94	89	82	77	75	74	71	64	58	43	30	25	15	12	1	0
Arm B	132	110	90	76	68	62	58	52	50	48	47	45	39	32	22	16	8	8	0	0

PD-L1 < 1% (excluding not evaluable/indeterminate)



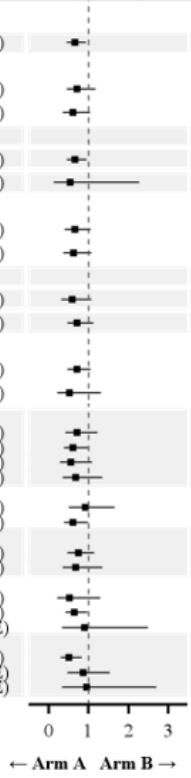
Number At Risk:

Arm A	89	77	67	59	52	50	50	47	45	44	43	35	32	25	18	13	5	4	1	0
Arm B	84	68	56	49	46	40	37	36	35	32	30	22	18	13	6	6	3	3	0	0

Data cutoff: 07 Mar 2025
Unstratified hazard ratio and its 95% CIs were estimated using a Cox regression model.

Figure 60: Forest Plot for Overall Survival (ITT) – at FA (DCO 07 Mar 2025)

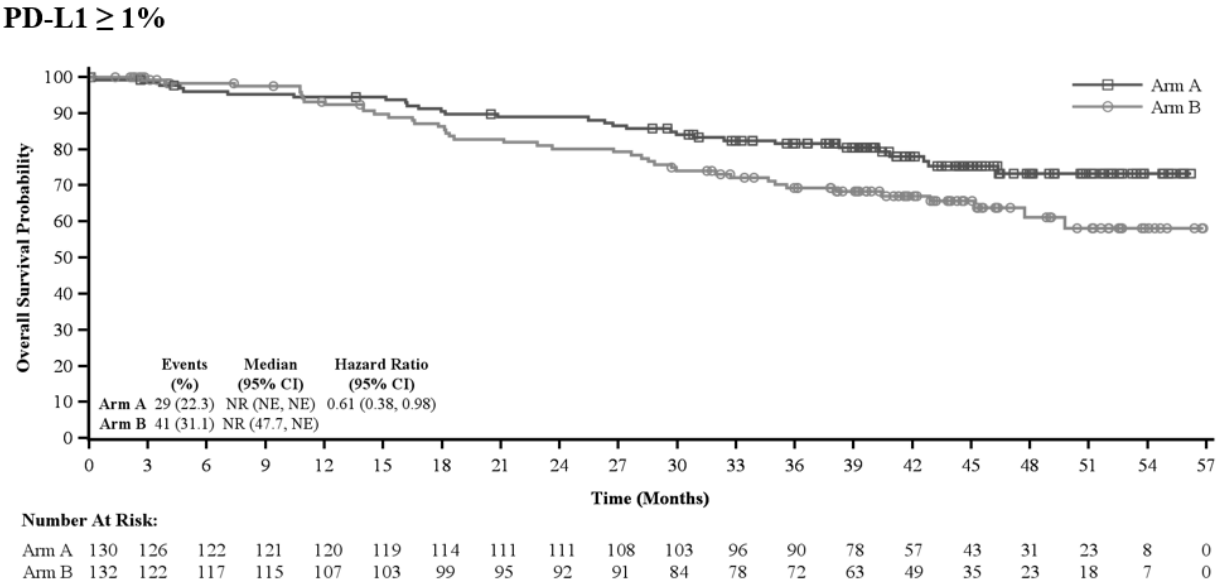
Subgroup	Event/Total Arm A	Event/Total Arm B	Median (95% CI) ARM A	Hazard Ratio (95% CI)	Median (95% CI) ARM B	Hazard Ratio (95% CI)
Overall	52/226	70/227	NR (NE, NE)		NR (NE, NE)	0.65 (0.45, 0.93)
Age Group						
< 65 Years	31/143	34/129	NR (NE, NE)		NR (NE, NE)	0.71 (0.44, 1.16)
>= 65 Years	21/83	36/98	NR (NE, NE)		NR (38.3, NE)	0.60 (0.35, 1.03)
Sex						
Male	49/205	65/205	NR (NE, NE)		NR (NE, NE)	0.66 (0.45, 0.95)
Female	3/21	5/22	NR (NE, NE)		NR (49.8, NE)	0.54 (0.13, 2.26)
ECOG Performance Status						
0	28/142	41/154	NR (NE, NE)		NR (NE, NE)	0.65 (0.40, 1.05)
1	24/83	29/73	NR (NE, NE)		NR (30.9, NE)	0.62 (0.36, 1.07)
Disease Stage at Baseline						
II	17/92	26/91	NR (NE, NE)		NR (NE, NE)	0.58 (0.31, 1.06)
IIIA	35/132	43/133	NR (NE, NE)		NR (49.8, NE)	0.71 (0.46, 1.11)
Histologic Type of Tumor						
Squamous	45/179	55/175	NR (NE, NE)		NR (47.7, NE)	0.70 (0.47, 1.04)
Non-squamous	7/45	13/50	NR (NE, NE)		NR (49.8, NE)	0.52 (0.21, 1.30)
PD-L1 Expression						
< 1% or not evaluable/indeterminate	23/96	29/95	NR (NE, NE)		NR (NE, NE)	0.70 (0.41, 1.22)
>= 1%	29/130	41/132	NR (NE, NE)		NR (47.7, NE)	0.61 (0.38, 0.98)
1-49%	14/59	23/70	NR (NE, NE)		NR (40.4, NE)	0.55 (0.28, 1.08)
>= 50%	15/71	18/62	NR (NE, NE)		NR (47.7, NE)	0.67 (0.34, 1.34)
PD-L1 Expression						
< 1% [excluding not evaluable/indeterminate]	22/89	22/84	NR (NE, NE)		NR (NE, NE)	0.91 (0.50, 1.64)
>= 1%	29/130	41/132	NR (NE, NE)		NR (47.7, NE)	0.61 (0.38, 0.98)
PD-L1 Expression						
< 50% [excluding not evaluable/indeterminate]	36/148	45/154	NR (NE, NE)		NR (NE, NE)	0.73 (0.47, 1.13)
>= 50%	15/71	18/62	NR (NE, NE)		NR (47.7, NE)	0.67 (0.34, 1.34)
Smoking Status						
Current	7/45	13/52	NR (NE, NE)		NR (47.7, NE)	0.51 (0.20, 1.28)
Former	38/148	49/138	NR (NE, NE)		NR (42.9, NE)	0.63 (0.41, 0.96)
Never	7/33	8/37	NR (42.6, NE)		NR (49.8, NE)	0.90 (0.33, 2.48)
Neoadjuvant Platinum Chemotherapy						
Cisplatin	23/120	40/124	NR (NE, NE)		NR (47.7, NE)	0.50 (0.30, 0.83)
Carboplatin	22/80	23/76	NR (45.2, NE)		NR (NE, NE)	0.85 (0.47, 1.52)
Switched From Cisplatin to Carboplatin	7/25	7/25	NR (35.0, NE)		NR (40.4, NE)	0.94 (0.33, 2.69)

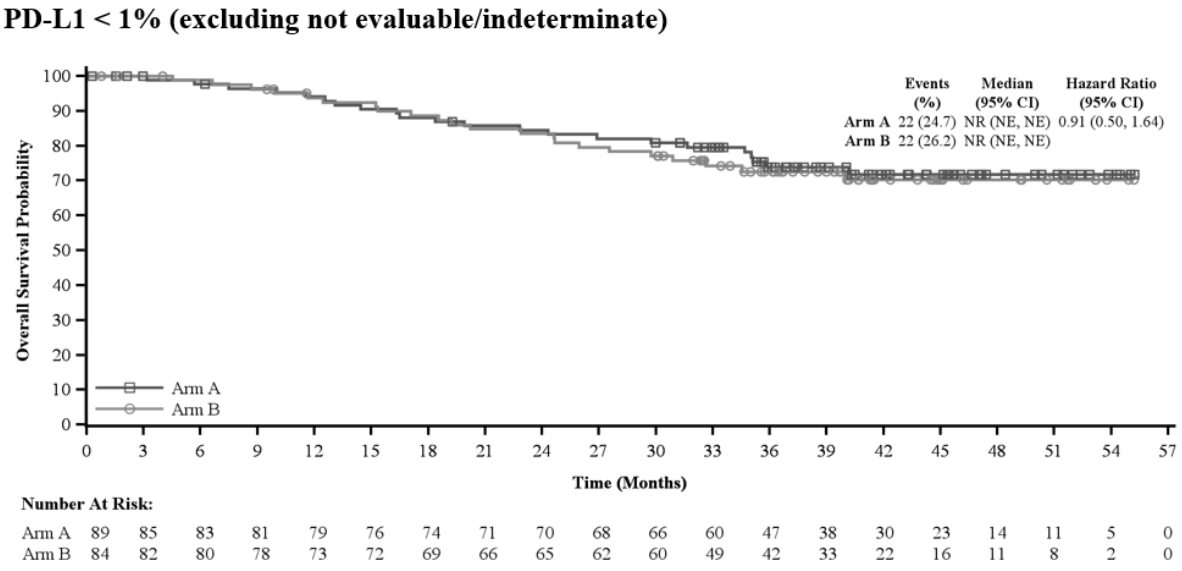


Data cutoff: 7MAR2025. Data extraction: 28MAR2025.

Unstratified hazard ratio and its 95% CIs were estimated using a Cox regression model.

Figure 61: KM Plots for OS by PD-L1 Status - 1% Threshold (ITT Analysis Set)

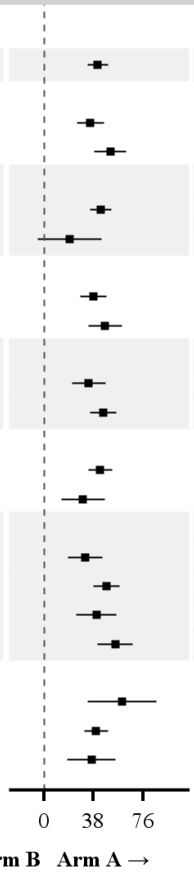




Data cutoff: 7MAR2025. Data extraction: 28MAR2025.
Unstratified hazard ratio and its 95% CIs were estimated using a Cox regression model.

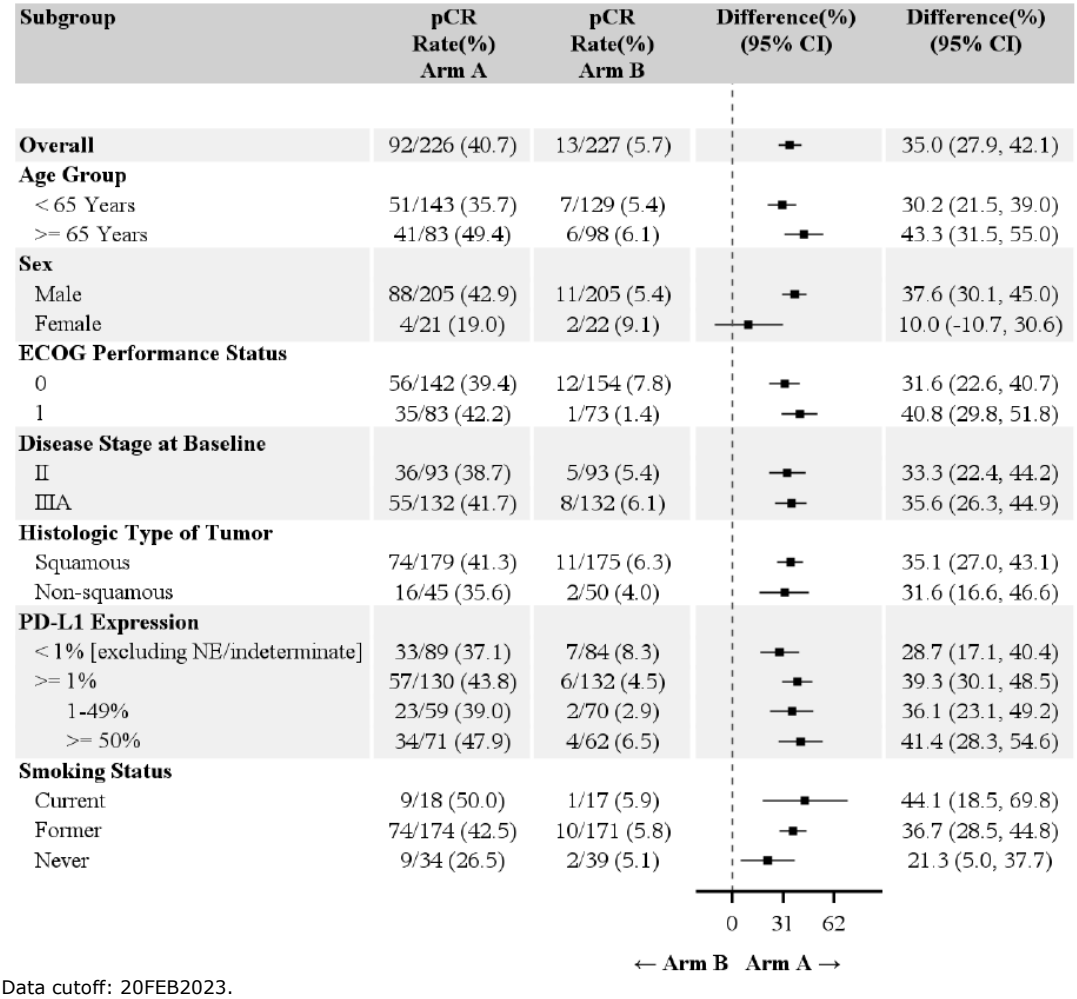
Figure 62: Forest Plot for Major Pathological Response by Blinded Independent Pathology Review

Subgroup	MPR Rate(%) Arm A	MPR Rate(%) Arm B	Difference(%) (95% CI)
Overall	127/226 (56.2)	34/227 (15.0)	41.2 (33.3, 49.2)
Age Group			
< 65 Years	72/143 (50.3)	19/129 (14.7)	35.6 (25.4, 45.8)
>= 65 Years	55/83 (66.3)	15/98 (15.3)	51.0 (38.5, 63.4)
Sex			
Male	120/205 (58.5)	31/205 (15.1)	43.4 (35.1, 51.8)
Female	7/21 (33.3)	3/22 (13.6)	19.7 (-5.0, 44.4)
ECOG Performance Status			
0	78/142 (54.9)	26/154 (16.9)	38.0 (27.9, 48.1)
1	48/83 (57.8)	8/73 (11.0)	46.9 (34.1, 59.7)
Disease Stage at Baseline			
II	49/93 (52.7)	17/93 (18.3)	34.4 (21.6, 47.2)
IIIA	77/132 (58.3)	17/132 (12.9)	45.5 (35.3, 55.6)
Histologic Type of Tumor			
Squamous	107/179 (59.8)	29/175 (16.6)	43.2 (34.2, 52.3)
Non-squamous	18/45 (40.0)	5/50 (10.0)	30.0 (13.4, 46.6)
PD-L1 Expression			
< 1% [excluding NE/indeterminate]	43/89 (48.3)	14/84 (16.7)	31.6 (18.6, 44.7)
>= 1%	81/130 (62.3)	19/132 (14.4)	47.9 (37.7, 58.2)
1-49%	33/59 (55.9)	11/70 (15.7)	40.2 (24.9, 55.5)
>= 50%	48/71 (67.6)	8/62 (12.9)	54.7 (41.0, 68.4)
Smoking Status			
Current	14/18 (77.8)	3/17 (17.6)	60.1 (33.7, 86.5)
Former	98/174 (56.3)	28/171 (16.4)	39.9 (30.7, 49.2)
Never	15/34 (44.1)	3/39 (7.7)	36.4 (17.8, 55.1)



Data cutoff: 20FEB2023. Data extraction: 24MAR2023.
Mantel-Haenszel common risk difference was estimated along with its 95% CIs constructed by a normal approximation and Sato's variance estimator without stratification.

Figure 63: Forest Plot for Pathological Complete Response by BIPR (ITT Analysis Set)



Data cutoff: 20FEB2023.
Mantel-Haenszel common risk difference was estimated along with its 95% CIs constructed by a normal approximation and Sato's variance estimator without stratification.

Post-hoc analysis by platinum chemotherapy

Table 45: Subgroup Analysis of EFS by BICR for Neoadjuvant Platinum Chemotherapy

	Event/Total		Median (95% CI)		
Subgroup	**Arm A (N = 226)**	**Arm B (N = 227)**	**Arm A (N = 226)**	**Arm B (N = 227)**	**Unstratified HR (95% CI)**
Overall	72/226	98/227	NR (50.3, NE)	30.6 (16.6, 45.3)	0.58 (0.43, 0.79)
Neoadjuvant Platinum Chemotherapy					
Cisplatin	36/120	56/124	NR (50.3, NE)	35.7 (12.7, NE)	0.53 (0.35, 0.81)
Carboplatin	27/80	33/76	NR (22.7, NE)	23.2 (15.2, NE)	0.62 (0.37, 1.04)
Switched From Cisplatin to Carboplatin	9/25	9/25	NR (16.2, NE)	NR (8.8, NE)	0.73 (0.29, 1.84)

Data cutoff: 7MAR2025. Data extraction: 28MAR2025.
Unstratified hazard ratio and its 95% CIs were estimated using a Cox regression model.

Table 46: Subgroup Analysis of OS by BICR for Neoadjuvant Platinum Chemotherapy

	Event/Total		Median (95% CI)		
Subgroup	**Arm A (N = 226)**	**Arm B (N = 227)**	**Arm A (N = 226)**	**Arm B (N = 227)**	**Unstratified HR (95% CI)**
Overall	52/226	70/227	NR (NE, NE)	NR (NE, NE)	0.65 (0.45, 0.93)
Neoadjuvant Platinum Chemotherapy					
Cisplatin	23/120	40/124	NR (NE, NE)	NR (47.7, NE)	0.50 (0.30, 0.83)
Carboplatin	22/80	23/76	NR (45.2, NE)	NR (NE, NE)	0.85 (0.47, 1.52)
Switched From Cisplatin to Carboplatin	7/25	7/25	NR (35.0, NE)	NR (40.4, NE)	0.94 (0.33, 2.69)

Data cutoff: 7MAR2025. Data extraction: 28MAR2025.
Unstratified hazard ratio and its 95% CIs were estimated using a Cox regression model.

- **Supplementary analyses**

Sensitivity analysis of **OS** (based on DCO of 07 Mar 2025)

showed consistent results with the primary OS analysis (stratified OS HR 0.65 [95% CI: 0.45, 0.93]):

- Sensitivity Analysis 1: Unstratified OS analysis

  -> HR 0.65 (95% CI: 0.45 to 0.93)

- Sensitivity Analysis 2: OS analysis with stratification factors from electronic data capture (EDC)

  -> stratified HR 0.64 (95% CI: 0.45 to 0.92)

Sensitivity and supplementary analysis of **EFS** (based on DCO of 21 Aug 2023)

A supplementary analysis of EFS was conducted ignoring any subsequent anticancer therapy to address the impact of subsequent anticancer therapy received as it excluded the start of subsequent anticancer therapy as a reason for EFS censoring. Any tumour assessments conducted after the start of subsequent anticancer therapy, including progressive disease or death, were considered when deriving EFS. The stratified HR was 0.57 (95% CI: 0.41 to 0.79), showing an EFS benefit that was consistent with the primary analysis (HR = 0.56; 95% CI: 0.40 to 0.79).

Further sensitivity and supplementary analysis of EFS

showed overall consistent results with the primary analysis (HR = 0.56; 95% CI: 0.40 to 0.79):

- Sensitivity Analysis 1: Unstratified EFS analysis

  -> HR 0.57 (95% CI: 0.41 to 0.80)

- Sensitivity Analysis 2: EFS analysis with stratification factors from electronic data capture

  ->HR 0.57 (95% CI: 0.41 to 0.80)

- Sensitivity Analysis 3: EFS analysis ignoring missed > 1 tumor assessments

  ->HR 0.56 (95% CI: 0.40 to 0.77)

- Supplementary Analysis 2: EFS analysis to adjust for baseline covariates

  -> HR 0.55 (95% CI: 0.39 to 0.77)

- Supplementary Analysis 3: COVID-19 EFS supplementary analysis

-> HR 0.55 (95% CI: 0.39 to 0.78)

- Supplementary Analysis 4: EFS analysis based on Max-Combo method

  ->HR 0.57 (95% CI, 0.39 to 0.83)

- Supplementary Analysis 5: EFS analysis based on restricted mean survival time method

  -> 4.69-month difference in EFS RMST (95% CI: 1.89 to 7.48), i.e. favourable EFS in Arm A vs Arm B

- Supplementary Analysis 6: EFS analysis including progression occurring before surgery but not precluding surgery -> HR was 0.56 (95% CI: 0.40 to 0.77)

An additional post-hoc supplementary analysis was performed in which a progression or death was not censored if it occurred after missing more than one tumour assessment or occurred after the start of new anti-cancer therapy.

Table 47: Analysis of EFS by BICR – Supplementary Analysis Ignoring Subsequent Anti-Cancer Therapy or Missed More Than One Tumour Assessments (ITT Analysis Set)

	Arm A (N = 226)	**Arm B (N = 227)**
Event-Free Survival		
Events, n (%)	63 (27.9)	98 (43.2)
Progressive Disease Precluding Study Surgery [a]	7 (3.1)	20 (8.8)
Progressive Disease [b]	44 (19.5)	63 (27.8)
Death	12 (5.3)	15 (6.6)
Censored, n (%)	163 (72.1)	129 (56.8)
No Baseline Assessment	5 (2.2)	5 (2.2)
No Post Surgery Assessment	6 (2.7)	7 (3.1)
Lost to Follow-up	1 (0.4)	0 (0.0)
Subject Withdrawal	3 (1.3)	6 (2.6)
Ongoing Without Events	148 (65.5)	111 (48.9)
Stratified Hazard Ratio (95% CI) [c]	0.55 (0.40, 0.76)	--
1-Sided Stratified p-Value [d]	< 0.0001	--
Event-Free Survival (Months) [e]		
Median (95% CI)	NR (NE, NE)	26.3 (16.6, NE)
Q1 (95% CI)	15.6 (11.5, 21.7)	8.9 (6.7, 11.2)
Q3 (95% CI)	NR (NE, NE)	NR (NE, NE)
Event-Free Survival Rate at, % (95% CI) [f]		
12 Months	79.7 (73.5, 84.7)	67.5 (60.6, 73.5)
24 Months	67.9 (60.4, 74.2)	50.4 (42.7, 57.5)
36 Months	62.6 (53.4, 70.5)	43.5 (34.4, 52.2)

Data cutoff: 21AUG2023. Data extraction: 18SEP2023.
[a] Progressive disease precluding surgery included radiographic disease progression per RECIST v1.1 precluding surgery or a disease progression not reaching the RECIST v1.1 criteria but which still precludes surgery (reason for no surgery is progressive disease or tumor unresectable).
[b] Progressive disease included patients who did not receive surgery but had disease progression after presurgical visit and patients receiving surgery with local or distant recurrence.
[c] Hazard ratio and 95% CIs were estimated using a Cox regression model stratified by histology (squamous vs nonsquamous), disease stage (stage II vs stage IIIA) and PD-L1 expression (<1%/not evaluable/indeterminate vs >=1%) from Interactive Response Technology.
[d] The descriptive p-value was calculated using a log-rank test stratified by histology (squamous vs nonsquamous), disease stage (stage II vs stage IIIA) and PD-L1 expression (<1%/not evaluable/indeterminate vs >=1%) from Interactive Response Technology.
[e] Medians and other quartiles were estimated by the Kaplan-Meier method with 95% CIs estimated using the Brookmeyer and

Crowley method with log-log transformation.
[f] Event-free rates were estimated using the Kaplan-Meier method with 95% CIs estimated using the Greenwood formula.

Table 48: Censoring Reason and Follow-up Time of the Patients with Early Censoring for Event-Free Survival by Blinded Independent Central Review (ITT Analysis Set)

	Arm A (N = 226)	Arm B (N = 227)
Event-Free Survival		
Censored, n (%)	32 (14.2)	46 (20.3)
No Baseline Assessment	5 (2.2)	5 (2.2)
No Postbaseline Assessment	0 (0.0)	1 (0.4)
No Post Surgery Assessment	6 (2.7)	13 (5.7)
New Anticancer Therapy Before Progression/Recurrence/Death	10 (4.4)	14 (6.2)
Progression/Recurrence/Death After > 1 Missed Assessment	2 (0.9)	3 (1.3)
Lost to Follow-up	1 (0.4)	0 (0.0)
Subject Withdrawal	3 (1.3)	6 (2.6)
Ongoing Without Events	5 (2.2)	4 (1.8)
Follow-up Time (Months) [a]		
Median (95% CI)	2.6 (1.5, 2.9)	2.6 (2.4, 3.1)
Min, Max	0.0, 5.9	0.0, 5.8

Data cutoff: 21AUG2023. Data extraction: 18SEP2023.
[a] Median was estimated by the reverse Kaplan-Meier method with 95% CIs estimated using the Brookmeyer and Crowley method.
Note: Early censoring is defined as any censoring occurring within the first 6 months following randomization, thereby capturing censoring during both the neoadjuvant and surgical phases.

Baseline characteristics and EFS by outcomes for pCR and MPR

Table 49: Demographic and Baseline Characteristics by pCR Status (ITT Analysis Set)

	pCR		Non-pCR	
Characteristic	**Arm A (N = 92)**	**Arm B (N = 13)**	**Arm A (N = 134)**	**Arm B (N = 214)**
Age (Years)				
Median	63.5	61.0	61.0	63.0
Min, Max	44, 78	52, 69	30, 80	36, 78
Age Group, n (%)				
< 65 Years	51 (55.4)	7 (53.8)	92 (68.7)	122 (57.0)
>= 65 Years	41 (44.6)	6 (46.2)	42 (31.3)	92 (43.0)
Sex, n (%)				
Male	88 (95.7)	11 (84.6)	117 (87.3)	194 (90.7)
Female	4 (4.3)	2 (15.4)	17 (12.7)	20 (9.3)
BMI (kg/m2)				
Median	23.54	22.27	23.28	23.21
Min, Max	16.5, 37.4	18.9, 29.4	16.3, 32.6	15.0, 36.3
ECOG Performance Status, n (%)				
0	56 (60.9)	12 (92.3)	86 (64.2)	142 (66.4)
1	35 (38.0)	1 (7.7)	48 (35.8)	72 (33.6)
Missing	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)
Smoking Status, n (%)				
Current	22 (23.9)	5 (38.5)	23 (17.2)	47 (22.0)
Former	61 (66.3)	6 (46.2)	87 (64.9)	132 (61.7)
Never	9 (9.8)	2 (15.4)	24 (17.9)	35 (16.4)
Histology From CRF, n (%)				
Squamous	74 (80.4)	11 (84.6)	105 (78.4)	164 (76.6)

Characteristic	pCR		Non-pCR	
	Arm A (N = 92)	Arm B (N = 13)	Arm A (N = 134)	Arm B (N = 214)
Nonsquamous	16 (17.4)	2 (15.4)	29 (21.6)	48 (22.4)
Other [a]	2 (2.2)	0 (0.0)	0 (0.0)	2 (0.9)
Disease Stage From CRF, n (%) [b]				
IB	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)
II	35 (38.0)	5 (38.5)	57 (42.5)	86 (40.2)
IIIA	55 (59.8)	8 (61.5)	77 (57.5)	125 (58.4)
IIIB	1 (1.1)	0 (0.0)	0 (0.0)	3 (1.4)
PD-L1 Expression From Central Lab, n (%)				
< 1%	33 (35.9)	7 (53.8)	56 (41.8)	77 (36.0)
>= 1%	57 (62.0)	6 (46.2)	73 (54.5)	126 (58.9)
1-49%	23 (25.0)	2 (15.4)	36 (26.9)	68 (31.8)
>= 50%	34 (37.0)	4 (30.8)	37 (27.6)	58 (27.1)
Not Evaluable/Indeterminate	2 (2.2)	0 (0.0)	5 (3.7)	11 (5.1)

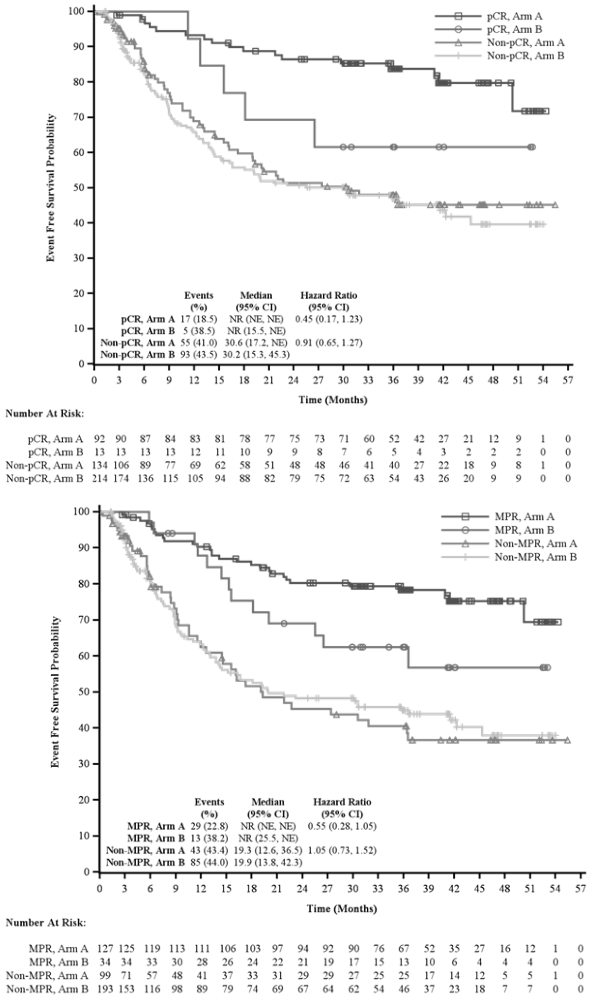
Source: Appendix Table 7. Data cutoff: 7MAR2025. Data extraction: 28MAR2025.
[a] Patients with mix histology were categorized into "Other" in CRF.
[b] Patients with stage IB and IIIB were enrolled mistakenly with protocol deviation reported.
Patients not having valid pathological value were considered as nonresponders where 90 patients did not have surgical resection and 2 patients had surgical resection but the pathological results were not collected.

Table 50: Demographic and Baseline Characteristics by MPR Status (ITT Analysis Set)

Characteristic	MPR		Non-MPR	
	Arm A (N = 127)	Arm B (N = 34)	Arm A (N = 99)	Arm B (N = 193)
Age (Years)				
Median	63.0	61.5	60.0	63.0
Min, Max	44, 78	51, 75	30, 80	36, 78
Age Group, n (%)				
< 65 Years	72 (56.7)	19 (55.9)	71 (71.7)	110 (57.0)
>= 65 Years	55 (43.3)	15 (44.1)	28 (28.3)	83 (43.0)
Sex, n (%)				
Male	120 (94.5)	31 (91.2)	85 (85.9)	174 (90.2)
Female	7 (5.5)	3 (8.8)	14 (14.1)	19 (9.8)
BMI (kg/m2)				
Median	23.43	22.33	23.44	23.32
Min, Max	16.5, 37.4	17.0, 29.4	16.3, 32.6	15.0, 36.3
ECOG Performance Status, n (%)				
0	78 (61.4)	26 (76.5)	64 (64.6)	128 (66.3)
1	48 (37.8)	8 (23.5)	35 (35.4)	65 (33.7)
Missing	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Smoking Status, n (%)				
Current	33 (26.0)	10 (29.4)	12 (12.1)	42 (21.8)
Former	80 (63.0)	21 (61.8)	68 (68.7)	117 (60.6)
Never	14 (11.0)	3 (8.8)	19 (19.2)	34 (17.6)
Histology From CRF, n (%)				
Squamous	107 (84.3)	29 (85.3)	72 (72.7)	146 (75.6)
Nonsquamous	18 (14.2)	5 (14.7)	27 (27.3)	45 (23.3)
Other [a]	2 (1.6)	0 (0.0)	0 (0.0)	2 (1.0)
Disease Stage From CRF, n (%) [b]				
IB	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
II	48 (37.8)	17 (50.0)	44 (44.4)	74 (38.3)
IIIA	77 (60.6)	17 (50.0)	55 (55.6)	116 (60.1)

	MPR		Non-MPR	
Characteristic	**Arm A (N = 127)**	**Arm B (N = 34)**	**Arm A (N = 99)**	**Arm B (N = 193)**
IIIB	1 (0.8)	0 (0.0)	0 (0.0)	3 (1.6)
PD-L1 Expression From Central Lab, n (%)				
< 1%	43 (33.9)	14 (41.2)	46 (46.5)	70 (36.3)
>= 1%	81 (63.8)	19 (55.9)	49 (49.5)	113 (58.5)
1-49%	33 (26.0)	11 (32.4)	26 (26.3)	59 (30.6)
>= 50%	48 (37.8)	8 (23.5)	23 (23.2)	54 (28.0)
Not Evaluable/Indeterminate	3 (2.4)	1 (2.9)	4 (4.0)	10 (5.2)

Figure 64: Kaplan-Meier Plot for Event-Free Survival by BICR by pCR/MPR Status (ITT Analysis Set)



Data cutoff: 7MAR2025. Data extraction: 28MAR2025.
Patients who did not receive surgical resection were considered as nonresponders in the analysis.
Unstratified hazard ratio and its 95% CIs were estimated using a Cox regression model.

Table 51: Summary of Treatment Status and Surgical Outcomes for Non-MPR and Non-pCR Patients

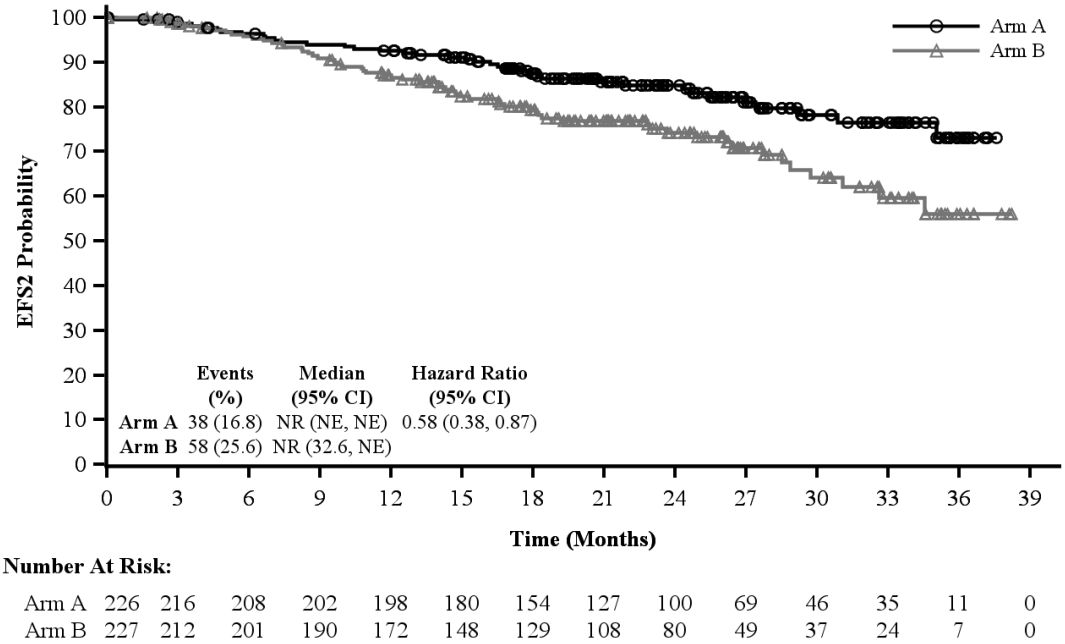
	Non-MPR		Non-pCR	
Characteristic	**Arm A (N = 99)**	**Arm B (N = 193)**	**Arm A (N = 134)**	**Arm B (N = 214)**
Neoadjuvant Treatment Complete, n (%)	87 (87.9)	176 (91.2)	121 (90.3)	197 (92.1)
Surgery Status, n (%)				
Completed	63 (63.6)	139 (72.0)	98 (73.1)	160 (74.8)
Cancelled	36 (36.4)	54 (28.0)	36 (26.9)	54 (25.2)
Pathological TNM Stage, n (%)				
0/I	16 (25.4)	48 (34.5)	29 (29.6)	62 (38.8)
II	16 (25.4)	44 (31.7)	33 (33.7)	48 (30.0)
III	31 (49.2)	45 (32.4)	36 (36.7)	48 (30.0)
IV	0 (0.0)	2 (1.4)	0 (0.0)	2 (1.3)
Resected Patients Who Dropout Before Adjuvant Treatment, n (%)	11 (11.1)	26 (13.5)	15 (11.2)	26 (12.1)

The denominator for the percentages of patients in each pathological TNM stage is the number of patients who completed surgical resection.

Exploratory Efficacy Analysis

Event-Free Survival on Next-Line of Treatment

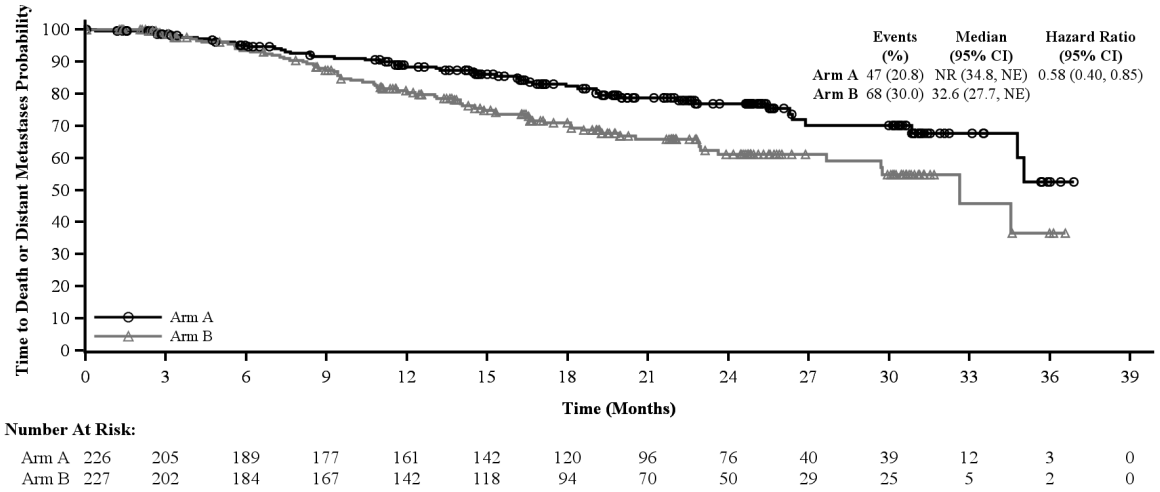
Figure 65 : KM Plot for EFS on Next Line of Therapy by Investigator (ITT Analysis Set)



Hazard ratio and 95% CIs were estimated using a Cox regression model stratified by histology (squamous vs non-squamous), disease stage (stage II vs stage IIIA) and PD-L1 expression (<1%/not evaluable/indeterminate vs >=1%) from Interactive Response Technology.

Time to Death or Distant Metastases

Figure 66 : KM Plot for Time to Death or Distant Metastases by Investigator



Hazard ratio and 95% CIs were estimated using a Cox regression model stratified by histology (squamous vs non-squamous), disease stage (stage II vs stage IIIA) and PD-L1 expression (<1%/not evaluable/indeterminate vs >=1%) from Interactive Response Technology.

- **Applicability of Study 315 Data to the EU Patient Population**

Considering all patients in the pivotal Study 315 were Chinese, the MAH performed three analyses to demonstrate the applicability of Study 315 to target population of EU resectable NSCLC population:

- Comparison of disease characteristics between Study 315 and European NSCLC patient population
- Quantification of the transferability of treatment effects observed in Study 315 to a European NSCLC patient population
- Population-adjusted treatment comparisons between Study 315 and other ICIs for patients with NSCLC in neoadjuvant/adjuvant setting

Comparison of Disease Characteristics Between European Patients with NSCLC and Study 315 Patient Population

Embase and PubMed databases were searched to identify scientific literature published over the past 5 years that reported baseline characteristics and disease status of patients with resectable NSCLC in pan-EU, EU regions, or single EU countries to conduct a comparison between the Study 315 patient population (Stage II to IIIA) and the EU resectable NSCLC patient population (across Stage I to III).

Seventeen relevant articles were included in the pooled literature analysis and the comparison is presented below.

Table 52: Comparison of Baseline and Disease Characteristics Between Study 315 and European Resectable NSCLC Patient Population

Characteristics	BGB-A317-315 Patient Population	EU Patient Population *
Age (years), Median	62.0	66.8
Gender Female (%)	**9.5**	**41.9**
Current/Former Smoker(%)	84.6	82.7

Characteristics	BGB-A317-315 Patient Population	EU Patient Population *
ECOG 0-1 (%)	100.0	84.6
Clinical TNM Stage 8th [a] (%)		
Stage II	40.4	28.0 (49.0 [b])
Stage III	59.4	29.5 (51.0 [b])
Histology Within NSCLC (%)		
Squamous cell carcinoma	**78.1**	**36.6**
Adenocarcinoma	**21.0**	**58.8**
PD-L1 Expression (%) [c]		
PD-L1 < 1%	38.2	35.7
Not evaluable/Indeterminate	4.0	18.9
PD-L1 ≥ 1%	57.8	45.4

[a] Stage I was not presented under this category to align with Study 315 population.
[b] The denominator in the brackets is the sum of clinical Stage II and III patients in the selected literature. As patients with Stage I NSCLC reported in the literature cannot be excluded from the pooled EU analysis for the whole comparison, the proportion of Stage II or III disease was also analysed using sum of Stage II + Stage III as denominator.
[c] References for PD-L1 expression summary are marked in the sources.

Quantification of the Transferability of Treatment Effects Observed in Study 315 to a European NSCLC Patient Population

Targeted Literature Reviews (TLR) were conducted that included a summary of relevant information related to RWE (TLR 1), target regulatory and HTA documents for multiregional RCTs (TLR 2), and potential effect modifiers (EM) (TLR 3).

In short, the European RWE population (TLR1) and the population of international trials (TLR2) were generally aligned with the Study 315 population in terms of age, ECOG status, and disease stage, but the proportion of men was higher in Study 315 (90.5%), and more patients with squamous histology (78.1%) were included in the study. Age, sex, smoking status, histology, disease stage, PD-L1 status, race, and geographical region were explored as potential EMs or predictive factors for clinical efficacy outcomes (TLR3). For each of the EMs, the efficacy results (EFS, MPR and pCR) were presented from the identified international trials. As a result of this analysis, no absolute EM was apparent, nor could they be ruled out as potential EMs.

In an additional analysis, EFS was predicted for a European target population adjusting for the potential EMs listed before. Since it was not feasible to adjust for race or region because Study 315 included Chinese patients only, a descriptive comparison of the treatment effect across various regions and races in multiple RCTs was presented.

Table 53: Subgroup Analysis by Race or Region Available for Outcomes in Resectable NSCLC

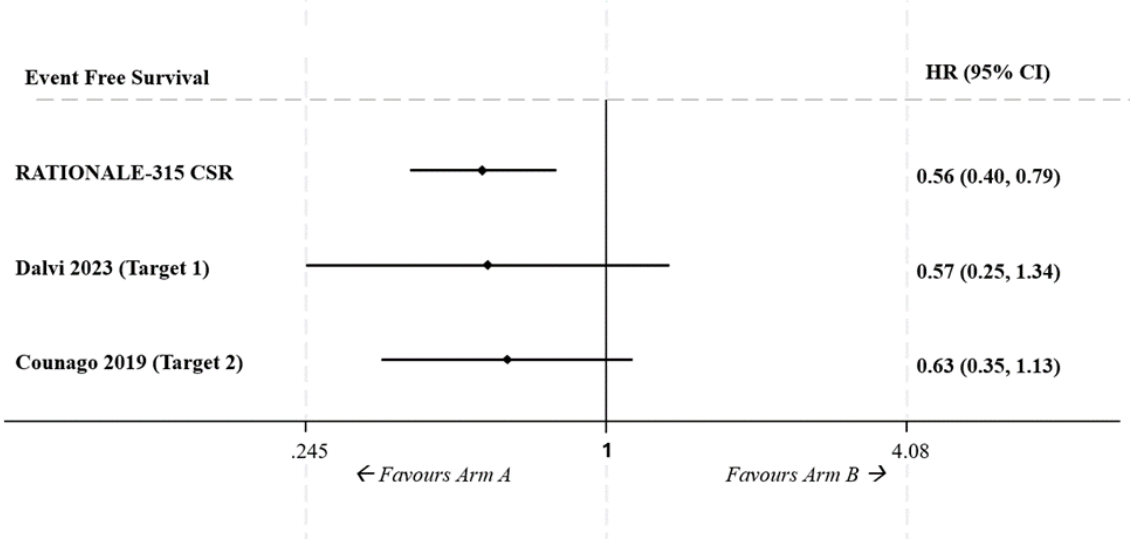
Study	Subgroup (sample size)	EFS HR (95% CI)
CheckMate- 77T	Region: North America (44)	0.59 (0.25, 1.38)
	Region: Europe (250)	0.61 (0.40, 0.92)
	Region: Asia (115)	0.47 (0.26, 0.86)
AEGEAN	Race: Asian (307)	0.60 (0.40, 0.90)
	Race: Non-Asian (433)	0.76 (0.54, 1.06)
	Region: Asia (305)	0.62 (0.41, 0.93)
	Region: Europe (281)	0.75 (0.49, 1.14)
	Region: North America (86)	0.69 (0.27, 1.62)
	Region: South America (68)	0.71 (0.33, 1.53)
KEYNOTE-671	Race: White (489)	0.54 (0.41, 0.72)
	Race: Other (279)	0.62 (0.42, 0.89)
	Region: East Asia (244)	0.66 (0.45, 0.99)
	Region: Other (553)	0.54 (0.41, 0.69)
Zhou et al (Neoadjuvant-adjuvant vs control)	Region: Non-Asia (986)	0.61 (0.50, 0.75)
	Region: Asia (551)	0.63 (0.47, 0.84)
CheckMate- 816	Region: North America (91)	0.78 (0.38, 1.62)
	Region: Europe (66)	0.80 (0.36, 1.77)
	Region: Asia (177)	0.45 (0.29, 0.71)

Abbreviations: CI = confidence interval; EFS = event-free survival; HR = hazard ratio; NSCLC = non-small cell lung cancer; pCR = pathological complete response; MPR = major pathological response

To predict the efficacy results for the European target population, 2 RWE studies (Dalvi, 2003 and Counago, 2019) were selected to represent the European target population and an outcome regression was performed using the following variables: age, sex, disease stage, histology, smoking status, and ECOG performance status.

The EFS results predicted for the two European target populations had similar point estimates, but wider CIs compared to Study 315:

Figure 67 : Treatment Effect for EFS by BIPR (TIS+CT Versus CT) Observed in Study 315 and Predicted in Target European Population



Outcome regression with adjustment for age, sex, disease stage, histology, smoking status, ECOG (not adjusted for sensitivity analysis due to lack of available data in the target population).

- **Population-adjusted treatment comparisons between Study 315 and other ICIs for patients with NSCLC in neoadjuvant/adjuvant setting**

Treatment comparisons based on EFS HRs were performed to further evaluate the benefit of perioperative tislelizumab plus neoadjuvant chemotherapy in the treatment of resectable NSCLC and how it compared to other global studies of perioperative ICI combination with similar design as Study 315. The publicly available summary level data from these global studies, including AEGEAN (durvalumab), CheckMate-77T (nivolumab), and Keynote 671 (pembrolizumab), were used to estimate the EFS HR in Study 315 after adjusting for differences in baseline characteristics according to the relevant perioperative ICI studies.

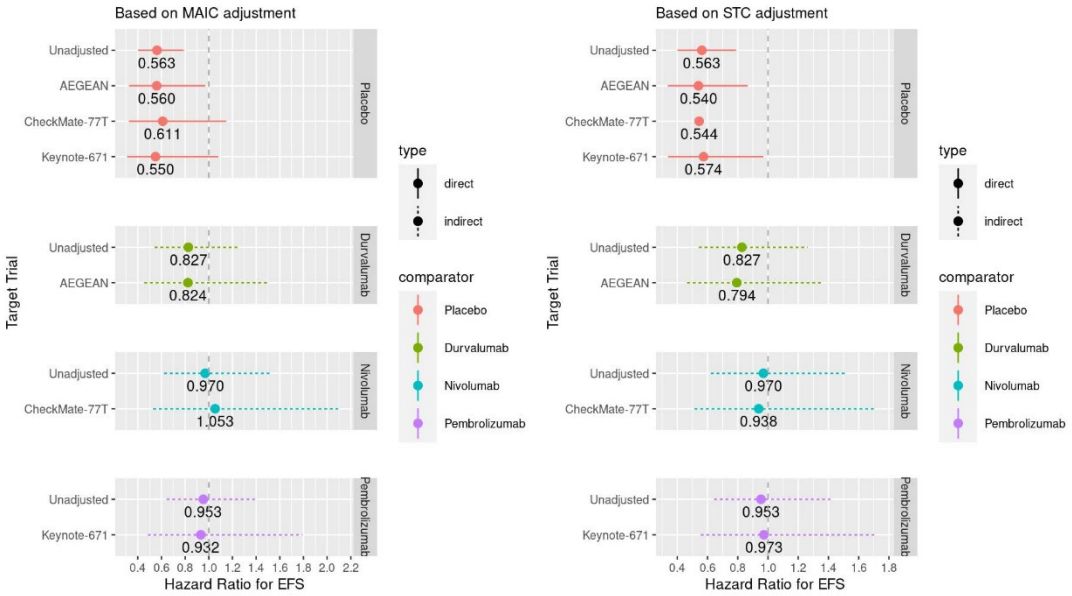
To address potential bias arising from indirect comparison of heterogeneous study populations, 2 well-established population adjustment methods, i.e., MAIC (Signorovitch et al 2012) and STC (Ishak et al 2015), were used. By matching the individual patient data from Study 315 to the summary data from the aforementioned perioperative ICI studies, the 2 methods, MAIC and STC, were utilized to adjust the direct treatment effects of perioperative tislelizumab plus neoadjuvant chemotherapy arm against the internal control arm, and to construct anchored indirect treatment effect of perioperative tislelizumab plus neoadjuvant chemotherapy arm against other perioperative ICI combination arms.

The following covariates were used for adjustment: sex (male versus female), prior smoking history (never versus former/current), disease stage (Stage III: yes versus no), histology (squamous: yes versus no), PD-L1 median expression (1% to 49%: yes versus no), and PD-L1 high expression (≥ 50%: yes versus no). Since Asian was the only race included in Study 315, it was not possible to reweight race against other perioperative ICI combination studies.

In the figure below, the upper panel depicting EFS HRs and corresponding 95% CIs, presented in red, shows the direct comparison between the perioperative tislelizumab plus neoadjuvant chemotherapy arm and the internal control arm, before (unadjusted) and after adjustment for baseline characteristics using MAIC for each of the perioperative ICI studies. After population adjustment, the analysis revealed a consistent EFS treatment benefit in favour of tislelizumab when compared with the unadjusted results.

Additional analyses presented in figure below show the EFS HRs and 95% CIs in green, blue, and violet corresponding to the indirect population-adjusted comparisons of tislelizumab experimental arms relative to other perioperative ICI combinations.

Figure 68: Population-Adjusted Hazard Ratios for Event-Free Survival and Indirect Treatment Comparisons With Other ICI Combinations in Resectable NSCLC – Study 315 (ITT Analysis Set)



Abbreviations: EFS, event-free survival; ICI, immune checkpoint inhibitor; ITT, intent-to-treat; MAIC, matching-adjusted indirect comparison; STC, simulated treatment comparison.

Summary of main study(ies)

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

Table 54: Summary of Efficacy for study 315

Title: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study to Compare the Efficacy and Safety of Neoadjuvant Treatment With Tislelizumab (BGB-A317, Anti PD-1 Antibody) or Placebo Plus Platinum-Based Doublet Chemotherapy Followed By Adjuvant Tislelizumab or Placebo in Resectable Stage II or IIIA Non-Small Cell Lung Cancer		
Study identifier	BGB-A317-315	
Design	Randomized, Double-Blind, Placebo-Controlled, Phase 3	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	First participant randomized: 08 June 2020; study ongoing Not applicable Not applicable
Hypothesis	Superiority	
Treatments groups	TIS Arm (tislelizumab + neoadjuvant chemotherapy/ tislelizumab) n=226 randomized, 226 treated	tislelizumab (200 mg) + platinum-based doublet chemotherapy on a 3-week cycle for 3 to 4 cycles, followed by surgical resection, and then adjuvant tislelizumab (400 mg) on a 6-week cycle for up to 8 cycles

	PBO Arm (placebo + neoadjuvant chemotherapy/ placebo) n=227 randomized, 226 treated		placebo + platinum-based doublet chemotherapy on a 3-week cycle for 3 to 4 cycles, followed by surgical resection, and then placebo on a 6-week cycle for up to 8 cycles
Endpoints and definitions	Dual-Primary endpoint	Major pathological response (MPR) rate by Blinded Independent Pathology Review (BIPR)	The proportion of patients with $\leqslant$ 10% residual viable tumour in the resected primary tumour and all resected lymph nodes after completion of neoadjuvant therapy
	Dual-Primary endpoint	Event-free survival (EFS) by Blinded Independent Central Review (BICR)	The time from randomization until any of the following events, whichever occurs first: disease progression precluding surgery, local or distant recurrence assessed by BICR, or death due to any cause
	Key secondary endpoint	Pathological complete response (pCR) rate by BIPR	The proportion of patients with absence of residual tumour in the resected primary tumour and all resected lymph nodes after completion of neoadjuvant therapy as assessed by BIPR
	Secondary endpoint	Overall survival (OS)	The time from the date of randomization to the date of death due to any cause
	Secondary endpoint	Objective response rate (ORR) by BICR	The proportion of patients who had complete or partial response before surgery as assessed by BICR per RECIST v1.1 in all randomized patients with measurable disease at baseline
	Secondary endpoint	Disease-free survival (DFS) by BICR	The time from the start date of surgery with outcome R0 resection to local or distant recurrence (by BICR) or death due to any cause, whichever occurs first after surgery
Database lock	Final analysis for MPR and pCR rate by BIPR: Data cutoff: 20 February 2023, Database lock: 24 March 2023 Interim Analysis for EFS and other efficacy endpoints: Data cutoff: 21 August 2023, Database lock: 18 September 2023		
Results and Analysis			
Analysis description	**Primary Analysis – EFS by BICR** EFS was formally tested with the multiplicity-adjusted, one-sided p-value boundary of 0.0105.		
Analysis population and time point description	Intent to treat Interim analysis; Data cutoff: 21 August 2023		
Descriptive statistics and estimate variability	Treatment group	TIS Arm	PBO Arm
	Number of subjects	226	227
	EFS by BICR (n events, %)	58 (25.7)	83 (36.6)
	EFS (median)	Not reached (NR)	NR
	95% confidence interval (CI)	Not evaluable (NE), NE	16.6 months, NE
		Comparison groups	TIS Arm vs PBO Arm

Effect estimate per comparison	EFS by BICR (dual primary endpoint)	Stratified Hazard Ratio (HR)	0.56
		95% CI	0.40, 0.79
		P-value (log-rank)	0.0003
Analysis description	**Primary Analysis – MPR rate by BIPR** MPR was formally tested with the multiplicity-adjusted, one-sided p-value boundary of 0.005.		
Analysis population and time point description	Intent to treat Final analysis; Data cutoff: 20 February 2023		
Descriptive statistics and estimate variability	Treatment group	TIS Arm	PBO Arm
	Number of subjects	226	227
	MPR rate by BIPR (%)	56.2	15.0
	95% CI	49.5, 62.8	10.6, 20.3
Effect estimate per comparison	MPR by BIPR (dual primary endpoint)	Comparison groups	TIS Arm vs PBO Arm
		Risk difference, %	41.1
		95% CI	33.2, 49.1
		P-value (Cochran-Mantel-Haenszel method)	< 0.0001
Analysis description	**Secondary Analysis – pCR rate by BIPR**		
Analysis population and time point description	Intent to treat Final analysis; Data cutoff: 20 February 2023		
Descriptive statistics and estimate variability	Treatment group	TIS Arm	PBO Arm
	Number of subjects	226	227
	pCR rate by BIPR (%)	40.7	5.7
	95% CI	34.2, 47.4	3.1, 9.6
Effect estimate per comparison	pCR by BIPR (key secondary endpoint)	Comparison groups	TIS Arm vs PBO Arm
		Risk difference, %	35.0
		95% CI	27.9, 42.1
		P-value (Cochran-Mantel-Haenszel method)	< 0.0001
Analysis description	**Secondary Analysis – OS** OS was formally tested with the multiplicity-adjusted, one-sided p-value boundary of 0.0001.		
Analysis population and time point description	Intent to treat Interim analysis; Data cutoff: 21 August 2023		
Descriptive statistics and estimate variability	Treatment group	TIS Arm	PBO Arm
	Number of subjects	226	227
	OS (n events, %)	31 (13.7%)	45 (19.8%)
	OS (median)	NR	NR
	95% CI	NE, NE	35.0 months, NE
		Comparison groups	TIS Arm vs PBO Arm

Effect estimate per comparison	OS (secondary endpoint)	Stratified HR	0.62
		95% CI	0.39, 0.98
		P-value (log-rank)	0.0193
Analysis description	**Secondary Analysis – ORR by BICR**		
Analysis population and time point description	Intent to treat Interim analysis; Data cutoff: 21 August 2023		
Descriptive statistics and estimate variability	Treatment group	TIS Arm	PBO Arm
	Number of subjects	226	227
	ORR by BICR, %	71.2	55.1
	95% CI	64.9, 77.0	48.3, 61.7
Effect estimate per comparison	ORR by BICR (secondary endpoint)	Comparison groups	TIS Arm vs PBO Arm
		Risk difference, %	15.9
		95% CI	7.3, 24.5
Analysis description	**Secondary Analysis – DFS by BICR**		
Analysis population and time point description	Patient who underwent resection R0 in the intent-to-treat population Interim analysis; Data cutoff: 21 August 2023		
Descriptive statistics and estimate variability	Treatment group	TIS Arm	PBO Arm
	Number of subjects	181	161
	DFS (n events, %)	41 (22.7%)	50 (31.1%)
	DFS (median)	NR	NR
	95% CI	NE, NE	NE, NE
Effect estimate per comparison	DFS by BICR (secondary endpoint)	Comparison groups	TIS Arm vs PBO Arm
		Stratified HR	0.76
		95% CI	0.49, 1.16
Notes	• The dual-primary endpoints of EFS by BICR and MPR rate by BIPR were met and statistically significant. • OS data were not mature at the time of interim analysis; however, the trend in OS benefit was observed in TIS Arm versus PBO Arm.		

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

A comparison of results across studies of tislelizumab is not applicable because Study 315 is the only study evaluating the efficacy of neoadjuvant tislelizumab plus platinum-based chemotherapy followed by adjuvant tislelizumab in patients with resectable Stage II or IIIA NSCLC.

Clinical studies in special populations

Table 55: Demographic and baseline characteristics (ITT analysis set)

Characteristic	Arm A (N = 226)	Arm B (N = 227)	Total (N = 453)
Age (Years)			
n	226	227	453
Mean (SD)	61.6 (7.61)	61.7 (8.05)	61.6 (7.83)
Median	62.0	63.0	62.0

Characteristic	Arm A (N = 226)	Arm B (N = 227)	Total (N = 453)
Q1, Q3	57.0, 67.0	56.0, 68.0	56.0, 67.0
Min, Max	30, 80	36, 78	30, 80
Age Group, n (%)			
< 65 Years	143 (63.3)	129 (56.8)	272 (60.0)
>= 65 Years	83 (36.7)	98 (43.2)	181 (40.0)

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Efficacy data supporting this application for extension of indication derive from the ongoing double-blind, randomised, placebo-controlled Asia-only study evaluating the efficacy and safety of neoadjuvant treatment with tislelizumab or placebo plus platinum-based doublet chemotherapy followed by adjuvant tislelizumab or placebo in resectable Stage II or IIIA NSCLC (Study 315). Eligible patients were randomized 1:1 according to the stratification factors disease stage (II vs. IIIA), histology (squamous vs. non squamous), and PD-L1 expression (≥ 1% vs. < 1% or not evaluable or indeterminate), which is considered adequate.

The way the study was designed, i.e. treatment of all patients with a neoadjuvant phase as well as an adjuvant treatment regimen, however does not allow to disentangle the contribution of the neoadjuvant versus the adjuvant treatment to the efficacy outcome of the study. Moreover, no conclusions may be drawn on the possibility of omission of one or the other treatment, while efficacy may be retained but toxicity of the therapy could be reduced. Conclusively, only the entire treatment strategy, i.e. the neoadjuvant in addition to the adjuvant treatment, is evaluable in this assessment procedure. This is considered a crucial deficiency of the study design which is further discussed with the exploratory analyses of EFS results by pCR / MPR status below.

Patient population

The study enrolled 453 stage II or IIIA NSCLC patients (by AJCC 8th ed) that were treatment-naïve for their current lung cancer and eligible for surgical resection with curative intent. The initially proposed indication wording was revised by replacing "patients with resectable (tumours ≥4 cm or node positive) NSCLC" with "patients with resectable NSCLC at high risk of recurrence (for selection criteria, see section 5.1)", in line with precedents in similar disease settings and since the initially proposed wording was not considered sufficiently accurate with regards to the exclusion of patients with certain T4 or N3 positive (Stage IIIB) tumours in Study 315. A detailed description was added in section 5.1 of the SmPC to define patients with a high risk of recurrence who are included in the therapeutic indication and are reflective of the patient population with Stage II – IIIA according to the 8th edition AJCC staging system.

Patients were enrolled regardless of PD-L1 expression. Assessment of PD-L1 expression at baseline (by central laboratory) was introduced and implemented as stratification factor (≥1% vs. <1%/not evaluable/indeterminate) with protocol amendment 1.0. This change was made prior to randomisation of the first patient on study and it is thus acceptable.

Only patients with a good clinical condition such as ECOG PS of 0 or 1 and adequate organ and cardiopulmonary function were enrolled. Patients were excluded in case of any prior treatment with a

checkpoint inhibitor and in case of known EGFR mutation or ALK gene translocation. The applied eligibility criteria are overall considered adequate and are reflected in section 5.1 of the SmPC.

Treatments

In the neoadjuvant phase, patients were treated with tislelizumab (at the approved posology of 200mg Q3W) or placebo in addition to cisplatin or carboplatin in combination with either pemetrexed (non-squamous histology) or paclitaxel (squamous histology) for 3 – 4 cycles. The chemotherapy regimen was selected based on investigator's choice (determined prior to randomization; a switch from cisplatin to carboplatin was allowed per investigator's discretion).

In the subsequent adjuvant treatment phase, the dosing regimen for tislelizumab was changed to 400mg Q6W, which was administered for up to 8 cycles.

Crossover between the tislelizumab and placebo arm was not allowed. This is endorsed, as it allows a more reliable assessment of OS. Furthermore, it is noted that immunotherapy was the most frequently administered post-treatment anticancer therapy (11.3%) in both treatment arms, with almost balanced rates comparing the tislelizumab (9.3%) and the placebo arm (13.2%). It is therefore not expected that post-treatment anticancer therapy has considerably confounded the OS results.

Postoperative radiotherapy (PORT) was allowed as option for patients with pathological N2+ disease after surgery. It was solely performed for 3 patients (1.3%) in the tislelizumab arm and 5 patients (2.2%) in the placebo arm. Due to the generally infrequent administration of PORT and comparable rate between the treatment arms, no relevant impact on efficacy results is anticipated.

Endpoints

Study 315 was designed with MPR rate by BIPR (≤ 10% residual viable tumour in the resected primary tumour and all resected lymph nodes after completion of neoadjuvant therapy) and EFS by BICR as dual primary endpoints. MPR rate as primary endpoint is not deemed adequate, as surrogacy with EFS or OS has not been sufficiently demonstrated so far. Many potential biases in determining MPR have been described, thereby preventing the use of MPR as a validated surrogate endpoint in the current setting.

The selection of EFS as primary endpoint is endorsed, as it is in accordance with the EMA guidance (EMA/CHMP/205/95 Rev. 6) and has been agreed as primary endpoint in preceding confirmatory studies in the (neo)adjuvant NSCLC setting. Importantly, the analysis of OS, which was implemented as secondary endpoint in the present study, is deemed highly relevant for demonstration of a favourable effect on the disease cure rate and ultimately, for the assessment of benefit-risk.

Further secondary (including pCR, ORR and DFS by BICR, investigator-assessed EFS) and exploratory efficacy endpoints (surgery outcome) are considered adequate.

Sample size

The sample size calculation was driven by the number of events required for the EFS analysis. Overall, 450 patients were planned to be enrolled over a 27 months recruitment period. A total of 184 EFS events were required to detect a HR of 0.65 with a power of 80% which would approximately occur at 51 months after the first patient randomized. In addition, one EFS interim analysis when approximately 75% of EFS events were observed was planned to occur at approximately 38 months after the first patient randomized. With this sample size, MPR and pCR were planned to have more than 95% power to detect a 20% difference in MPR rate, and 15% difference in pCR rate. The study was not sized to power OS, which is planned to be analysed at interim and final analysis of EFS.

Statistical analysis

MPR and pCR rates were planned to be analysed after the last operable patient had a pathological result after neoadjuvant treatment using the Cochran-Mantel-Haenszel method and stratification factors as used for randomisation. Patients who did not receive surgical resection or started new anticancer therapy prior to surgery were handled using a composite strategy, i.e. considered non-responders in the analysis.

For time-to-event outcomes EFS and OS a stratified log-rank test and Kaplan-Meier estimates were planned.

An EFS event includes disease progression precluding surgery, local or distant recurrence assessed by BICR and death due to any cause. Withdrawal from surgery and discontinuation from treatment were handled using a treatment policy strategy, and a new anticancer therapy prior to an EFS events was handled using a hypothetical strategy. Supplemental and sensitivity analyses were defined in the SAP to evaluate the different censoring rules.

OS was defined as the time from the date of randomisation to the date of death due to any cause. Patients who did not die at the time of analysis were censored at the date last known to be alive.

The overall type I error of 0.025 was split among the primary endpoints as follows: 0.005 was assigned to testing MPR, and 0.02 was assigned to testing EFS. An alpha-recycling scheme was implemented to test the primary and secondary endpoints with OS to be tested only if MPR, pCR and EFS were tested positive.

Overall, two interim analyses and one final analysis were planned. At the first interim analysis, MPR and pCR were tested once the last patient received surgery. At the second interim analysis, EFS and OS were tested approximately after 138 EFS events (75% information) were observed. A final analysis of EFS and OS was to be performed after 184 EFS events were observed. Updated OS data, including the PD-L1 subgroup results, will be provided by the MAH in Q1 2026 (**Recommendation**).

The testing strategy and multiplicity control is acceptable from a technical perspective. However, the relevance of testing pCR and MPR and in particular, only testing OS depending on positive results for MPR and pCR is questionable in light of limited evidence for their surrogacy.

Participant flow

At the data cut-off date of the prespecified IA of EFS (21 August 2023), almost all patients had completed treatment (4.9% vs. 3.5% of patients remained on adjuvant treatment in the tislelizumab vs. placebo arm). The majority of patients completed the neoadjuvant treatment phase (tislelizumab vs. placebo: 93.4% vs. 92.5%). Approximately 20% of patients did not undergo surgery, but this affected less patients in the tislelizumab as compared to the placebo arm (15.9% vs. 23.8%). Primary reasons for surgery cancellation included subject withdrawal (tislelizumab vs. placebo: 8.8% vs. 12.3%), progressive disease (tislelizumab vs. placebo: 2.7% vs. 7.5%) and adverse events (tislelizumab vs. placebo: 2.7% vs. 0.9%). All patients enrolled in Study 315 were required to be eligible for R0 resection as per inclusion criteria, therefore neoadjuvant treatment can be considered a loss of chance for cure for those patients determined to be inoperable after the neoadjuvant treatment phase. However, this is merely a general issue with neoadjuvant therapy still not considered standard of care for patients with (clearly) resectable early-stage NSCLC. Although there are several suggested benefits of neoadjuvant therapy in resectable NSCLC (e.g. early attacking of micro-metastases or sparing of critical organs by performing less invasive surgery of smaller tumours), adjuvant chemotherapy after surgery has generally been the preferred option, mainly because of the theoretical concern about resectable tumours becoming unresectable due to progressive disease during neoadjuvant chemotherapy (Upreti et al. 2020; Kalvapudi et al. 2023). Evidence from literature revealing no difference between preoperative and postoperative chemotherapy must however be considered (Upreti et al. 2020; Kalvapudi et al. 2023). From a mechanistic point of view, it appears

much more rational to use immunotherapy in the neoadjuvant setting when the tumour mass and antigen burden is large, thereby yielding a stronger antitumor T-cell response. In consideration of the aforementioned, and accounting for the fact that other studies in the same setting reported similar rates of (initially) resectable NSCLC patients not undergoing surgery after neoadjuvant treatment, neoadjuvant (immuno)-chemotherapy is deemed an acceptable approach.

Of those patients that underwent surgery, the vast majority of patients had R0 resection which was well distributed between treatment arms (tislelizumab vs. placebo: 95.3% vs. 93.1%). A higher proportion of patients in the tislelizumab arm had a delay in surgery (16.3%) compared to placebo (12.7%); 6.3% vs. 3.5% (for tislelizumab vs. placebo) had a delay due to adverse events. Subsequent to surgery, 74.3% of patients in the tislelizumab arm vs. 64.8% of patients in the placebo arm were treated in the adjuvant treatment phase. At the DCO date (21 August 2023), adjuvant treatment was completed by solely 46.9% of patients in the tislelizumab arm and 44.5% of patients in the placebo arm. Discontinuations of the adjuvant treatment were more frequent in the tislelizumab arm (22.6% vs 16.7%), mainly due to higher rates of discontinuations due to adverse event (6.6% vs. 1.8%), subject withdrawal (4.0% vs. 0.9%), and physician decision (3.1% vs. 0%), while discontinuation due to progressive disease was less frequent in the tislelizumab vs. placebo arm (8.8% vs. 14.1%).

Overall, a higher percentage of patients discontinued from study in the placebo arm (tislelizumab vs. placebo: 41 patients (18.1%) vs. 68 patients (30.0%)). Most common reason for patient discontinuation from study was death in both study arms, with lower frequency in the tislelizumab as compared to the placebo arm (13.7% vs. 20.3%), indicative of a beneficial treatment effect.

Conduct of the study

The original protocol for Study 315 (dated 09 August 2019) was amended three times, although protocol amendment 1.0 was issued prior to the first patients was randomized on study. Major changes were introduced with amendments 2.0 and 3.0: revision of pCR from a secondary to a primary endpoint and increase of sample size from 380 to 450 patients based on revised assumptions for the dropout patterns (amendment 2.0), and update of the EFS definition to include disease progression that does not reach RECIST v1.1 criteria but still precludes surgery as an event (amendment 3.0). By the time amendment 2.0 was implemented, around 80% of patients were already recruited, and amendment 3.0 was implemented after recruitment was completed, shortly before the primary analysis of MPR and pCR. The MAH confirmed that the revisions of amendment v2.0 were based on external evidence from other studies in the neoadjuvant / adjuvant treatment that showed a strong correlation of pCR with OS and / or informed on specific dropout patterns. Amendment v3.0 was made to align the EFS definition with those of similar studies. At the time of finalization of amendment v3.0, 92 (20.3%) EFS events have been observed. Overall, 87 patients (19.2%) had surgery cancellation. At least 5 patients across both arms were known to be impacted by the revised EFS definition, these were reclassified from censored to EFS events. The largest number of patients that were possibly affected by the revised EFS definition was 17 (3.8%), for whom physician decision was reported as reason for surgery cancellation. The distribution among both arms was not provided, however, this range of numbers (5 to up to 17 patients) is not assumed to have a clinically meaningful impact on the study outcomes.

Furthermore, the MAH outlined the implemented strategies to protect the data integrity and to maintain the blinding of the study data until the IDMC communicated that the study crossed the pre-specified p-value boundary for superiority testing of the primary endpoint of EFS. After a positive result from the MPR/pCR analysis, an unblinded team was established for the MPR/pCR publication and health authority consultation. While any publication of efficacy results that might be correlated to EFS or OS before these endpoints were formally analysed could increase the risk for bias, this risk is considered

to be low given that the study was otherwise blinded, EFS was analysed centrally and the EFS interim analysis was performed within 6 months.

Overall, the provided information supports the assumptions that the implemented protocol revisions were likely triggered by external studies rather than by knowledge of internal results of Study 315.

A numerically slightly higher rate of protocol deviations in the tislelizumab arm compared to the placebo arm (28.8% vs 23.3%) was primarily attributed to the category of Protocol Compliance (26.1% vs. 18.9%) and the subcategory of Study Assessments and Procedures (11.1% vs 5.3% in the tislelizumab vs the placebo arm, respectively). A more detailed review provided during the procedure did not raise any concerns that the reported imbalance of missed tumor assessments during follow-up or the missed safety evaluations had any meaningful impact on the interpretation of the study results.

Baseline characteristics

The study population included in Study 315 was predominantly male (90.5%) and had a median age of 62.0 years. Median age at diagnosis seems to be lower compared to other studies in similar populations, corresponding to data from the literature describing that Asian NSCLC patients are in general younger than Caucasian patients at diagnosis (Zhou & Christiani 2011: East meets West: ethnic differences in epidemiology and clinical behaviours of lung cancer between East Asians and Caucasians). Slightly more patients in the tislelizumab arm as compared to the placebo arm were < 65 years old (63.3% vs. 56.8%). Given that older patients were found to have a worse prognosis (Sheikh et al. 2023), this imbalance may have been in favour of the tislelizumab treatment arm. However, referring to the subgroup analysis by age group, no meaningful differences between patients aged below or above 65 years are apparent.

The majority of patients that were enrolled had ECOG PS 0 (65.3%), stage IIIA disease (58.6%), PD-L1 expression status ≥1% (57.8%), and squamous tumour histology (78.1%). In clinical studies with other checkpoint inhibitors in the same indication the distribution of histology types was approx. 50:50. Patients with non-squamous histology are thus somewhat underrepresented in Study 315. However, similar to the observations in other preceding trials with checkpoint inhibitors in the same indication, subgroup analysis of EFS do not indicate a differential treatment effect of study treatment in patients with squamous or non-squamous NSCLC.

Overall, demographics and baseline disease characteristics were comparable between the treatment groups.

It is noted that 85.2% of patients had unknown ALK gene translocation status and 71.1% of patients have not been tested for EGFR mutation status. However, determination of EGFR mutation status was solely required for patients with non-squamous NSCLC, and testing for ALK fusion oncogene status was generally not required in patients with unknown status. Wild type EGFR was confirmed for all patients with non-squamous NSCLC by a tissue-based test either locally or by central testing before randomization. In further consideration that the proportion of patients with non-squamous histology in the study was rather low (21.0%), the high rate of patients with unknown EGFR mutation and ALK rearrangement status can be explained.

Efficacy data and additional analyses

The provided efficacy results are based on three data cutoff dates.

At the first DCO of 20 February 2023, after the surgery of the last patient who was operated, the final analyses of Major Pathological Response (MPR) and Pathological Complete Response (pCR) were performed. Both endpoints were assessed by Blinded Independent Pathology Review (BIPR).

MPR rates, one of the dual primary endpoints, were statistically significant in the TIS arm compared to the PBO Arm (56.2% vs 15.0%, 1-sided p-Value <0.0001). At that time, also the secondary endpoint **pCR** was met, pCR rates were 40.7% in the TIS Arm compared to 5.7% in the PBO Arm (1-sided p-Value < 0.0001).
These results can be considered supportive to indicate a direct antitumor activity of tislelizumab in combination with chemotherapy in the neoadjuvant treatment setting of resectable NSCL. Nonetheless, the clinical value of these improvements in MPR and pCR remain currently unclear, as their use as surrogate markers for disease cure has not been demonstrated yet.

The interim efficacy analysis of Event Free Survival (**EFS**) by BICR, the second of the dual primary endpoints, was performed together with other efficacy endpoints at the DCO of 21 August 2023. EFS was statistically significant with an EFS HR of 0.56 (95% CI: 0.40, 0.79; 1-sided p-Value 0.0003). The analysis was based on 141 events with an event/patient ratio of 27.7% in the TIS Arm and 36.6% in the PBO Arm and a median study follow-up time of 22 months. A post-hoc supplementary analysis in line with EMA guidance[1] following the intention-to-treat principle, in which a progression or death was not censored if it occurred after missing more than one tumour assessment or occurred after the start of new anti-cancer therapy, showed consistent results (EFS HR 0.55, 95% CI: 0.40 to 0.76). Detailed censoring tables were provided. The number of patients censored due to non-administrative censoring were mostly equally distributed among both arms. For "no post-surgery assessment", a slight imbalance was observed with 2.7% and 5.7% of patients in Arm A and Arm B being censored. Early censoring, defined as any censoring within the first 6 months following randomization, occurred in 14.2% and 20.3% of patients in Arm A and Arm B. The imbalance was mainly driven by patients censored due to "no post-surgery assessment" with 2.7% and 5.7% in Arm A and Arm B, and due to "subject withdrawal" with 1.3% and 2.6% in Arm A and Arm B. The MAH argued the first may be due to less favourable pathological response after neoadjuvant treatment in Arm B (non-MPR: 4/6 patients in Arm A and 13/13 patients in Arm B). In both arms, the median follow-up time for early censored patients was 2.6 months. The remaining reasons for early censoring were balanced between both arms. Given that the imbalance due to "no post-surgery assessment" and "subject withdrawal" affected only a small number of patients, this is expected to have a low impact on the efficacy results.

At this IA, a favourable OS trend was observed in the TIS Arm versus the PBO Arm (stratified HR 0.62, 95% CI: 0.39, 0.98, with non-significant 1-sided p value of 0.0193). 31 death events (13.7%) occurred in the TIS Arm and 45 (19.8%) occurred in the PBO Arm.

The final analyses of EFS and OS were conducted at the DCO of 07 March 2025 with a median study follow-up time of 38.47 months. The final EFS results (HR 0.58; 95% CI: 0.43, 0.79) remained consistent with those of the interim analysis, the KM curves indicated an improvement of about 20% in the EFS rate at 48 months. The EFS final analysis was performed after 170 EFS events despite a targeted number of 184 events. The MAH clarified that the selection of the final analysis data cut-off (FA DCO) as 07 Mar 2025 took place already in June 2024. Due to a decrease in the EFS event occurrence rate and due to operational logistic complexity of the BICR process that hampered the performance of event prediction on an ongoing basis and quick adjustments of the FA DCO, the predicted 184 events EFS events were not reached at the FA. This is however not considered a critical issue.

The **OS** results reached statistical significance at the final OS analysis (HR 0.65; 95% CI: 0.45, 0.93, with 1-sided p-value of 0.0093 [prespecified boundary of 0.024997]). Despite a still high rate of censoring beyond month 30, OS KM curves remain separated after about 10 months and suggest a 10% difference of OS rate at 36 months (79.3% vs 69.3% in the tislelizumab vs the placebo arm). The demonstrated EFS and OS improvements are regarded as clinically meaningful and the data are

[1] Appendix 1 to the guideline on the evaluation of anticancer medicinal products in man; EMA/CHMP/27994/2008/Rev.1

considered sufficiently mature at the FA to conclude on a benefit in the overall study population (data maturity 37.5% for EFS and 26.9% for OS).

Other secondary endpoints that were not included in the statistical testing hierarchy provided overall favourable trends. **ORR** (assessed per RECIST 1.1 by BICR before surgery) were improved in the TIS Arm compared to the PBO Arm (71% vs 55%, respectively). **DFS** results showed a HR of 0.76 (95% CI 0.49, 1.16) in favour of tislelizumab. **EFS assessed by Investigator** supported the results of the primary EFS analysis (HR 0.55; 95% CI 0.39, 0.77).

Results of patient reported outcomes (**PRO**) showed no consistent clinically meaningful differences between both treatment arms. Since the analysis testing of the PRO results are only descriptive and not controlled for multiplicity, CHMP did not support to present these results in the SmPC.

Exploratory analysis on EFS on next-line of treatment and time to death or distant metastases showed supportive results in favour of treatment with tislelizumab: HR for EFS2 0.58 (95% CI: 0.38, 0.87) and HR for distant metastases free survival 0.58 (95% CI: 0.40, 0.85).

Determination of tumour PD-L1 expression status is considered overall reliable; PD-L1 status was determined on tumour cells by central IHC analysis using the VENTANA PD-L1 (SP263) assay and was included as a stratification factor. PD-L1 expression status < 1% was determined in a relevant proportion of 38.2% of study population.
Efficacy results showed a consistent trend for a less favourable outcome in the PD-L1 <1% subgroup across all evaluated endpoints (EFS, OS, MPR and PCR).While the difference was less pronounced for EFS (HR 0.70 [95% CI: 0.43, 1.14] vs HR 0.53 [95% CI: 0.35, 0.79] in the PD-L1 <1% vs the ≥1% subgroups), the OS data showed no clear clinically meaningful benefit for patients with PD-L1 status <1% based on the latest DCO (HR 0.91 [95% CI: 0.50, 1.64] vs HR 0.61 [95% CI: 0.38, 0.98] in the PD-L1 <1% vs the ≥1% subgroups). OS KM curves in the PD-L1 <1 subgroup showed only a minimal separation after 24 months until 36 months, when both curves overlapped again and were not interpretable given the high rate of censoring. Since an increase in cure rate is the ultimate treatment aim in a curative disease setting (see EMA anticancer guideline; EMA/CHMP/205/95 Rev.6), the uncertainty regarding an improvement in overall survival for patients with tumour PD-L1 expression < 1% is considered a deficiency. However, in view of the EFS benefit that is shown also for the lower PD-L1 expression subgroup (although at a lower extent compared to the PD-L1 ≥ 1 subgroup), a restriction of the indication to patients with PD-L1 ≥1 with a more favourable B/R is not warranted. Nonetheless, EFS and OS subgroup results by PD-L1 status are adequately reflected in section 5.1 of the SmPC to support physicians and patients in informed treatment decisions based on individual benefit/risk evaluations.
From a clinical point of view, it was considered relevant to learn, whether the observed delay of recurrence will finally translate into a clinically more relevant OS improvement also in the PD-L1 <1% subgroup. Thus, the MAH is requested to provide updated OS data, including the PD-L1 subgroup results based on a longer follow-up for study 315, in Q1 2026 **(Recommendation).**

Efficacy in other subgroups

EFS and OS results in pre-specified subgroups were overall consistent with the ITT analyses. Results are less reliable in some subgroups with small sample sizes, such as females, patients with non-squamous histology or never smokers. Nonetheless, the results do not raise concerns on a lack of treatment effect in these subgroups; although the point estimates of the EFS HR for females and the OS HR for never smokers are numerically higher than in the complementary subgroups, the event numbers are similar across the treatment arms and the confidence intervals are very large in these subgroups.

The results of subgroup analyses by age showed overall a consistent treatment effect for patients below and above 65 years. However, the number of elderly patients with ≥ 75 years are too limited (3.3% of patients) to draw conclusions on a potentially different treatment effect in this subgroup (6 and 8 patients in the TIS Arm and the PBO Arm, respectively).

156 patients (34.4%) received carboplatin-based regimens, and 294 patients (64.9%) received at least one dose of cisplatin, among which 50 patients (11%) switched from cisplatin to carboplatin per investigators discretion. Subgroup results showed a generally consistent EFS benefit across the platinum-based subgroups, while a more favourable OS benefit was observed in the cisplatin subgroup (unstratified OS HR 0.50 [95% CI: 0.30, 0.83] for cisplatin, 0.85 [95% CI: 0.47, 1.52] for carboplatin, and 0.94 [95% CI: 0.33, 2.69] for patients who switched from cisplatin to carboplatin). However, platinum-based regimen was not a pre-defined subgroup and the patient number especially in the platinum-switch subgroup is small, which hampers reliable conclusions on these results.

As the pivotal study was conducted in China only, exploratory analyses were provided to justify the applicability of Chinese Study 315 data to the EU patient population. A comparison of measured baseline and disease characteristics indicated a lower proportion of females and non-squamous histology (as discussed above). The MAH provided analysis to evaluate the treatment effect of tislelizumab predicted in a European population represented by two selected RWE studies. In addition, the MAH provided direct and indirect comparisons to compare event-free survival in the tislelizumab arm against the internal control arm and experimental arms from studies with other products conducted with European patients. Different methods to account for measured imbalances (MAIC, STC) suggest better outcome in the tislelizumab arm as compared to the internal control in Study 315 after adjustment for baseline characteristics for each of these studies. No population-adjusted analysis on Overall Survival was provided.

These exploratory analyses have methodological uncertainties and limitations, for example, these analyses require the assumption that all relevant differences between the populations are measured and that they can be accounted for. Therefore, results should be interpreted with caution as these analyses cannot fully compensate the limitations that arise from a pivotal study conducted only in China. Nonetheless, the provided additional analyses can be considered supportive that the conclusions on the study outcome would not be substantially different in a global study. In this context, it is acknowledged that within the observed range of patient characteristics, no strong signals for inconsistent effects were observed in Study 315 or other immunotherapy studies in the same setting (e.g. Study 315 does not suggest substantially different efficacy across gender or histology and thus results may not depend on the distribution of these characteristics). Subgroup analysis from global immunotherapy studies indicated a benefit across race and regions (although with some variability). In conclusion, it appears justified that the effect of tislelizumab of Study 315 can be extrapolated to European patients.

EFS results by pCR / MPR status

The MAH provided baseline characteristics and EFS results by pCR and MPR status. The limitations of these post-hoc, exploratory analyses that are based on comparisons of non-randomized subgroups are fully acknowledged.

Summaries of the baseline characteristics by pCR /MPR positive versus negative outcomes were generally balanced across treatment arms apart from numerical differences in age, sex, ECOG PS (higher proportion of PS 0 in the placebo arm for patients with pCR and MPR) and PD-L1 status (a lower proportion of PD-L1 negative patients in the tislelizumab arm in the PCR and MPR groups and a higher proportion of PD-L1 negative patients in the tislelizumab arm in the non-pCR and non-MPR groups). Overall, these imbalances are not considered clinically relevant or rather favour the control arm (as the distribution of ECOG PS). However, the observed differences in PD-L1 status might reflect the impact of PD-L1 expression on response status as a post-baseline factor.

Exploratory EFS analysis by pCR and MPR status showed an improved outcome for both treatment arms among patients who achieved MPR or pCR compared to those who did not achieve MPR or pCR. Among patients who achieved pCR and / or MPR, the EFS benefit appeared to be improved by the addition of tislelizumab as compared to the placebo arm: unstratified EFS HR 0.45 [95% CI: 0.17 to 1.23] for patients who achieved pCR status and HR 0.55 [95% CI: 0.28 to 1.05] for patients who achieved MPR status. On the contrary, no clinically meaningful EFS improvements were observed for tislelizumab versus placebo for patients who did not achieve pCR status (unstratified HR 0.91 [95% CI: 0.65 to 1.27]) or who did not achieve MPR status (unstratified HR 1.05 [95% CI: 0.73 to 1.52]). As these analyses were performed using a post-hoc defined variable and imbalances in baseline characteristics were observed among the post-hoc defined subgroups, the resulting estimates may be confounded by (unknown) factors and hamper any reliable conclusions. Unfortunately, the interpretability of the data is too limited to compensate for any deficiencies of the study design that cannot inform on the distinct value of the pre- vs postoperative treatment phases of tislelizumab.

2.4.4. Conclusions on the clinical efficacy

The perioperative treatment with tislelizumab in Study 315 demonstrated statistically significant and clinically meaningful improvements in EFS and OS in the overall study population of patients with resectable NSCLC based on a median study follow-up time of 38.47 months.
Efficacy results were less favourable in the PD-L1 <1% subgroup (38.2% of study population) as compared to the PD-L1 ≥ 1% subgroup. While for patients with a PD-L1 tumour expression of <1% the OS data showed no clear meaningful benefit at the latest data cutoff, a numerically smaller but still relevant delay in recurrence could be observed. The subgroup results by PD-L1 expression status are reflected in section 5.1 of the SmPC.

2.5. Clinical safety

Introduction

The safety analysis is primarily based on the Phase 3 Study 315 at the EFS interim analysis (data cutoff: 21 August 2023) and is focused on the data for the overall treatment phase of Study 315.
Patients with resectable Stage II or IIIA A NSCLC were randomized in a 1:1 ratio to receive neoadjuvant treatment with tislelizumab plus platinum-based chemotherapy followed by adjuvant tislelizumab treatment (TIS Arm) or neoadjuvant treatment with placebo plus platinum-based chemotherapy followed by placebo (PBO Arm).
The safety evaluation (including ADR determination) is also supported by integrated safety data from 9 tislelizumab monotherapy studies (N = 1952, hereafter referred to as tislelizumab monotherapy pool) and 9 tislelizumab combination therapy studies (N = 1950, hereafter referred to as tislelizumab combination therapy pool) which includes study 315. These pooled safety data provide a reference of the safety profile of tislelizumab administered as monotherapy and in combination with chemotherapy.

Table 56: Safety Analysis Populations

Analysis Set	N	Definition	Purpose
Study 315 Safety Analysis Set	452	All randomized patients from Study 315 who received any amount of any study drugs	Primary source of safety data for the intended indication

Analysis Set	N	Definition	Purpose
Tislelizumab monotherapy pool	1952	Patients with solid tumours 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 solid tumours who received tislelizumab 200 mg Q3W in combination with chemotherapy in Studies 315, 312, 309, 307, 306, 305, 304, 206, and 205	Reference population for the known safety profile of tislelizumab in combination with chemotherapy

Table 57: Studies that provide Safety Data

Study number	Disease type	Study design	Countries	Dosing Regimen	Safety Analysis Set (N)	Study Statues/ Data Cutoff Date
Primary Study Providing Safety Data						
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/carboplatin plus pemetrexed (for nonsquamous) or paclitaxel (for squamous)	Total: 452 TIS Arm: 226 PBO Arm: 226	Ongoing/ 21-Aug-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 • 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	13	Completed/ 12 August 2020
102	ST (NSCLC, MM, GC, ESCC, OC, UC, HNSCC, RCC, TNBC, CRC, SCNEC or other tumours with known MSIH or dMMR, NPC, Child-Pugh Class A HCC)	• Phase 1/2 • Open-label, multicentre study	China	Tisle 200mg Q3W, 200mg W1D1, W5+D1 Q3W (PK sub-study)	300	Completed/ 31 May 2020
203	R/R cHL	• Phase 2 • Open-label, multicentre, single-arm study	China	Tisle 200 mg Q3W	70	Completed/ 02 November 2020
204	Previously treated UC	• Phase 2 • Single-arm, multicentre study	China, South Korea	Tisle 200 mg Q3W	113	Completed/ 11 March 2021

208	Previously treated, unresectable HCC	• Phase 2 • Open-label, multicentre study	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, Russia, Slovakia, Turkey	Tisle 200 mg Q3W	534 in Tisle arm	Completed/ 18 January 2024
Tislelizumab* Combination Therapy *Pool Providing Supportive Safety Data						
205	Locally advanced or metastatic 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)	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	54	Completed/ 31-Dec-2019
304	Stage IIIB or IV nonsquamous NSCLC	• Phase 3 • Randomised, open-label, multicentre	China	Tisle 200 mg Q3W Cisplatin or carboplatin and pemetrexed	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,	Tisle 200 mg Q3W Fluoropyrimidine-(capecitabine or 5-FU) and platinum-(oxaliplatin or cisplatin) based chemotherapy	498	Ongoing/ 28-Feb-2023

			Spain, Turkey, and USA			
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, UK, USA, and Australia	Tisle 200 mg Q3W Platinum-containing chemotherapy doublet (cisplatin or oxaliplatin) with fluoropyrimidine (capecitabine or 5-FU) or paclitaxel	324	Ongoing/ 28-Feb-2022
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 and cisplatin	131	Completed/ 08-Dec-2023
312	Untreated extensive-stage SCLC	• Phase 3 • Randomised, double-blind, placebo-controlled, multicentre	China	Tisle 200 mg Q3W Cisplatin or carboplatin and etoposide	227	Completed/ 29-Dec-2023
315	Resectable Stage II or IIIA NSCLC	See above	China	See above	226	See above

Abbreviations: ST, Advanced solid tumour

Patient exposure

Exposure to Tislelizumab – Overall Study Treatment

Table 58: Summary of Treatment Exposure to Tislelizumab (Overall Phase)

	Study 315		
	Tislelizumab + Chemotherapy (N = 226)	**Tislelizumab Monotherapy (N = 1952)**	**Tislelizumab Combination Therapy (N = 1950)**
Duration of Exposure (Months) [a]			
Mean (SD)	9.75 (5.375)	9.78 (12.386)	11.09 (11.011)
Median	12.63	4.14	7.20
Min, Max	0.4, 18.7	0.2, 63.2	0.1, 53.9
Duration of Exposure (Months), n (%)			
< 3	53 (23.5)	789 (40.4)	402 (20.6)
3 to < 6	19 (8.4)	368 (18.9)	447 (22.9)
6 to < 9	12 (5.3)	222 (11.4)	296 (15.2)
9 to < 12	24 (10.6)	90 (4.6)	182 (9.3)

	Study 315		
	Tislelizumab + Chemotherapy (N = 226)	Tislelizumab Monotherapy (N = 1952)	Tislelizumab Combination Therapy (N = 1950)
12 to < 18	117 (51.8)	127 (6.5)	290 (14.9)
18 to < 24	1 (0.4)	87 (4.5)	90 (4.6)
≥ 24	0 (0.0)	269 (13.8)	243 (12.5)
Number of Cycles Received [b]			
Mean (SD)	8.2 (3.74)	13.5 (16.96)	14.1 (14.61)
Median	10.0	6.0	9.0
Min, Max	1, 12	1, 88	1, 77
Cumulative Dose Administered (mg)			
Mean (SD)	2629.2 (1432.09)	2706.1 (3389.94)	2944.6 (2922.88)
Median	3400.0	1200.0	2000.0
Min, Max	200, 4000	200, 17600	200, 15400
Actual Dose Intensity (mg/week)			
Mean (SD)	62.64 (5.252)	64.57 (4.439)	61.72 (6.018)
Median	64.62	66.67	63.64
Min, Max	33.3, 68.9	30.8, 71.8	23.1, 71.8
Relative Dose Intensity (%)			
Mean (SD)	93.97 (7.877)	96.94 (6.549)	92.57 (9.026)
Median	96.92	100.00	95.45
Min, Max	50.0, 103.3	46.2, 107.7	34.7, 107.7

[a] For study 315, the duration of exposure of overall phase is the total of duration of exposure in neoadjuvant phase and adjuvant phase.
[b] For study 315, number of cycles received is defined as the sum of number of cycles received in neoadjuvant phase and adjuvant phase. Assessor's note: In Study 315, patients received tislelizumab neoadjuvant for 3 or 4 cycles (200 mg every 3 weeks) and adjuvant for up to 8 cycles (400 mg every 6 weeks). Number of cycles in the Tislelizumab Monotherapy and Tislelizumab Combination Therapy Pool refer to Tislelizumab 200 mg Q3W cycles.

Exposure to Chemotherapy

Comparable exposures to each component of chemotherapies (ie, cisplatin, carboplatin, paclitaxel, and pemetrexed) were observed between the 2 arms, with respect to the duration of exposure and RDI (please see data for exposure to chemotherapy overall).

Table 59: Summary of Treatment Exposure to Chemotherapy (Safety Analysis Set)

	Study 315		
	Tislelizumab + Chemotherapy (N = 226)	Placebo + Chemotherapy (N = 226)	Tislelizumab Combination Therapy (N = 1950)
Duration of Exposure (Months) [a]			
n	226	226	1950
Mean (SD)	2.39 (0.576)	2.40 (0.542)	6.01 (7.054)
Median	2.23	2.20	4.01
Q1, Q3	2.07, 2.79	2.10, 2.79	2.76, 5.78
Min, Max	0.4, 4.4	0.7, 3.9	0.1, 52.6
Number of Cycles Received			
n	226	226	1950
Mean (SD)	3.2 (0.69)	3.3 (0.67)	8.0 (9.39)
Median	3.0	3.0	5.0
Q1, Q3	3.0, 4.0	3.0, 4.0	4.0, 8.0
Min, Max	1, 4	1, 4	1, 69
Relative Dose Intensity (%) [b]			
n	224	225	1945
Mean (SD)	91.09 (11.011)	91.64 (10.456)	86.41 (13.346)
Median	95.13	94.78	89.69
Q1, Q3	85.30, 99.06	86.57, 98.93	77.77, 97.76
Min, Max	44.0, 104.9	53.4, 120.8	34.6, 112.2

Adverse event

Methodology for Analysing Treatment-Emergent Adverse Events

Note: In the SCS, a harmonized TEAE definition was used for analysis of safety parameters for the safety pools as well as the pivotal Study 315; i.e., immune-related AEs were considered if occurring up to 90 days after the last dose of study treatment regardless of whether or not the patient started a new anticancer therapy. This differs from the Study 315 CSR analyses where imAEs starting beyond the 30-day time window after the last dose of study treatment were not considered as a TEAE. Thus, sometimes reported incidences of TEAEs of the same category differ between Tables from the CSR and the SCS.

Adverse event summary

A summary of Treatment-Emergent Adverse Events (TEAEs) (including related TEAEs) in the Overall Phase is presented below.

Table 60: Overview of TEAEs – Overall Phase (Safety Analysis Set)

	Study 315			Tislelizumab Combination Therapy (N = 1950) n (%)
	Tislelizumab + Chemotherapy (N = 226) n (%)	Placebo + Chemotherapy (N = 226) n (%)	Tislelizumab Monotherapy (N = 1952) n (%)	
Patients with Any TEAE	225 (99.6)	226 (100.0)	1886 (96.6)	1943 (99.6)
Treatment-Related	224 (99.1)	225 (99.6)	1472 (75.4)	1918 (98.4)
to Tislelizumab/Placebo	155 (68.6)	125 (55.3)	1472 (75.4)	1446 (74.2)
to Any Chemotherapy	221 (97.8)	225 (99.6)	NA	1908 (97.8)
≥ Grade 3	177 (78.3)	166 (73.5)	916 (46.9)	1531 (78.5)
Treatment-Related	164 (72.6)	150 (66.4)	364 (18.6)	1352 (69.3)
to Tislelizumab/Placebo	65 (28.8)	42 (18.6)	364 (18.6)	594 (30.5)
to Any Chemotherapy	153 (67.7)	149 (65.9)	NA	1276 (65.4)
Serious	70 (31.0)	55 (24.3)	683 (35.0)	822 (42.2)
Treatment-Related	43 (19.0)	18 (8.0)	241 (12.3)	502 (25.7)
to Tislelizumab/Placebo	36 (15.9)	11 (4.9)	241 (12.3)	351 (18.0)
to Any Chemotherapy	16 (7.1)	13 (5.8)	NA	342 (17.5)
Leading to Death	6 (2.7)	3 (1.3)	150 (7.7)	128 (6.6)
Treatment-Related	4 (1.8)	2 (0.9)	21 (1.1)	42 (2.2)
to Tislelizumab/Placebo	4 (1.8)	2 (0.9)	21 (1.1)	37 (1.9)
to Any Chemotherapy	2 (0.9)	2 (0.9)	NA	29 (1.5)
Leading to Treatment Discontinuation	36 (15.9)	24 (10.6)	253 (13.0)	478 (24.5)
Treatment-Related	32 (14.2)	21 (9.3)	118 (6.0)	400 (20.5)
Tislelizumab/Placebo Discontinuation	24 (10.6)	7 (3.1)	253 (13.0)	281 (14.4)
Any Chemotherapy Discontinuation	17 (7.5)	19 (8.4)	NA	374 (19.2)
Leading to Treatment Modification	107 (47.3)	90 (39.8)	582 (29.8)	1386 (71.1)
Treatment-Related	93 (41.2)	73 (32.3)	350 (17.9)	1295 (66.4)

	Study 315			
	Tislelizumab + Chemotherapy (N = 226) n (%)	Placebo + Chemotherapy (N = 226) n (%)	Tislelizumab Monotherapy (N = 1952) n (%)	Tislelizumab Combination Therapy (N = 1950) n (%)
Modification of Tislelizumab/Placebo	79 (35.0)	60 (26.5)	582 (29.8)	1006 (51.6)
Modification of Any Chemotherapy	67 (29.6)	66 (29.2)	NA	1270 (65.1)
Immune-Mediated AE	90 (39.8)	40 (17.7)	659 (33.8)	778 (39.9)
ImAE ≥ Grade 3	21 (9.3)	6 (2.7)	105 (5.4)	173 (8.9)
Infusion-Related Reaction	10 (4.4)	8 (3.5)	58 (3.0)	123 (6.3)
IRR ≥ Grade 3	1 (0.4)	1 (0.4)	2 (0.1)	12 (0.6)

Abbreviations: AE, adverse event; TEAE, treatment-emergent adverse event; imAE, immune-mediated adverse event.
Dose modification for Tislelizumab/Placebo includes dose interruption, dose delay, dose temporary discontinuation in neoadjuvant phase and infusion rate decrease. Dose modification for chemotherapy includes dose reduction, dose interruption, dose delay and infusion rate decrease.
Adverse events were graded for severity using CTCAE (v5.0 for studies 315, 209, 304, 305, 307, 309, and 312, v4.03 for studies 001, 102, 203, 204, 205, 206, 208, 301, 302, 303, and 306).
Treatment-related TEAEs include those events considered by the investigator to be related or with missing assessment of the causal relationship.

Most common and Grade ≥3 Adverse Events

Table 61: TEAEs With Incidence ≥ 20% by Preferred Term (Any Grade)

	Study 315			
Preferred Term	Tislelizumab + Chemotherapy (N = 226) n (%)	Placebo + Chemotherapy (N = 226) n (%)	Tislelizumab Monotherapy (N = 1952) n (%)	Tislelizumab Combination Therapy (N = 1950) n (%)
Patients With Any TEAE	225 (99.6)	226 (100.0)	1886 (96.6)	1943 (99.6)
Neutrophil count decreased	180 (79.6)	177 (78.3)	113 (5.8)	988 (50.7)
White blood cell count decreased	144 (63.7)	152 (67.3)	160 (8.2)	961 (49.3)
Anaemia	124 (54.9)	120 (53.1)	511 (26.2)	1291 (66.2)
Incision site pain	113 (50.0)	103 (45.6)	0 (0.0)	113 (5.8)
Alopecia	106 (46.9)	118 (52.2)	11 (0.6)	558 (28.6)
Alanine aminotransferase increased	72 (31.9)	57 (25.2)	430 (22.0)	597 (30.6)
Nausea	63 (27.9)	61 (27.0)	196 (10.0)	844 (43.3)
Aspartate aminotransferase increased	61 (27.0)	47 (20.8)	482 (24.7)	590 (30.3)
Cough	56 (24.8)	59 (26.1)	298 (15.3)	293 (15.0)
Platelet count decreased	51 (22.6)	50 (22.1)	157 (8.0)	651 (33.4)
Decreased appetite	49 (21.7)	52 (23.0)	290 (14.9)	782 (40.1)
Constipation	47 (20.8)	47 (20.8)	227 (11.6)	511 (26.2)
Hypoaesthesia	47 (20.8)	49 (21.7)	26 (1.3)	240 (12.3)
Hypoalbuminaemia	39 (17.3)	44 (19.5)	244 (12.5)	395 (20.3)
Vomiting	27 (11.9)	32 (14.2)	166 (8.5)	533 (27.3)
Diarrhoea	24 (10.6)	17 (7.5)	196 (10.0)	394 (20.2)
Leukopenia	6 (2.7)	3 (1.3)	63 (3.2)	414 (21.2)
Thrombocytopenia	3 (1.3)	2 (0.9)	68 (3.5)	394 (20.2)
Neutropenia	0 (0.0)	0 (0.0)	31 (1.6)	533 (27.3)

Adverse events were classified based on MedDRA 26.1.
Patients with multiple events for a given Preferred Term were counted once at the Preferred Term level.
Events were sorted by decreasing frequency of Preferred Term in the 'Tislelizumab + Chemotherapy' of Study 315 group. Events were cut per Preferred Term ≥ 20% of any column.

Table 62: TEAEs with ≥ 10% by PT (Any Grade and ≥ Grade 3) – Study 315 - overall phase

	Arm A (N = 226) n (%)		Arm B (N = 226) n (%)	
Preferred Term	**Any Grade**	**>= Grade 3**	**Any Grade**	**>= Grade 3**
Patients With Any TEAE	225 (99.6)	176 (77.9)	226 (100.0)	165 (73.0)
Neutrophil count decreased	180 (79.6)	139 (61.5)	177 (78.3)	134 (59.3)
White blood cell count decreased	144 (63.7)	39 (17.3)	152 (67.3)	32 (14.2)
Anaemia	124 (54.9)	18 (8.0)	120 (53.1)	23 (10.2)
Incision site pain	113 (50.0)	1 (0.4)	103 (45.6)	1 (0.4)
Alopecia	106 (46.9)	1 (0.4)	118 (52.2)	1 (0.4)
Alanine aminotransferase increased	72 (31.9)	3 (1.3)	57 (25.2)	1 (0.4)
Nausea	63 (27.9)	1 (0.4)	61 (27.0)	0 (0.0)
Aspartate aminotransferase increased	61 (27.0)	4 (1.8)	47 (20.8)	0 (0.0)
Cough	56 (24.8)	0 (0.0)	59 (26.1)	0 (0.0)
Platelet count decreased	51 (22.6)	6 (2.7)	50 (22.1)	6 (2.7)
Decreased appetite	49 (21.7)	2 (0.9)	52 (23.0)	0 (0.0)
Constipation	47 (20.8)	0 (0.0)	47 (20.8)	0 (0.0)
Hypoaesthesia	47 (20.8)	0 (0.0)	49 (21.7)	0 (0.0)
Pneumonia	41 (18.1)	17 (7.5)	37 (16.4)	10 (4.4)
Hypoalbuminaemia	39 (17.3)	0 (0.0)	44 (19.5)	0 (0.0)
Arthralgia	38 (16.8)	1 (0.4)	39 (17.3)	1 (0.4)
Hyponatraemia	38 (16.8)	1 (0.4)	24 (10.6)	4 (1.8)
Productive cough	38 (16.8)	0 (0.0)	30 (13.3)	0 (0.0)
Rash	36 (15.9)	4 (1.8)	23 (10.2)	0 (0.0)
Fatigue	32 (14.2)	1 (0.4)	31 (13.7)	0 (0.0)
Hypothyroidism	31 (13.7)	2 (0.9)	7 (3.1)	0 (0.0)
Blood creatinine increased	30 (13.3)	0 (0.0)	28 (12.4)	0 (0.0)
Dyspnoea	30 (13.3)	1 (0.4)	30 (13.3)	1 (0.4)
Pain in extremity	30 (13.3)	0 (0.0)	34 (15.0)	0 (0.0)
Vomiting	27 (11.9)	0 (0.0)	32 (14.2)	0 (0.0)
Asthenia	26 (11.5)	0 (0.0)	26 (11.5)	1 (0.4)
Pyrexia	25 (11.1)	0 (0.0)	21 (9.3)	0 (0.0)
Diarrhoea	24 (10.6)	0 (0.0)	17 (7.5)	0 (0.0)
Hypokalaemia	23 (10.2)	5 (2.2)	30 (13.3)	6 (2.7)
Malaise	23 (10.2)	0 (0.0)	18 (8.0)	0 (0.0)
Lymphocyte count decreased	15 (6.6)	3 (1.3)	23 (10.2)	9 (4.0)

A TEAE for "overall phase" is an AE happened from the first dose of study treatment to 30 days after the last dose of study treatment or surgery (whichever comes later), data cutoff date, death date, end of study date, or new-anticancer therapy date whichever comes first.

Table 63: TEAEs by SOC and PT (Any Grade and ≥ Grade 3)

	Arm A (N = 226) n (%)		Arm B (N = 226) n (%)	
System Organ Class Preferred Term	**Any Grade**	**>= Grade 3**	**Any Grade**	**>= Grade 3**
Patients With Any TEAE	225 (99.6)	176 (77.9)	226 (100.0)	165 (73.0)
Investigations	212 (93.8)	149 (65.9)	209 (92.5)	143 (63.3)
Skin and subcutaneous tissue disorders	137 (60.6)	7 (3.1)	133 (58.8)	4 (1.8)
Blood and lymphatic system disorders	135 (59.7)	23 (10.2)	127 (56.2)	27 (11.9)

Gastrointestinal disorders	128 (56.6)	4 (1.8)	121 (53.5)	1 (0.4)
Injury, poisoning and procedural complications	127 (56.2)	2 (0.9)	114 (50.4)	4 (1.8)
Metabolism and nutrition disorders	124 (54.9)	18 (8.0)	121 (53.5)	14 (6.2)
Respiratory, thoracic and mediastinal disorders	107 (47.3)	10 (4.4)	104 (46.0)	7 (3.1)
General disorders and administration site conditions	106 (46.9)	3 (1.3)	95 (42.0)	4 (1.8)
Musculoskeletal and connective tissue disorders	90 (39.8)	1 (0.4)	91 (40.3)	2 (0.9)
Infections and infestations	74 (32.7)	22 (9.7)	64 (28.3)	14 (6.2)
Nervous system disorders	71 (31.4)	1 (0.4)	59 (26.1)	2 (0.9)
Endocrine disorders	39 (17.3)	2 (0.9)	15 (6.6)	0 (0.0)
Cardiac disorders	31 (13.7)	6 (2.7)	34 (15.0)	5 (2.2)
Psychiatric disorders	21 (9.3)	0 (0.0)	24 (10.6)	0 (0.0)
Vascular disorders	21 (9.3)	8 (3.5)	15 (6.6)	2 (0.9)
Hypertension	13 (5.8)	5 (2.2)	8 (3.5)	1 (0.4)
Renal and urinary disorders	12 (5.3)	2 (0.9)	7 (3.1)	2 (0.9)
Hepatobiliary disorders	8 (3.5)	4 (1.8)	5 (2.2)	5 (2.2)
Eye disorders	7 (3.1)	1 (0.4)	5 (2.2)	0 (0.0)
Reproductive system and breast disorders	5 (2.2)	0 (0.0)	3 (1.3)	0 (0.0)
Immune system disorders	3 (1.3)	1 (0.4)	3 (1.3)	1 (0.4)

Postoperative complications were reported with similar incidences in both treatment arms (66.3% in the TIS Arm vs 63.0% in the PBO Arm). The most frequently reported events assessed as postoperative complication with an incidence of ≥ 10% in either arm were Incision site pain (42.1% in Arm A and 33.5% in Arm B), Cough (17.9% and 20.8%, respectively), Productive cough (13.7% and 12.7%, respectively), Anaemia (12.1% and 15.0%, respectively), Pneumonia (12.1% and 9.2%, respectively), and Dyspnoea (10.5% and 15.6%, respectively).

Treatment-related Adverse Events

Table 64: Treatment-Related TEAEs with ≥ 10% by PT (Any Grade and ≥ Grade 3) – Study 315

	Arm A (N = 226) n (%)		Arm B (N = 226) n (%)	
Preferred Term	**Any Grade**	**>= Grade 3**	**Any Grade**	**>= Grade 3**
Patients With Any Treatment-Related TEAE	224 (99.1)	163 (72.1)	225 (99.6)	150 (66.4)
Neutrophil count decreased	177 (78.3)	138 (61.1)	176 (77.9)	134 (59.3)
White blood cell count decreased	143 (63.3)	38 (16.8)	152 (67.3)	32 (14.2)
Alopecia	106 (46.9)	1 (0.4)	118 (52.2)	1 (0.4)
Anaemia	91 (40.3)	11 (4.9)	96 (42.5)	15 (6.6)
Alanine aminotransferase increased	65 (28.8)	2 (0.9)	48 (21.2)	1 (0.4)
Nausea	60 (26.5)	1 (0.4)	59 (26.1)	0 (0.0)
Aspartate aminotransferase increased	53 (23.5)	2 (0.9)	38 (16.8)	0 (0.0)
Platelet count decreased	47 (20.8)	5 (2.2)	49 (21.7)	6 (2.7)
Hypoaesthesia	44 (19.5)	0 (0.0)	47 (20.8)	0 (0.0)
Decreased appetite	40 (17.7)	1 (0.4)	47 (20.8)	0 (0.0)
Rash	32 (14.2)	4 (1.8)	22 (9.7)	0 (0.0)
Hypothyroidism	31 (13.7)	2 (0.9)	5 (2.2)	0 (0.0)
Arthralgia	30 (13.3)	1 (0.4)	35 (15.5)	0 (0.0)
Blood creatinine increased	28 (12.4)	0 (0.0)	26 (11.5)	0 (0.0)
Hyponatraemia	28 (12.4)	1 (0.4)	20 (8.8)	4 (1.8)
Fatigue	27 (11.9)	1 (0.4)	27 (11.9)	0 (0.0)
Constipation	26 (11.5)	0 (0.0)	24 (10.6)	0 (0.0)
Pain in extremity	26 (11.5)	0 (0.0)	29 (12.8)	0 (0.0)
Vomiting	21 (9.3)	0 (0.0)	28 (12.4)	0 (0.0)

Treatment Related TEAEs include TEAEs that were considered by the Investigator to be related to any study drug or TEAEs with a missing causality.

TEAEs Related to Tislelizumab/Placebo

The incidence rates of any grade TEAEs related to tislelizumab/placebo were higher in the TIS Arm compared to those in the PBO Arm (all grade 67.7% versus 55.3%, respectively); higher incidence with a difference ≥ 5% were Aspartate aminotransferase increased (19.0% in Arm A versus 13.7% in Arm B), Hypothyroidism (13.7% versus 2.2%) and Nausea (8.5% versus 3.5%).

More patients in the TIS Arm experienced tislelizumab/placebo-related TEAEs of ≥ Grade 3 compared with those in the PBO Arm (27.0% versus 18.6%, respectively). The most frequently reported tislelizumab/placebo-related treatment-emergent adverse event of ≥ Grade 3 with an incidence ≥ 10% in either arm was Neutrophil count decreased (14.6% in Arm A and 12.8% in Arm B). A higher incidence of ≥ Grade 3 TEAEs suspected to be related to tislelizumab/placebo (difference > 2%) in the TIS Arm compared with the PBO Arm was reported for White blood cell count decreased (4.9% vs 2.2%) and Pneumonia (3.1% vs 0.4%).

Table 65: TEAEs Related to Tislelizumab/Placebo ≥ 10% by PT (Any Grade and ≥ Grade 3)

	Arm A (N = 226) n (%)		Arm B (N = 226) n (%)	
Preferred Term	**Any Grade**	**>= Grade 3**	**Any Grade**	**>= Grade 3**
Patients With Any TEAE Related to Tislelizumab/Placebo	153 (67.7)	61 (27.0)	125 (55.3)	42 (18.6)
Alanine aminotransferase increased	46 (20.4)	1 (0.4)	37 (16.4)	0 (0.0)
Aspartate aminotransferase increased	43 (19.0)	1 (0.4)	31 (13.7)	0 (0.0)
Neutrophil count decreased	43 (19.0)	33 (14.6)	40 (17.7)	29 (12.8)
White blood cell count decreased	39 (17.3)	11 (4.9)	32 (14.2)	5 (2.2)
Hypothyroidism	31 (13.7)	2 (0.9)	5 (2.2)	0 (0.0)
Rash	28 (12.4)	4 (1.8)	20 (8.8)	0 (0.0)
Anaemia	26 (11.5)	3 (1.3)	31 (13.7)	3 (1.3)

Serious adverse event/death/other significant events

Serious Adverse Events (SAEs)

Table 66: Serious TEAEs With Incidence ≥ 1% by Preferred Term

	Study 315			
Preferred Term	**Tislelizumab + Chemotherapy (N = 226) n (%)**	**Placebo + Chemotherapy (N = 226) n (%)**	**Tislelizumab Monotherapy (N = 1952) n (%)**	**Tislelizumab Combination Therapy (N = 1950) n (%)**
Patients With Any Serious TEAE	70 (31.0)	55 (24.3)	683 (35.0)	822 (42.2)
Pneumonia	15 (6.6)	10 (4.4)	85 (4.4)	86 (4.4)
Pneumonitis	9 (4.0)	1 (0.4)	25 (1.3)	58 (3.0)
Hypothyroidism	4 (1.8)	0 (0.0)	2 (0.1)	7 (0.4)
Immune-mediated lung disease	4 (1.8)	0 (0.0)	15 (0.8)	11 (0.6)
Febrile neutropenia	3 (1.3)	1 (0.4)	0 (0.0)	20 (1.0)
Neutrophil count decreased	2 (0.9)	1 (0.4)	0 (0.0)	26 (1.3)
Death	1 (0.4)	0 (0.0)	18 (0.9)	21 (1.1)
Decreased appetite	1 (0.4)	1 (0.4)	12 (0.6)	20 (1.0)
Platelet count decreased	1 (0.4)	1 (0.4)	4 (0.2)	42 (2.2)
Pyrexia	1 (0.4)	0 (0.0)	19 (1.0)	24 (1.2)
Anaemia	0 (0.0)	3 (1.3)	6 (0.3)	23 (1.2)
Dysphagia	0 (0.0)	0 (0.0)	18 (0.9)	23 (1.2)
Neutropenia	0 (0.0)	0 (0.0)	1 (0.1)	21 (1.1)
Thrombocytopenia	0 (0.0)	0 (0.0)	2 (0.1)	34 (1.7)
Upper gastrointestinal haemorrhage	0 (0.0)	0 (0.0)	19 (1.0)	9 (0.5)

All serious TEAEs in the TIS Arm in the above table were assessed as related to any component of the study treatment apart from death (not related) and pneumonia that was reported in a lower incidence as related (3.1%).

Deaths

Table 67: Summary of All Death

	Study 315			Tislelizumab Combination Therapy (N = 1950) n (%)
Category	**Tislelizumab + Chemotherapy (N = 226) n (%)**	**Placebo + Chemotherapy (N = 226) n (%)**	**Tislelizumab Monotherapy (N = 1952) n (%)**	
Total Number of Deaths	31 (13.7)	46 (20.4)	1412 (72.3)	1171 (60.1)
Cause of Death				
Disease Under Study	16 (7.1)	33 (14.6)	1181 (60.5)	914 (46.9)
Adverse Event	9 (4.0)	7 (3.1)	87 (4.5)	85 (4.4)
Concurrent Illness	0 (0.0)	0 (0.0)	9 (0.5)	0 (0.0)
Indeterminate/Unknown	0 (0.0)	0 (0.0)	62 (3.2)	97 (5.0)
Other	6 (2.7)	6 (2.7)	73 (3.7)	75 (3.8)
Death Within 30 Days After Last Dose of Study Drug	1 (0.4)	0 (0.0)	140 (7.2)	98 (5.0)
Cause of Death				
Adverse Event	1 (0.4)	0 (0.0)	58 (3.0)	54 (2.8)
Concurrent Illness	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Disease Under Study	0 (0.0)	0 (0.0)	78 (4.0)	43 (2.2)
Indeterminate/Unknown	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	30 (13.3)	46 (20.4)	1272 (65.2)	1072 (55.0)
Cause of Death				
Disease Under Study	16 (7.1)	33 (14.6)	1103 (56.5)	871 (44.7)
Adverse Event	8 (3.5)	7 (3.1)	29 (1.5)	31 (1.6)
Concurrent Illness	0 (0.0)	0 (0.0)	8 (0.4)	0 (0.0)
Indeterminate/Unknown	0 (0.0)	0 (0.0)	60 (3.1)	96 (4.9)
Other	6 (2.7)	6 (2.7)	72 (3.7)	74 (3.8)
Study 315:				
Death Within 90 Days After Surgery	3 (1.3)	4 (1.8)		
Cause of Death				
Disease Under Study	0 (0.0)	1 (0.4)		
Adverse Event	3 (1.3)	3 (1.3)		

Death causes 'Progression of Disease' and 'Disease Progression' were reported under 'Disease Under Study'.
Deaths with complete missing death dates were only counted in total number of deaths.

Table 68: TEAEs with ≥ 1 event in Study 315 by Preferred Term

	Study 315			Tislelizumab Combination Therapy (N = 1950) n (%)
Preferred Term	**Tislelizumab + Chemotherapy (N = 226) n (%)**	**Placebo + Chemotherapy (N = 226) n (%)**	**Tislelizumab Monotherapy (N = 1952) n (%)**	
Patients with Any TEAE Leading to Death	6 (2.7)	3 (1.3)	150 (7.7)	128 (6.6)
Death	1 (0.4)	0 (0.0)	18 (0.9)	21 (1.1)
Immune-mediated lung disease	1 (0.4)	0 (0.0)	1 (0.1)	1 (0.1)
Infection	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)
Multiple organ dysfunction syndrome	1 (0.4)	0 (0.0)	11 (0.6)	3 (0.2)
Pneumonia	1 (0.4)	0 (0.0)	12 (0.6)	8 (0.4)
Pneumonitis	1 (0.4)	0 (0.0)	1 (0.1)	4 (0.2)

	Study 315			
Preferred Term	Tislelizumab + Chemotherapy (N = 226) n (%)	Placebo + Chemotherapy (N = 226) n (%)	Tislelizumab Monotherapy (N = 1952) n (%)	Tislelizumab Combination Therapy (N = 1950) n (%)
Cardiac failure	0 (0.0)	1 (0.4)	1 (0.1)	0 (0.0)
Respiratory tract haemorrhage	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Suspected COVID-19	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)

In Study 315, treatment-related TEAEs leading to death were reported in a numerically higher incidence of patients in the TIS Arm than PBO Arm (4 patients [1.8%] versus 2 patients [0.9%]). The PTs reported in TIS Arm included Infection, Pneumonia, Immune-mediated lung disease, and Pneumonitis in 1 patient each (0.4%) (multiple organ dysfunction following intraoperatively subclavian artery rupture and death at home on Study Day 11 of unknow cause were considered as not related).

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

Immune-mediated Adverse Event

Table 69: Overview of Immune-Mediated Adverse Events

	Study 315			
	Tislelizumab + Chemotherapy (N = 226) n (%)	Placebo + Chemotherapy (N = 226) n (%)	Tislelizumab Monotherapy (N = 1952) n (%)	Tislelizumab Combination Therapy (N = 1950) n (%)
Patients with Any Immune-Mediated Adverse Event	90 (39.8)	40 (17.7)	659 (33.8)	778 (39.9)
≥ Grade 3	21 (9.3)	6 (2.7)	105 (5.4)	173 (8.9)
Leading to Death	2 (0.9)	0 (0.0)	2 (0.1)	11 (0.6)
Serious	23 (10.2)	5 (2.2)	113 (5.8)	177 (9.1)
Leading to Treatment Discontinuation	15 (6.6)	0 (0.0)	66 (3.4)	121 (6.2)
Leading to Treatment Discontinuation of Tislelizumab/Placebo	13 (5.8)	0 (0.0)	66 (3.4)	113 (5.8)
Leading to Treatment Modification	30 (13.3)	6 (2.7)	144 (7.4)	242 (12.4)
Leading to Treatment Modification of Tislelizumab/Placebo	30 (13.3)	6 (2.7)	144 (7.4)	215 (11.0)
Treated with Systemic Corticosteroids	33 (14.6)	7 (3.1)	183 (9.4)	242 (12.4)
Treated with Other Immunosuppressant	2 (0.9)	0 (0.0)	11 (0.6)	18 (0.9)
Treated with Hormone Therapy	34 (15.0)	3 (1.3)	199 (10.2)	232 (11.9)

Patients with imAEs treated with hormone therapy by selected categories were counted under 'Treated with Hormone Therapy'.
Selected Categories are Immune-mediated diabetes mellitus, Immune-mediated hypothyroidism, Immune-mediated hyperthyroidism, and Immune-mediated thyroiditis.
Immune-mediated AEs were identified based on BeiGene standard process as defined in Immune-Mediated Adverse Event Identification Charter v1.2, imAE CCQ v2.4.

Two patients (0.9%) in the TIS Arm died due to imAEs (Pneumonitis and Immune-mediated lung disease, see above), and both were reported in the neoadjuvant phase.

Table 70: Immune-Mediated Adverse Events by Category (incidence ≥1 in Study 315)

	Study 315			
Category	**Tislelizumab + Chemotherapy (N = 226) n (%)**	**Placebo + Chemotherapy (N = 226) n (%)**	**Tislelizumab Monotherapy (N = 1952) n (%)**	**Tislelizumab Combination Therapy (N = 1950) n (%)**
Patients with Any Immune-Mediated AE	90 (39.8)	40 (17.7)	659 (33.8)	778 (39.9)
Skin adverse reaction	39 (17.3)	24 (10.6)	247 (12.7)	327 (16.8)
Hypothyroidism	33 (14.6)	6 (2.7)	269 (13.8)	296 (15.2)
Pneumonitis	18 (8.0)	4 (1.8)	101 (5.2)	151 (7.7)
Hyperthyroidism	16 (7.1)	7 (3.1)	100 (5.1)	107 (5.5)
Thyroiditis	5 (2.2)	0 (0.0)	21 (1.1)	14 (0.7)
Hepatitis	5 (2.2)	5 (2.2)	23 (1.2)	29 (1.5)
Adrenal insufficiency	3 (1.3)	0 (0.0)	10 (0.5)	15 (0.8)
Diabetes mellitus	2 (0.9)	1 (0.4)	12 (0.6)	28 (1.4)
Colitis	1 (0.4)	0 (0.0)	11 (0.6)	20 (1.0)
Hypophysitis	1 (0.4)	0 (0.0)	5 (0.3)	11 (0.6)
Myocarditis/Pericarditis	1 (0.4)	0 (0.0)	15 (0.8)	23 (1.2)
Myositis/Rhabdomyolysis	1 (0.4)	0 (0.0)	16 (0.8)	13 (0.7)
Nephritis and Renal dysfunction	1 (0.4)	0 (0.0)	4 (0.2)	8 (0.4)

Table 71: Summary of Immune-Mediated AEs in ≥ 1% of Patients in TIS Arm of Study 315 by Category

imAE Category	Total / ≥ G3 n (%)	Led to Modified Treatment n (%)	Led to Discontinued Treatment n (%)	Treated With Corticosteroids			Treated With Immune-suppressants n (%) [a]	Treated With Hormone replacement n (%) [a]	Patients recovered n (%) [a, b]	Median (months)		
				Treated n (%) [a]	Median					Time to first onset	Duration of event	Duration of resolved event
					Initial dose (mg/day)	Duration (months)						
Skin adverse reaction [c]												
	39 (17.3) / 5 (2.2)	7 (3.1)	2 (0.9)	11 (28.2)	48.333	0.378	0 (0.0)	--	34 (87.2)	0.427	1.117	0.986
Hypothyroidism [d]												
	33 (14.6) / 2 (0.9)	8 (3.5)	1 (0.4)	0 (0.0)	--	--	0 (0.0)	29 (87.9)	8 (24.2)	4.107	NR	2.661
Pneumonitis [e]												
	18 (8.0) / 7 (3.1)	7 (3.1)	6 (2.7)	16 (88.9)	50.000	0.838	1 (5.6)	--	8 (44.4)	4.041	8.345	3.992
Hyperthyroidism [f]												
	16 (7.1) / 1 (0.4)	1 (0.4)	2 (0.9)	0 (0.0)	--	--	0 (0.0)	6 (37.5)	14 (87.5)	1.396	2.842	2.579
Thyroiditis [g]												
	5 (2.2) / 0 (0.0)	2 (0.9)	1 (0.4)	2 (40.0)	82.500	2.251	1 (20.0)	2 (40.0)	4 (80.0)	2.070	1.117	1.002
Hepatitis [h]												
	5 (2.2) / 4 (1.8)	4 (1.8)	2 (0.9)	2 (40.0)	125.000	3.088	1 (20.0)	--	5 (100.0)	2.957	0.690	0.690
Adrenal insufficiency [i]												
	3 (1.3) / 1 (0.4)	0 (0.0)	0 (0.0)	1 (33.3)	25.000	NR	0 (0.0)	--	0 (0.0)	2.333	NR	--

[a] Percentages were based on the number of patients in the category.
[b] Patient was considered as recovered from a category only if all events in the category were recovered or recovered with sequalae.

[c] For *immune-mediated skin adverse reaction*, the PTs reported in Study 315 Safety Analysis Set were Rash, Eczema, Rash maculo-papular, Dermatitis exfoliative, Psoriasis, Rash erythematous, and Dermatitis allergic.
[d] For *immune-mediated endocrinopathies (hypothyroidism)*, the PT reported in Study 315 Safety Analysis Set was Hypothyroidism.
[e] For *immune-mediated pneumonitis,* the PTs reported in Study 315 Safety Analysis Set were Pneumonitis and Immune-mediated lung disease.
[f] For *immune-mediated endocrinopathies (hyperthyroidism)*, the PTs reported in Study 315 Safety Analysis Set were Hyperthyroidism, Immune-mediated hyperthyroidism, and Thyroxine free increased.
[g] For *immune-mediated endocrinopathies (thyroiditis)*, the PTs reported in Study 315 Safety Analysis Set were Autoimmune thyroiditis, Thyroiditis, and Immune-mediated thyroiditis.
[h] For *immune-mediated Hepatitis*, the PTs reported in Study 315 Safety Analysis Set were Drug-induced liver injury, Immune-mediated hepatitis, and Hepatitis.
[i] For *immune-mediated endocrinopathies (adrenal insufficiency)*, the PT reported in Study 315 Safety Analysis Set was Adrenal insufficiency.

Infusion-Related Reactions

Table 72: Overview of IRR

	Study 315			
	Tislelizumab + Chemotherapy (N = 226)	Placebo + Chemotherapy (N = 226)	Tislelizumab Monotherapy (N = 1952)	Tislelizumab Combination Therapy (N = 1950)
Patients With Any IRR	10 (4.4)	8 (3.5)	58 (3.0)	123 (6.3)
>= Grade 3	1 (0.4)	1 (0.4)	2 (0.1)	12 (0.6)
Leading to Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Serious	0 (0.0)	1 (0.4)	2 (0.1)	1 (0.1)
Leading to Treatment Discontinuation of Tislelizumab/Placebo	1 (0.4)	1 (0.4)	1 (0.1)	1 (0.1)
Leading to Treatment Modification of Tislelizumab/Placebo	1 (0.4)	0 (0.0)	4 (0.2)	5 (0.3)
Treated With Systemic Corticosteroids	3 (1.3)	1 (0.4)	12 (0.6)	29 (1.5)
Treated With High Dose Systemic Corticosteroids	1 (0.4)	1 (0.4)	5 (0.3)	17 (0.9)

In Study 315, 1 patient each in the 2 arms experienced ≥ Grade 3 IRR (TIS Arm: Grade 3 Drug hypersensitivity; PBO Arm: Grade 4 Drug hypersensitivity).

The most commonly reported IRR by PT was Infusion related reaction (2.7% in TIS Arm and 1.8% in PBO Arm); the other reported PTs were Chills (0.9% and 0.0%), Drug hypersensitivity (0.9% and 0.4%), Rash (0.4% and 0.9%), and Face oedema (0.0% and 0.4%). All IRR events had resolved.

Laboratory findings

In Study 315, at baseline, the mean values for haematology and serum chemistry parameters were similar between the 2 arms and were all within the normal ranges.
Haematology abnormalities that worsened from baseline were generally comparable between the 2 arms.

Table 73: Summary of Laboratory Abnormalities Worsened from Baseline: Hematology

		Study 315							
		Tislelizumab + Chemotherapy (N = 226)		Placebo + Chemotherapy (N = 226)		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	11/225 (4.9)	0/225 (0.0)	9/224 (4.0)	0/224 (0.0)	86/1914 (4.5)	2/1914 (0.1)	39/1901 (2.1)	0/1901 (0.0)
Hemoglobin (g/L)	Low	171/225 (76.0)	17/225 (7.6)	179/224 (79.9)	21/224 (9.4)	752/1914 (39.3)	85/1914 (4.4)	1559/1901 (82.0)	269/1901 (14.2)
Leukocytes (10^9/L)	Low	163/225 (72.4)	43/225 (19.1)	170/224 (75.9)	35/224 (15.6)	321/1914 (16.8)	18/1914 (0.9)	1454/1901 (76.5)	443/1901 (23.3)
Lymphocytes (10^9/L)	High	12/225 (5.3)	0/225 (0.0)	6/224 (2.7)	0/224 (0.0)	40/1890 (2.1)	3/1890 (0.2)	38/1161 (3.3)	1/1161 (0.1)
Lymphocytes (10^9/L)	Low	112/225 (49.8)	17/225 (7.6)	118/224 (52.7)	23/224 (10.3)	776/1890 (41.1)	169/1890 (8.9)	714/1161 (61.5)	208/1161 (17.9)

		Study 315				Tislelizumab Monotherapy (N = 1952)		Tislelizumab Combination Therapy (N = 1950)	
		Tislelizumab + Chemotherapy (N = 226)		Placebo + Chemotherapy (N = 226)					
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 (%)
Neutrophils (10^9/L)	Low	197/225 (87.6)	143/225 (63.6)	197/224 (87.9)	137/224 (61.2)	258/1891 (13.6)	39/1891 (2.1)	1499/1881 (79.7)	887/1881 (47.2)
Platelets (10^9/L)	Low	77/225 (34.2)	6/225 (2.7)	70/224 (31.3)	8/224 (3.6)	315/1914 (16.5)	24/1914 (1.3)	1148/1900 (60.4)	267/1900 (14.1)

n is the number of patients for whom the grade worsened from baseline in the 'All Grades' or 'Grades 3-4' category.
M is the number of patients treated with any dose of the study drug and with baseline and any postbaseline assessment.
Percentages were calculated based on M.
Laboratory results were reported up to 30 days of the last dose of study treatment.

In Study 315, **clinical chemistry** abnormalities that worsened from baseline were generally comparable between the 2 arms for majority of the parameters with differences (≥ 5%) noted only for the increase of creatine kinase and creatinine (higher incidence in TIS Arm), and increase of glucose (higher incidence in PBO Arm).

Table 74: Summary of Laboratory Abnormalities Worsened from Baseline: Serum Chemistry

		Study 315				Tislelizumab Monotherapy (N = 1952)		Tislelizumab Combination Therapy (N = 1950)	
		Tislelizumab + Chemotherapy (N = 226)		Placebo + Chemotherapy (N = 226)					
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	92/225 (40.9)	6/225 (2.7)	89/224 (39.7)	4/224 (1.8)	628/1911 (32.9)	49/1911 (2.6)	794/1898 (41.8)	66/1898 (3.5)
Albumin (g/L)	Low	99/225 (44.0)	0/225 (0.0)	91/224 (40.6)	0/224 (0.0)	639/1911 (33.4)	6/1911 (0.3)	887/1898 (46.7)	9/1898 (0.5)
Alkaline Phosphatase (IU/L)	High	59/225 (26.2)	0/225 (0.0)	58/224 (25.9)	0/224 (0.0)	610/1910 (31.9)	52/1910 (2.7)	593/1896 (31.3)	15/1896 (0.8)
Aspartate Aminotransferase (U/L)	High	87/225 (38.7)	5/225 (2.2)	78/224 (34.8)	1/224 (0.4)	708/1911 (37.0)	92/1911 (4.8)	883/1899 (46.5)	58/1899 (3.1)
Bilirubin (umol/L)	High	54/225 (24.0)	1/225 (0.4)	52/223 (23.3)	0/223 (0.0)	452/1910 (23.7)	54/1910 (2.8)	500/1898 (26.3)	38/1898 (2.0)
Creatine Kinase (ukat/L)	High	46/225 (20.4)	3/225 (1.3)	31/222 (14.0)	0/222 (0.0)	259/1254 (20.7)	24/1254 (1.9)	433/1808 (23.9)	41/1808 (2.3)
Creatinine (umol/L)	High	66/225 (29.3)	2/225 (0.9)	54/224 (24.1)	1/224 (0.4)	253/1911 (13.2)	23/1911 (1.2)	420/1898 (22.1)	35/1898 (1.8)
Glucose (mmol/L)	High	93/225 (41.3)	0/225 (0.0)	112/223 (50.2)	0/223 (0.0)	865/1905 (45.4)	83/1905 (4.4)	926/1894 (48.9)	23/1894 (1.2)
Glucose (mmol/L)	Low	9/225 (4.0)	0/225 (0.0)	5/223 (2.2)	1/223 (0.4)	208/1905 (10.9)	9/1905 (0.5)	252/1894 (13.3)	9/1894 (0.5)

		Study 315							
		Tislelizumab + Chemotherapy (N = 226)		Placebo + Chemotherapy (N = 226)		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 (%)
Potassium (mmol/L)	High	40/225 (17.8)	0/225 (0.0)	29/224 (12.9)	2/224 (0.9)	191/1906 (10.0)	17/1906 (0.9)	263/1901 (13.8)	24/1901 (1.3)
Potassium (mmol/L)	Low	46/225 (20.4)	7/225 (3.1)	47/224 (21.0)	7/224 (3.1)	296/1906 (15.5)	55/1906 (2.9)	571/1901 (30.0)	144/1901 (7.6)
Sodium (mmol/L)	High	9/225 (4.0)	0/225 (0.0)	2/224 (0.9)	0/224 (0.0)	131/1906 (6.9)	2/1906 (0.1)	127/1901 (6.7)	5/1901 (0.3)
Sodium (mmol/L)	Low	153/225 (68.0)	20/225 (8.9)	150/224 (67.0)	16/224 (7.1)	662/1906 (34.7)	123/1906 (6.5)	1025/1901 (53.9)	219/1901 (11.5)

In Study 315, a higher incidence of patients in the TIS Arm than in the PBO Arm had postbaseline **thyroid parameters** consistent with hypothyroidism (13.5% versus 1.4%) or hyperthyroidism (8.4% versus 0.9%).

Table 75: Summary of Thyroids Laboratory Tests

	Study 315			
Laboratory Parameter	Tislelizumab + Chemotherapy (N = 226) n/M (%)	Placebo + Chemotherapy (N = 226) n/M (%)	Tislelizumab Monotherapy (N = 1952) n/M (%)	Tislelizumab Combination Therapy (N = 1950) n/M (%)
Post-baseline TSH > ULN and T4 < LLN	29/215 (13.5)	3/216 (1.4)	216/1577 (13.7)	236/1706 (13.8)
Baseline TSH and T4 within normal range	19/215 (8.8)	2/216 (0.9)	128/1577 (8.1)	155/1706 (9.1)
Post-baseline TSH < LLN and T4 > ULN	18/215 (8.4)	2/216 (0.9)	102/1577 (6.5)	87/1706 (5.1)
Baseline TSH and T4 within normal range	13/215 (6.0)	2/216 (0.9)	81/1577 (5.1)	69/1706 (4.0)

n is the number of patients with the worst postbaseline value and baseline value.
M is the number of patients treated with any dose of the study drug and with baseline and any postbaseline assessment. Percentages were calculated based on M.

For information on the **immunogenicity** of tislelizumab, see Section 5.3.

Safety in special populations

Study 315 was carried out in an exclusively Chinese population. An overview of safety is provided for subgroups by age, sex, baseline hepatic and renal function, ECOG PS and smoking status.

Table 76: Overview of TEAEs by Age in Study 315

	Study 315							
	Tislelizumab + Chemotherapy				Placebo + Chemotherapy			
	< 65 (N=143) n (%)	65-<75 (N=77) n (%)	>=75 (N=6) n (%)	All (N=226) n (%)	< 65 (N=128) n (%)	65-<75 (N=89) n (%)	>=75 (N=9) n (%)	All (N=226) n (%)
Patients With Any TEAE	142 (99.3)	77 (100.0)	6 (100.0)	225 (99.6)	128 (100.0)	89 (100.0)	9 (100.0)	226 (100.0)
Treatment-Related	141 (98.6)	77 (100.0)	6 (100.0)	224 (99.1)	128 (100.0)	88 (98.9)	9 (100.0)	225 (99.6)
>=Grade 3	106 (74.1)	66 (85.7)	5 (83.3)	177 (78.3)	96 (75.0)	62 (69.7)	8 (88.9)	166 (73.5)
Treatment-Related	98 (68.5)	61 (79.2)	5 (83.3)	164 (72.6)	87 (68.0)	56 (62.9)	7 (77.8)	150 (66.4)
Serious	43 (30.1)	25 (32.5)	2 (33.3)	70 (31.0)	21 (16.4)	31 (34.8)	3 (33.3)	55 (24.3)
Treatment-Related	25 (17.5)	16 (20.8)	2 (33.3)	43 (19.0)	7 (5.5)	9 (10.1)	2 (22.2)	18 (8.0)

Leading to Death	0 (0.0)	6 (7.8)	0 (0.0)	6 (2.7)	1 (0.8)	0 (0.0)	2 (22.2)	3 (1.3)
Treatment-Related	0 (0.0)	4 (5.2)	0 (0.0)	4 (1.8)	1 (0.8)	0 (0.0)	1 (11.1)	2 (0.9)
Leading to Treatment Discontinuation	22 (15.4)	12 (15.6)	2 (33.3)	36 (15.9)	16 (12.5)	4 (4.5)	4 (44.4)	24 (10.6)
Leading to Treatment Modification	67 (46.9)	37 (48.1)	3 (50.0)	107 (47.3)	50 (39.1)	34 (38.2)	6 (66.7)	90 (39.8)
Treatment-Related	59 (41.3)	31 (40.3)	3 (50.0)	93 (41.2)	41 (32.0)	26 (29.2)	6 (66.7)	73 (32.3)
Immune-Mediated AE	62 (43.4)	28 (36.4)	0 (0.0)	90 (39.8)	28 (21.9)	10 (11.2)	2 (22.2)	40 (17.7)
Immune-Mediated AE >= Grade 3	14 (9.8)	7 (9.1)	0 (0.0)	21 (9.3)	3 (2.3)	2 (2.2)	1 (11.1)	6 (2.7)

Table 77: Overview of TEAEs by Age for Tislelizumab Monotherapy and Combination Therapy

	Tislelizumab Monotherapy				Tislelizumab Combination Therapy			
	< 65 (N=1286) n (%)	65-<75 (N=552) n (%)	>=75 (N=114) n (%)	All (N=1952) n (%)	< 65 (N=1274) n (%)	65-<75 (N=616) n (%)	>=75 (N=60) n (%)	All (N=1950) n (%)
Patients With Any TEAE	1244 (96.7)	534 (96.7)	108 (94.7)	1886 (96.6)	1268 (99.5)	615 (99.8)	60 (100.0)	1943 (99.6)
Treatment-Related	979 (76.1)	418 (75.7)	75 (65.8)	1472 (75.4)	1250 (98.1)	610 (99.0)	58 (96.7)	1918 (98.4)
>=Grade 3	584 (45.4)	277 (50.2)	55 (48.2)	916 (46.9)	975 (76.5)	512 (83.1)	44 (73.3)	1531 (78.5)
Treatment-Related	233 (18.1)	114 (20.7)	17 (14.9)	364 (18.6)	838 (65.8)	474 (76.9)	40 (66.7)	1352 (69.3)
Serious	428 (33.3)	211 (38.2)	44 (38.6)	683 (35.0)	499 (39.2)	288 (46.8)	35 (58.3)	822 (42.2)
Treatment-Related	152 (11.8)	76 (13.8)	13 (11.4)	241 (12.3)	284 (22.3)	193 (31.3)	25 (41.7)	502 (25.7)
Leading to Death	92 (7.2)	49 (8.9)	9 (7.9)	150 (7.7)	75 (5.9)	48 (7.8)	5 (8.3)	128 (6.6)
Treatment-Related	12 (0.9)	8 (1.4)	1 (0.9)	21 (1.1)	23 (1.8)	19 (3.1)	0 (0.0)	42 (2.2)
Leading to Treatment Discontinuation	149 (11.6)	85 (15.4)	19 (16.7)	253 (13.0)	280 (22.0)	181 (29.4)	17 (28.3)	478 (24.5)
Treatment-Related	64 (5.0)	46 (8.3)	8 (7.0)	118 (6.0)	234 (18.4)	151 (24.5)	15 (25.0)	400 (20.5)
Leading to Treatment Modification	362 (28.1)	175 (31.7)	45 (39.5)	582 (29.8)	890 (69.9)	453 (73.5)	43 (71.7)	1386 (71.1)
Treatment-Related	221 (17.2)	105 (19.0)	24 (21.1)	350 (17.9)	831 (65.2)	424 (68.8)	40 (66.7)	1295 (66.4)
Immune-Mediated AE	423 (32.9)	199 (36.1)	37 (32.5)	659 (33.8)	503 (39.5)	256 (41.6)	19 (31.7)	778 (39.9)
Immune-Mediated AE >= Grade 3	60 (4.7)	40 (7.2)	5 (4.4)	105 (5.4)	92 (7.2)	75 (12.2)	6 (10.0)	173 (8.9)

Table 78: Overview of TEAEs by Age Group - Tislelizumab Combination Studies (excerpt)

	Tislelizumab Combination Studies							
	Tislelizumab + Chemotherapy				Placebo + Chemotherapy			
	<65 (N = 1274) n (%)	65-<75 (N = 616) n (%)	≥75 (N = 60) n (%)	All (N = 1950) n (%)	<65 (N = 1009) n (%)	65-<75 (N = 548) n (%)	≥75 (N = 70) n (%)	All (N = 1627) n (%)
Patients With Any TEAE	1268 (99.5)	615 (99.8)	60 (100.0)	1943 (99.6)	1001 (99.2)	544 (99.3)	69 (98.6)	1614 (99.2)
Treatment-Related	1250 (98.1)	610 (99.0)	58 (96.7)	1918 (98.4)	988 (97.9)	537 (98.0)	66 (94.3)	1591 (97.8)
>= Grade 3	975 (76.5)	512 (83.1)	44 (73.3)	1531 (78.5)	747 (74.0)	417 (76.1)	53 (75.7)	1217 (74.8)
Treatment-Related	838 (65.8)	474 (76.9)	40 (66.7)	1352 (69.3)	649 (64.3)	366 (66.8)	40 (57.1)	1055 (64.8)
Serious	499 (39.2)	288 (46.8)	35 (58.3)	822 (42.2)	304 (30.1)	198 (36.1)	28 (40.0)	530 (32.6)
Treatment-Related	284 (22.3)	193 (31.3)	25 (41.7)	502 (25.7)	158 (15.7)	95 (17.3)	12 (17.1)	265 (16.3)
Related to Tislelizumab/Placebo	195 (15.3)	143 (23.2)	13 (21.7)	351 (18.0)	68 (6.7)	3 7 (6.8)	4 (5.7)	109 (6.7)
Related to Any Component of Chemotherapies	193 (15.1)	129 (20.9)	20 (33.3)	342 (17.5)	144 (14.3)	89 (16.2)	12 (17.1)	245 (15.1)
Leading to Death	75 (5.9)	48 (7.8)	5 (8.3)	128 (6.6)	45 (4.5)	35 (6.4)	8 (11.4)	88 (5.4)
Treatment-Related	23 (1.8)	19 (3.1)	0 (0.0)	42 (2.2)	11 (1.1)	6 (1.1)	1 (1.4)	18 (1.1)
Leading to Treatment Discontinuation	280 (22.0)	181 (29.4)	17 (28.3)	478 (24.5)	112 (11.1)	82 (15.0)	19 (27.1)	213 (13.1)
Treatment-Related	234 (18.4)	151 (24.5)	15 (25.0)	400 (20.5)	89 (8.8)	62 (11.3)	12 (17.1)	163 (10.0)

	Tislelizumab Combination Studies							
	Tislelizumab + Chemotherapy				Placebo + Chemotherapy			
	<65 (N = 1274) n (%)	65-<75 (N = 616) n (%)	≥75 (N = 60) n (%)	All (N = 1950) n (%)	<65 (N = 1009) n (%)	65-<75 (N = 548) n (%)	≥75 (N = 70) n (%)	All (N = 1627) n (%)
Leading to Treatment Modification	890 (69.9)	453 (73.5)	43 (71.7)	1386 (71.1)	618 (61.2)	376 (68.6)	54 (77.1)	1048 (64.4)
Treatment-Related	831 (65.2)	424 (68.8)	40 (66.7)	1295 (66.4)	567 (56.2)	350 (63.9)	50 (71.4)	967 (59.4)
Immune-mediated AE	503 (39.5)	256 (41.6)	19 (31.7)	778 (39.9)	177 (17.5)	85 (15.5)	8 (11.4)	270 (16.6)
Immune-mediated AE >= Grade 3	92 (7.2)	75 (12.2)	6 (10.0)	173 (8.9)	9 (0.9)	13 (2.4)	1 (1.4)	23 (1.4)
Infusion-Related Reaction	78 (6.1)	44 (7.1)	1 (1.7)	123 (6.3)	40 (4.0)	26 (4.7)	2 (2.9)	68 (4.2)
Infusion-Related Reaction >= Grade 3	8 (0.6)	4 (0.6)	0 (0.0)	12 (0.6)	4 (0.4)	4 (0.7)	0 (0.0)	8 (0.5)

Table 79: Overview of TEAEs by Sex, Hepatic / Renal Function, ECOG PS and smoking status

Subgroup Category	Study 315			
	Tislelizumab + Chemotherapy		Placebo + Chemotherapy	
Sex	**Female (N=21) n (%)**	**Male (N=205) n (%)**	**Female (N=22) n (%)**	**Male (N=204) n (%)**
Patients with Any TEAE	20 (95.2)	205 (100.0)	22 (100.0)	204 (100.0)
≥ Grade 3	17 (81.0)	160 (78.0)	15 (68.2)	151 (74.0)
Serious	1 (4.8)	69 (33.7)	3 (13.6)	52 (25.5)
Leading to Death	0 (0.0)	6 (2.9)	0 (0.0)	3 (1.5)
Leading to Treatment Discont.	5 (23.8)	31 (15.1)	0 (0.0)	24 (11.8)
Leading to Treatment Modification	11 (52.4)	96 (46.8)	10 (45.5)	80 (39.2)
Immune-Mediated AE	6 (28.6)	84 (41.0)	2 (9.1)	38 (18.6)
Hepatic Function	**Normal (N=216) n (%)**	**Impairment (N=10) n (%)**	**Normal (N=214) n (%)**	**Impairment (N=11) n (%)**
Patients with Any TEAE	215 (99.5)	10 (100.0)	214 (100.0)	11 (100.0)
≥ Grade 3	170 (78.7)	7 (70.0)	155 (72.4)	10 (90.9)
Serious	66 (30.6)	4 (40.0)	51 (23.8)	4 (36.4)
Leading to Death	6 (2.8)	0 (0.0)	3 (1.4)	0 (0.0)
Leading to Treatment Discont.	34 (15.7)	2 (20.0)	24 (11.2)	0 (0.0)
Leading to Treatment Modification	102 (47.2)	5 (50.0)	87 (40.7)	3 (27.3)
Immune-Mediated AE	86 (39.8)	4 (40.0)	38 (17.8)	2 (18.2)
Renal Function	**Normal (N=177) n (%)**	**Impairment (N=49) n (%)**	**Normal (N=170) n (%)**	**Impairment (N=56) n (%)**
Patients with Any TEAE	177 (100.0)	48 (98.0)	170 (100.0)	56 (100.0)
≥ Grade 3	130 (73.4)	47 (95.9)	122 (71.8)	44 (78.6)
Serious	51 (28.8)	19 (38.8)	39 (22.9)	16 (28.6)
Leading to Death	3 (1.7)	3 (6.1)	1 (0.6)	2 (3.6)
Leading to Treatment Discont.	26 (14.7)	10 (20.4)	12 (7.1)	12 (21.4)
Leading to Treatment Modification	84 (47.5)	23 (46.9)	63 (37.1)	27 (48.2)
Immune-Mediated AE	68 (38.4)	22 (44.9)	30 (17.6)	10 (17.9)
ECOG PS	**0 (N=142) n (%)**	**1 (N=83) n (%)**	**0 (N=153) n (%)**	**1 (N=73) n (%)**
Patients with Any TEAE	141 (99.3)	83 (100.0)	153 (100.0)	73 (100.0)
≥ Grade 3	106 (74.6)	71 (85.5)	105 (68.6)	61 (83.6)
Serious	39 (27.5)	31 (37.3)	26 (17.0)	29 (39.7)
Leading to Death	1 (0.7)	5 (6.0)	1 (0.7)	2 (2.7)
Leading to Treatment Discont.	20 (14.1)	16 (19.3)	18 (11.8)	6 (8.2)
Leading to Treatment Modification	68 (47.9)	39 (47.0)	58 (37.9)	32 (43.8)
Immune-Mediated AE	53 (37.3)	37 (44.6)	27 (17.6)	13 (17.8)
Smoking Status	**Smoked (N=193)**	**Never Smoked (N=33)**	**Smoked (N=189)**	**Never Smoked (N=37)**
Patients with Any TEAE	193 (100.0)	32 (97.0)	189 (100.0)	37 (100.0)
≥ Grade 3	155 (80.3)	22 (66.7)	139 (73.5)	27 (73.0)
Serious	65 (33.7)	5 (15.2)	45 (23.8)	10 (27.0)
Leading to Death	5 (2.6)	1 (3.0)	3 (1.6)	0 (0.0)

Leading to Treatment Discont.	29 (15.0)	7 (21.2)	23 (12.2)	1 (2.7)
Leading to Treatment Modification	91 (47.2)	16 (48.5)	78 (41.3)	12 (32.4)
Immune-Mediated AE	77 (39.9)	13 (39.4)	37 (19.6)	3 (8.1)

Adverse drug reactions

The SmPC section 4.8 reflects the safety data from the tislelizumab combination therapy pool, including study 315 (N=1950) which was already updated in the context of variation EMEA/H/C/005919/II/0016. No new ADRs are identified. New PTs reflecting already established ADR group terms are highlighted bold in the footnote.

Table 80: ADRs by SOC, Group Term and Frequency Category (Safety Analysis Set)

	Study 315						Tislelizumab Monotherapy (N = 1952)			Tislelizumab Combination Therapy (N = 1950)		
	Tislelizumab + Chemotherapy (N = 226)			Placebo + Chemotherapy (N = 226)								
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]	41 (18.1)	16 (7.1)	Very Common	37 (16.4)	10 (4.4)	Very Common	186 (9.5)	70 (3.6)	Common	227 (11.6)	78 (4.0)	Very Common
Blood and lymphatic system disorders												
Anaemia[2]	125 (55.3)	18 (8.0)	Very Common	121 (53.5)	23 (10.2)	Very Common	541 (27.7)	94 (4.8)	Very Common	1311 (67.2)	282 (14.5)	Very Common
Thrombocytopenia[3]	53 (23.5)	6 (2.7)	Very Common	52 (23.0)	7 (3.1)	Very Common	212 (10.9)	21 (1.1)	Very Common	949 (48.7)	275 (14.1)	Very Common
Neutropenia[4]	180 (79.6)	139 (61.5)	Very Common	177 (78.3)	134 (59.3)	Very Common	136 (7.0)	28 (1.4)	Common	1397 (71.6)	882 (45.2)	Very Common
Lymphopenia[5]	15 (6.6)	3 (1.3)	Common	24 (10.6)	9 (4.0)	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

	Study 315											
	Tislelizumab + Chemotherapy (N = 226)			Placebo + Chemotherapy (N = 226)			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)
Endocrine disorders												
Hypothyroidism[6]	33 (14.6)	2 (0.9)	Very Common	7 (3.1)	0 (0.0)	Common	276 (14.1)	2 (0.1)	Very Common	311 (15.9)	5 (0.3)	Very Common
Hyperthyroidism[7]	18 (8.0)	1 (0.4)	Common	9 (4.0)	0 (0.0)	Common	128 (6.6)	0 (0.0)	Common	152 (7.8)	1 (0.1)	Common
Thyroiditis[8]	5 (2.2)	0 (0.0)	Common	0 (0.0)	0 (0.0)		21 (1.1)	0 (0.0)	Common	14 (0.7)	1 (0.1)	Uncommon
Adrenal insufficiency[9]	4 (1.8)	2 (0.9)	Common	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]	22 (9.7)	3 (1.3)	Common	21 (9.3)	0 (0.0)	Common	186 (9.5)	30 (1.5)	Common	204 (10.5)	18 (0.9)	Very Common
Hyponatraemia[12]	38 (16.8)	1 (0.4)	Very Common	26 (11.5)	5 (2.2)	Very Common	182 (9.3)	56 (2.9)	Common	364 (18.7)	90 (4.6)	Very Common
Hypokalaemia[13]	23 (10.2)	5 (2.2)	Very Common	30 (13.3)	6 (2.7)	Very Common	158 (8.1)	36 (1.8)	Common	334 (17.1)	88 (4.5)	Very Common
Diabetes mellitus[14]	3 (1.3)	2 (0.9)	Common	4 (1.8)	2 (0.9)	Common	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

	Study 315											
	Tislelizumab + Chemotherapy (N = 226)			Placebo + Chemotherapy (N = 226)			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)
Cardiac disorders												
Myocarditis[17]	1 (0.4)	1 (0.4)	Uncommon	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												
Hypertension[18]	15 (6.6)	5 (2.2)	Common	9 (4.0)	2 (0.9)	Common	117 (6.0)	47 (2.4)	Common	115 (5.9)	37 (1.9)	Common
Respiratory, thoracic and mediastinal disorders												
Cough	56 (24.8)	0 (0.0)	Very Common	59 (26.1)	0 (0.0)	Very Common	298 (15.3)	5 (0.3)	Very Common	293 (15.0)	5 (0.3)	Very Common
Dyspnoea	30 (13.3)	1 (0.4)	Very Common	30 (13.3)	1 (0.4)	Very Common	136 (7.0)	21 (1.1)	Common	180 (9.2)	13 (0.7)	Common
Pneumonitis[19]	18 (8.0)	5 (2.2)	Common	4 (1.8)	0 (0.0)	Common	101 (5.2)	33 (1.7)	Common	151 (7.7)	37 (1.9)	Common
Gastrointestinal disorders												
Diarrhoea[20]	24 (10.6)	0 (0.0)	Very Common	17 (7.5)	0 (0.0)	Common	197 (10.1)	13 (0.7)	Very Common	395 (20.3)	35 (1.8)	Very Common
Nausea	63 (27.9)	1 (0.4)	Very Common	61 (27.0)	0 (0.0)	Very Common	196 (10.0)	4 (0.2)	Very Common	844 (43.3)	28 (1.4)	Very Common
Stomatitis[21]	6 (2.7)	0 (0.0)	Common	7 (3.1)	0 (0.0)	Common	64 (3.3)	6 (0.3)	Common	181 (9.3)	22 (1.1)	Common
Pancreatitis[22]	0 (0.0)	0 (0.0)		1 (0.4)	0 (0.0)	Uncommon	18 (0.9)	13 (0.7)	Uncommon	54 (2.8)	19 (1.0)	Common
Colitis[23]	1 (0.4)	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												

	Study 315						Tislelizumab Monotherapy (N = 1952)			Tislelizumab Combination Therapy (N = 1950)		
	Tislelizumab + Chemotherapy (N = 226)			Placebo + Chemotherapy (N = 226)								
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)**
Hepatitis[24]	5 (2.2)	4 (1.8)	Common	5 (2.2)	5 (2.2)	Common	54 (2.8)	28 (1.4)	Common	73 (3.7)	33 (1.7)	Common
Skin and subcutaneous tissue disorders												
Rash[25]	44 (19.5)	5 (2.2)	Very Common	27 (11.9)	0 (0.0)	Very Common	319 (16.3)	26 (1.3)	Very Common	418 (21.4)	57 (2.9)	Very Common
Pruritus	19 (8.4)	0 (0.0)	Common	13 (5.8)	1 (0.4)	Common	215 (11.0)	1 (0.1)	Very Common	198 (10.2)	3 (0.2)	Very Common
Vitiligo[26]	1 (0.4)	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	39 (17.3)	1 (0.4)	Very Common	39 (17.3)	1 (0.4)	Very Common	180 (9.2)	4 (0.2)	Common	227 (11.6)	3 (0.2)	Very Common
Myalgia	14 (6.2)	0 (0.0)	Common	11 (4.9)	0 (0.0)	Common	35 (1.8)	0 (0.0)	Common	80 (4.1)	3 (0.2)	Common
Arthritis[27]	2 (0.9)	0 (0.0)	Uncommon	1 (0.4)	0 (0.0)	Uncommon	18 (0.9)	2 (0.1)	Uncommon	21 (1.1)	4 (0.2)	Common
Myositis[28]	1 (0.4)	1 (0.4)	Uncommon	0 (0.0)	0 (0.0)		16 (0.8)	5 (0.3)	Uncommon	14 (0.7)	4 (0.2)	Uncommon
Renal and urinary disorders												
Nephritis[29]	1 (0.4)	0 (0.0)	Uncommon	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 315						Tislelizumab Monotherapy (N = 1952)			Tislelizumab Combination Therapy (N = 1950)		
	Tislelizumab + Chemotherapy (N = 226)			Placebo + Chemotherapy (N = 226)								
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]	73 (32.3)	1 (0.4)	Very Common	66 (29.2)	1 (0.4)	Very Common	481 (24.6)	41 (2.1)	Very Common	796 (40.8)	81 (4.2)	Very Common
Pyrexia[31]	25 (11.1)	0 (0.0)	Very Common	21 (9.3)	0 (0.0)	Common	314 (16.1)	7 (0.4)	Very Common	360 (18.5)	11 (0.6)	Very Common
Decreased appetite	49 (21.7)	2 (0.9)	Very Common	52 (23.0)	0 (0.0)	Very Common	290 (14.9)	16 (0.8)	Very Common	782 (40.1)	51 (2.6)	Very Common
Investigations												
Aspartate aminotransferase increased	61 (27.0)	4 (1.8)	Very Common	47 (20.8)	0 (0.0)	Very Common	482 (24.7)	72 (3.7)	Very Common	590 (30.3)	42 (2.2)	Very Common
Alanine aminotransferase increased	72 (31.9)	3 (1.3)	Very Common	57 (25.2)	1 (0.4)	Very Common	430 (22.0)	37 (1.9)	Very Common	597 (30.6)	41 (2.1)	Very Common
Blood bilirubin increased[32]	19 (8.4)	0 (0.0)	Common	16 (7.1)	0 (0.0)	Common	303 (15.5)	54 (2.8)	Very Common	271 (13.9)	18 (0.9)	Very Common
Blood alkaline phosphatase increased	9 (4.0)	0 (0.0)	Common	10 (4.4)	0 (0.0)	Common	165 (8.5)	26 (1.3)	Common	132 (6.8)	5 (0.3)	Common
Blood creatinine increased	30 (13.3)	0 (0.0)	Very Common	28 (12.4)	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]	10 (4.4)	1 (0.4)	Common	8 (3.5)	1 (0.4)	Common	58 (3.0)	2 (0.1)	Common	123 (6.3)	12 (0.6)	Common

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, the group terms were ranked by the decreasing frequency of 'All Grades' of monotherapy and then by the decreasing frequency of 'Grade 3-4' of monotherapy.
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 1 hypersensitivity, and Urticaria.

Immune-Mediated ADRs

The data below reflect information for imADRs (summarized by imAE category) for tislelizumab monotherapy since there were no clinically relevant differences noted between the monotherapy and combination therapy.

Table 81: Summary of Immune-Mediated ADRs in Patients Treated in Tislelizumab Monotherapy Pool

				Treated With Corticosteroids			Treated With Immuno-suppressants n (%) [a]	Treated With Hormone Replacement n (%) [a]	Patients Recovered n (%) [a,b]	Median (months)		
					Median							
imADR Category	Total / ≥ Gr 3 n (%)	Led to Modified Treatment n (%)	Led to Discontinued Treatment n (%)	Treated / High-dose n (%) [a]	Initial Dose (mg/day)	Duration (months)				Time to First Onset	Duration of Event	Duration of Resolved Event
Pneumonitis [c]	100 (5.1) / 34 (1.7)	37 (1.9)	36 (1.8)	69 (69.0) / 63 (63.0)	63.750	1.643	2 (2.0)	--	47 (47.0)	4.123	6.275	2.793
Hepatitis	23 (1.2) / 18 (0.9)	15 (0.8)	5 (0.3)	18 (78.3) / 17 (73.9)	100.000	2.168	2 (8.7)	--	14 (60.9)	0.723	2.103	1.084
Skin Adverse Reaction	246 (12.6) / 22 (1.1)	25 (1.3)	2 (0.1)	37 (15.0) / 13 (5.3)	30.000	0.690	1 (0.4)	--	177 (72.0)	1.544	2.004	1.068
Colitis	11 (0.6) / 4 (0.2)	8 (0.4)	2 (0.1)	11 (100.0) / 6 (54.5)	30.000	0.936	0 (0.0)	--	9 (81.8)	6.045	1.380	0.920
Myositis/Rhabdomyolysis	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

Endocrinopathies	Hypothyroidism	269 (13.8) / 2 (0.1)	12 (0.6)	2 (0.1)	2 (0.7) / (0.0)	10.000	1.938	0 (0.0)	174 (64.7)	98 (36.4)	4.008	7.524	2.070
	Hyperthyroidism	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
	Thyroiditis	21 (1.1) / 0 (0.0)	4 (0.2)	0 (0.0)	2 (9.5) / 0 (0.0)	22.500	1.446	0 (0.0)	14 (66.7)	8 (38.1)	2.037	5.552	1.971
	Adrenal Insufficiency	10 (0.5) / 5 (0.3)	8 (0.4)	0 (0.0)	10 (100.0) / 2 (20.0)	25.000	NR	0 (0.0)	--	3 (30.0)	10.283	NR	1.938
	Hypophysitis	5 (0.3) / 0 (0.0)	0 (0.0)	0 (0.0)	4 (80.0) / 0 (0.0)	12.500	NR	0 (0.0)	--	1 (20.0)	9.002	NR	2.300
	Diabetes Mellitus	12 (0.6) / 6 (0.3)	3 (0.2)	3 (0.2)	0 (0.0) / 0 (0.0)	--	--	0 (0.0)	10 (83.3)	1 (8.3)	6.489	NR	0.723
Nephritis and Renal Dysfunction		4 (0.2) / 1 (0.1)	2 (0.1)	1 (0.1)	3 (75.0) / 3 (75.0)	90.000	NR	1 (25.0)	--	2 (50.0)	1.544	NR	0.296
Myocarditis/ Pericarditis		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
Other immune-mediated	Ocular	2 (0.1) / 0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0) / 0 (0.0)	--	--	0 (0.0)	--	1 (50.0)	1.413	NR	0.723
	Pancreatitis	5 (0.3) / 5 (0.3)	5 (0.3)	0 (0.0)	2 (40.0) / 1 (20.0)	33.333	0.230	0 (0.0)	--	5 (100.0)	9.068	0.608	0.608
	Central Nervous System	1 (0.1) / 1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0) / 0 (0.0)	--	--	1 (100.0)	--	1 (100.0)	4.271	1.971	1.971
	Musculoskeletal	15 (0.8) / 2 (0.1)	2 (0.1)	2 (0.1)	10 (66.7) / 4 (26.7)	22.500	1.478	1 (6.7)	--	6 (40.0)	3.023	NR	1.380

[a] Percentages were based on the number of patients in the category.
[b] Patient was considered as recovered from a category only if all events in the category were recovered or recovered with sequalae.
[c] The *immune-mediated pneumonitis* was reported in 53 (8.4%) of 633 patients with prior radiotherapy and 47 (3.6%) of 1319 patients without prior radiotherapy.

ADRs leading to death

Table 82: Adverse Drug Reactions Leading to Death by SOC and Group Term (Safety Analysis Set)

System Organ Class Group Term Preferred Term	Study 315 Tislelizumab + Chemotherapy (N = 226) n (%)	Study 315 Placebo + Chemotherapy (N = 226) n (%)	Tislelizumab Monotherapy (N = 1952) n (%)	Tislelizumab Combination Therapy (N = 1950) n (%)
Patients With ADRs Leading to Death	3 (1.3)	0 (0.0)	19 (1.0)	25 (1.3)
Infections and infestations	1 (0.4)	0 (0.0)	12 (0.6)	9 (0.5)
Pneumonia	1 (0.4)	0 (0.0)	12 (0.6)	9 (0.5)
Respiratory, thoracic and mediastinal disorders	2 (0.9)	0 (0.0)	3 (0.2)	9 (0.5)
Pneumonitis	2 (0.9)	0 (0.0)	2 (0.1)	6 (0.3)
Dyspnoea	0 (0.0)	0 (0.0)	1 (0.1)	3 (0.2)
Hepatobiliary disorders	0 (0.0)	0 (0.0)	2 (0.1)	1 (0.1)
Hepatitis	0 (0.0)	0 (0.0)	2 (0.1)	1 (0.1)
Blood and lymphatic system disorders	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)
Thrombocytopenia	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)
General disorders and administration site conditions	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Decreased appetite	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Cardiac disorders	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.2)
Myocarditis	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.2)
Gastrointestinal disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Colitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Metabolism and nutrition disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Hypokalaemia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Musculoskeletal and connective tissue disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Myositis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)

Safety related to drug-drug-interactions and other interactions

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

Discontinuation due to adverse events

TEAEs Leading to Discontinuation of Any Component of Study Treatment

Table 83: TEAEs Leading to Treatment Discontinuation with Incidence ≥ 0.5% by Preferred Term

	Study 315			
Preferred Term	Tislelizumab + Chemotherapy (N = 226) n (%)	Placebo + Chemotherapy (N = 226) n (%)	Tislelizumab Monotherapy (N = 1952) n (%)	Tislelizumab Combination Therapy (N = 1950) n (%)
Patients With Any TEAE Leading to Treatment Discontinuation	36 (15.9)	24 (10.6)	253 (13.0)	478 (24.5)
Blood creatinine increased	6 (2.7)	13 (5.8)	1 (0.1)	27 (1.4)
Pneumonitis	4 (1.8)	0 (0.0)	16 (0.8)	39 (2.0)
Pneumonia	3 (1.3)	0 (0.0)	19 (1.0)	16 (0.8)

	Study 315			
Preferred Term	**Tislelizumab + Chemotherapy (N = 226) n (%)**	**Placebo + Chemotherapy (N = 226) n (%)**	**Tislelizumab Monotherapy (N = 1952) n (%)**	**Tislelizumab Combination Therapy (N = 1950) n (%)**
Drug hypersensitivity	2 (0.9)	1 (0.4)	0 (0.0)	6 (0.3)
Hyperthyroidism	2 (0.9)	0 (0.0)	1 (0.1)	2 (0.1)
Immune-mediated lung disease	2 (0.9)	0 (0.0)	11 (0.6)	6 (0.3)
Rash	2 (0.9)	0 (0.0)	1 (0.1)	7 (0.4)
Death	1 (0.4)	0 (0.0)	11 (0.6)	12 (0.6)
Decreased appetite	1 (0.4)	0 (0.0)	1 (0.1)	9 (0.5)
Fatigue	1 (0.4)	0 (0.0)	2 (0.1)	11 (0.6)
Neutrophil count decreased	1 (0.4)	2 (0.9)	0 (0.0)	17 (0.9)
Vomiting	1 (0.4)	2 (0.9)	1 (0.1)	4 (0.2)
Anaemia	0 (0.0)	4 (1.8)	1 (0.1)	37 (1.9)
Blood urea increased	0 (0.0)	2 (0.9)	0 (0.0)	1 (0.1)
Interstitial lung disease	0 (0.0)	0 (0.0)	9 (0.5)	6 (0.3)
Malaise	0 (0.0)	1 (0.4)	3 (0.2)	10 (0.5)
Myocarditis	0 (0.0)	0 (0.0)	4 (0.2)	9 (0.5)
Peripheral sensory neuropathy	0 (0.0)	0 (0.0)	0 (0.0)	29 (1.5)
Platelet count decreased	0 (0.0)	1 (0.4)	3 (0.2)	16 (0.8)
Thrombocytopenia	0 (0.0)	0 (0.0)	1 (0.1)	23 (1.2)
Upper gastrointestinal haemorrhage	0 (0.0)	0 (0.0)	11 (0.6)	2 (0.1)
White blood cell count decreased	0 (0.0)	2 (0.9)	0 (0.0)	11 (0.6)

Drug hypersensitivity in both arms (2 patients in Arm A and 1 patient in Arm B) were related to chemotherapy.

TEAEs Leading to Tislelizumab/Placebo Discontinuation

Table 84: TEAEs Leading to Tislelizumab/Placebo Discontinuation by SOC and PT (≥1% SOC in Arm A)

System Organ Class Preferred Term	Arm A (N = 226) n (%)	Arm B (N = 226) n (%)
Patients With Any TEAE Leading to Tislelizumab/Placebo Discontinuation	21 (9.3)	7 (3.1)
Respiratory, thoracic and mediastinal disorders	5 (2.2)	2 (0.9)
Immune-mediated lung disease	2 (0.9)	0 (0.0)
Pneumonitis	2 (0.9)	0 (0.0)
Respiratory failure	1 (0.4)	0 (0.0)
Bronchopleural fistula	0 (0.0)	1 (0.4)
Respiratory tract haemorrhage	0 (0.0)	1 (0.4)
Cardiac disorders	4 (1.8)	1 (0.4)
Acute myocardial infarction	1 (0.4)	0 (0.0)
Cardiac failure	1 (0.4)	1 (0.4)
Cardiac failure acute	1 (0.4)	0 (0.0)
Immune-mediated myocarditis	1 (0.4)	0 (0.0)
Infections and infestations	4 (1.8)	1 (0.4)
Pneumonia	3 (1.3)	0 (0.0)
Infection	1 (0.4)	0 (0.0)
Lower respiratory tract infection	1 (0.4)	0 (0.0)
Pneumonia aspiration	1 (0.4)	0 (0.0)
Suspected COVID-19	0 (0.0)	1 (0.4)
Endocrine disorders	3 (1.3)	0 (0.0)
Hyperthyroidism	1 (0.4)	0 (0.0)
Hypothyroidism	1 (0.4)	0 (0.0)
Immune-mediated thyroiditis	1 (0.4)	0 (0.0)

TEAEs Leading to Dose Modification of Any Component of Study Treatment

Table 85: TEAEs Leading to Treatment Modification with Incidence ≥ 2% by Preferred Term

	Study 315			
Preferred Term	Tislelizumab + Chemotherapy (N = 226) n (%)	Placebo + Chemotherapy (N = 226) n (%)	Tislelizumab Monotherapy (N = 1952) n (%)	Tislelizumab Combination Therapy (N = 1950) n (%)
Patients With Any TEAE Leading to Treatment Modification	107 (47.3)	90 (39.8)	582 (29.8)	1386 (71.1)
Neutrophil count decreased	29 (12.8)	34 (15.0)	4 (0.2)	352 (18.1)
White blood cell count decreased	17 (7.5)	14 (6.2)	4 (0.2)	266 (13.6)
Hypothyroidism	8 (3.5)	0 (0.0)	12 (0.6)	39 (2.0)
Alanine aminotransferase increased	7 (3.1)	4 (1.8)	53 (2.7)	82 (4.2)
Anaemia	6 (2.7)	10 (4.4)	14 (0.7)	287 (14.7)
Aspartate aminotransferase increased	6 (2.7)	4 (1.8)	67 (3.4)	72 (3.7)
Infusion related reaction	6 (2.7)	4 (1.8)	0 (0.0)	17 (0.9)
Platelet count decreased	6 (2.7)	8 (3.5)	9 (0.5)	228 (11.7)
Blood creatinine increased	5 (2.2)	7 (3.1)	6 (0.3)	41 (2.1)
Pneumonia	5 (2.2)	2 (0.9)	47 (2.4)	71 (3.6)

	Study 315			
Preferred Term	**Tislelizumab + Chemotherapy (N = 226) n (%)**	**Placebo + Chemotherapy (N = 226) n (%)**	**Tislelizumab Monotherapy (N = 1952) n (%)**	**Tislelizumab Combination Therapy (N = 1950) n (%)**
Pneumonitis	5 (2.2)	2 (0.9)	22 (1.1)	47 (2.4)
Rash	5 (2.2)	1 (0.4)	13 (0.7)	35 (1.8)
Fatigue	4 (1.8)	1 (0.4)	14 (0.7)	49 (2.5)
Pyrexia	4 (1.8)	1 (0.4)	23 (1.2)	61 (3.1)
Decreased appetite	2 (0.9)	0 (0.0)	7 (0.4)	58 (3.0)
Diarrhoea	1 (0.4)	0 (0.0)	11 (0.6)	40 (2.1)
Nausea	1 (0.4)	0 (0.0)	7 (0.4)	61 (3.1)
Vomiting	1 (0.4)	2 (0.9)	6 (0.3)	66 (3.4)
Leukopenia	0 (0.0)	1 (0.4)	3 (0.2)	141 (7.2)
Neutropenia	0 (0.0)	0 (0.0)	3 (0.2)	225 (11.5)
Palmar-plantar erythrodysaesthesia syndrome	0 (0.0)	0 (0.0)	0 (0.0)	55 (2.8)
Thrombocytopenia	0 (0.0)	2 (0.9)	4 (0.2)	157 (8.1)

Safety by Treatment Phase

Exposure to Tislelizumab by Treatment Phase

In Study 315, the exposure to tislelizumab / placebo treatment was longer in the adjuvant phase than in the neoadjuvant phase (48.14 weeks versus 9.57 weeks for TIS Arm). The median duration of exposure to tislelizumab and placebo was similar both in the neoadjuvant phase (9.57 weeks for tislelizumab and 9.43 weeks for placebo) and the adjuvant phase (48.14 weeks in either arm); the median number of treatment cycles was identical for both arms in both the neoadjuvant phase (3.0 in either arm) and the adjuvant phase (8.0 in either arm); the RDIs were also similar for both arms in the neoadjuvant phase (98.44% in either arm) and the adjuvant phase for tislelizumab and placebo (97.17% and 97.96%, respectively).

Overview of TEAs by Treatment Phase

Table 86: Overview of TEAEs - Neoadjuvant Phase and Adjuvant Phase in Study 315

	Neoadjuvant Phase		Adjuvant Phase	
	Tislelizumab + Chemotherapy (N = 226) n (%)	**Placebo + Chemotherapy (N = 226) n (%)**	**Tislelizumab (N = 168) n (%)**	**Placebo (N = 147) n (%)**
Patients with **Any TEAE**	224 (99.1)	225 (99.6)	125 (74.4)	101 (68.7)
Treatment-Related	223 (98.7)	225 (99.6)		
Related to Tislelizumab/Placebo	123 (54.4)	108 (47.8)	73 (43.5)	44 (29.9)
Related to Any Component of Chemotherapies	221 (97.8)	225 (99.6)		
≥ Grade 3	159 (70.4)	152 (67.3)	26 (15.5)	16 (10.9)
Treatment-Related	155 (68.6)	148 (65.5)		

Related to Tislelizumab/Placebo	44 (19.5)	38 (16.8)	13 (7.7)	3 (2.0)
Related to Any Chemotherapy	152 (67.3)	148 (65.5)		
Serious	25 (11.1)	24 (10.6)	26 (15.5)	18 (12.2)
Treatment-Related				
Related to Tislelizumab/Placebo	18 (8.0)	14 (6.2)	11 (6.5)	2 (1.4)
Related to Any Chemotherapy	14 (6.2)	11 (4.9)		
Leading to Death	3 (1.3)	0 (0.0)	0 (0.0)	1 (0.7)
Treatment-Related	2 (0.9)	0 (0.0)		
Related to Tislelizumab/Placebo	2 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
Leading to Treatment Discontinuation	20 (8.8)	19 (8.4)		
Tislelizumab/Placebo Discontinuation	7 (3.1)	2 (0.9)	9 (5.4)	2 (1.4)
Chemotherapy Discontinuation	17 (7.5)	19 (8.4)	Related 9 (5.4)	Related 0 (0.0)
Leading to Dose Modification	71 (31.4)	69 (30.5)		
Dose Modification of Tislelizumab/Placebo	36 (15.9)	38 (16.8)	35 (20.8)	24 (16.3)
Dose Modification of Any Chemotherapy	67 (29.6)	66 (29.2)	Related 19 (11.3)	Related 8 (5.4)
Immune-Mediated AE	61 (27.0)	31 (13.7)	36 (21.4)	12 (8.2)
AE ≥ Grade 3	12 (5.3)	5 (2.2)	9 (5.4)	1 (0.7)
Leading to death	2 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
Serious	10 (4.4)	5 (2.2)	12 (7.1)	0 (0.0)
Infusion-Related Reaction	6 (2.7)	4 (1.8)	2 (1.2)	0 (0.0)

Table 87: Exposure-Adjusted Incidence Rate of TEAEs and ImAEs by Category in Study 315

	Neoadjuvant Phase		Adjuvant Phase	
AE Category	**Tislelizumab + Chemotherapy (N=226)**	**Placebo + Chemotherapy (N=226)**	**Tislelizumab + Chemotherapy (N=168)**	**Placebo + Chemotherapy (N=147)**
All TEAE				
Number of Patients Experiencing the Event, n (%)	224 (99.1)	225 (99.6)	125 (74.4)	101 (68.7)
EAIR (Person per 100 Person-Months), 95% CI	388.3 (339.1, 442.6)	377.7 (330.0, 430.5)	16.8 (14.0, 20.1)	14.9 (12.1, 18.1)
Treatment-Related TEAE				
Number of Patients Experiencing the Event, n (%)	223 (98.7)	225 (99.6)	76 (45.2)	47 (32.0)
EAIR (Person per 100 Person-Months), 95% CI	367.9 (321.2, 419.5)	369.4 (322.7, 420.9)	6.9 (5.4, 8.6)	4.5 (3.3, 5.9)
TEAE >= Grade 3				
Number of Patients Experiencing the Event, n (%)	159 (70.4)	152 (67.3)	26 (15.5)	16 (10.9)
EAIR (Person per 100 Person-Months), 95% CI	50.5 (42.9, 59.0)	46.5 (39.4, 54.6)	1.8 (1.2, 2.6)	1.2 (0.7, 2.0)
Treatment-Related TEAE >= Grade 3				
Number of Patients Experiencing the Event, n (%)	155 (68.6)	148 (65.5)	13 (7.7)	3 (2.0)
EAIR (Person per 100 Person-Months), 95% CI	48.1 (40.8, 56.3)	44.3 (37.5, 52.1)	0.8 (0.4, 1.4)	0.2 (0.0, 0.6)
Serious TEAE				
Number of Patients Experiencing the Event, n (%)	25 (11.1)	24 (10.6)	26 (15.5)	18 (12.2)
EAIR (Person per 100 Person-Months), 95% CI	4.0 (2.6, 5.9)	3.9 (2.5, 5.8)	1.7 (1.1, 2.5)	1.4 (0.8, 2.1)
Serious Treatment-Related TEAE				
Number of Patients Experiencing the Event, n (%)	18 (8.0)	14 (6.2)	11 (6.5)	2 (1.4)
EAIR (Person per 100 Person-Months), 95% CI	2.9 (1.7, 4.5)	2.2 (1.2, 3.8)	0.7 (0.3, 1.2)	0.1 (0.0, 0.5)

All Immune-Mediated AE				
Number of Patients Experiencing the Event, n (%)	61 (27.0)	31 (13.7)	36 (21.4)	12 (8.2)
EAIR (Person per 100 Person-Months), 95% CI	7.7 (5.9, 9.8)	3.5 (2.4, 5.0)	2.1 (1.5, 3.0)	0.8 (0.4, 1.3)
Immune-Mediated AE >= Grade 3				
Number of Patients Experiencing the Event, n (%)	12 (5.3)	5 (2.2)	9 (5.4)	1 (0.7)
EAIR (Person per 100 Person-Months), 95% CI	1.3 (0.7, 2.2)	0.5 (0.2, 1.2)	0.5 (0.2, 0.9)	0.1 (0.0, 0.3)
Serious Immune-Mediated AE				
Number of Patients Experiencing the Event, n (%)	10 (4.4)	5 (2.2)	12 (7.1)	0 (0.0)
EAIR (Person per 100 Person-Months), 95% CI	1.0 (0.5, 1.9)	0.5 (0.2, 1.2)	0.6 (0.3, 1.1)	0.0 (0.0, 0.2)

Abbreviations: EAIR, exposure-adjusted incidence rate

Serious TEAEs (PTs in ≥ 2 patients in either arm) in the neoadjuvant phase were Pneumonia (1.8% in TIS Arm and 2.2% in PBO Arm), Pneumonitis (1.3% and 0.4%), Febrile neutropenia (1.3% and 0.4%), Anaemia (0.0% and 1.3%), Neutrophil count decreased (0.9% and 0.4%), and Immune-mediated hepatitis (0.0% and 0.9%).

SAEs in the adjuvant phase were Pneumonia (3.6% in TIS Arm and 2.0% in PBO Arm), Pneumonitis (1.2% and 0.0%), Type 2 diabetes mellitus (1.2% and 0.0%), Hypothyroidism (1.2% and 0.0%), and Cataract (1.2% and 0.0%).

Serious imAEs categories in the neoadjuvant phase in TIS Arm were Pneumonitis (2.2%, 5 patients), Hepatitis (0.9%, 2 patients), and Skin adverse reaction, Myositis/Rhabdomyolysis, Hyperthyroidism, Thyroiditis, Adrenal insufficiency, Myocarditis/Pericarditis (0.4% each, 1 patient). 2 events were of Grade 5 (PT: Pneumonitis and Immune-mediated lung disease), the others were resolved or being resolving except 1 event of Adrenal insufficiency which was not resolved.

In the adjuvant phase, serious imAEs in TIS Arm were immune-mediated Pneumonitis (4.8%, 8 patients), Hypothyroidism (1.8%, 3 patients), Hepatitis, and Hypophysitis (0.6% each, 1 patient), all of which were of Grade 3.

Surgery

A total of 80.1% patients had curative surgery performed and more patients having underwent surgery in Arm A compared with Arm B (190 patients [84.1%] versus 173 patients [76.2%], respectively).

TEAEs Leading to **Surgery Delay / Cancellation and Postoperative Complication**

Table 88: Overview of TEAEs - Leading to Surgery Cancellation or Delay and Postoperative Complication

	Study 315	
	Tislelizumab + Chemotherapy (N = 226) n (%)	**Placebo + Chemotherapy (N = 226) n (%)**
Patients With Any TEAE	225 (99.6)	226 (100.0)
Leading to Surgery Cancellation	5 (2.2)	2 (0.9)
Treatment-Related	1 (0.4)	1 (0.4)
Related to Tislelizumab/Placebo	1 (0.4)	0 (0.0)
Related to Any Component of Chemotherapies	0 (0.0)	1 (0.4)
Leading to Surgery Delay	17 (7.5)	8 (3.5)

	Study 315	
	Tislelizumab + Chemotherapy (N = 226) n (%)	Placebo + Chemotherapy (N = 226) n (%)
Treatment-Related	12 (5.3)	4 (1.8)
Related to Tislelizumab/Placebo	11 (4.9)	1 (0.4)
Related to Any Component of Chemotherapies	5 (2.2)	3 (1.3)
Postoperative Complication, n/M[a]	121/190 (63.7)	106/173 (61.3)

[a] M is the number of patients performed study surgery.

Table 89: TEAEs Leading to Surgery Delay by SOC and PT (Any Grade and ≥ Grade 3), n ≥2 for SOC Arm A

	Arm A (N = 226) n (%)		Arm B (N = 226) n (%)	
System Organ Class Preferred Term	Any Grade	>= Grade 3	Any Grade	>= Grade 3
Patients With Any TEAE Leading to Surgery Delay	17 (7.5)	8 (3.5)	8 (3.5)	4 (1.8)
Respiratory, thoracic and mediastinal disorders	6 (2.7)	3 (1.3)	0 (0.0)	0 (0.0)
Pneumonitis	3 (1.3)	1 (0.4)	0 (0.0)	0 (0.0)
Asthma	1 (0.4)	1 (0.4)	0 (0.0)	0 (0.0)
Immune-mediated lung disease	1 (0.4)	1 (0.4)	0 (0.0)	0 (0.0)
Respiratory failure	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders	4 (1.8)	1 (0.4)	0 (0.0)	0 (0.0)
Rash	4 (1.8)	1 (0.4)	0 (0.0)	0 (0.0)
Endocrine disorders	3 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Hypothyroidism	3 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Infections and infestations	2 (0.9)	1 (0.4)	2 (0.9)	0 (0.0)
Pneumonia	1 (0.4)	1 (0.4)	2 (0.9)	0 (0.0)
Upper respiratory tract infection	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)

Table 90: TEAEs Leading to Surgery Cancellation by SOC and PT (Any Grade and ≥ Grade 3)

	Arm A (N = 226) n (%)		Arm B (N = 226) n (%)	
System Organ Class Preferred Term	Any Grade	>= Grade 3	Any Grade	>= Grade 3
Patients With Any TEAE Leading to Surgery Cancellation	5 (2.2)	4 (1.8)	2 (0.9)	0 (0.0)
Cardiac disorders	2 (0.9)	2 (0.9)	1 (0.4)	0 (0.0)
Acute myocardial infarction	1 (0.4)	1 (0.4)	0 (0.0)	0 (0.0)
Cardiac failure	1 (0.4)	1 (0.4)	0 (0.0)	0 (0.0)
Myocardial infarction	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	2 (0.9)	1 (0.4)	0 (0.0)	0 (0.0)
Immune-mediated lung disease	1 (0.4)	1 (0.4)	0 (0.0)	0 (0.0)
Respiratory failure	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
General disorders and administration site conditions	1 (0.4)	1 (0.4)	0 (0.0)	0 (0.0)
Death	1 (0.4)	1 (0.4)	0 (0.0)	0 (0.0)
Blood and lymphatic system disorders	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Anaemia	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)

Table 91: AEs Assessed as Postoperative Complication ≥ 5% by SOC and PT (Any and ≥ Grade 3)

	Arm A (N = 190) n (%)		Arm B (N = 173) n (%)	
System Organ Class Preferred Term	Any Grade	>= Grade 3	Any Grade	>= Grade 3
Patients With Any Postoperative Complication	121 (63.7)	21 (11.1)	106 (61.3)	27 (15.6)
Injury, poisoning and procedural complications	84 (44.2)	1 (0.5)	60 (34.7)	0 (0.0)
Incision site pain	80 (42.1)	1 (0.5)	56 (32.4)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	57 (30.0)	3 (1.6)	61 (35.3)	7 (4.0)
Cough	33 (17.4)	0 (0.0)	35 (20.2)	0 (0.0)
Productive cough	25 (13.2)	0 (0.0)	22 (12.7)	0 (0.0)
Dyspnoea	16 (8.4)	0 (0.0)	27 (15.6)	1 (0.6)
Blood and lymphatic system disorders	28 (14.7)	3 (1.6)	25 (14.5)	4 (2.3)
Anaemia	22 (11.6)	3 (1.6)	20 (11.6)	4 (2.3)
Leukocytosis	13 (6.8)	0 (0.0)	12 (6.9)	0 (0.0)
Infections and infestations	26 (13.7)	11 (5.8)	18 (10.4)	6 (3.5)
Pneumonia	23 (12.1)	10 (5.3)	16 (9.2)	5 (2.9)
Metabolism and nutrition disorders	19 (10.0)	2 (1.1)	18 (10.4)	2 (1.2)
Hypoalbuminaemia	14 (7.4)	0 (0.0)	11 (6.4)	0 (0.0)
Gastrointestinal disorders	17 (8.9)	1 (0.5)	17 (9.8)	1 (0.6)
Constipation	10 (5.3)	0 (0.0)	11 (6.4)	0 (0.0)
Investigations	17 (8.9)	2 (1.1)	24 (13.9)	3 (1.7)
Neutrophil count increased	3 (1.6)	0 (0.0)	9 (5.2)	0 (0.0)

All adverse events assessed as postoperative complications from the date of surgery up to 90 days after surgery were included.

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 data to support the new indication of tislelizumab for the perioperative treatment of patients with resectable NSCLC are primarily based on the pivotal, placebo-controlled Study 315. Tislelizumab (or placebo) was given neoadjuvant (200 mg Q3W for 3 or 4 cycles) in combination with platinum-containing chemotherapy and then continued as monotherapy as adjuvant treatment (400 mg Q6W for up to 8 cycles). Safety assessment is based mainly on 226 patients only which were randomized in the Tislelizumab + Chemotherapy Arm (TIS Arm) compared to 226 patients randomized in the Placebo + Chemotherapy Arm (PBO Arm). Safety data are based on the EFS interim analysis (data cutoff: 21 August 2023) with a median study follow-up time of 23.15 months for the TIS Arm and 21.04 months for the PBO Arm. The follow-up time can be considered acceptable to characterize the safety data in this setting.

Supportive safety data from the tislelizumab monotherapy pool (N=1952) and the tislelizumab combination therapy pool (N=1950) are provided as reference. These integrated safety data from 9 tislelizumab monotherapy studies and 9 combination therapy studies (including study 315) serve also as basis for the presentation of ADRs in Section 4.8 of the SmPC, which is endorsed.

The median duration of **exposure** to tislelizumab in the TIS Arm was 12.63 months with a high Relative Dose Intensity (median RDI 97%). The median duration of exposure to tislelizumab and placebo and the number of treatment cycles were similar for both arms in both the neoadjuvant phase (about 9.5 weeks and 3.0 cycles in either arm) and the adjuvant phase (48 weeks and 8.0 cycles in either arm). The exposure to chemotherapy was comparable between the 2 arms in Study 315 (median number of 3 cycles, RDI 95%).
More patients underwent **surgery** in the TIS Arm compared with the PBO Arm (190 patients [84.1%] versus 173 patients [76.2%], respectively). Surgery cancellation due to adverse event was infrequent (6 patients [2.7%] in TIS Arm versus 2 patients [0.9%] in PBO arm). A higher proportion of patients experienced surgery delays in the TIS Arm (n=31, 16.3%) than in the PBO Arm (n=22, 12.7%), with more delays due to AEs in the TIS Arm (n=12, 6.3% vs n=6, 3.5%). Most surgery delays were within 2 weeks, only 2 patients in the TIS Arm had a delay of more than 6 weeks (surgery was to be performed within 6 weeks of last neoadjuvant treatment date).
Despite these delays, the similar exposure to chemotherapy and the reported surgical procedures/ outcomes in both treatment arms indicated that the addition of tislelizumab did not have a significant negative impact on the ability to receive neoadjuvant chemotherapy and the feasibility and risk of surgery. Overall, 168 patients in the TIS Arm and 147 patients in the PBO Arm started adjuvant treatment with tislelizumab / placebo.

The adverse event summary in the overall treatment phase demonstrated that the majority of patients in Study 315 experienced ≥ 1 TEAE (≥ 99%). The **most common TEAEs** were (incidence rate ≥ 30% in either arm): Neutrophil count decreased (79.6% in TIS Arm versus 78.3% in PBO Arm), White blood cell count decreased (63.7% vs 67.3%), Anaemia (54.9% and 53.1%), Incision site pain (50.0% vs 45.6%), Alopecia (46.9% vs 52.2%), and Alanine aminotransferase increased (31.9% vs 25.2%). Preferred Terms (PTs) that occurred at a higher incidence (difference ≥ 5%) in the TIS Arm compared with the PBO Arm were Alanine aminotransferase increased (31.9% versus 25.2%), Aspartate aminotransferase increased (27.0% versus 20.8%), Hyponatraemia (16.8% versus 10.6%), Rash (15.9% versus 10.2%), and Hypothyroidism (13.7% versus 3.1%).
Almost all TEAEs of any grade were assessed as related to any component of the study treatment. A higher incidence (difference ≥ 5%) in the TIS Arm compared with the PBO Arm was reported for the PTs Alanine aminotransferase increased (28.8% versus 21.2%), Aspartate aminotransferase increased (23.5% versus 16.8%), and Hypothyroidism (14.6% versus 2.2%).

The overall incidence rates of **severe TEAEs** (CTCAE ≥ Grade 3) were numerically higher in the TIS Arm than in the PBO Arm (77.9% vs 73.0%). The most commonly reported severe events were (incidence

rate ≥ 2% in either arm): Neutrophil count decreased (61.5% in TIS Arm versus 59.3% in PBO Arm), White blood cell count decreased (17.3% vs 14.2%), Anaemia (8.0% vs 10.2%), Pneumonia (7.5% vs 4.4%), and Platelet count decreased (2.7% in both Arms). Severe TEAEs by Preferred Term with a higher incidence rate in the TIS Arm compared with the PBO Arm (difference ≥ 2%) were Pneumonia, White blood cell count decreased, and Neutrophil count decreased. As with all cause severe TEAEs, also the incidence of treatment-related TEAEs of ≥ Grade 3 was numerically higher in the TIS Arm (72.1%) than in the PBO Arm (66.4%) with Neutrophil and White blood cell count decreased being the most frequently reported.

The incidence of **serious** TEAEs in the TIS Arm was higher than in the PBO Arm (31.0% versus 24.3%). The most frequently reported (incidence ≥ 1% in either arm) serious TEAEs were Pneumonia (6.6% in TIS Arm and 4.4% in PBO Arm), Pneumonitis (4.0% and 0.4%), immune-mediated lung disease (1.8% vs 0%), and Hypothyroidism (1.8% vs 0%), all with higher rates in the TIS Arm. Related SAEs were observed in 19.0% in the TIS Arm and 8.0% in the PBO Arm; the most frequent were Pneumonitis (4.0% in TIS Arm and 0.4% in PBO Arm) and Pneumonia (3.1% and 0.9%).

In both arms of Study 315, almost all **deaths** occurred > 30 days after the last dose of study treatment. The most frequently reported cause of death in both arms was disease under study, with a lower incidence in the TIS Arm than PBO Arm (7.1% versus 14.6%).
9 patients in the TIS Arm and 7 patients in the PBO Arm died due to AEs, among which 6 patients (2.7%) in the TIS Arm and 3 patients (1.3%) in the PBO Arm were accounted for as TEAEs leading to death; the remaining events had an onset of > 30 days after the last dose of study treatment or surgery, whichever occurred later, and were thus not considered treatment emergent. TEAEs leading to death in the TIS Arm were Pneumonitis, Immune-mediated lung disease, Infection, and Pneumonia (all treatment-related) as well as Death and Multiple organ dysfunction syndrome (not related). In the PBO Arm, Respiratory tract haemorrhage and Cardiac failure were considered treatment-related and Suspected COVID-19 was an unrelated TEAE leading to death.
The above described adverse event profile overall 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 neoadjuvant and adjuvant treatment with tislelizumab increases however the rate of severe and serious adverse events by adding haematological toxicities, clinically relevant immune-mediated pneumonitis/lung disease and increasing the rates of severe and serious pneumonia in patients with resectable NSCLC; in 23 out of 43 patients with pneumonia, this was reported as postoperative complication. Pneumonitis /Immune-mediated lung disease and Pneumonitis were also reported as TEAEs leading to death.

A higher proportion of subjects **discontinued treatment due to an AE** in the TIS Arm (15.9%) compared to PBO Arm (10.6%). The most frequently reported AEs (in ≥ 2 patients) resulting in treatment discontinuation in the TIS Arm were Blood creatinine increased, Pneumonitis, Pneumonia, Drug hypersensitivity, Hyperthyroidism, Immune-mediated lung disease and Rash.

The overall incidence of **immune-mediated** adverse events (imAEs) was higher in the TIS Arm (39.8%) compared to the PBO Arm (17.7%). Immune-mediated AEs in the TIS Arm were Skin adverse reaction (17.3%), Hypothyroidism (14.6%), Pneumonitis (8.0%), Hyperthyroidism (7.1%), Thyroiditis and Hepatitis (2.2% each), Adrenal insufficiency (1.3%), Diabetes mellitus (0.9%), Colitis, Hypophysitis, Myocarditis, Myositis and Nephritis (0.4% each). Of these, 9.3% were ≥ G3 imAEs, 10.2% SAEs, 5.8% led to discontinuation of tislelizumab and two patients died due to imAEs (Pneumonitis and Immune-mediated lung disease, both in the neoadjuvant phase).

Evaluation of **safety data by treatment phase** showed generally higher incidences of most TEAE categories in the neoadjuvant phase than in the adjuvant phase without chemotherapy-associated toxicities. In contrast, serious TEAE (15.5% in the adjuvant phase versus 11.1% in the neoadjuvant

phase in TIS Arm) and serious imAE (7.1% versus 4.4% in TIS Arm) were reported with a higher incidence in the adjuvant phase than in the neoadjuvant phase. Exposure-adjusted incidence rates were lower in all categories in the adjuvant phase than in the neoadjuvant phase, including serious TEAE and serious imAE.

Safety in special populations

An overview of TEAEs was provided for subgroups by age, sex, baseline hepatic and renal function, ECOG PS and smoking status. However, no reliable conclusions can be derived from these analyses that are limited by small patient populations and the retrospective analysis of non-randomized subgroups. Inclusion criteria required adequate hepatic/renal function and an ECOG PS of 0/1, only 9.5% of the study participants were female, only 15.5% were never-smokers, and only 15 patients were ≥75 years of age across both treatment arms in Study 315. Overall, there was no new safety signal identified for tislelizumab in any of these subgroups that was consistently observed across several safety categories (and would be also reflected in the larger Tislelizumab combination therapy pool).

In the tislelizumab combination therapy pool, the incidences of all cause and related SAEs increased with age (SAE rate 58.3% for patients ≥ 75 years of age as compared to 38.6% in the Tislelizumab Monotherapy pool). To further evaluate the safety profile of tislelizumab in combination with chemotherapy in elderly, the MAH provided an overview of TEAEs by age group (<65 vs ≥65-<75 vs ≥75 years) for the tislelizumab + chemotherapy group (N=1950) in comparison with the placebo + chemotherapy group (N=1627) in the tislelizumab combination therapy pool across indications.

Serious TEAEs showed an increased incidence with age in the tislelizumab + chemotherapy group (39.2% vs 46.8% vs 58.3%), whereas a less pronounced trend was observed in the placebo + chemotherapy group (30.1% vs 36.1% vs 40.0%). The high incidences of SAEs in the ≥ 75 years age group in the tislelizumab + chemotherapy group were considered related to chemotherapy in 33% and related to tislelizumab in 22%, suggesting that both components of the combination contribute to the increased rate of serious AEs. It is however acknowledged that for other categories, such as the rate of Grade ≥3 AEs, TEAEs leading to death, treatment discontinuation or treatment modification, no meaningful differences were reported between the age groups of patients ≥75 years and patients of 65-<75 years. Overall, the sample size of patients with an age of ≥75 (N=60) is still too limited to draw reliable conclusions despite the pooled datasets. This is reflected in Section 4.8 the SmPC.

Only Chinese patients were enrolled in Study 315; however, no clinically meaningful differences attributable to ethnic background were identified in other global studies with tislelizumab across various indications. Therefore, the extrapolation of the safety data of the Chinese study population in Study 315 to the European patient population can be considered acceptable.

No new adverse reactions were identified and the SmPC section 4.8 reflects the safety data from the tislelzumab combination therapy pool (N=1950), including study 315 (N=226) which was already updated in the context of variation EMEA/H/C/005919/II/0016.

2.5.2. Conclusions on clinical safety

The safety profile for tislelizumab as neoadjuvant chemotherapy combination therapy and as adjuvant monotherapy following surgery for the treatment of resectable NSCLC overall reflects the well-known toxicities of the individual components. There were no new safety concerns identified. The addition of tislelizumab did not have a significant negative impact on the ability to receive neoadjuvant chemotherapy and the feasibility and risk of surgery. Nonetheless, the neoadjuvant and adjuvant treatment with tislelizumab increases the rate of severe and serious adverse events by adding haematological toxicities, clinically relevant immune-mediated pneumonitis/lung disease and increasing

the rates of severe and serious pneumonia in patients with resectable NSCLC.

2.5.3. PSUR cycle

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

2.6. Risk management plan

The MAH submitted/was requested to submit an updated RMP version 6.0 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 6.0 is acceptable.

The CHMP endorsed the Risk Management Plan version 6.0 with the following content:

Safety concerns

Table 92: 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

None.

Risk minimisation measures

Table 93: 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		

The safety concerns, pharmacovigilance plan and risk minimisations measures remain unchanged.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 5.1 and 6.6 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

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 was performed as part of the marketing authorisation for the treatment of NSCLC and a bridging was conducted to cover the second-line treatment OSCC. The current changes in the package leaflet are related to the extension of the indication "a type of lung cancer called non-small cell lung cancer, which can be removed by surgery, and continued alone after surgery".

In Section 1 'What Tevimbra is and what it is used for' a revised wording was included and to add the new indication in patient friendly terms and to simplify the previous indications. The Section 4 'Possible side effects' contains an update of new side effects and frequencies for the proposed new indication.

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.

3. Benefit-Risk Balance

3.1. Therapeutic Context

The approved indication is:

Tevimbra, in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment, is indicated for the treatment of adult patients with resectable NSCLC at high risk of recurrence (for selection criteria, see Section 5.1)".

3.1.1. Disease or condition

The MAH applied for an extension of indication for resectable (Stage IIA-IIIA) NSCLC (staged per the AJCC staging system for lung cancer 8th Edition). Lung cancer is the second most common cause of cancer morbidity and the most common cause of cancer-related death worldwide, with 2.2 million new cases and 1.8 million deaths observed in 2020. In Europe, an estimated 477,534 new cases of lung cancer were diagnosed with approximately 384,176 deaths related to lung cancer. NSCLC is the predominant subtype of lung cancer, accounting for approximately 85% of all cases. About one-third of NSCLC cases present with surgically resectable disease, including most Stage I to IIIA cases and a small proportion of Stage IIIB cases (Chansky et al 2017).

3.1.2. Available therapies and unmet medical need

In the adjuvant treatment setting randomized studies of platinum-based chemotherapy demonstrated an improvement in OS in patients with resected NSCLC. The Lung Adjuvant Cisplatin Evaluation meta-analysis of pooled data from the five largest trials of cisplatin-based chemotherapy after NSCLC complete resection indicated a 5.4% absolute benefit in 5-year survival for chemotherapy vs no chemotherapy. The benefit of adjuvant chemotherapy was different depending on stage, with higher stage correlating with an increased magnitude of benefit (HR 1.4 [95%CI: 0.95 to 2.06] for Stage IA disease; HR = 0.93 for Stage IB disease [95%CI: 0.78 to 1.10]; HR 0.83 for Stage II disease [95%CI: 0.73 to 0.95]; and HR 0.83 for Stage III disease [95%CI: 0.72 to 0.94]) (Pignon et al 2008). However, the recurrence rate remains high, ranging from 62% in patients with Stage II and 76% of patients with Stage III disease (Pignon et al 2008), which in turn is associated with poor survival rates in this patient population (Goldstraw et al 2016). Multiple trials have demonstrated comparable outcomes between neoadjuvant and adjuvant therapy. However, due to its simpler implementation as well as earlier availability of survival data from clinical trials, adjuvant chemotherapy was more widely adopted than neoadjuvant chemotherapy (Kalvapudi et al 2023).

The addition of anti-PD-1/PD-L1 inhibitors to the neoadjuvant and adjuvant phases of treatment to resectable NSCLC has shown EFS and DFS benefits, conducting to a European approval of immune-chemotherapy combinations with Tecentriq (II-64 adjuvant setting, PD-L1 ≥ 50%), Keytruda (II-134 perioperative and II 121 adjuvant setting, PD-L1 unrestricted), Opdivo (II-140 perioperative and II-117 neoadjuvant setting, tumours PD-L1 ≥ 1%), and Imfinzi (II-64 perioperative, PD-L1 unrestricted).

3.1.3. Main clinical study

The efficacy data of tislelizumab plus platinum-based chemotherapy followed by adjuvant tislelizumab is based on the China-only pivotal Study 315. Overall, 453 patients with resectable NSCLC were randomized 1:1 to receive 3-4 three-weekly cycles of Tislelizumab + Chemotherapy (TIS Arm) or Placebo + Chemotherapy (PBO Arm) followed by adjuvant tislelizumab or placebo for up to 8 six-weekly cycles.

Patients were stratified by disease stage (II vs. IIIA), histology (squamous vs. non-squamous), and PD-L1 expression (≥ 1% v s. < 1% or not evaluable or indeterminate).

Efficacy results were provided from three data cutoff dates,

- 20 Feb 2023 as DCO for primary analysis of Major Pathological Response (MPR) and Pathological Complete Response (pCR),
- 21 Aug 2023 as DCO for the EFS interim analysis and other endpoints, and
- 07 Mar 2025 as DCO for final analysis of EFS and OS.

3.2. Favourable effects

At the 20 Feb 2023 DCO, the study demonstrated statistically significant improvements for **MPR**, one of the dual primary endpoints (MPR rate 56.2% vs 15.0% in the TIS and PBO arms respectively, 1-sided p-Value <0.0001) and for the secondary endpoint of pCR (pCR rate 40.7% vs 5.7%, respectively, 1-sided p-Value < 0.0001).

At the IA DCO 21 Aug 2023, **EFS by BICR**, the other primary endpoint, was statistically significant with an EFS HR of 0.56 (95% CI: 0.40, 0.79; 1-sided p-Value 0.0003) based on 141 EFS events and a median study follow-up time of 22 months.

EFS results showed a consistent benefit at the final analysis (HR 0.58; 95% CI 0.43, 0.79) based on 170 events and a median study follow-up time of 38.5 months (07 March 2025 DCO).

At the 07 Mar 2025 DCO of the FA, **OS results** reached statistical significance with an OS HR of 0.65 (95% CI: 0.45, 0.93; p-value 0.0093).

3.3. Uncertainties and limitations about favourable effects

Efficacy results showed a consistent trend for a less pronounced benefit in the PD-L1 <1% subgroup (38.2% of study population) across all evaluated endpoints (EFS, OS, MPR and PCR). PD-L1 expression status by central assessment was included as a stratification factor. The EFS HR for the PD-L1 < 1% subgroup was 0.70 (95% CI: 0.43, 1.14) compared to 0.53 (95% CI: 0.35, 0.79) in the PD-L1 ≥ 1% subgroup. The OS HR was 0.91 (95% CI: 0.50 to 1.64) in the PD-L1 < 1% subgroup and 0.61 (95% CI: 0.38, 0.98) in the PD-L1 ≥ 1% subgroup. EFS and OS subgroup results by PD-L1 status are adequately reflected in section 5.1 of the SmPC to support physicians and patients in informed treatment decisions based on individual benefit/risk evaluations. In addition, a recommendation "to provide updated OS data (including PD-L1 subgroup results) based on longer follow-up for the study BGB-A317-315" will be provided by the Applicant by Q1 2026. (**REC**).

The study design does not allow to disentangle the contribution of neoadjuvant versus adjuvant treatment with tislelizumab on the clinically relevant endpoints of EFS and OS. Therefore, study results can only be discussed in the context of an overall peri-surgical strategy i.e. including neoadjuvant AND adjuvant treatment for NSCLC.

Study 315 recruited only Chinese patients with low proportions of non-squamous histology (21%) and females (9.5%). Although the efficacy results are considered less reliable in these subgroups due to the small sample sizes, they do not raise concerns on a lack of treatment effect. Additional exploratory analyses overall support that the efficacy conclusions of Study 315 can be extrapolated to European patients.

3.4. Unfavourable effects

The incidence rates of TEAEs grade ≥ 3 and serious AEs were higher in the TIS Arm compared to the PBO Arm in Study 315 (all cause G ≥3 AEs 78.3% vs. 73.5%, related G ≥3 AEs 72.6 vs 66.4%, all cause SAEs 31.0% vs 24.3%, related SAEs 19.0% vs 8.0%).

Severe (G ≥ 3) immune-mediated TEAEs were reported in 9.3% and 2.7% in the TIS and the PBO Arms. All grade im Pneumonitis occurred in 8% vs 1.8% of patients in the TIS and the PBO Arms (with serious pneumonitis in 5.8% vs 0.4% and 2 patients (0.9%) in the TIS Arm who died due to pneumonitis in the neoadjuvant phase).

In the TIS Arm, numerically higher rates of pneumonia were observed (18.1% vs 16.4% in the TIS and the PBO Arm, the majority of which were reported as post-operative complication (12.1% vs 9.2%). Severe and serious pneumonitis events were also more frequently in the TIS Arm as compared to the PBO Arm (G ≥ 3 AEs 7.5% vs 4.4% and SAEs 6.6% vs 4.4%). The safety profile of tislelizumab given in combination with chemotherapy in the neoadjuvant treatment phase is generally comparable to the known safety profile of tislelizumab in combination with chemotherapy.

3.5. Uncertainties and limitations about unfavourable effects

None.

3.6. Effects Table

Table 94: Effects Table for Tevimbra as neoadjuvant /adjuvant treatment of resectable NSCLC; Study 315 (data cut-off: 21 AUG 2023 IA, 07 Mar 2025 FA)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects (EFS interim analysis, DCO 21 Aug 2023)						
EFS	Based on BIRC*	Events n (%)	58 (25.7)	83 (36.6)	Randomized, double-blind study; statistically significant results for EFS at IA and for OS at FA	SCE
		HR [95% CI]	0.56 [0.40, 0.79]			
Favourable Effects (Final analysis for EFS / OS, DCO 07 Mar 2025)						
EFS	Based on BIRC*	Events n (%)	72 (31.9)	98 (43.2)		
		HR [95% CI]	0.58 [0.43, 0.79]			
OS	Time from randomization until death	Events n (%)	52 (23.0)	70 (30.8)		
		HR [95% CI]	0.65 [0.45, 0.93]			
Unfavourable Effects						
TEAEs G ≥ 3	All causality	%	78.3	73.5	The size of the safety data is overall limited;	SCS
	Related	%	72.6	66.4		SCS
Serious TEAEs	All causality	%	31.0	24.3		SCS

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
	Related	%	19.0	8.0	in the TIS Arm n=226 started neoadjuvant treatment and n=168 started adjuvant treatment	SCS
im TEAEs	All causality	%	39.8	17.7		SCS
	G ≥ 3	%	9.3	2.7		SCS
im Pneumonitis**	Total	%	8	1.8		ISS Table 2.7.4.2.2.2
	Serious	%	5.8	0.4		ISS Table 2.7.4.2.2.5
	Leading to death	%	0.9	0.0		ISS Table 2.7.4.2.2.8
Pneumonia	Total	%	18.1	16.4		CSR Table 32
	postoperative	%	12.1	9.2		CSR Table 57
	G ≥ 3	%	7.5	4.4		CSR Table 32
	serious	%	6.6	4.4		SCS Table 12

Abbreviations: BICR - Blinded Independent Central Review; im – immune-mediated; TEAE- Treatment-emergent adverse event; SCS – Summary of Clinical Safety; ISS – integrated summary of safety
Notes:
* EFS by BICR is defined as the time from randomization until any of the following events, whichever occurs first: disease progression precluding surgery, local or distant recurrence, or death due to any cause.
**for imPneumonitis PTs reported in Study 315 were Pneumonitis and im lung disease

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The perioperative treatment with tislelizumab in Study 315 demonstrated statistically significant and clinically meaningful improvements in EFS and OS in the overall study population of patients with resectable NSCLC based on a median study follow-up time of 38.47 months.

The safety profile for tislelizumab as neoadjuvant chemotherapy combination therapy and as adjuvant monotherapy following surgery overall reflects the well-known toxicities of the individual components. There were no new safety concerns identified. Importantly, the addition of tislelizumab did not have a significant negative impact on the ability to receive neoadjuvant chemotherapy and the feasibility and risk of surgery. Nonetheless, increased incidences of severe and serious adverse events were observed related to treatment with tislelizumab, including higher incidences of immune-mediated pneumonitis and pneumonia. In addition, long-term adverse events may occur, including in patients also potentially cured.

3.7.2. Balance of benefits and risks

The provided efficacy data are considered mature enough to conclude on a clinically meaningful benefit that encompasses an increased cure rate in the overall study population. The additional toxicities of a perioperative treatment with tislelizumab can be considered justified in view of the improvement in overall survival.

3.8. Conclusions

The overall B/R of Tevimbra in combination with platinum-containing chemotherapy as neoadjuvant treatment and then continues as monotherapy as adjuvant treatment, for the treatment of adult patients with resectable NSCLC is positive.

4. Recommendations

Outcome

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

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

Extension of indication for Tevimbra in combination with platinum-containing chemotherapy as neoadjuvant treatment and then continued as monotherapy as adjuvant treatment, for the treatment of adult patients with resectable NSCLC based on interim results from study BGB-A317-315. Study BGB-A317-315 is a phase 3 randomized, placebo-controlled, double-blind study to compare the efficacy and safety of neoadjuvant treatment with tislelizumab plus platinum-based doublet chemotherapy followed by adjuvant tislelizumab versus neoadjuvant treatment with placebo plus platinum-based doublet chemotherapy followed by adjuvant placebo in patients with resectable Stage II or IIIA NSCLC. As a consequence, sections 4.1, 4.2, 5.1, and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 6.0 of the RMP has also been agreed.

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

Amendments to the marketing authorisation

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