22 February 2024
EMA/116407/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tizveni

International non-proprietary name: Tislelizumab

Procedure No. EMEA/H/C/005542/0000

Note

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

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List of abbreviations

ADA	Anti-drug antibodies
ADCC	Antibody-dependent cellular cytotoxicity
ADCP	Antibody-dependent cellular phagocytosis
ADME	Absorption, distribution, metabolism and excretion
AET	Analytical evaluation threshold
AEX	Anion exchange chromatography
APG	Acidic peak group
AUC	Area under the curve
BICN-PB	Boehringer Ingelheim Biopharmaceuticals (Lishizhen Road) China
Biolab BICN	Boehringer Ingelheim Biopharmaceuticals (Halei Road) China
BIP Biberach	Boehringer Ingelheim Pharma Germany
BPG	Basic peak group
CAPA	Corrective action and preventive action
CCIT	Container closure integrity testing
CCS	Container closure system
CD	Cluster of differentiation, such as CD274, CD279, CD3 and etc.
CDC	Complement-dependent cytotoxicity
CEX	Cation exchange chromatography
CFU	Colony forming unit
CGE	Capillary gel electrophoresis
cGMP	Current good manufacturing practice
CHMP	Committee for Evaluation of Human Medicinal Products
CHO	Chinese hamster ovary
ChP	Chinese Pharmacopoeia
CL	Clearance
C_{max}	Maximum (plasma or tissue) concentration
CPP	Critical process parameter
CZE	Capillary zone electrophoresis
DNA	Deoxyribonucleic acid
ECD	Extracellular domain
ECG	Electrocardiogram
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOPCB	End-of-production cell bank
EP	European Pharmacopoeia
EU	Endotoxin unit
EU	European Union
EVA	Ethylene-vinyl acetate
Fab	Antigen-binding fragment
FACS	Fluorescence activated cell sorting
Fc	Fragment crystallizable region (typically, of immunoglobulin G)
FcγR	Fc gamma receptor
FDA	Food and Drug Administration
FMEA	Failure modes and effect analysis
FMP	Final manufacturing process
G/P	Growth and production
GLP	Good laboratory practice
HC	Heavy chain

HCB	Host Cell bank
HCP	Host cell protein
HMW	High molecular weight
HPSEC	Size-exclusion chromatography using high-performance liquid chromatography
IC50	Inhibitory concentration 50%
ICH	International Council For Harmonization Of Technical Requirements For Pharmaceuticals For Human Use
IFN-γ	Interferon-gamma
IgG4	Immunoglobulin G4
IL	Interleukin, such as IL-2, IL-6, and more
INN	International non-proprietary name
IPC	In-process control
IV	Intravenously
JP	Japanese Pharmacopoeia
KD	Dissociation constant
Kindos	Kindos Pharmaceuticals Co., Ltd., Chengdu
Koff	Constant for off-rate
KPP	Key process parameter
LAL	Limulus amebocyte lysate
LC	Light chain
LER	Low endotoxin recovery
LIVCA	Limit of in vitro cell age
LMW	Low molecular weight
MAA	Marketing authorisation application
MCB	Master cell bank
mGM-CSF	Murine granulocyte-macrophage colony-stimulation
MHCB	Master host cell bank
MO	Major objection
MOA	Mechanism of action
MP	Main peak
NANA	N-acetylneuraminic acid
NGNA	N-glycolylneuraminic acid
NOR	Normal operating range
NSCLC	Non-small cell lung cancer
NTU	Nephelometric turbidity unit
OC	Overall concern
OD	Optical density
OECD	Organization for Economic Cooperation and Development
OMP	Original manufacturing process
PACMP	Post-approval change management protocol
PAR	Proven acceptable range
PBMC	Peripheral blood mononuclear cell
PD-1	Programmed cell death protein 1
PDE	Permitted daily exposure
PD-L1	Programmed -death ligand-1
PD-L2	Programmed-death ligand-2
PE	Polyethylene
PES	Polyethersulfone
Ph. Eur.	European Pharmacopoeia
pI	Isoelectric pH

PK	Pharmacokinetic
PP	Process parameter
PPQ	Process performance qualification
PRS	Primary reference standard
PVC	Polyvinyl chloride
QA	Quality attribute
QbD	Quality by design
QW	Every week
Q2W	Every 2 week
Q3W	Every 3 week
RH	Relative humidity
RRF	Risk-ranking and filtering
RS	Reference standard
SCB	Safety cell bank
SCID	Severe combined immunodeficiency (mouse)
SPR	Surface plasmon resonance
SUB	Single-use bioreactor
TGI	Tumour growth inhibition
TK	Toxicokinetic
TSE	Transmissible spongiform encephalopathy
USAN	United States adopted name
USP	United States Pharmacopoeia
UV	Ultraviolet
VCD	Viable cell density
WCB	Working cell bank
WRS	Working reference standard
WT	wild-type

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Novartis Europharm Limited submitted on 3 March 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for Tizveni, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication:

Tizveni in combination with pemetrexed and platinum-containing chemotherapy is indicated for the first-line treatment of locally advanced or metastatic non-squamous non-small cell lung cancer in adults whose tumours have no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) positive mutation.

Tizveni in combination with carboplatin and either paclitaxel or nab-paclitaxel is indicated for the first-line treatment of locally advanced or metastatic squamous non-small cell lung cancer in adults.

Tizveni as monotherapy is indicated for the treatment of locally advanced or metastatic non-small cell lung cancer after prior chemotherapy in adults.

During the procedure, the applicant has changed from Novartis Europharm Limited to Beigene Ireland limited. Relevant documents for the change of applicant have been provided, validated and agreed.

Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0142/2019 on the granting of a (product-specific) waiver.

1.2. Information relating to orphan market exclusivity

1.2.1. Similarity

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

1.3. Applicant's request(s) for consideration

1.3.1. New active substance status

The applicant requested the active substance Tislelizumab contained in the above medicinal product to be considered as a new active substance, as the applicant claimed that it was not a constituent of a medicinal product previously authorised within the European Union.

1.4. Scientific advice

The applicant did not seek scientific advice from the CHMP.

1.5. Steps taken for the assessment of the product

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

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: Aaron Sosa Mejia

The Rapporteur appointed by the PRAC was:

PRAC Rapporteur: Bianca Mulder

The application was received by the EMA on	3 March 2022
The procedure started on	24 March 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	13 June 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	27 June 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	21 July 2022
The applicant submitted the responses to the CHMP consolidated List of Questions on	25 January 2023
The following GMP and GCP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
GCP inspections were requested and conducted at one investigator site in Turkey between 29 August to 2 September 2022, the sponsor site in the USA, between 9 and 17 November 2022 and two investigator sites in China between 6 and 17 November 2023. The outcome of the inspections carried out was issued on:	20 January 2023 and 04 January 2024
A GMP inspection at Boehringer Ingelheim Biopharmaceuticals (China) Ltd., 1090 Halei Road, Pilot Free Trade Zone, Shanghai, 201203, China for Drug Substance and Drug Product manufacturing and testing, Drug Product Primary packaging, between 13-17 March 2023. The outcome of the inspection carried out was issued on:	08 May 2023

The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	10 March 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	16 March 2023
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	30 March 2023
The applicant submitted the responses to the CHMP List of Outstanding Issues on	16 January 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	24 March 2023
The CHMP, in light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Tizveni on:	22 February 2024
Furthermore, the CHMP adopted a report on new active substance (NAS) status of the active substance contained in the medicinal product	22 February 2024

2. Scientific discussion

2.1. Problem statement

The initially claimed therapeutic indication was: "*Tislelizumab as monotherapy is indicated for the treatment of patients with locally advanced or metastatic NSCLC after prior chemotherapy in adults.*

Tislelizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel for the first-line treatment of patients with locally advanced or metastatic squamous NSCLC.

Tislelizumab in combination with pemetrexed and platinum- containing chemotherapy for the first-line treatment of patients with locally advanced or metastatic nonsquamous NSCLC with no EGFR or ALK genomic tumor aberrations."

2.1.1. Disease or condition

Lung cancer is the second most common cancer worldwide (after breast cancer) and is associated with the highest cancer mortality. As per GLOBOCAN data in 2020, there were approximately 2.2 million new cases and 1.8 million deaths (Sung et al 2021). Based on the estimates from GLOBOCAN 2020, the age-adjusted incidence rate (IR) of lung cancer in 2020 was 33.1 per 100000 in the United States of America (US) and was 29.4 per 100000 in 2020 in Europe (Ferlay et al 2020). The leading cause of lung cancer is smoking in both men and women, irrespective of geographic region. Emerging economies vary widely in smoking practices and cancer incidence but commonly also harbour risks from environmental exposures (Barta et al 2019).

Non-small cell lung cancer (NSCLC) accounts for 80%-85% of all lung cancers (Bareschino et al 2011) and based on this assumption, the estimated incidence of NSCLC in Europe is approximately 25.0 per 100000 and was 28.1 per 100000 in USA (Goldstraw et al 2016). The main histological subtypes are adenocarcinoma (40%), squamous cell carcinoma (25-30%), and large cell carcinoma (10-15%) (National Cancer Institute 2017). Lung cancer is often diagnosed at an advanced stage, resulting in a poor prognosis; the 5-year OS rate for patients with advanced NSCLC ranges from 19% in patients with Stage IIIB to 6% with Stage IV disease (Goldstraw et al 2016).

2.1.2. Epidemiology

The highest incidence rates of lung cancer in males are observed in Micronesia/Polynesia, Eastern and Southern Europe, and Eastern and Western Asia, and among women in North America, Northern and Western Europe, Micronesia/Polynesia, and Australia/New Zealand (Sung et al 2021). In the US, according to SEER-18 data (2017), the incidence of NSCLC was 37.5 per 100,000 (42.4 per 100,000 in men and 33.8 per 100,000 in women), and the 5-year survival overall was 26.4% (21.9% in men and 31.3% in women) (Ganti et al 2021). In Europe, the age-standardised incidence rate of all lung cancers is 63.5 per 100,000 (97.6 per 100,000 among men and 38.3 per 100,000 among women) (Dyba et al 2021).

2.1.3. Biologic features

Non-small cell lung cancer (NSCLC) is the predominant subtype, accounting for approximately 85% of all cases. NSCLC can be divided into two major histologic types: non-squamous and squamous cell carcinoma. Non-squamous histology accounts for more than half of all NSCLC, whereas squamous histology accounts for approximately 30% (Brambilla et al, 2014 and Schrump DS et al. NSCLC; Principles and Practice of Oncology. 9th Edition. 2011) in Europe.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

More than half of the patients are diagnosed at an advanced stage of disease, which directly contributes to poor survival, as expressed by an untreated median OS of 4 months and a metastatic 5-

year survival rate of <5% (Lindsey A. et al, 2016). Poor prognostic factors for survival in patients with NSCLC include advanced stage of disease at the time of initial diagnosis, poor performance status (PS), and a history of unintentional weight loss. More than half of the patients with NSCLC are diagnosed with distant metastatic disease, which directly contributes to poor survival prospects.

2.1.5. Management

Over the past decade, there have been considerable advances in the management of NSCLC. Improved understanding of the biology and molecular subtypes of NSCLC has led to development of a number of biomarker-directed therapies for patients with metastatic disease, including drugs targeting EGFR mutations, ALK rearrangements, and other molecular aberrations. These therapies have improved OS for patients with metastatic NSCLC with an oncogenic driver (Arbour and Riely 2019). For patients with metastatic NSCLC with no actionable oncogenic driver (notably without EGFR mutations and ALK rearrangements), the development of immune checkpoint inhibitors (ICIs) has transformed the care, providing a survival benefit when administered as monotherapy following disease progression on platinum-based chemotherapy (Borghaei et al 2015, Brahmer et al 2015, Herbst et al 2016, Rittmeyer et al 2017) or when administered with or without chemotherapy in the first-line setting (Borghaei et al 2017, Gandhi et al 2018, Paz-Ares et al 2018, Socinski et al 2018, West et al 2019, Jotte et al 2020, Nishio et al 2021, Paz-Ares et al 2021).

Second-/third-line treatment options for advanced or metastatic NSCLC without oncogenic driver mutations

Before ICI therapy was available, there were 2 established chemotherapeutic agents available globally for the treatment of locally advanced or metastatic NSCLC with no actionable oncogenic driver after prior chemotherapy: docetaxel for patients with either nonsquamous or squamous NSCLC and pemetrexed for patients with nonsquamous NSCLC who did not receive pemetrexed as first-line treatment (Planchard et al 2018, Ettinger et al 2019). Erlotinib can also be considered for patients who cannot receive cytotoxic chemotherapy due to poor performance status (Tarceva USPI 2010, Planchard et al 2018). Overall, the therapeutic benefit of these further lines of treatment has been restricted by limited improvements in survival, low response rates, and significant toxicities (Stinchcombe and Socinski 2008, Al-Farsi and Ellis 2014, Nadler et al 2018).

PD-1/PD-L1 ICIs were first approved beginning in 2015 for patients with second- or later-line locally advanced or metastatic NSCLC lacking sensitizing EGFR or ALK mutations, and over time, access has expanded globally from early approvals in the US and EU (Novello et al 2016, Ettinger et al 2019). As access in other parts of the world arrived later, docetaxel remained a commonly used standard treatment option for both squamous and nonsquamous NSCLC in the second- and third-line treatment settings until recently. Presently, pembrolizumab (Keytruda), nivolumab (Opdivo), and atezolizumab (Tecentriq) are approved in the EU for the second-line treatment of metastatic NSCLC (Keytruda SmPC 2021, Opdivo SmPC 2021, Tecentriq SmPC 2021).

First-line treatment options for advanced or metastatic NSCLC without oncogenic driver mutations

Before ICI therapy became available as the first-line treatment for advanced or metastatic NSCLC, platinum-based doublet therapy was the recommended treatment option in patients with no actionable oncogenic driver and an ECOG performance status of 0 to 2. Pemetrexed use is restricted to nonsquamous cell carcinoma in first- (or later-) line of treatment in advanced disease, and is preferred to gemcitabine- or docetaxel-based combinations in nonsquamous NSCLC (Planchard et al 2018).

The approval of ICIs has now been extended to first-line treatment therapy for NSCLC with no actionable oncogenic driver, either as monotherapy or in combination with chemotherapy (Reck et al 2016, Paz-Ares et al 2018, Mok et al 2019). Pembrolizumab in combination with platinum and pemetrexed has since become a new standard of care for patients with first-line nonsquamous NSCLC,

irrespective of PD-L1 status (Gandhi et al 2018). ICI monotherapy has been approved for patients with PD-L1 positive expression (≥50%) and, in some countries, the approval was also extended to the patients with tumour PD-L1 expression ≥1% (Reck et al 2016, Mok et al 2019, Keytruda SmPC 2021).

Similarly, in the first-line squamous NSCLC setting, pembrolizumab has been approved as first-line treatment therapy for squamous NSCLC, either as monotherapy for the "PD-L1 high" (≥50%) population (and also for the population with PD-L1 ≥1% in the US) (Reck et al 2016) or in combination with chemotherapy irrespective of PD-L1 expression (Paz-Ares et al 2018). More recently, nivolumab/ipilimumab with platinum-doublet chemotherapy has been approved as first-line treatment for NSCLC irrespective of histology, and nivolumab/ipilimumab combination therapy alone was approved in tumours expressing PD-L1 ≥1% (Opdivo SmPC 2021). Other ICIs approved for treatment in the first-line setting include atezolizumab and cemiplimab as monotherapy for first-line treatment of NSCLC whose tumours have high PD-L1 expression irrespective of histology, and atezolizumab as first-line treatment of metastatic nonsquamous NSCLC with no EGFR or ALK genomic tumour aberrations in combination with bevacizumab, paclitaxel, and carboplatin as well as with paclitaxel protein-bound and carboplatin (Tecentriq SmPC 2021, Libtayo SmPC 2021).

2.2. About the product

Tislelizumab is a humanised IgG4 variant monoclonal antibody that binds to the T-cell surface receptor programmed cell death protein 1 (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. As such, upregulation of PD-1 ligands occurs in some tumours and signalling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumours, which is counteracted by the administration of PD-1 inhibitors like tislelizumab. The antibody does not bind to Fc gamma receptors and C1q and therefore does not induce antibody-dependent cellular cytotoxicity or complement-dependent cytotoxicity.

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

The approved indication is:

Tizveni in combination with pemetrexed and platinum-containing chemotherapy is indicated for the first-line treatment of adult patients with non-squamous non-small cell lung cancer whose tumours have PD-L1 expression on ≥50% of tumour cells with no EGFR or ALK positive mutations and who have:

- locally advanced NSCLC and are not candidates for surgical resection or platinum-based chemoradiation, or
- metastatic NSCLC.

Tizveni in combination with carboplatin and either paclitaxel or nab-paclitaxel is indicated for the first-line treatment of adult patients with squamous non-small cell lung cancer who have:

- locally advanced NSCLC and are not candidates for surgical resection or platinum-based chemoradiation, or
- metastatic NSCLC.

Tizveni as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer after prior platinum-based therapy. Patients with EGFR mutant or ALK positive NSCLC should also have received targeted therapies before receiving tislelizumab.

Tislelizumab concentrate for solution for infusion is formulated in vials of 10 mL containing 100 mg tislelizumab. Tislelizumab treatment must be initiated and supervised by physicians experienced in the

treatment of cancer. The recommended dose of tislelizumab is 200 mg administered by intravenous infusion once every 3 weeks. Tislelizumab treatment should be continued until disease progression or unacceptable toxicity. No dose reductions of Tizveni as monotherapy are recommended. Tizveni should be withheld or discontinued as described in Table below. Detailed guidelines for the management of immune-related adverse reactions are described in section 4.4.

Table 1. Recommended treatment modifications for Tizveni

Immune-related adverse reaction	**Severity[1]**	**Tizveni treatment modification**
Pneumonitis	Grade 2	Withhold[2,3]
	Recurrent grade 2; grade 3 or 4	Permanently discontinue[3]
Hepatitis	ALT or AST >3 to 8 x ULN or total bilirubin >1.5 to 3 x ULN	Withhold[2,3]
	ALT or AST >8 x ULN or total bilirubin >3 x ULN	Permanently discontinue[3]
Rash	Grade 3	Withhold[2,3]
	Grade 4	Permanently discontinue[3]
Severe cutaneous adverse reactions (SCARs)	Suspected SCARs, including SJS or TEN	Withhold[2,3] For suspected SJS or TEN, do not resume unless SJS/TEN has been ruled out in consultation with appropriate specialist(s).
	Confirmed SCARs, including SJS or TEN	Permanently discontinue
Colitis	Grade 2 or 3	Withold[2,3]
	Recurrent grade 3; grade 4	Permanently discontinue[3]
Myositis/rhabdomyolysis	Grade 2 or 3	Withhold[2,3]
	Recurrent grade 3; grade 4	Permanently discontinue[3]
Hypothyroidism	Grade 2, 3 or 4	Hypothyroidism may be managed with replacement therapy without treatment interruption.
Hyperthyroidism	Grade 3 or 4	Withhold[2] For grade 3 or 4 that has improved to grade ≤2 and is controlled with anti-thyroid therapy, if indicated continuation of Tizveni may be considered after corticosteroid taper. Otherwise, treatment should be discontinued.
Adrenal insufficiency	Grade 2	Consider withholding treatment until controlled by HRT.
	Grade 3 or 4	Withhold[3] For grade 3 or 4 that has improved to grade ≤2 and is controlled with HRT, if indicated continuation of Tizveni may be considered after corticosteroid taper. Otherwise, treatment should be discontinued.[3]

Hypophysitis	Grade 2	Consider withholding treatment until controlled by HRT.
	Grade 3 or 4	Withhold[2,3] For grade 3 or 4 that has improved to grade ≤2 and is controlled with HRT, if indicated continuation of Tizveni may be considered after corticosteroid taper. Otherwise, treatment should be discontinued.[3]
Type 1 diabetes mellitus	Type 1 diabetes mellitus associated with grade ≥3 hyperglycaemia (glucose >250 mg/dl or >13.9 mmol/l) or associated with ketoacidosis	Withhold For grade 3 or 4 that has improved to grade ≤2 with insulin therapy, if indicated continuation of Tizveni may be considered once metabolic control is achieved. Otherwise, treatment should be discontinued.
Nephritis with renal dysfunction	Grade 2 (creatinine >1.5 to 3 x baseline or >1.5 to 3 x ULN)	Withhold[2,3]
	Grade 3 (creatinine >3 x baseline or >3 to 6 x ULN) or grade 4 (creatinine >6 x ULN)	Permanently discontinue[3]
Myocarditis	Grade 2, 3 or 4	Permanently discontinue[3]
Neurological toxicities	Grade 2	Withhold[2,3]
	Grade 3 or 4	Permanently discontinue[3]
Pancreatitis	Grade 3 pancreatitis or grade 3 or 4 serum amylase or lipase levels increased (>2 x ULN)	Withhold[2,3]
	Grade 4	Permanently discontinue[3]
Other immune-related adverse reactions	Grade 3	Withhold[2,3]
	Recurrent grade 3; grade 4	Permanently discontinue[3]
Other adverse drug reactions		
Infusion-related reactions	Grade 1	Consider pre-medication for prophylaxis of subsequent infusion reactions. Slow the rate of infusion by 50%.
	Grade 2	Interrupt infusion. Resume infusion if resolved or decreased to grade 1, and slow rate of infusion by 50%.
	Grade 3 or 4	Permanently discontinue

ALT = alanine aminotransferase, AST = aspartate aminotransferase, HRT= hormone replacement therapy, SJS = Stevens-Johnson syndrome, TEN = toxic epidermal necrolysis, ULN = upper limit normal

1 Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI-CTCAE v4.0). Hypophysitis grade is in accordance with NCI-CTCAE v5.0.

2 Resume in patients with complete or partial resolution (grade 0 to 1) after corticosteroid taper over at least 1 month. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating corticosteroids or inability to reduce prednisone to ≤10 mg/day (or equivalent) within 12 weeks of initiating corticosteroids.

3 Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper to ≤10 mg/day (or equivalent) over at least 1 month is recommended, except for pneumonitis, where initial dose of 2 to 4 mg/kg/day is recommended.

2.3. Type of application and aspects on development

The legal basis for this application refers to: Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as concentrate for solution for infusion containing 100 mg/10 mL of tislelizumab as active substance.

Other ingredients are: sodium citrate dihydrate, citric acid monohydrate, L-histidine hydrochloride monohydrate, L-histidine, trehalose dihydrate, polysorbate 20 and water for injections.

The product is available in a 20 mL type 1 glass vial, with a grey chlorobutyl stopper with FluroTec coating and seal cap with a flip-off button. The product is available in unit packs containing 1 vial and in multipacks containing 2 (2 x 1) vials.

2.4.2. Active Substance

2.4.2.1. General Information

Tislelizumab is a Fc engineered humanised immunoglobulin G4 (IgG4) variant monoclonal antibody produced in recombinant Chinese Hamster Ovary (CHO) cells. The antibody binds to the programmed cell death protein 1 (PD-1) receptor on the T-cell surface, preventing interaction with PD-1 ligands PD-L1 and PD-L2, thereby blocking PD-1-mediated inhibitory signalling.

Tislelizumab consists of two heterodimers, each composed of a heavy and a light polypeptide chain. The amino acid sequences of the light chain (LC) and heavy chain (HC) in tislelizumab are shown in Figure 1. The theoretical molecular weight calculated from the amino acid sequence is 144,080 Dalton. Tislelizumab is composed of 1318 amino acid residues, 445 in the HC and 214 in the LC. Each HC contains one N-glycosylation site at asparagine 295. Post-translational modifications concern the N-termini with a N-term pyroglutamate, or Pyr-Q, and the C-termini with a C-term lysine clipped, -K, as well as a glycosylation at the conserved Fc glycosylation site. Due to the modulations in the Fc region, tislelizumab does not bind to Fc gamma receptors and C1q. Therefore, it does not include antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP) and/or complement-dependent cytotoxicity (CDC).

Figure 1: Primary structure of tislelizumab

The physicochemical properties of tislelizumab active substance are provided in the dossier. The general information is considered sufficient.

2.4.2.2. Manufacture, process controls and characterisation

The active substance is manufactured, tested and released in accordance with good manufacturing practice (GMP). The site responsible for the manufacture of the active substance is Boehringer Ingelheim Biopharmaceuticals (China) Ltd., 1090 Halei Road Pilot Free Trade Zone, 201203 Shanghai, China.

During the procedure, a major objection (MO) was raised for the lack of proof of EU GMP compliance for several of the active substance manufacturing sites. Following remote inspection and/or agreement to conduct a post-approval inspection at the concerned sites from the responsible supervisory authorities, EU GMP compliance for the active substance manufacturing sites has been confirmed.

Description of manufacturing process and process controls

The overall active substance manufacturing process is adequately presented in the dossier. The tislelizumab active substance is expressed in the CHO cell expression system. The manufacturing process is divided into cell culture/harvest (upstream) and purification (downstream) steps.

To initiate the tislelizumab cell culture process, working cell bank (WCB) is thawed and cells are cultivated under controlled conditions. After vial thaw, a series of sequential passages are performed to expand and scale-up the tislelizumab cell culture before being finally transferred into the production bioreactor.

During the harvest unit operation, cells and cell debris are separated from the cell culture fluid of the production bioreactor containing tislelizumab active substance to provide harvested cell culture fluid for purification.

The purification of the active substance starts with a Protein A affinity chromatography to remove process-related impurities. Viral reduction follows during a virus inactivation and pH adjustment step. Turbidities are removed by depth filtration subsequently. Process-related impurities are removed further by several other chromatography techniques. Virus filtration is conducted as a second orthogonal method specifically dedicated for viral clearance that provides additional assurance of viral safety by the physical removal of potential adventitious viruses by size. After ultrafiltration and diafiltration during tangential flow filtration, the tislelizumab active substance is supplemented with spike buffer and formulation buffer to achieve the target product concentration and excipient composition.

Lastly, the filtration and storage unit operation include filtration of the active substance into a mixing bag with subsequent transfer into bags for long-term storage.

The container closure system (CCS) for tislelizumab active substance is a single-use pre-sterilised bag that complies with the compendial requirements. Sufficient details on the CCS, including materials, dimensions and technical drawings are provided in the dossier.

Adequate definition of a batch of tislelizumab active substance is included in the dossier. Reprocessing is claimed for several manufacturing steps and the proposed approach is considered acceptable.

An extractables assessment was performed based on extractables study data to identify potential leachables present in both tislelizumab active substance and finished product manufacturing processes, which may adversely affect patient safety. Polymeric materials used throughout the manufacturing processes were assessed by review of associated extractables data available for each material. The leachable study results, by all analyses, detected no elemental impurities with a concentration greater than or equal to the corresponding Permitted Daily Exposure (PDE) limits and no organic compounds with a concentration greater than or equal to the corresponding Analytical Evaluation Threshold (AET) limits. Therefore, the leachables study supports the conclusion that potential leachables present in the tislelizumab active substance/finished product manufacturing processes and/or in the active substance CCS pose no risk to patient safety.

Overall, the active substance manufacturing process has been adequately described and the in-process controls (IPCs) are indicated for each step, with adequately justified acceptance criteria. It is mentioned that a deviation procedure, which includes an investigation, is followed when any normal operating range (NOR) or proven acceptable range (PAR) limits for process parameters (PP) are exceeded or when excursions for critical (CPP), key (KPP) and non-key (non-KPP) process parameters occur. This approach is endorsed.

In conclusion, the active substance manufacturing process is considered acceptable.

Control of materials

Sufficient information on raw materials has been submitted by the applicant. Raw materials and reagents for the manufacture of tislelizumab active substance are commercial or prepared from commercially available materials and are qualified. Compendial raw materials comply with their respective monographs. None of the raw materials of the manufacturing process are of animal or human origin. The composition of media for cell banking, growth and production, feed is provided and process parameters for media preparation are indicated.

Tislelizumab is expressed in CHO cells. Sufficient information regarding cell line development has been presented in the dossier. Master cell bank (MCB), working cell bank (WCB) and end-of-production cell banks (EOPCBs) were tested for identity, sterility, mycoplasma, endogenous and adventitious viruses.

The limit of in vitro cell age (LIVCA) has been established for the tislelizumab production cell line in accordance with ICH Q5B.

Control of critical steps and intermediates

A comprehensive overview of critical in-process controls and critical in-process tests performed throughout the tislelizumab active substance manufacturing process is given. Acceptable information has been provided on the control system in place to monitor and control the active substance manufacturing process with regard to critical, as well as non-critical operational parameters and in-process tests. Actions taken if limits are exceeded are specified. The critical manufacturing controls are supported by process characterisation studies, additional supportive studies and manufacturing experience. Hold time CPPs through both harvest and purification processes are established and considered acceptable.

Process validation

Process validation follows a master validation plan to control consistent and robust quality of the active substance. A three-stage approach to validation was followed: Stage 1 - Process Design, Stage 2 - Process Performance Qualification (PPQ) and Stage 3 - Continued Process Verification.

Process characterisation studies and scale down models were conducted to support the commercial manufacturing process control strategy and to ensure robust process performance and consistent product quality. Quality attributes (QA) are established and the criticality of each quality attribute is assessed with respect to impact on biological activity, pharmacokinetics, pharmacodynamics, and immunogenicity and safety, which are directly linked to product efficacy and safety.

Impact of non-conformities to the product quality or to the validation execution was assessed and corrective and preventive actions (CAPAs) were initiated as appropriate.

Results of the process performance qualification (PPQ) demonstrated that the tislelizumab manufacturing process is consistently capable of producing product meeting predefined criteria for each PPQ batch, including repeatability and consistency of all PPQ batches manufactured. Reprocessing, hold times and resin reuse are validated within supporting validation studies.

In conclusion, the active substance manufacturing process is adequately validated.

Manufacturing process development

The commercial active substance manufacturing process was developed in parallel with the clinical development program. Several important changes have been introduced during the development of the manufacturing process. These include changes to manufacturing site, scale and to the process itself.

The tislelizumab final manufacturing process (FMP) is the process intended for commercial manufacturing and was the only source of active substance used in the pivotal study for the Marketing Authorisation Application (MAA).

Comparability studies were performed at every major stage of development to assure product quality and performance. The comparability assessment showed no impact to purity and potency. All active substance batches met the predetermined comparability criteria. The additional characterisation confirmed the consistent higher-order structure and biophysical properties. Slight differences in glycosylation were observed, which were attributed to variability in the cell culture medium used.

Despite these differences, no changes in functional attributes were correlated to an increase or decrease of specific glycan forms or charge variant groups. Therefore, tislelizumab manufacturing process was demonstrated to be comparable throughout development.

Characterisation

Structure, physicochemical characteristics and biological properties of tislelizumab were elucidated by release tests and additional characterisation assays. The analytical results are consistent with the proposed structure.

Primary, secondary and higher order structure has been thoroughly characterised applying various orthogonal methods, revealing that the active substance has the expected structure of a human IgG4-type antibody. Furthermore, heterogeneity of the active substance was adequately characterised by analysing size and charge variants, glycosylation and other product-related substances and impurities.

Biological characterisation of tislelizumab indicates that this antibody has a high affinity for human PD-1 and binds to the extracellular domain of PD-1, as well as to the native PD-1 expressed on cell surface, in a dose-dependent manner. Binding activities of tislelizumab to Fc gamma receptors and C1q protein were analysed and results show that tislelizumab does not bind to different Fc gamma receptors and has little or no binding to C1q. ADCC and CDC activity of tislelizumab was characterised by cell-based assays and neither ADCC, nor CDC activity were detected, as expected for IgG4 construct.

Process-related impurities comprise of impurities originating from the cell substrates, cell culture and purification processing. During process characterisation studies and process validation campaigns, sufficient clearance of certain process-related impurities was shown. Based on the provided data, it is acceptable that tests for these impurities are not included as in-process controls or in the tislelizumab active substance release specification. In summary, the characterisation data presented are considered appropriate for this type of molecule.

2.4.2.3. Specification

The release and stability specification for tislelizumab active substance are set based on regulatory guidelines, analytical capability, process capability and clinical experience. The tislelizumab release/stability specification includes general tests, test for identity, purity and impurity tests for product-related impurities, test for process-related impurities, test for protein content, biological activity, as well as tests for safety parameters.

During the assessment, the applicant was requested to tighten the acceptance criteria for several quality attributes (bacterial endotoxin and biological activity). Additionally, inclusion of a quantitative acceptance criteria for glycan content was requested. A recommendation to monitor the glycan content, until a sufficient number of active substance batches is manufactured to document manufacturing process consistency and determine if the quantitative control of glycan content for tislelizumab release testing is required, has been given (Recommendation).

Overall, the parameters included in the active substance release and shelf-life specification are found adequate to control the quality of tislelizumab.

Analytical methods

Method descriptions for all non-compendial analytical procedures are provided and validations are performed according to ICH Q2(R1). The compendial methods have been verified to demonstrate the suitability for the intended purpose. The biological activity of tislelizumab is determined by a cell-based assay, measuring the ability of the active substance to block PD-1 receptor from engaging with the target ligand PD-L1.

Batch analysis

Batch analysis data of the active substance were provided, cover early-stage batches produced by the original manufacturing process and late-stage batches produced by the final manufacturing process. All batch analysis data were in line with the acceptance criteria that applied at the time of testing. The results for batch release demonstrate a high level of batch-to-batch consistency.

Reference materials

A 2-tiered reference standard (RS) system has been established with a primary reference standard (PRS) and a working reference standard (WRS).

The information provided is found sufficient and the extent of the qualification of the standards is adequate.

Future WRS will be prepared form representative commercial active substance batches. A detailed protocol for the characterisation and qualification of future WRS has been provided, including sufficient description of potency assignment. Requalification protocols for the PRS and WRS have been included and are found acceptable.

2.4.2.4. Stability

The proposed shelf-life for the tislelizumab active substance is 24 months in the defined CCS and at the proposed long-term storage condition.

The active substance stability program is conducted according to ICH Q1A (R2) and ICH Q5C. Primary data are derived from PPQ batches and from additional representative clinical batches, manufactured at the proposed commercial site. All primary stability batches were manufactured using the final manufacturing process and the CCS used is representative of the commercial container closure. In addition to data from the primary stability studies, data from supportive stability batches manufactured using the original manufacturing process are also provided.

In summary, the stability data demonstrate that the active substance is stable at the recommended long-term storage condition for all attributes tested, supporting the proposed shelf-life of 24 months. All stability data remain within the clinical specifications in place at the time of testing, indicating that there have been no significant changes in terms of potency, quality or purity of the active substance when stored at the long-term condition. No change has been observed relative to the initial time point and the results meet the acceptance criteria for all analytical procedures applied. In addition, data from stability studies conducted under accelerated and stressed conditions are also included in the dossier and results are adequately discussed.

Additionally, forced degradation studies were performed to further characterise the active substance and to build knowledge around specific molecular degradation pathways and resilience of the molecule under various stressed conditions. The results obtained demonstrate that selected analytical methods are stability indicating.

The applicant commits to conduct and complete the ongoing long-term stability studies of the primary batches, which includes stability studies for process validation batches, according to the stability protocols. This approach is endorsed.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

The finished product is presented as a 10 mL concentrate for solution for infusion in a 20 mL vial, consisting of 10 mg/mL tislelizumab formulated in citrate, histidine, trehalose, polysorbate 20. The concentrate is a clear to slightly opalescent, colourless to slightly yellowish solution, that contains no preservative and is intended for intravenous infusion as single use only.

Acceptable description of the finished product composition has been provided. All excipients are of Ph. Eur. compendial grade and specifications for the excipients have been provided, including additional testing of polysorbate 20 and trehalose dihydrate for residual solvents. No novel excipients and no excipients of human or animal origin are used in the finished product formulation. Compatibility between the excipients and the tislelizumab active substance is considered demonstrated by the long-term stability data.

The primary packaging is a Type I glass vial, with a grey chlorobutyl stopper with FluroTec-coating and secured with aluminium flip-off seal caps. The finished product CCS complies with compendial requirements. Suitability of the CCS is supported by the chemical resistance of the selected components, container closure integrity testing (CCIT) and stability data. In addition, extractable and leachables studies were performed, in line with ICH Q3D guideline. The extractables study identified no extractables requiring further investigation. The leachables study results indicate that all elemental analyses were below the PDE and all organic compounds were below the AET, with the exception of two substances of interest. However, as both compounds were detected at levels well below the safety threshold, no further toxicology evaluation was needed. In summary, test results support the conclusion that the selected CCS is compatible with the finished product and adequate for the intended use of the product throughout the shelf-life.

The commercial formulation of the finished product was established in formulation screening and robustness studies. The objective of the finished product formulation development program was to develop a formulation sufficiently stable and robust for manufacturing, storage, transportation and administration of tislelizumab by intravenous infusion. There have been no changes in the formulation of tislelizumab finished product between the toxicology batches used for nonclinical safety studies, clinical batches and the planned commercial batches.

Over the course of manufacturing process development, the manufacturing process has undergone several changes as appropriate for each development stage. These changes were primarily associated with the transfer to the commercial manufacturing site, process scale-up and change of the CCS. Process characterisation, process transfer and comparability studies were conducted to support the commercial manufacturing process control strategy and to ensure robust process performance and consistent finished product quality.

The clinical dose of 200 mg is delivered using two 100 mg vials via intravenous administration with a 0.22 µm filter, upon dilution with saline solution. Compatibility with representative infusion bags, infusion lines and in-line filter has been investigated in-use stability studies and results demonstrate that the diluted tislelizumab injection solution is stable for 24 hours at refrigerated conditions (2°C to 8°C), as well as 4 hours at 25°C ± 2°C, when in contact with clinically representative plastics. Further

studies demonstrate that no microbial proliferation occurred in spiked 0.9% saline bags for 48 hours at the refrigerated conditions (2°C to 8°C) and for 8 hours at room temperature conditions (25°C ± 2°C). The proposed in-use period and storage conditions stated in the SmPC are therefore supported.

2.4.3.2. Manufacture of the product and process controls

The manufacture, control, packaging and release of tislelizumab finished product is performed, in accordance with GMP. The sites responsible for the batch release of the finished product are: Novartis Farmacéutica, S.A., Gran Via de les Corts Catalanes, 764, 08013 Barcelona, Spain and Novartis Pharma GmbH, Roonstrasse 25, 90429 Nuremberg, Germany.

During the procedure, a major objection (MO) was raised for the lack of proof of EU GMP compliance for several of the finished product manufacturing sites. The MO was resolved, reference is made to the active substance section.

The tislelizumab finished product manufacturing process consists of the following unit operations: thawing, bioburden reduction filtration and pooling, sterile filtration, filling and stoppering, capping and visual inspection.

The finished product manufacturing process includes no additional formulation steps, hence all physicochemical and biological properties of the finished product are the same as those for the active substance. Controls for CPPs and IPCs (including microbiologic contamination control) with process limits and acceptance criteria are established for the finished product manufacturing process to ensure consistent process performance and product quality. Hold times for thawing and pooled active substance have been adequately defined.

A three-stage approach to validation of the finished product manufacturing process was followed: Stage 1 - Process Design, Stage 2 - Process Performance Qualification (PPQ) and Stage 3 - Continued Process Verification. The predefined PPQ requirement of the finished product batches was determined based on platform experience, process development knowledge and manufacturing history. PPQ batches are subject to increased scrutiny of process performance and extended sampling and testing, and encompass all unit operations of the finished product manufacturing process. The PPQ campaign was performed under cGMP conditions, with defined targets and/or ranges for process parameters equivalent to the NORs. All CPPs and KPPs were assessed per PPQ protocol. All process parameters were within all NORs and all outputs met all process validation limits and acceptance criteria. As a consequence, all validated ranges or limits are implemented as the commercial process NORs, PARs and IPCs process limits or IPC acceptance criteria.

The consistency and reproducibility of the intermediate hold times were successfully validated during the PPQ campaign with the demonstration that the intermediate hold validation batches met all predefined validation criteria.

Taken together, the finished product manufacturing process is considered validated and it has been demonstrated that the process is capable of producing a product of intended quality in a reproducible manner.

Results of shipping qualification for non-simulated shipment over a worst-case distance of the bulk finished product between China and a site in the US and back to China for testing have been further provided. It is concluded that there is no adverse effect on the tislelizumab finished product. The same conclusion results upon risk assessment of the second shipping configuration and associated shipment of bulk finished product from China to a secondary packaging site in Switzerland.

2.4.3.3. Product specification

The release and shelf-life specification includes general tests, test for protein content, test for identity, purity and impurity tests for product-related impurities and heterogeneity, biological activity, as well as tests for safety parameters. Polysorbate 20 content is tested at both release and stability. Further, container closure integrity is tested during stability.

The general approach for selection of the attributes included in the finished product release and stability specification is based on clinical safety, efficacy, and pharmacokinetic analysis, statistical analysis of release and stability data and historical understanding of the finished product performance/formulation robustness studies. Further, compendial requirements are considered. Overall, the selection of specification attributes and setting of the acceptance criteria are in line with ICH Q6B and are found adequate to control the quality of the tislelizumab finished product. However, similar to the active substance specification, some adjustments/tightening of the acceptance criteria for biological activity, visible particles and bacterial endotoxin were performed upon request.

No additional process or product-related impurities are introduced or expected to form as a result of the finished product manufacturing. Therefore, finished product impurities are expected to be the same as those described in the active substance section.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed, considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary. In addition, the risk of extractable, leachables and elemental impurities is found sufficiently addressed and no additional controls are necessary, as stated in the active substance section.

Analytical methods

The finished product is tested using both compendial and non-compendial methods. Many of the methods used to test the finished product are equivalent to the methods used to test the active substance, since there is no compositional difference between the active substance and the finished product with respect to protein concentration or formulation. The only non-compendial method which is unique to finished product is determination of polysorbate 20 content, for which appropriate validation data in accordance with ICH guidelines have been provided.

The applicant has declared that a new method employing a demasking procedure coupled with endotoxin determination is currently under development. Therefore, the applicant is recommended to communicate the outcome of method evaluation to the authority immediately upon finalisation (to be submitted as a Recommendation).

Batch analysis

The data for all tislelizumab finished product batches used during clinical development and manufactured at the commercial manufacturing facility, demonstrate that all batches met the specifications in place at the time of release, are comparable across production sites and scales and confirm consistency of the manufacturing process.

Reference materials

Reference is made to the corresponding active substance section.

2.4.3.4. Stability of the product

The applicant claims a shelf-life for the finished product of 36 months when stored at 2°C to 8°C in the defined CCS.

Stability results for tislelizumab finished product stored under recommended long-term conditions (5°C ± 3°C) and under accelerated conditions (25°C ± 2°C, 60% ± 5% RH) are provided. Primary stability data are derived from finished product PPQ batches and from representative clinical finished product batches, all batches being manufactured at the commercial site and packaged in the CCS. Data from supportive stability clinical batches are also provided. All the primary and supportive stability finished product batches have the same formulation composition and protein concentration.

A photostability study was conducted in line with ICH Q1B and data obtained show no significant impact on the finished product quality after exposure to light. Nevertheless, the SmPC statement "Store in the original carton in order to protect from light" is kept as a precaution due to optimal storage. This approach is considered acceptable.

As discussed in the Pharmaceutical Development section, in-use stability of the diluted finished product solution has been demonstrated for 24 hours at 2°C to 8°C. The 24 hours include storage of the diluted solution under refrigeration (2°C to 8°C) for no more than 20 hours, time required for returning to room temperature (25°C or below) and time to complete the infusion within 4 hours.

In summary, the stability data demonstrate that the tislelizumab finished product is stable at the recommended long-term storage condition of 2°C to 8°C, as mentioned in the SmPC, supporting the proposed shelf-life of 36 months.

The applicant commits to conduct and complete the ongoing stability studies, which includes stability studies for process validation batches, according to the stability protocols. This approach is endorsed.

2.4.3.5. Post approval change management protocol(s)

Two post-approval change management protocols (PACMPs) are included in Module 3.2.R of the dossier. The protocols concern:

1. Introduction of an additional active substance manufacturing and testing site.
2. Introduction of an additional finished product manufacturing site, as well as introduction of two additional finished product testing sites.

Overall, the strategies provided in both PACMPs are considered adequate. Provided that the PACMPs are fulfilled and successfully implemented, it is agreed that the changes can be accepted.

2.4.3.6. Adventitious agents

Transmissible spongiform encephalopathy (TSE) compliance

No animal-derived or human-derived components were used in the manufacture of the MCB and WCB. No animal-derived or human-derived components were used during cell line development and generation of the MCB. None of the raw materials used during manufacturing of active substance or finished product are of animal or human origin. No human or animal-derived excipients are used at formulation of the finished product. One animal-derived material, sheep-wool–derived cholesterol, was used in the development of the MHCB, which was transfected to generate MCB, for which a TSE Certificate was provided.

In summary, compliance with "Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev.3)" requirement has been demonstrated.

Virus safety

The antibody is produced in a cell culture medium, free of animal or human-derived components. MCB and WCB and cells from end of production have been sufficiently tested for adventitious and endogenous viruses. The tests demonstrate the absence of viral contaminants. Only retrovirus-like particles have been detected, which is expected for this type of cells. A retroviral risk assessment demonstrated an excess reduction capacity for retroviral particles within manufacturing process. The presence of retroviral particles is therefore justified. The purification process includes four steps, including virus filtration, which all have been validated for their virus removal capacity of enveloped and non-enveloped viruses.

Overall, sufficient virus inactivation/removal capacity has been demonstrated.

2.4.3.7. GMO

Not applicable.

2.4.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The applicant has applied QbD principles in the development of the active substance and/or finished product and their manufacturing process. However, no design spaces were claimed for the manufacturing process of the active substance, nor for the finished product.

One major objection was raising during the assessment for the lack of valid EU GMP certificates for active substance and finished product sites, which has been adequately addressed by the end of the procedure.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the benefit/risk ratio of the product, which pertain to the: 1) requirement to continue monitoring the glycan content at the active substance level until a sufficient number of batches has been manufactured to document manufacturing process consistency and 2) requirement to update the dossier with an optimised endotoxin test procedure once validation of the new procedure is finalised. These points are put forward and agreed as recommendations for future quality development.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.4.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. The Applicant proposes to monitor glycan content through a continued process verification protocol in which glycan content can be quantitatively monitored in all commercially manufactured active substance lots for the first year of manufacture, and trending analysis performed to ensure levels are not drifting or changing in a meaningful manner over time. A determination can then be made after the first year as to whether continued quantitative control of glycan content for active substance release testing is required. This approach is supported, provided that a sufficient number of active substance batches is manufactured to document manufacturing process consistency. The Applicant is recommended to follow this approach and submit a suitable variation application when sufficient data is available to support discontinued quantitative control of glycan content for active substance release testing.
2. For the determination of bacterial endotoxin, low endotoxin recovery (LER) was observed in the finished product. The Applicant has declared that a new method employing a demasking procedure coupled with endotoxin determination is currently under development. The Applicant is recommended to communicate the outcome of method evaluation to the authorities immediately upon finalisation.

Non-clinical aspects

2.4.7. Introduction

Tislelizumab is a humanised IgG4 variant antibody derived from a murine hybridoma clone. The proposed mode of action consists in binding to the check-point molecule PD-1, blocking its signal transduction and consequently enhancing immune cell functions, possibly leading to inhibition of tumour growth in vivo. Tislelizumab has been mutated in the Fc region, in order to minimise the binding to Fc gamma receptors.

Non-clinical studies are based on the requirements of the ICH S6 and S9 guidelines; therefore, a reduced package of studies was submitted.

2.4.8. Pharmacology

2.4.8.1. Primary pharmacodynamic studies

The Applicant performed a wide panel of *in vitro* studies to characterise tislelizumab binding to its target PD.1 and its subsequent whished effect (i.e. re-activation of immune response). From the results shown, tislelizumab seems to specifically bind to PD-1 (and to cynomolgus PD-1, but not to murine PD-1) with KD in the order of 0.1-0.2 nM. EC50 values were calculated with different methods and in different experimental settings (e.g. ELISA and FACS) and they were in low nM order. Competition with PD-L1 and PD-L2 molecules was also tested with IC50 values of approximatively 0.5nM. Functional assays showed variable activity but with IC50 or EC50 again in low nM order (0.4-1.5 nM).

The activity of tislelizumab was investigated in several in vivo experiments. The experiments include also allogeneic xenograft models of epidermoid carcinoma, colon and lung cancers. In all studies

presented, treatment with tislelizumab (10mg/kg, i.p QW or less) showed a decrease in tumour growth compared to controls. Although, animal survival was not an endpoint, in most of the studies tumour regression (not always long lasting) could be observed in some animals (Reports: R01-vivo-127 and 125 colon cancers). Of note, tumour inoculation had only marginal effect on animal weight and no significant difference could be noted between treated animals and controls.

2.4.8.2. Secondary pharmacodynamic studies

Since tislelizumab contains mutations to reduce Fc effector functions, several experiments were performed to verify a reduced binding to FcγRs and lack of ADCC and CDC activity.

Dahan et al. 2015 report that Fcγ receptor engagement augments the anti-tumour activity of anti-PD-L1 antibodies (Abs), but compromises the anti-tumour activity of anti-PD-1 Abs. These findings provide rationale for Fc engineering of these Abs to optimise anti-tumour efficacy. Lack of binding of tislelizumab to FcγR as compared to pembrolizumab and nivolumab was demonstrated in vitro. These interactions between anti-PD-1 antibodies with competent Fc have shown to significantly reduce their therapeutic efficacy for cancer treatment, likely due to the killing of T cells by antibody-mediated effector functions (such as ADCC).

2.4.8.3. Safety pharmacology programme

Safety pharmacology parameters were assessed during the toxicology studies, please refer to the Toxicology section.

2.4.8.4. Pharmacodynamic drug interactions

No pharmacodynamic drug interactions studies were submitted as part of this application.

2.4.9. Pharmacokinetics

The PK behaviour of tislelizumab was investigated after single or repeat intravenous infusion administration to cynomolgus monkeys. The study P14-057-YD included three groups with single dose administrations of 3/10/30 mg/kg tislelizumab and one group with repeat-dose administration of tislelizumab 10mg/kg once weekly for four weeks with a total of five doses. There was no control group in this study. In the single dose groups, C_{max} and exposure increased approximatively dose-proportional. In the repeat-dose group, some accumulation could be noticed between d1 and d289, at least in male animals. Slight differences in PK parameters between female and male animals were observed. ADA were detected in the vast majority of the animals with possible impact on tislelizumab concentration.

Toxicokinetics: In the single dose study in monkeys, tislelizumab C_{max} and AUC increased slightly more than dose-proportionally. T ½ ranged from 7-11 days, approximatively. In the 13-week repeat-dose study in monkeys, tislelizumab C_{max} and AUC increased approximatively dose proportional at day 1. Slight accumulation between d1, d29 and d71 could be seen in the mid and high dose groups in male animals. The presence of ADA may have affected C_{max} and AUC especially in the low dose group and potentially AUC for the mid and high-dose groups, nevertheless exposure was still present in the majority of the animals. Of note, results of the nAb assay indicate that the ADA were neutralising. Serum exposure in male and female monkeys was generally comparable after a single dose on Day 1 across the two IV dose groups. Serum exposure to tislelizumab in female monkeys was generally lower compared with those measured for male monkeys after repeated once every two weeks IV bolus doses on Day 71 across the two IV dose groups.

Overall, PK parameters were compatible with the ones expected for monoclonal antibodies.

Distribution

No specific tissue-cross reactivity with tislelizumab was noted in cynomolgus monkey or human tissues. (study Nos O14-057-2ZJ and O14-057-1ZJ). A Retrogenix assay, was also performed, please refer to the section "other toxicity studies".

No animal studies have been conducted to assess the impact of tislelizumab on milk production or its presence in breast milk.

Metabolism and excretion

No metabolism and excretion studies were performed.

Pharmacokinetic drug interactions

As there is minimal involvement of the cytochrome P450 system in the metabolism of monoclonal antibodies it is endorsed that no in vitro drug interaction studies with tislelizumab are conducted.

2.4.10. Toxicology

2.4.10.1. Single dose toxicity

The Applicant performed a single-dose toxicology study in mice (m14-057-jd), where 0/30/100 mg/kg tislelizumab was administered IV once to 10 female and 10 male animal/group and followed by a 28-day recovery period. Only a limited set of parameters was analysed: clinical observations, body weight, food consumption, upon necropsy: macroscopic evaluation (gross findings), the Applicant did not observe any sign of toxicity. Of note, no TK analysis performed so the exposure not known in this study. Importantly, the mouse is not the relevant animal species, since tislelizumab does not bind to murine PD-1.

Moreover, the Applicant performed a single-dose toxicology study in monkeys (p14-057-jd), where 0/10/30/100 mg/kg tislelizumab was administered IV once to one female and one male animal/group and followed by a 28-day recovery period. The Applicant did not observe any sign of toxicity and set the MTD at 100mg/kg. ADA were detected in about 50% of the animals.

2.4.10.2. Repeat dose toxicity

The Applicant performed a repeat-dose toxicology study in monkeys (p14-057-cd), where 0/3/10/30 mg/kg tislelizumab was administered IV once biweekly for 13 weeks to 6 animals/sex/group followed by a 6-week recovery period (the first 4 monkeys/sex/group were euthanised after 13-week of dosing on Day 91 and the remaining 2 monkeys/sex/group were euthanised on Day 133) following a 6-week recovery period. The Applicant did not observe any sign of toxicity and set the NOAEL at 30 mg/kg. Safety pharmacology parameters were incorporated in the toxicology studies and no effects were noted on parameters evaluating respiratory, neural or cardiovascular system. Importantly, the outcome of the triggered GLP inspection was negative. Results of an additional repeat-dose toxicity study in cynomolgus monkeys were submitted during the procedure. Doses of 0/30/60 mg/kg tislelizumab was administered IV once every two weeks for 13 weeks to 3 animals/sex/group or as two single doses (14 days apart to 3 males only) via subcutaneous injection (SQ). No sign of toxicity was observed at 30mg/kg, which was confirmed to be the NOAEL. However, in the 60 mg/kg IV group, a female had to be euthanised early at day 31. The causes were possibly attributed to immunogenicity.

2.4.10.3. Genotoxicity

No genotoxicity studies were performed as part of this application.

2.4.10.4. Carcinogenicity

No carcinogenicity studies were performed as part of this application.

2.4.10.5. Reproductive and developmental toxicity

No dedicated in vivo studies reproductive and developmental toxicity studies were submitted as part of this application The applicant submitted a literature review on the effects of PD-1/PD-L1 on embryo-foetal toxicity. The risk-assessment highlighted the important role of the PD-1/PD-L1 axes in pregnancy and foetal loss. Tislelizumab may cause foetal harm, increase rates of abortion or stillbirth or altering the normal immune response in foetuses if administered to a pregnant woman, which is acknowledged. Moreover, the effects of PD-1/PD-L1 on prenatal and postnatal development, including maternal function, suggest that inhibition of PD-1/PD-L1 pathway during pregnancy may cause or potentiate autoimmune diseases in infants. Examination of reproductive organs was performed during the 13-week repeat dose study, where no findings were reported.

2.4.10.6. Toxicokinetic data

2.4.10.7. Local tolerance

Local tolerance endpoints were included in the repeated dose toxicity study and no findings were reported. This is considered acceptable.

2.4.10.8. Other toxicity studies

Other in vitro toxicity studies were performed in order to evaluate tislelizumab antigenicity, immunotoxicity and potential to induce cytokine release.

The Applicant performed two tissue cross-reactivity studies on 30 human normal tissues (O14-057-1ZJ) and 30 monkey normal tissues (O14-057-2ZJ). The GLP TCR studies submitted in the original application were not considered GLP compliant therefore the study results were replaced with Retrogenix assay. The Applicant performed a Retrogenix assay showing binding of tislelizumab to PD-1 on fixed and live human cells (HEK293 transfectants). The positive signals were further verified by FACS. Although for tislelizumab an Ab concentration much higher than the one of the positive control rituximab was used (20µg/ml versus 1µg/ml respectively), the signal appears to be strong and specific. The results of the Retrogenix assay identified a specific, although weak, off-target binding to TREML1, which was not sufficiently addressed in the current answer and the Applicant was asked to further investigate. In response, the Applicant provided an additional study investigating the potential binding of tislelizumab to TREML-1 via SPR. Two different assay formats were tested, one format had the antigen in solution (monovalent format) the other format had the antigen bound to the surface (avid format). None of the formats could confirm tislelizumab binding to TREML-1. Of note, the respective positive controls resulted in positive signals, as expected. Therefore, it is unlikely that VDT482 shows significant competition against the natural ligand of TREML1 and thus the weak interaction observed in the Retrogenix in vitro assay is not expected to have any physiological implication."

2.4.11. Ecotoxicity/environmental risk assessment

A justification for not performing an environmental risk assessment was provided. As tislelizumab is a protein composed of natural amino acids, and proteins are expected to biodegrade in the environment and not pose a significant risk. Therefore, tislelizumab is exempt from preparation of an Environmental Risk Assessment as per the "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (EMEA/CHMP/SWP/4447/00).

2.4.12. Discussion on non-clinical aspects

Overall, the primary pharmacodynamic studies provided evidence that tislelizumab can bind to PD-1 receptor and can prevent the interaction with PD-1 ligands PD-L1 and PD-L2, avoiding PD-1-mediated

inhibitory signalling. However, most experiments were performed in very artificial conditions showing binding to PD-1 transfectants, believed to have a very high target expression. Lack of binding of tislelizumab to FcγR as compared to pembrolizumab and nivolumab was demonstrated in vitro. These interactions between anti-PD-1 antibodies with competent Fc have shown to significantly reduce their therapeutic efficacy for cancer treatment, likely due to the killing of T cells by antibody-mediated effector functions (such as ADCC). However, how this would pan out in a disease animal model is not known. Therefore, a comparative study with nivolumab and pembrolizumab in an animal model to determine the lack of antibody effector function in vivo would have been supportive of the non-clinical proof of concept of tislelizumab. Therefore, more data on binding to unstimulated PBMCs (performed, but not shown) were requested. *In vivo* studies using murine xenograft tumour models and human PBMCs showed tislelizumab efficacy against several tumour cell lines.

The pharmacokinetics of tislelizumab were assessed in cynomolgus monkeys in a single-dose PK study and in the repeat-dose toxicity study after IV administration. This is appropriate as it reflects the clinical route of administration. ADA were detected in most of the animals and determined to be mostly neutralising. An impact on C_{max} and AUC was evident especially in the low dose group and potentially also on AUC for the mid and high-dose group, nevertheless exposure was still present. Overall, these studies indicate that tislelizumab has pharmacokinetics typical for a mAb. The newly developed validation methods are considered fit for purpose and suitable to be used in support of the pivotal GLP toxicology study. As tislelizumab is expected to be degraded to small peptides and individual amino acids, the omission of metabolism and excretion studies is supported.

As there is minimal involvement of the cytochrome P450 system in the metabolism of monoclonal antibodies it is endorsed that no in vitro drug interaction studies with tislelizumab are conducted.

The toxicity of tislelizumab was evaluated in a single dose toxicology study in mice (not relevant species) and in two studies in cynomolgus monkeys, the relevant species.

The studies in monkeys were a single-dose toxicology study with tislelizumab IV up to 100 mg/kg, a first 13-week repeat-dose study with tislelizumab IV biweekly up to 30 mg/kg and an additional repeat-dose study, where 0/30/60 mg/kg tislelizumab was administered IV once every two weeks for 13 weeks to 3 animals/sex/group or as two single doses (14 days apart to 3 males only) via subcutaneous injection (SQ)+. In the first two studies, no signs of toxicity were observed. A MTD of 100mg/kg for the single dose study in monkeys and a no observed adverse effect level (NOAEL) at 30mg/kg for the repeat-dose study were set. In the additional repeat-dose study (Labcorp, USA) no sign of toxicity at 30mg/kg were observed, which was confirmed to be the NOAEL. However, in the 60 mg/kg IV group, a female has to be euthanised early at day 31. The causes were possibly attributed to immunogenicity. ADA were detected in most of animals at low doses and in individual animals at mid and higher doses, however the exposure was maintained in almost all animals. In conclusion, in repeat-dose toxicology studies in cynomolgus monkeys with intravenous dose administration for 13 weeks at doses of 3, 10, 30 or 60 mg/kg every 2 weeks for 13 weeks (7 dose administrations), no apparent treatment-related toxicity or histopathological changes were observed at doses up to 30 mg/kg every 2 weeks, corresponding to 4.3 to 6.6 times the exposure in humans with the clinical dose of 200 mg. This is reflected in section 5.3 of the SmPC. Reproductive and developmental toxicity studies have not been conducted with tislelizumab. In line with ICH S9, omission of fertility/early embryonic development studies and of pre-/post-natal development studies is accepted. A weight of evidence approach, as outlined in ICH S6(R1) was applied to describe the potential risk of tislelizumab to human pregnancy, which is acceptable. Given the role of the PD-1/PD-L1 pathway in maintaining materno-fetal tolerance (in murine models of pregnancy, blockade of PD-1/PD-L1 signalling has been shown to disrupt tolerance to the foetus and to result in increased foetal loss, treatment with tislelizumab during pregnancy may lead to abortion or still births. Furthermore, tislelizumab is a monoclonal antibody and is expected to be present in breast milk. Because of the potential for serious

adverse drug reactions in breast-fed infants breastfeeding is not recommended during tislelizumab treatment and for at least 4 months after stopping treatment with tislelizumab.

This is reflected in section 4.6 of the SmPC.

No studies have been performed to assess the potential of tislelizumab for carcinogenicity or genotoxicity in line with ICH guideline S9 and ICH S6(R1).

Moreover, two tissue cross reactivity studies on cynomolgus and human normal tissues were performed, but their sensitivity was questioned. Therefore, a Retrogenix assay was performed in order to address the concerns. Results from this assay show binding to tislelizumab to PD-1 on fixed and live human cells (HEK293 transfectants). The positive signals were further verified by FACS. Although for tislelizumab an Ab concentration much higher than the one of the positive control Rituximab was used (20 µg/ml versus 1 µg/ml respectively), the signal appears to be strong and specific. These results, together with the data provided contributed to clear up the doubts about tislelizumab possible insufficient binding. However, the results of the Retrogenix assay identified a specific, although weak, off-target binding to TREML1, which needed to be further investigated. In response, an additional study investigating the potential binding of tislelizumab to TREML-1 via SPR was provided. Two different assay formats were tested, one format had the antigen in solution (monovalent format), the other format had the antigen bound to the surface (avid format). None of the formats could confirm tislelizumab binding to TREML-1. Of note, the respective positive controls resulted in positive signals, as expected. Therefore, in conclusion, it is unlikely that VDT482 shows significant competition against the natural ligand of TREML1 and thus the weak interaction observed in the Retrogenix in vitro assay is not expected to have any physiological implication.

Importantly, the TCR and the first toxicological studies were performed in the facility of JOINN Laboratories (Beijing, China), which was not part of a compliance monitoring program of an EU monitoring authority and located in a non-OECD MAD country. A study-specific GLP inspection was triggered for studies P14-057-CD (13-week repeat-dose toxicity in monkeys), O14-057-2ZJ (TCR in monkey tissues) and O14-057-1ZJ (TCR in human tissues) A remote inspection was performed from 14/11/2022 to 18/11/2022. The final inspection report, dated 20/01/2023, indicated several critical and major findings and declared all the three studies as non OECD- GLP compliant. Several actions to mitigate the negative inspection outcome were proposed. A new in vivo 13-week repeat-dose toxicology study for tislelizumab in a GLP-compliant facility (Labcorp, USA) was initiated. Considering the new study results confirming the NOAEL at 30mg/kg, the results of additional tests confirming the specific binding of tislelizumab to PD-1, the well-known target and that "nonclinical toxicity studies in nonhuman primates have been poor in predicting clinical toxicities for antibodies mediating immune checkpoint blockade (Wang et al 2014)", the GLP inspections findings were considered solved.

Several other in vitro toxicity studies were performed in order to evaluate tislelizumab antigenicity, immunotoxicity and potential to induce cytokine release. Beside the potential of tislelizumab to induce neutralising ADA and to possibly induce an enhanced recall response to the re-challenge antigen, no other toxicities were detected.

Regarding ecotoxicity, the active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, tislelizumab is not expected to pose a risk to the environment.

2.4.13. Conclusion on the non-clinical aspects

Overall, the package of in vitro and in vivo non-clinical studies with tislelizumab is adequate and is supportive of market approval for Tizveni.

2.5. Clinical aspect

2.5.1. Introduction

GCP aspects

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

The applicant 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**

Overview of main studies and their status:

Study ***Status***	**Study Design**	**Treatments and target dose regimen**	**Patients randomised (N)**
001 *Completed*	Phase I, open-label, multiple-dose, dose-escalation and expansion study investigating the safety, tolerability, PK, and antitumour activity of tislelizumab in patients with advanced tumours, including NSCLC. **Participating countries:** Australia, New Zealand, South Korea, Taiwan, United States (27 centres)	0.5/2/5/10 mg/kg Q2W, 2/5 mg/kg Q3W, and 200 mg Q3W	451 enrolled (49 with NSCLC)
102 *Completed*	Phase I/II multicentre, open-label, study in Chinese patients with advanced solid tumours. The Phase I portion assessed safety, tolerability, PK characteristics, preliminary antitumour activity, and determined the MTD and/or RP2D of tislelizumab. The Phase II portion was conducted as an indication-expansion study to further assess the safety, PK, and preliminary efficacy in patients with malignant solid tumours, including cohorts in patients with NSCLC. **Participating country:** China (16 centres)	200mg Q3W	300 enrolled (56 with NSCLC)
303 *Ongoing*	Phase III, randomised, open-label, multicentre study in adult patients with histologically confirmed, locally advanced or metastatic NSCLC (squamous or nonsquamous) who had disease progression during or after a platinum-containing regimen to investigate the efficacy and safety of tislelizumab compared with docetaxel. **Participating countries:** China, Bulgaria, Brazil, Lithuania, Mexico, New Zealand, Poland, Russia, Slovakia, Turkey.	Tislelizumab 200 mg iv Q3W Docetaxel 75 mg/m^2 iv Q3W	535 270 Total: 805
307	Phase III, multicentre, randomised, open-label study to compare the efficacy and	Arm T+PC	T+PC: 120

Ongoing	safety of tislelizumab combined with paclitaxel plus carboplatin or nab-paclitaxel plus carboplatin vs. paclitaxel plus carboplatin alone as first-line treatment for untreated advanced squamous NSCLC. **Participating country:** China	Tislelizumab 200 mg iv D1 Q3W Paclitaxel 175 mg/m^2 D1 Q3W Carboplatin AUC 5 D1 Q3W (Paclitaxel and carboplatin administered 4-6 cycles) Arm T+nPC Tislelizumab 200 mg iv D1 Q3W Nab-paclitaxel 100 mg/m^2 D1, 8, 15 Q3W Carboplatin AUC 5 D1 Q3W (Nab-paclitaxel and carboplatin administered 4-6 cycles) Arm PC* Paclitaxel 175 mg/m^2 D1 Q3W Carboplatin AUC 5 D1 Q3W (Paclitaxel and carboplatin administered 4-6 cycles) *Optional crossover to receive tislelizumab 200 mg iv upon disease progression.	T+nPC: 119 PC: 121 Total: 360
304 *Ongoing*	Phase III, multicentre, randomised study to investigate the efficacy and safety of tislelizumab combined with platinum-pemetrexed vs. platinum-pemetrexed alone as first-line treatment for patients with Stage IIIB or IV nonsquamous NSCLC. **Participating country:** China	*Induction Phase:* Arm T+PP Tislelizumab 200 mg iv D1 Q3W Cisplatin 75 mg/m^2 or carboplatin AUC 5 Pemetrexed 500 mg/m^2 (Chemotherapy administered 4-6 cycles Q3W) Arm PP Cisplatin 75 mg/m^2 or carboplatin AUC 5 Pemetrexed 500 mg/m^2 (Chemotherapy administered 4-6 cycles q3w) *Maintenance Phase:* Arm T+PP Tislelizumab 200 mg iv D1 Q3W Pemetrexed 500 mg/m^2 Q3W Arm PP* Pemetrexed 500 mg/m^2 Q3W *Optional crossover to receive tislelizumab 200 mg iv upon disease progression.	T+PP: 223 PP: 111 Total:334

2.5.2. Clinical pharmacology

2.6.2.1 Pharmacokinetics

Clinical studies that contributed to the characterisation of the clinical pharmacology properties of tislelizumab are presented in Table 2. Dose ranges from 0.5 to 10 mg/kg Q2W, 2 and 5 mg/kg Q3W, and 200 mg Q3W, all administered as intravenous infusions over 30 to 60 minutes were studied. Sparse PK samples were collected in Phase I, II, and III studies that tested the recommended dose of 200 mg Q3W. PK data from the studies presented in Table 2 were also used in the popPK analysis and to characterise ER relationships.

Table 2: Overview of studies with clinical pharmacology components in patients

Study number, phase type of study (objectives)	Population	Number of PK evaluable patients	Clinical pharmacology assessments with study data	Tislelizumab Dosage regimen
Tislelizumab monotherapy				
BGB-A317-001, Phase IA/IB Open-label, multiple-dose, multicenter, 2-part, dose escalation, and indication expansion (safety, tolerability, anti-tumor activity, and determine MTD and RP2D)	Patients with advanced or refractory solid tumors (TN)	108 (NCA) 450 (PopPK) 0.5 mg/kg Q2W (n = 3) 2 mg/kg Q2W (n = 26) 5 mg/kg Q2W (n = 26) 10 mg/kg Q2W (n = 7) 2 mg/kg Q3W (n = 21) 5 mg/kg Q3W (n = 354) 200 mg Q3W (n = 13)	NCA PopPK Exposure-safety ADA	Phase IA Part 1 (Dose escalation): 0.5, 2, 5, and 10 mg/kg Q2W Phase IA Part 2 (Schedule expansion): 2 and 5 mg/kg Q2W or Q3W Phase IA Part 3 (Flat-dose evaluation): 200 mg Q3W Phase IB (Indication expansion): 5 mg/kg Q3W
BGB-A317-102, Phase I/II Open-label, multicenter, 2-part, dose-verification and indication expansion (safety, tolerability, antitumor activity, and determine MTD and RP2D)	Chinese patients with advanced solid tumors (TN)	20 (NCA) 300 (PopPK)	NCA PopPK Exposure-safety ADA	Phase I (Dose verification): 200 mg Q3W Phase I (PK substudy): 200 mg for the first dose, and 200 mg Q3W started at Week 5 Day 1 Phase II (Indication expansion): 200 mg Q3W
BGB-A317-203, Phase II Open-label, single-arm, and multicenter (efficacy, safety and tolerability)	Chinese patients with R/R cHL	69 (Sparse PK) 70 (PopPK)	PopPK Exposure-safety ADA	200 mg Q3W
BGB-A317-204, Phase II Single-arm, multicenter, and multinational (efficacy, safety and tolerability)	Chinese/Korean patients with PD-L1+ locally advanced or metastatic UC who had progressed during or following a platinum-containing regimen	109 (Sparse PK) 112 (PopPK)	PopPK Exposure-safety ADA	200 mg Q3W
BGB-A317-205, Phase II Open-label, single-arm, multi-cohort, multicenter (efficacy, safety, tolerability and antitumor activity)	Chinese patients with inoperable, locally advanced or metastatic esophageal, gastric, or gastroesophageal junction carcinoma	30 (PopPK)	PopPK	200 mg Q3W
BGB-A317-208, Phase II Open-label, single-arm, multicenter, and multinational (efficacy, safety, and tolerability)	Patients with previously-treated unresectable HCC	241 (Sparse PK) 248 (PopPK)	PopPK Exposure-safety ADA	200 mg Q3W
BGB-A317-209, Phase II Open-label, single-arm and multicenter (efficacy, safety, and tolerability)	Chinese patients with previously-treated locally advanced unresectable or metastatic MSI-H or dMMR solid tumors	76 (PopPK)	PopPK	200 mg Q3W
BGB-A317-302, Phase III Randomized, controlled, open-label, two-arm multicenter, and multinational (efficacy, safety, and tolerability)	Patients with advanced, unresectable or metastatic esophageal squamous cell carcinoma	245 (Sparse PK) 264 (PopPK)	PopPK Exposure-safety ADA	200 mg Q3W
BGB-A317-303, Phase III Open-label, two-arm, randomized, multicenter, and multinational (efficacy, safety, and tolerability)	Patients with locally advanced or metastatic NSCLC with disease progression on or after prior chemotherapy	519 (Sparse PK) 532 (PopPK)	PopPK Exposure-efficacy Exposure-safety ADA	200 mg Q3W

Study number, phase type of study (objectives)	Population	Number of PK evaluable patients	Clinical pharmacology assessments with study data	Tislelizumab Dosage regimen
Tislelizumab combination therapy				
BGB-A317-206, Phase II Open-label, multi-cohort and multicenter (efficacy, safety, tolerability and antitumor activity)	Chinese patients with locally advanced or metastatic lung cancer	54 (PopPK)	PopPK Exposure-safety ADA	200 mg Q3W
BGB-A317-304, Phase III Open-label, two-arm, randomized and multicenter (efficacy, safety and tolerability)	Chinese patients with locally advanced or metastatic non-squamous NSCLC	222 (PopPK)	PopPK Exposure-efficacy Exposure-safety ADA	200 mg Q3W
BGB-A317-307, Phase III Open-label, multi-arm, multicenter, and randomized (efficacy, safety and tolerability)	Chinese patients with locally advanced or metastatic squamous NSCLC	238 (PopPK)	PopPK Exposure-efficacy Exposure-safety ADA	200 mg Q3W
Abbreviations: ADA, antidrug antibody; cHL, classical Hodgkin lymphoma; dMMR, deficient mismatch repair; HCC, hepatocellular carcinoma; MSI-H, microsatellite instability-high; MTD, maximum tolerated dose; NCA, noncompartmental analysis; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death ligand-1; PopPK, population pharmacokinetic(s); Q2W, once every 2 weeks; Q3W, once every 3 weeks; RP2D, recommended Phase 2 dose; R/R, relapsed or refractory; TN, treatment-naive; UC, urothelial carcinoma. Note: All doses were administered intravenously. Source: [Study 001], [Study 102], [Study 203], [Study 204], [Study 205], [Study 208], [Study 209], [Study 302], [Study 303], [Study 206], [Study 304], [Study 307],[PopPK Report-Table 6], [BGB-A317-CP-009], [ER Report]				

The number of patients by age group for the 12 studies of the PopPK dataset is provided in the table below.

Table 3: Number of patients by age group in the 12 studies included in the PopPK dataset

	Study number	001	102	203	204	205	206	208	209	302	303	304	307	All
Age group	≤64	285	223	66	69	20	39	148	63	164	363	163	147	1750
	65-74	125	72	4	37	10	14	75	11	87	155	56	91	737
	75-84	40	5	0	6	0	1	24	2	13	13	3	0	107
	≥85	0	0	0	0	0	0	1	0	0	1	0	0	2

Analytical methods

Two quantitative indirect enzyme immunoassay methods were validated and used for measurement of tislelizumab in human serum. The first analytical laboratory method in serum was developed and fully validated at Australia CPR Pharma Service (VAL136). This method was then transferred to Covance and fully validated at their Shanghai laboratory (8354-363). In addition, a formal cross-validation has been performed to verify that PK data obtained at different laboratories (method VAL136 and method 8354-363) are reliable and comparable.

A validated antidrug antibody (ADA) electro-chemiluminescent (ECL) immunoassay utilizing the Meso Scale Discovery (MSD) technology was used for determination of anti-tislelizumab antibodies in human serum from clinical studies. Detection of ADAs was performed in 3 steps: a screening assay; a confirmation assay and a titration assay to estimate the level of antibody in confirmed positive samples.

A validated competitive ECL ligand-binding assay utilizing MSD technology was applied for detection of neutralizing antibodies (NAbs) to tislelizumab.

PK data analysis

In the early studies (BGB-A317-001 and BGB-A317-102), PK parameters were derived using standard noncompartmental methods with WinNonlin Professional or SAS.

In addition, a popPK model was developed from the full PK analysis dataset consisting of 12 studies (Studies 001, 102, 203, 204, 205, 206, 208, 209, 302, 303, 304, and 307, see Table 4) to quantitatively describe the PK properties of tislelizumab and identify sources of interindividual variability.

Table 4: Summary of studies included in the PopPK analysis

Region	Study No.	Title	Phase	Dose Regimen	Planned N
Global	BGB-A317-001	A Phase 1A/1B, Open Label, Multiple Dose, Dose Escalation and Expansion Study to Investigate the Safety, Pharmacokinetics and Antitumor Activities of the anti-PD-1 Monoclonal Antibody BGB-A317 in Subjects with Advanced Tumors	1a/1b	0.5 mg/kg, 2 mg/kg, 5 mg/kg, or 10 mg/kg Q2W; 2 mg/kg or 5 mg/kg Q3W; and 200 mg Q3W	451
China	BGB-A317-102	Phase I/II Study Investigating Safety, Tolerability, Pharmacokinetics and Preliminary Antitumor Activities of Anti-PD-1 Monoclonal Antibody BGB-A317 in Chinese Patients with Advanced Solid Tumors	1/2	200 mg Q3W	300
China	BGB- A317-203	A Single Arm, Multicenter, Phase 2 Study of BGB-A317 as Monotherapy in Relapsed or Refractory Classical Hodgkin Lymphoma	2	200 mg Q3W	70
China/ Korea	BGB- A317-204	A Single-Arm, Multicenter Phase 2 Study of BGB-A317 in Patients with Previously Treated PD-L1+ Locally Advanced or Metastatic Urothelial Bladder Cancer	2	200 mg Q3W	113
China	BGB- A317-205	A Phase 2, Multi-Cohort Study to Investigate the Safety, Pharmacokinetics and Preliminary Antitumor Activity of the anti-PD-1 Monoclonal Antibody BGB-A317 in Combination with Chemotherapy as First-Line Treatment in Adults with Inoperable, Locally Advanced or Metastatic Esophageal, Gastric, or Gastroesophageal Junction Carcinoma	2	200 mg Q3W	30
China	BGB- A317-206	A Phase II, Open-Label, Multi-Cohort Study to Investigate the Preliminary Antitumor Activity, Safety, and Pharmacokinetics of the anti-PD-1 Monoclonal Antibody BGB-A317 in Combination with Chemotherapy as First-Line Treatment in Chinese Subjects with Locally Advanced or Metastatic Lung Cancer	2	200 mg Q3W	54
Global	BGB- A317-208	A Phase 2, Open-label, Multicenter Study to Investigate the Efficacy, Safety, and Pharmacokinetics of the Anti-PD-1 Monoclonal Antibody BGB-A317 in Patients with Previously Treated Hepatocellular Unresectable Carcinoma	2	200 mg Q3W	249
China	BGB- A317-209	A Single-Arm, Multi-Center, Open-Label, Phase 2 Study to Evaluate Efficacy and Safety of Tislelizumab (BGB-A317), an anti-PD-1 Monoclonal Antibody, as Monotherapy in Patients with Previously-Treated Locally Advanced Unresectable or Metastatic Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Solid Tumors	2	200 mg Q3W	78
Global	BGB- A317-302	A Randomized, Controlled, Open-label, Global Phase 3 Study Comparing the Efficacy of the anti-PD-1 Antibody Tislelizumab (BGB-A317) versus Chemotherapy as Second Line Treatment in Patients with Advanced Unresectable/Metastatic Esophageal Squamous Cell Carcinoma	3	200 mg Q3W	264
Global	BGB- A317-303	A Phase 3, Open-Label, Multicenter, Randomized Study to Investigate the Efficacy and Safety of BGB-A317 (Anti-PD1 Antibody) Compared with Docetaxel in Patients with Non-Small Cell Lung Cancer Who Have Progressed on a Prior Platinum-Containing Regimen	3	200 mg Q3W	532
China	BGB- A317-304	A Phase 3, Open-Label, Multicenter, Randomized Study to Investigate the Efficacy and Safety of Tislelizumab (BGB-A317) (Anti-PD1 Antibody) Combined With Platinum-Pemetrexed Versus Platinum-Pemetrexed Alone as First-line Treatment for Patients With Stage IIIB or IV Non-Squamous Non-Small Cell Lung Cancer	3	200 mg Q3W	238
China	BGB- A317-307	A Phase 3, Multicenter, Randomized Open-Label Study to Compare the Efficacy and Safety of Tislelizumab (BGB-A317, Anti-PD1 Antibody) Combined With Paclitaxel Plus Carboplatin or Nab-Paclitaxel Plus Carboplatin Versus Paclitaxel Plus Carboplatin Alone as First-Line Treatment for Untreated Advanced Squamous Non-Small Cell Lung Cancer	3	200 mg Q3W	238

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

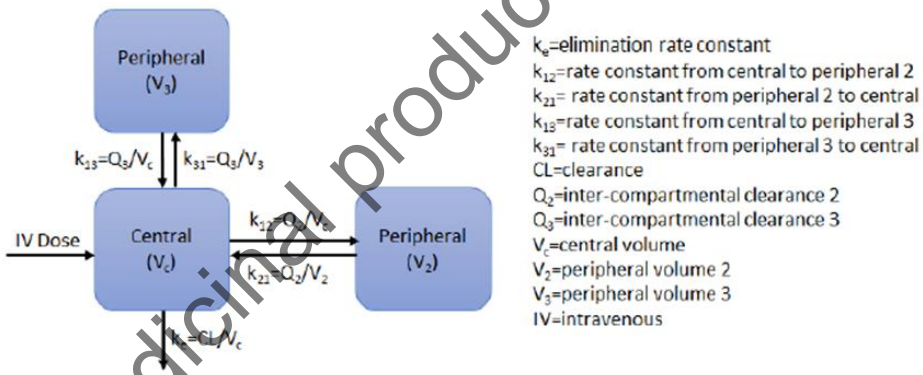


Figure 2: PopPK model diagram for tislelizumab

Parameter estimates for the final PopPK model for tislelizumab are presented in Table 5.

Table 5: Summary of final population PK parameters

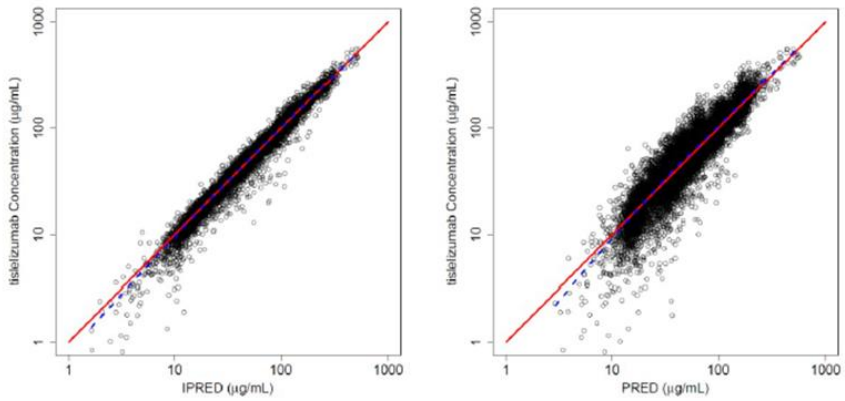
Parameter	Parameter Description	Final PopPK Model		
		Estimate (% RSE)	Median (95% CI) from bootstrapping	Shrinkage (%)
$exp(\theta_1)*24$	Clearance, CL (L/day)	0.153 (0.816%)	0.154 (0.151, 0.157)	15.9%
θ_7	Influence of WT on CL	0.565 (5.95%)	0.562 (0.491, 0.631)	-
θ_{10}	Influence of ALB on CL	-0.457 (11.2%)	-0.443 (-0.648, -0.229)	-
θ_{11}	Influence of TUMSZ on CL	0.0735 (10.4%)	0.0757 (0.056, 0.0953)	-
θ_{13}	Influence of ADA on CL	0.111 (13.8%)	0.110 (0.0783, 0.146)	-
θ_{14}	Influence of TUMTP of GC on CL	0.069 (48.2%)	0.0778 (-0.00319, 0.161)	-
θ_{15}	Influence of TUMTP of cHL on CL	-0.216 (17.1%)	-0.215 (-0.294, -0.137)	-
$exp(\theta_2)$	Central volume, V_c (L)	3.05 (0.498%)	3.05 (3.02, 3.08)	15.7%
θ_8	Influence of WT on V_c	0.397 (5.50%)	0.395 (0.354, 0.437)	-
θ_9	Influence of Sex on V_c	-0.116 (8.30%)	-0.116 (-0.135, -0.0997)	-
θ_{12}	Influence of Age on V_c	0.0966 (51.7%)	0.0957 (0.0602, 0.132)	-
$exp(\theta_3)*24$	Inter-compartmental clearance, Q_2 (L/day)	0.740 (4.55%)	0.746 (0.616, 0.944)	-
$exp(\theta_4)$	Peripheral volume, V_2 (L)	1.27 (2.02%)	1.27 (1.14, 1.43)	55.8%
$exp(\theta_5)*24$	Inter-compartmental clearance, Q_3 (L/day)	0.092 (3.23%)	0.0923 (0.0796, 0.104)	-
$exp(\theta_6)$	Peripheral volume, V_3 (L)	2.10 (3.89%)	2.06 (1.81, 2.30)	44.4%
$\omega^2_{Cl,Vc}$	Covariance (CL,V_c)	0.020 (6.43%)	0.0198 (0.0167, 0.0227)	-
Inter-Individual Variability (%RSE)	CL	26.3 (1.84%)	26.4 (25.2, 27.7)	-
	V_c	16.7 (2.05%)	16.7 (15.8, 17.6)	-
	V_2	74.7 (1.88%)	76.3 (65.0, 86.8)	-
	V_3	99.9 (4.06%)	97.3 (85.7, 110)	-
σ_p	Proportional residual error (%)	12.6 (1.08%)	12.6 (12.0, 13.2)	17.8%
σ_a	Additive residual error (µg/mL)	2.09 (9.31%)	2.06 (1.79, 2.33)	17.8%

In Amendment 1 to the popPK report, discrepancies regarding the baseline body weight of two subjects from BGB-A317-302 study were corrected and PK parameters were re-estimated using the final PopPK model and the updated PopPK dataset with corrected weights. The estimated PK parameters using updated dataset were almost identical to those reported in the original PopPK report, with some minor differences in second decimal place.

Evaluation and Qualification of popPK model

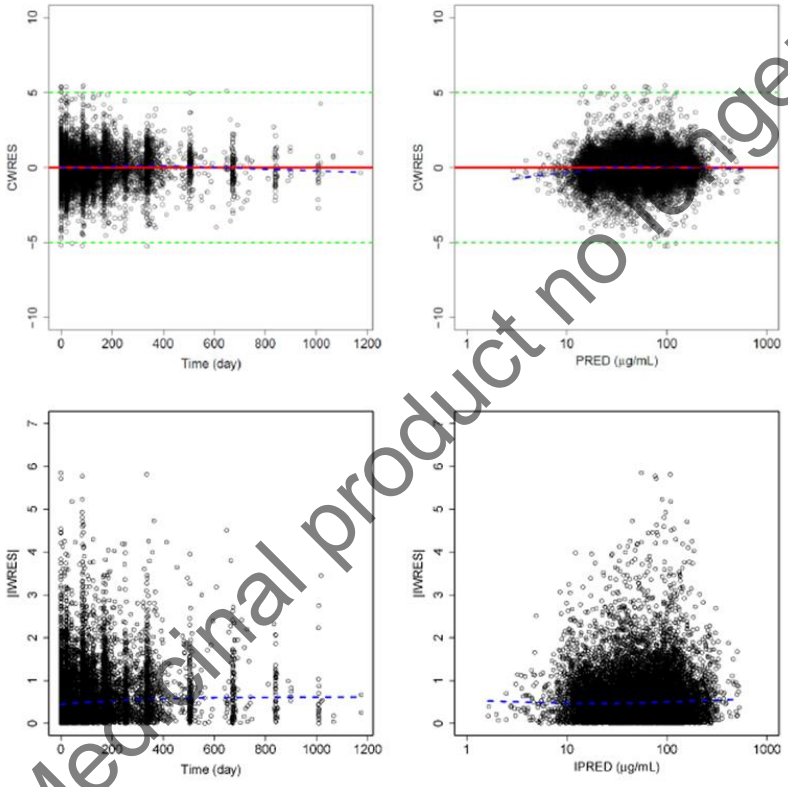
The final PopPK model was evaluated with multiple model qualification/validation methods, including goodness-of-fit (GOF) plots, prediction-corrected visual predictive check (pcVPC), numerical predictive check (NPC), bootstrap, and shrinkage assessments.

The general goodness-of-fit plots of the final PopPK model are shown in Figure 7 and Figure 8, where a good agreement between the predicted concentrations and the observed concentrations was observed and no apparent bias was observed in the residuals plots over time and across predicted concentrations.



Observed vs individual predicted concentrations (IPRED, left) and observed vs population predicted concentrations (PRED, right) for the final popPK model. Points are individual data and red lines represent the unit diagonal. The blue dashed lines are smooth curves (lowess) showing the relationship between 2 variables.

Figure 3: Predicted versus observed concentration for the final PopPK model



Conditional weighted residuals (CWRES) vs time (top left) and population predicted concentrations (PRED, top right). Absolute individual weighted residuals (|IWRES|) vs time (bottom left) and individual predicted concentrations (IPRED, bottom right). Points are individual data. Red solid lines represent the unit line at zero. Green dotted lines represent |CWRES| of 5. The blue dashed lines are smooth curves (lowess) showing the relationship between 2 variables.

Figure 4: Residual diagnostic plots for the final PopPK model

The ability of the final popPK model to reproduce the distribution of the tislelizumab concentration data over time was evaluated using pcVPC based on 1000 simulated replicates of the original dataset. 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. These results suggest that the

final popPK model adequately predicted the central tendency and variability of the serum tislelizumab concentrations following IV administration.

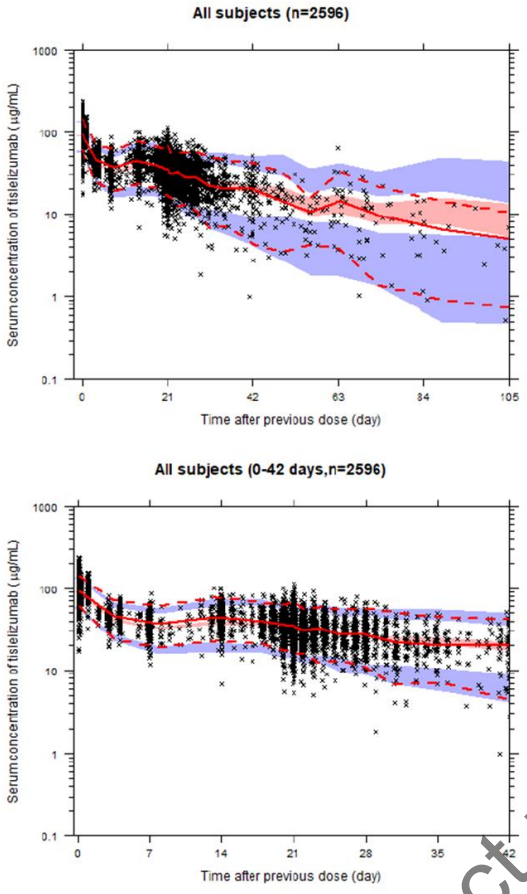


Figure 5: Prediction-corrected visual predictive check of tislelizumab serum concentration time profiles across all studies

Absorption

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

The estimate for steady-state C_{max} derived by population PK analysis was 110 µg/mL.

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

Distribution

Noncompartmental analysis:

In study 102, geometric mean VSS (Cycle 5) was determined to be 4.04 L.

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

Noncompartmental analysis:

After 200 mg intravenous tislelizumab dosing, mean CL determined in Cycle 1 and Cycle 5 of study 001 were 0.186 and 0.242 L/day. The apparent terminal t½ estimated in Cycle 1 and Cycle 5 was 15.9 days and 14.9 days, respectively.

In study 102, clearance values determined in Cycle 1 and Cycle 5 after dosing with 200 mg tislelizumab Q3W were 0.233 and 0.186 L/day, respectively. The apparent half-lives (t½ values) estimated in Cycle 1 and Cycle 5 were 12.9 and 16.6 days, respectively.

Population PK analysis:

The geometric mean elimination half-life was estimated to be 23.8 days. Clearance was estimated to be 0.153 L/day.

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

Dose proportionality and time dependencies

In study 001, drug exposure (C_{max} and AUC0-14d) increased in a dose-proportional manner from 0.5 mg/kg to 10 mg/kg both after the first dose administration and at Cycle 4/5, corresponding to steady state.

The accumulation indices in study 001 were 1.21 and 1.60 determined by the ratio of steady-state and first dose of C_{max} and AUC0-tau, respectively. In study 102, the accumulation index ranged between 1.87 and 2.13 determined by PK exposures (ratio of steady-state and first dose of AUC0-tau, C_{max}, and predose Ctrough). Referring to the population PK analysis, the accumulation ratios are 2.14, 1.62, and 2.49 for AUCss, C_{max},ss and Cmin,ss.

PK in target population

Study BGB-A317-303 (Study 303)

A Phase 3, Open-Label, Multicenter, Randomized Study to Investigate the Efficacy and Safety of BGB-A317 (Anti-PD-1 Antibody) Compared With Docetaxel in Patients with Non-Small Cell Lung Cancer Who Have Progressed on a Prior Platinum-Containing Regimen.

A total of 534 patients received tislelizumab at a dose of 200 mg administered intravenously Q3W. Study treatment continued until disease progression as assessed by the investigator per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, unacceptable toxicity, or withdrawal of informed consent, whichever occurred first.

As of the data cutoff date, geometric means of predose (Cycle 1, 2, 5, 9, and 17) and postdose (Cycle 1 and 5) serum concentrations after the intravenous doses of tislelizumab 200 mg Q3W, summarised by study cycles up to Cycle 17, are presented in Table 6. A total of 532 patients were included in the PK data analysis set.

Table 6. Summary of tislelizumab serum concentrations in study 303 (PK analysis set)

	Tislelizumab concentrations (µg/mL)	
Visit	Predose (C_{min}) GM (GCV%)	Postdose (C_{max}) GM (GCV%)
Cycle 1	NC [a] (n = 519)	68.4 (27.3%) (n = 517)
Cycle 2	16.0 (36.9%) (n = 493)	NA
Cycle 5	33.8 (38.3%) (n = 329)	100.8 (27.5%) (n = 329)
Cycle 9	40.7 (48.0%) (n = 224)	NA
Cycle 17	47.1 (33.7%) (n = 102)	NA

Source: [Study 303-Table 14.4.1, Listing 16.2.9.1 and Listing 16.2.9.2] (Data cutoff 28-May-2020). [Study 303-Table 20]

Abbreviations: C_{max}, maximum serum concentration (end of infusion, postdose); C_{min}, minimum serum concentration (predose); GCV, geometric coefficient of variation; GM, geometric mean; M/F, male/female; NA, not available; NC, not calculated.

Notes: Population: 532 patients; sex (M/F): 414/118; age: 59.9 (28-88); body weight: 67.7 (35-130) kg.

2.7% (77/2841) of samples were excluded from the summary due to aberrant sample collection information.

[a] Eleven patients with a measurable predose concentration at Cycle 1 were excluded from the summary.

Study BGB-A317-304 (Study 304)

A Phase 3, Open-Label, Multicenter, Randomized Study to Investigate the Efficacy and Safety of Tislelizumab (BGB-A317) (Anti-PD1 Antibody) Combined With Platinum-Pemetrexed Versus Platinum-Pemetrexed Alone as First-line Treatment for Patients With Stage IIIB or IV NonSquamous Non-Small Cell Lung Cancer.

Study 304 is an ongoing, open-label, multicentre, randomised Phase III study designed to compare the efficacy and safety of tislelizumab combined with platinum (cisplatin or carboplatin) and pemetrexed versus platinum (cisplatin or carboplatin) and pemetrexed alone as first-line treatment in patients who have Stage IIIB or IV non-squamous NSCLC, whereby the choice of platinum (cisplatin or carboplatin) was at the investigator's discretion. As of the data cutoff date, total of 334 patients were randomised of which 222 patients received 200 mg of tislelizumab in combination with pemetrexed and platinum.

Pharmacokinetic data were available for a total of 222 patients (1185 samples with 961 observed values and 224 below the limit of quantification samples) following treatment with tislelizumab 200 mg every 3 weeks administered as an iv infusion over 30 to 60 minutes (60 minutes for the first dose; if well-tolerated, 30 minutes for the rest of doses). The exclusion percentage for tislelizumab was 3.71% (44/1185 samples). As of the data cutoff date, the mean (± standard deviation), Ctrough (predose), and C_{max} (postdose) following the iv doses of tislelizumab 200 mg every 3 weeks up to Cycle 17, were presented in Table 7.

Table 7: Summary of tislelizumab serum concentration (mean Plus/Minus standard deviation) (PK analysis set)

	Tislelizumab Concentrations (µg/mL)	
Time point	**Cycle**	**T+PP**
Pre-Dose	Cycle 1	NC [a] (n=219)
	Cycle 2	16.4 ± 5.75 (n=202)
	Cycle 5	38.2 ± 14.39 (n=162)
	Cycle 9	47.8 ± 17.46 (n=107)
	Cycle 17	61.3 ± 19.85 (n=18)
Post-Dose	Cycle 1	69.1 ± 16.81 (n=219)
	Cycle 5	103.5 ± 26.24 (n=160)

Source: [Study 304-Table 18] (Data cutoff 19-Dec-2019).

Abbreviations: T+PP, Tislelizumab+Pemetrexed+Platinum; NC, not calculated.

Population: 222 patients; Sex (M/F): 167/55; Age: 60(27-75) years; Body weight: 65 (41-100) kg. 3.71% (44/1185) of samples were excluded from the summary due to aberrant sample collection information.

[a] 3 patients with a predose measurable concentration at Cycle 1 were excluded from the summary.

Study BGB-A317-307 (Study 307)

Study 307 is an ongoing open-label, randomised, multicentre Phase III study designed to compare the efficacy and safety of tislelizumab combined with carboplatin and either paclitaxel (Arm T+PC) or nab-paclitaxel (Arm T+nPC) versus paclitaxel plus carboplatin alone (Arm PC) as first-line treatment in patients with untreated Stage IIIB or IV squamous NSCLC. As of the data cutoff date, total of 360 patients were randomised of which 120 patients received 200 mg of tislelizumab in combination with paclitaxel and 118 patients received 200 mg of tislelizumab in combination with nab-paclitaxel.

Pharmacokinetic data were available for a total of 238 patients (1222 samples with 983 observed values and 239 below the limit of quantification samples) following treatment with tislelizumab 200 mg every 3 weeks administered as an intravenous infusion over 30 to 60 minutes (60 minutes for the first dose; if well-tolerated, 30 minutes for the rest of doses).

As of the data cutoff date, the mean (±SD) Ctrough (predose) and C_{max} (postdose) following the intravenous doses of tislelizumab 200 mg every 3 weeks, stratified by treatment cohorts up to Cycle 17, were presented in the below table.

Table 8: Summary of tislelizumab serum concentration (mean +/- standard deviation) (PK analysis set)

	Tislelizumab concentrations (µg/mL)			
Time point	**Cycle**	**T+PC**	**T+*n*PC**	**All**
Pre-Dose	Cycle 1	NC [a] (n=117)	NC [a] (n=115)	NC [a] (n=232)
	Cycle 2	15.2 ± 4.47 (n=110)	13.1 ± 3.63 (n=109)	14.1 ± 4.21 (n=219)
	Cycle 5	37.7 ± 11.39 (n=83)	28.4 ± 9.21 (n=77)	33.2 ± 11.36 (n=160)
	Cycle 9	44.3 ± 14.23 (n=59)	41.9 ± 13.45 (n=50)	43.2 ± 13.87 (n=109)
	Cycle 17	47.5 ± 34.76 (n=3)	41.5 ± 12.41 (n=5)	43.8 ± 21.05 (n=8)
Post-Dose	Cycle 01	70.2 ± 16.77 (n=118)	65.4 ± 11.45 (n=117)	67.8 ± 14.54 (n=235)
	Cycle 05	98.9 ± 23.16 (n=82)	89.3 ± 17.82 (n=78)	94.2 ± 21.21 (n=160)

Source: [Study 307-Table 16] (Data cutoff 31-Oct-2019).

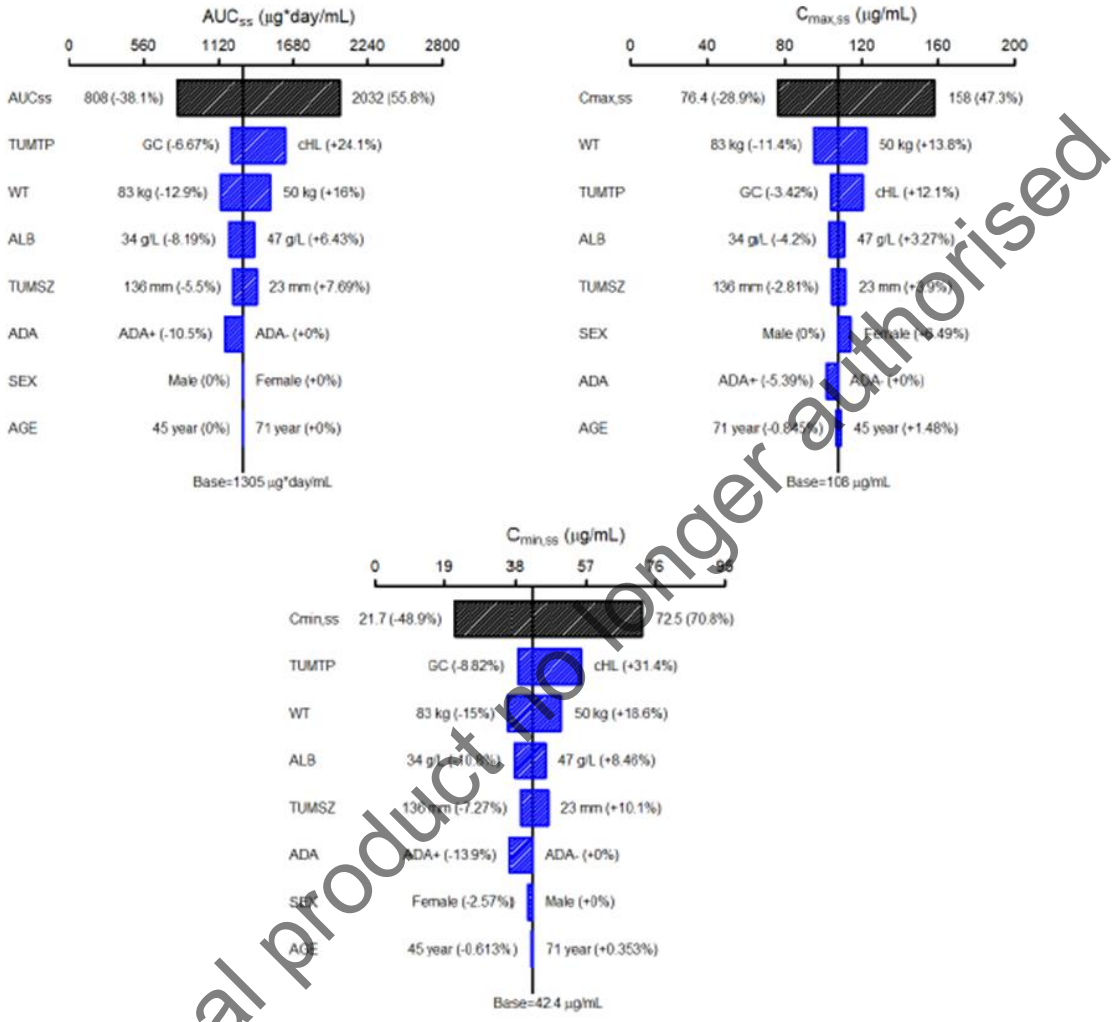
Abbreviations: T+PC, Tislelizumab+Paclitaxel+Carboplatin; T+*n*PC, Tislelizumab+*nab*-Paclitaxel+Carboplatin; NC, not calculated.

Population: 238 patients; Sex (M/F): 218/20; Age: 62 (38-74) years; Body weight: 62 (45-113) kg. 4.91% (60/1222) of samples were excluded from the summary due to aberrant sample collection information.

[a] 6 patients with a predose measurable concentration at Cycle 1 were excluded from the summary.

PK in special populations

In the population PK model, baseline body weight, albumin level, tumour size of solid tumours, ADA status (treatment-emergent ADA), and tumour type were identified as significant covariates on CL. Baseline body weight, sex, and age were identified as significant covariates on Vc.



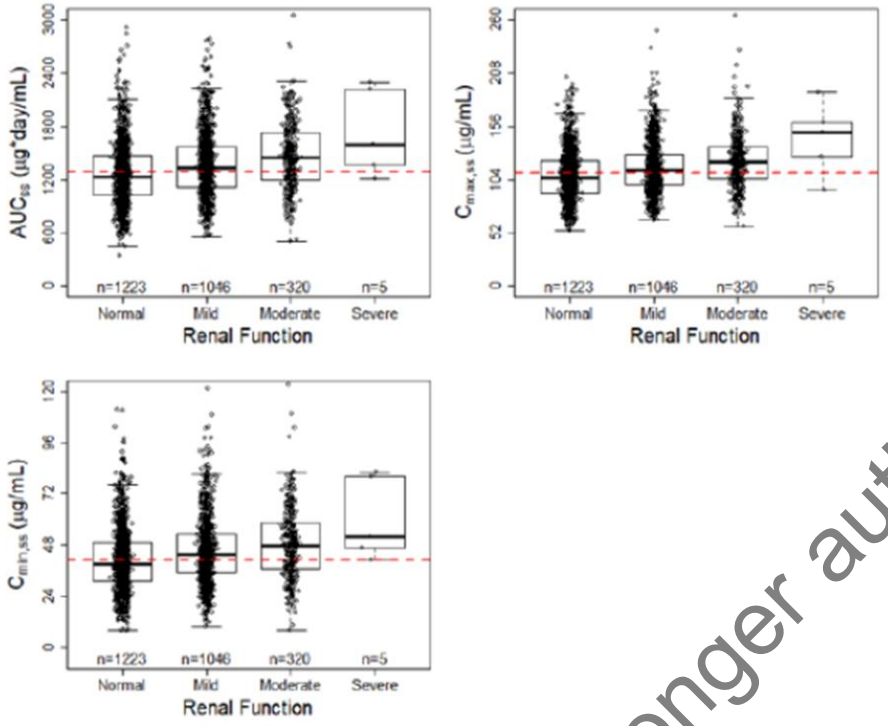
The black vertical line refers to the predicted exposure (AUC_{ss}, $C_{max,ss}$, and $C_{min,ss}$) of tislelizumab in a typical subject after 200 mg Q3W for 30 weeks which serve as the reference values. All percentage values shown in each plot are the relative changes in exposure relative to the reference value. The black shaded bar with values at each end shows the 5th to 95th percentile exposure range across the study population. Each blue shaded bar represents the magnitude of influence of the respective covariate on the exposure. The length of each bar represents the range of predicted tislelizumab exposure between the high/low or possible values of the covariate (indicated at each end of the bar). The covariates shown in each plot are ordered from the most influential covariate at the top to the least influential covariate at the bottom.

Figure 6: Sensitivity analysis plot comparing the effect of covariates on tislelizumab steady state exposure (AUCss, C_{max}ss and Cminss)

<u>Impaired renal function</u>

Renal function was not identified as a significant covariate. No dedicated studies of tislelizumab have been conducted in patients with renal impairment. In the population PK analyses of tislelizumab, no clinically relevant differences in the clearance of tislelizumab were found between patients with mild

renal impairment (CLCr 60 to 89 ml/min, n = 1 046) or moderate renal impairment (CLCr 30 to 59 ml/min, n = 320) and patients with normal renal function (CLCr ≥90 ml/min, n = 1 223) (Figure 7).



Source: [PopPK Report-Figure 25].

Abbreviations: AUC_{ss}, area under the serum concentration-time curve at steady state; CL, clearance; $C_{min,ss}$, minimum serum concentration at steady state; PK, pharmacokinetic(s).

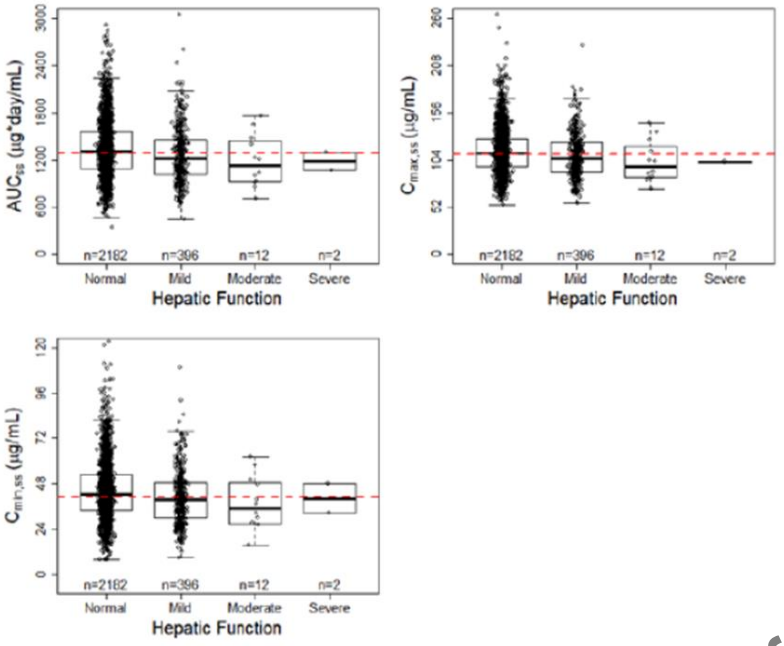
Notes: The steady-state exposures ($C_{min,ss}$ and AUC_{ss}) of tislelizumab were computed for each patient. AUC_{ss} was calculated as dose/CL. $C_{min,ss}$ was calculated as the minimum concentration on the 21st days after the 10th consecutive doses of tislelizumab Q3W [PopPK Report-Section 5.5 and Section 5.6].

The dashed red horizontal line represents the mean of the overall population.

Figure 7: Steady-state tislelizumab exposure by renal function

Impaired hepatic function

No dedicated studies of tislelizumab have been conducted in patients with hepatic impairment. The liver function laboratory tests (AST, ALT, or total bilirubin) were not found to be significant covariates on tislelizumab PK in the popPK analysis. The mean simulated exposures (AUCss, C_{max},ss and Cmin,ss) in mild, moderate, or severe hepatic impairment were up to 8.71% lower, 15.4% lower, and 9.12% lower, respectively, compared with those of subjects with normal hepatic function. Comparing popPK model-predicted exposures between different impairment groups, no clinically relevant effect of hepatic function was noticeable on the PK of tislelizumab.



Source: [PopPK Report-Figure 26].

Abbreviations: AUC_{ss}, area under the serum concentration-time curve at steady-state; CL, clearance; $C_{min,ss}$, minimum serum concentration at steady state; PK, pharmacokinetic(s).

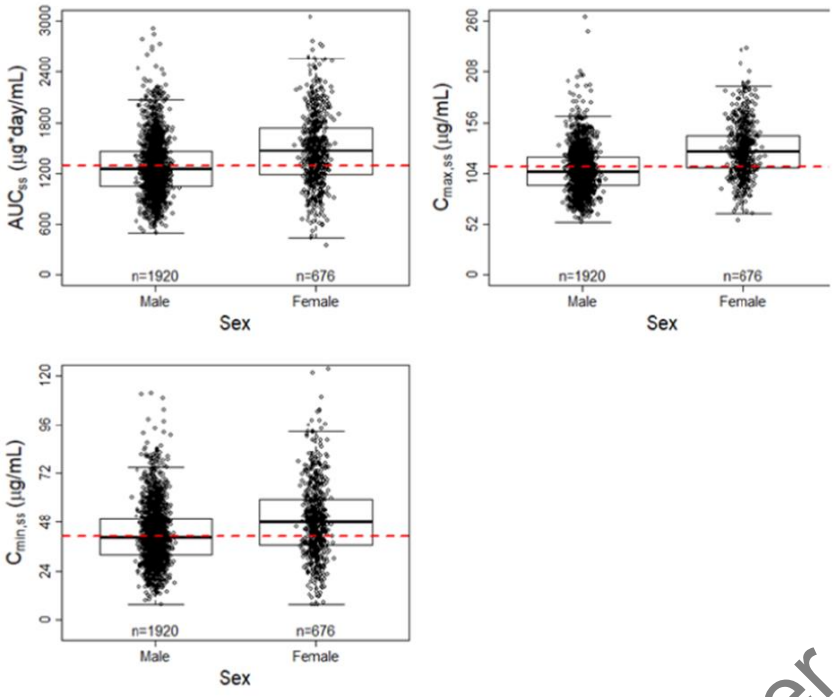
Notes: The steady-state exposures ($C_{min,ss}$ and AUC_{ss}) of tislelizumab were computed for each patient. AUC_{ss} was calculated as dose/CL. $C_{min,ss}$ was calculated as the minimum concentration on the 21st days after the 10th consecutive doses of tislelizumab Q3W [PopPK Report-Section 5.5 and Section 5.6].

Horizontal red dashed line represents the median value based on the overall population.

Figure 8: Steady-state tislelizumab exposure by hepatic function

Gender

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



Source: [PopPK Report-Figure 21].

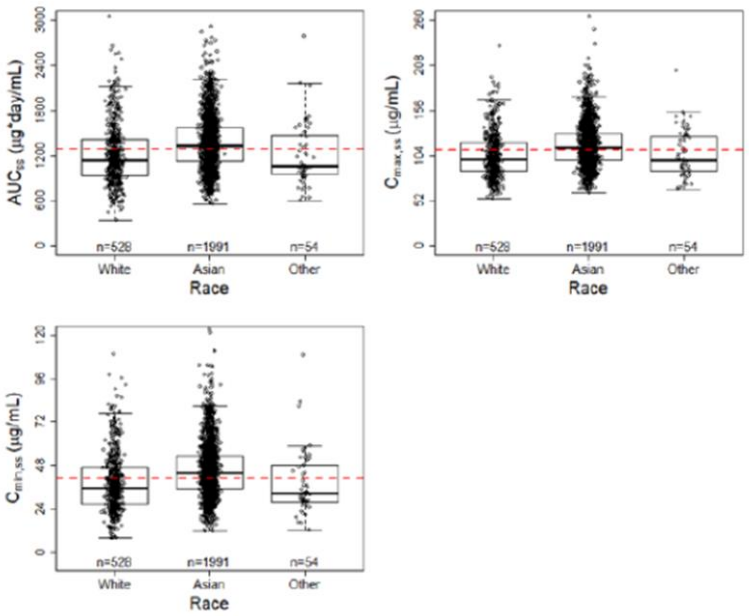
Circles are the simulated steady state tislelizumab exposure in individual subjects. The boxes represent the 25th to 75th percentiles (the interquartile range). The solid black horizontal line in the middle of each box represents the median. The whiskers represent the range of data points within 1.5 times the interquartile range. The dashed red horizontal line represents the mean of the overall population.

Figure 9: Simulated steady-state exposures of tislelizumab by gender following 200mg and Q3W dosing

Race

The popPK analysis showed that race was not a significant covariate on the PK parameters (CL and Vc) of tislelizumab and had no clinical relevance on tislelizumab PK exposure.

Subsequent simulations indicated that overall range of tislelizumab exposure after 200 mg Q3W is largely overlapped between the Asian and white patients, as shown below. The simulated geometric mean exposures (AUCss, C_{max},ss, and Cmin,ss) of the Asian patient population (the majority of Asian patients are Chinese) from 12 studies were approximately 12% to 21% higher than those of white patients.



Source: [PopPK Report-Figure 22].

Abbreviations: AUC_{ss}, area under the serum concentration-time curve at steady-state; CL, clearance; $C_{min,ss}$, minimum serum concentration at steady-state; PK, pharmacokinetic(s).

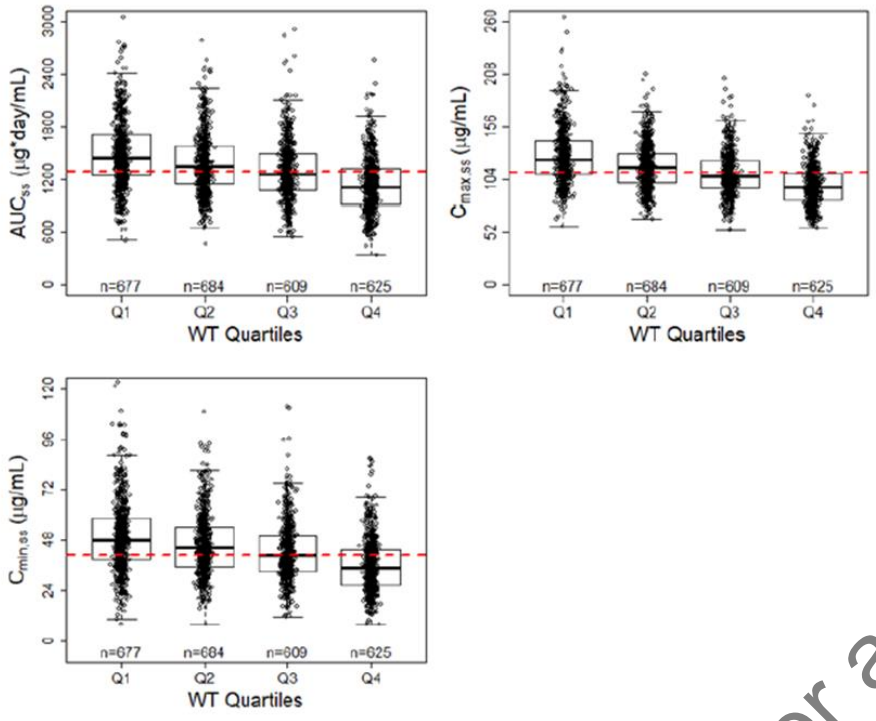
Notes: The steady-state exposures ($C_{min,ss}$ and AUC_{ss}) of tislelizumab were computed for each patient. AUC_{ss} was calculated as dose/CL. $C_{min,ss}$ was calculated as the minimum concentration on the 21st day after 10 consecutive doses of tislelizumab 200 mg Q3W [PopPK Report-Section 5.5 and Section 5.6].

The dashed red horizontal line represents the mean of the overall population.

Figure 10: Simulated steady-state exposures of tislelizumab by race following 200mg Q3W dosing

Weight

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



Circles are the simulated steady state tislelizumab exposure in individual subjects. The boxes represent the 25th to 75th percentiles (the interquartile range). The solid black horizontal line in the middle of each box represents the median. The whiskers represent the range of data points within 1.5 times the interquartile range. The dashed red horizontal line represents the mean of the overall population.

Figure 11: Simulated steady-state exposures of tislelizumab by body weight quartiles following 200mg and Q3W dosing

Because body weight was identified as a significant covariate on clearance, simulations were performed to compare the exposure produced with the 200 mg Q3W flat dose regimen with those produced with a hypothetical 3 mg/kg Q3W body weight based dose to further understand the effect of body-weight distribution on dosing.

The overall difference in geometric means of all summary exposure measures between the two dosing scenarios was <4%, with similar variability (% CV) (Table 9). Although predicted exposures were higher in patients with lower body weight receiving the flat dosing regimen, the median and 90% prediction intervals of tislelizumab summary exposures across the body weight range was maintained well within the range of 2 -5 mg/kg Q3W (therapeutic range established in FIH study 001), and well below the corresponding median exposures observed with tislelizumab 10 mg/kg Q2W, the clinically established highest, safe and tolerable dose.

Table 9: Comparison of summary of exposures between flat and body weight-based dosing regimens

Summary exposure	3 mg/kg Q3W		200 mg Q3W	
	Geometric Mean (% CV)	Median [P05, P95]	Geometric Mean (% CV)	Median [P05, P95]
AUC_1 (µg*day/mL)	583 (20.7)	584 [418, 818]	601 (17.7)	601 [446, 799]
C_{max1} (µg/mL)	65.8 (18.9)	65.4 [49.0, 89.4]	67.8 (18.1)	67.3 [51.1, 92.1]
C_{min1} (µg/mL)	16.0 (28.3)	16.2 [10.1, 24.3]	16.5 (27.0)	16.7 [10.6, 24.9]
AUC_{ss} (µg*day/mL)	1245 (27.9)	1245 [784, 1946]	1283 (28.7)	1297 [808, 2032]
$C_{max,ss}$ (µg/mL)	107 (21.7)	107 [75.0, 152]	110 (22.2)	110 [76.4, 158]
$C_{min,ss}$ (µg/mL)	39.8 (36.6)	40.5 [21.6, 68.7]	41.0 (38.3)	42.1 [21.7, 72.5]

Additionally, the predicted steady state exposures stratified by body weight quartiles are presented in Table below. The geometric mean simulated exposures (AUCss, C_{max},ss and Cmin,ss) in the lowest or highest quartile of body weight were up to 14.5% higher and 17.3% lower, respectively, compared with those of the overall population.

Table 10: Comparison of the predicted steady-state exposures in patients stratified by body weight quartiles

		Body weight quartiles							
		Q1		Q2		Q3		Q4	
Summary exposure		200 mg	3 mg/kg	200 mg	3 mg/kg	200 mg	3 mg/kg	200 mg	3 mg/kg
No of subjects (%)		677 (26.1)		685 (26.4)		610 (23.5)		624 (24.0)	
AUCss (µg*day/mL)	Geometric mean (%CV)	1406 (27.2)	1070 (27.3)	1309 (24.8)	1204 (24.8)	1232 (25.2)	1283 (25.4)	1079 (26.8)	1347 (26.5)
	% difference [a]	12.0	-12.1	4.32	-1.07	-1.86	5.36	-14	10.62
Cmax,ss (µg/mL)	Geometric mean (%CV)	122 (20.7)	93 (20.3)	113 (18.8)	104 (18.8)	106 (19.4)	110 (19.4)	95 (19.8)	118 (19.8)
	% difference [a]	12.4	-11.8	3.6	-1.8	-2.5	4.7	-13.1	11.8
Cmin,ss (µg/mL)	Geometric mean (%CV)	46 (37.2)	35 (37.2)	42 (33.7)	39 (33.7)	39 (34.8)	41 (34.9)	33 (37.5)	42 (36.8)
	% difference [a]	13.8	-10.7	5.8	0.3	-2.0	5.3	-16.7	7.2
Body weight (kg) [min, median, max]		[31.9; 52; 57]		[57.2; 61; 65]		[65.2; 70; 74]		[74.1; 81; 130]	

[a] % difference from the geometric mean simulated exposures of the subjects in the overall population

Further data were provided demonstrating that observed concentrations and the medians across various dose levels are in a similar range between patients with BW < 89 kg and ≥ 89 kg (p95 of body weight).

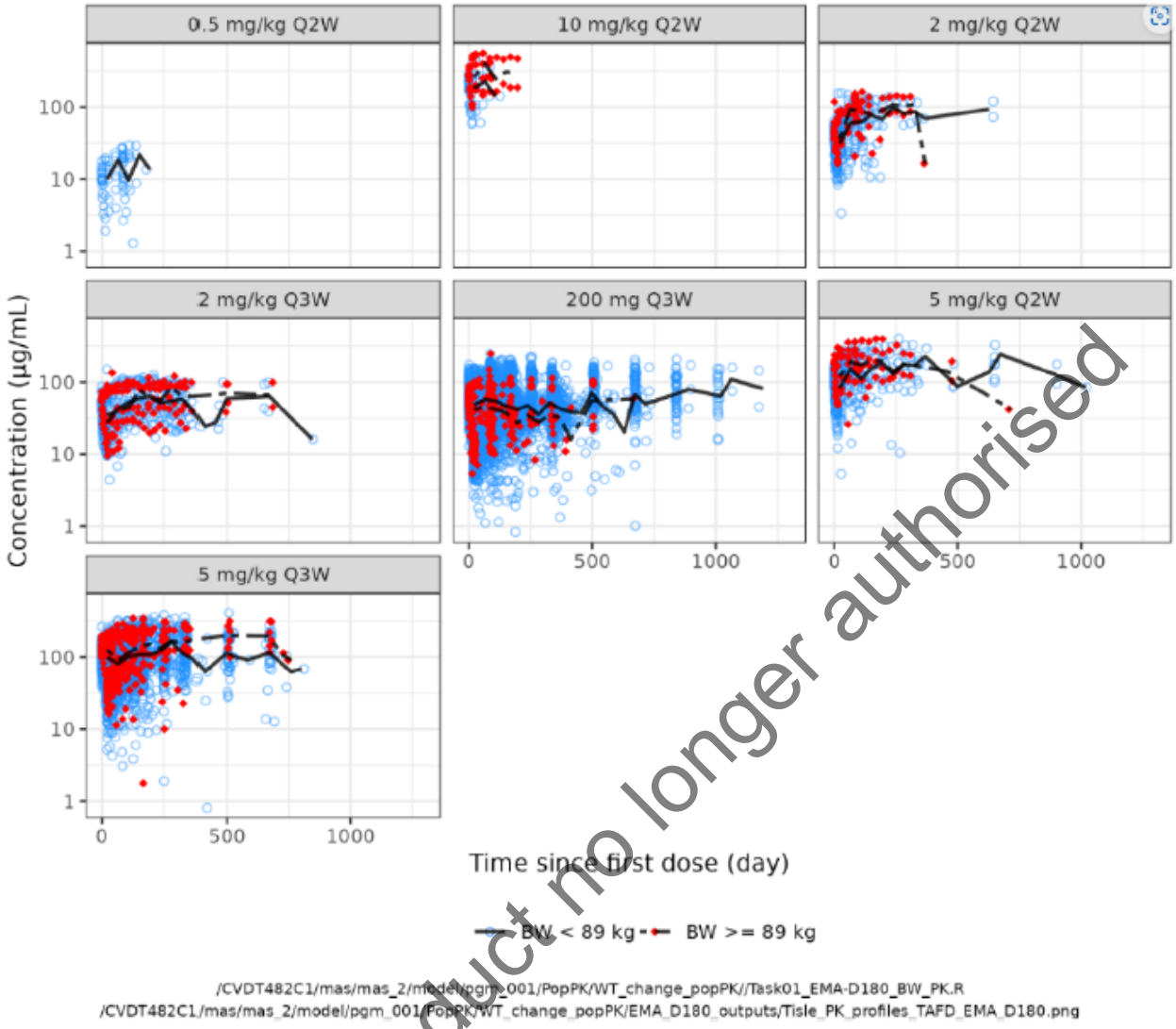


Figure 12: Observed tislelizumab concentrations stratified by dose and body weight groups (PopPK dataset)

Further, PopPK-predicted tislelizumab exposure metrics (AUC, C_{max}, Cmin, and Cavg) after 200 mg Q3W at dose 1 and steady-state in patients with 2L ESCC (Study 302) and NSCLC (Studies 303, 304, and 307) are shown in Figure 2-5 and Figure 2-6. These figures further show the overlapping exposure in patients with BW < 89 kg and BW > 89 kg, suggesting that BW is not the only covariate that affects tislelizumab PK. Other factors, such as baseline albumin level, tumour size, ADA status, tumour type, gender, and age, also contribute to the difference in PK.

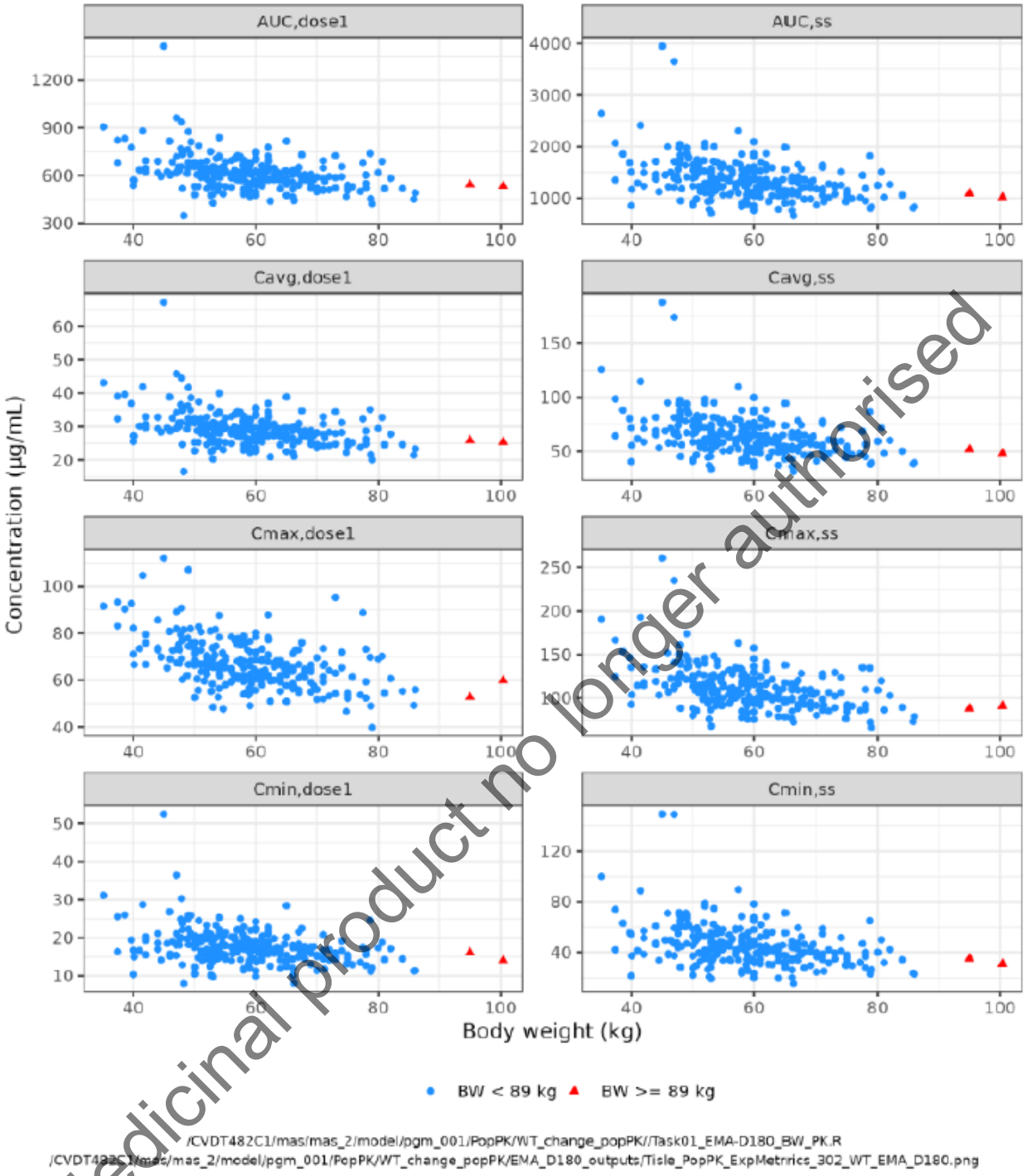


Figure 13: popPK predicted exposure metrics of patients from study 302 (2L ESCC)

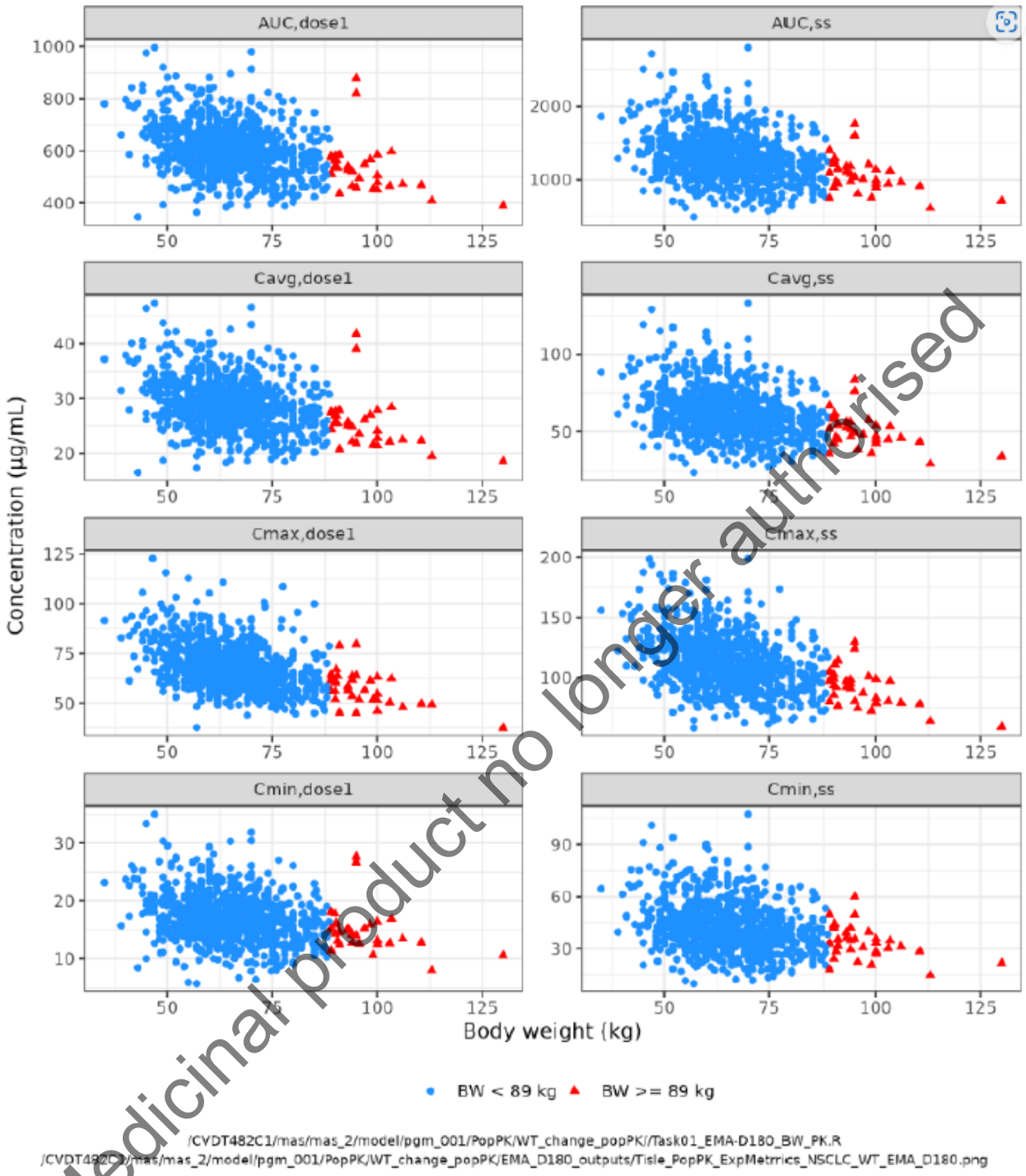


Figure 14: PopPK predicted exposure metrics of patients from study 303, 304 and 307 (NSCLC)

Geometric mean (%CV) of simulated steady-state exposure metrics of tislelizumab at 200 mg Q3W for all patients in the PopPK dataset comparing BW < 89 kg and BW ≥ 89 kg.

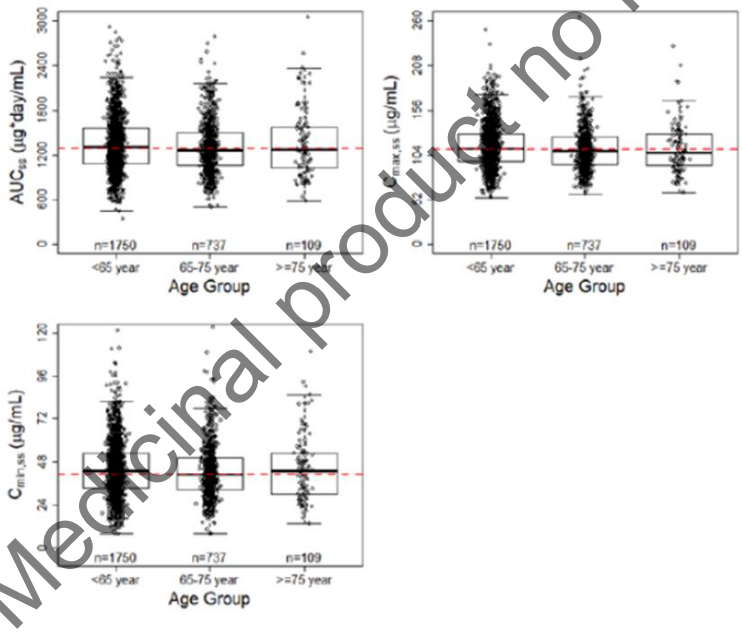
Table 11: Geometric mean (%CV) of simulated steady-state exposure metrics of tislelizumab at 200 mg Q3W

Characteristics	BW < 89 kg	BW ≥ 89 kg
No. of subjects, N (%)	2463 (94.9)	133 (5.1)
Cmin,ss (µg/mL)	40.67 (37.05)	30.34 (40.12)
Cmax,ss (µg/mL)	110.03 (21.4)	88.43 (19.6)
AUC,ss (µg*day/mL)	1270.49 (27.32)	1002.57 (28.11)
CL (L/day)	0.15 (28.06)	0.2 (28.52)
BW (kg) – min, median, max	31.9, 64, 88.9	89, 95.5, 130
Albumin (g/L) – min, median, max	17, 41.1, 435	22, 40.9, 61.3
Age (year) – min, median, max	18, 60, 90	29, 59, 81
Tumor size (mm) – min, median, max	10, 63, 408	10, 68, 252
Sex - M/F, n (%)	1815 (73.7), 648 (26.3)	105 (78.9), 28 (21.1)
ADA negative/positive/missing, n (%)	2031 (82.5), 406 (16.5), 26 (1.1)	105 (78.9), 26 (19.5), 2 (1.5)

Source: /CVDT482C1/mas/mas_2/model/pgm_001/PopPK/WT_change_popPK/EMA_D180_outputs/GeoMean_PK_DoseSS_WT_EMA_D180.pdf

Elderly

Baseline age was identified as a significant covariate on the Vc of tislelizumab in the final popPK model. The estimates of Vc at 10th and 90th percentile of age distribution (45 to 71-year-old) were within 3% of the typical estimate of Vc at median age of 60. The predicted steady-state exposures after 200 mg Q3W dosing for subjects stratified by age groups are presented in Figure below.



Source: [PopPK Report-Figure 20]

Abbreviations: AUC_{ss}, area under the serum concentration-time curve at steady-state; CL, clearance; $C_{min,ss}$, minimum serum concentration at steady-state; PK, pharmacokinetic(s).

Notes: The steady-state exposures ($C_{min,ss}$ and AUC_{ss}) of tislelizumab were computed for each patient. AUC_{ss} was calculated as dose/CL. $C_{min,ss}$ was calculated as the minimum concentration on the 21st day after the 10th consecutive doses of tislelizumab 200 mg Q3W [PopPK Report-Section 5.5 and Section 5.6].

The dashed red horizontal line represents the mean of the overall population.

Figure 15: simulated steady-state exposures of tislelizumab by age group after 200 mg Q3W dosing

Children

Tislelizumab has no study conducted in paediatric subjects.

In the presentation of variability in special populations, the Applicant notes in several instances that "These differences were small relative to the overall variability of exposures and are not considered clinically significant". The variability values were obtained by taking the largest differences between the 5th and 95th percentile exposures in the overall population compared to the typical individual, which are ~ 55.8%, 47.3%, and 70.8% for AUC,ss, C_{max},ss, and Cmin,ss, respectively. Based on the data provided, it is agreed that the variability in the special populations is small compared to the overall variability.

Impact of ADA on PK

In the Phase III Studies 302, 303, 304, and 307, patients who tested positive for treatment-emergent ADA had slightly lower trough tislelizumab concentrations as compared to patients who were ADA negative. However, the serum concentrations in the treatment-emergent ADA-positive patients were within the range observed in ADA-negative patients.

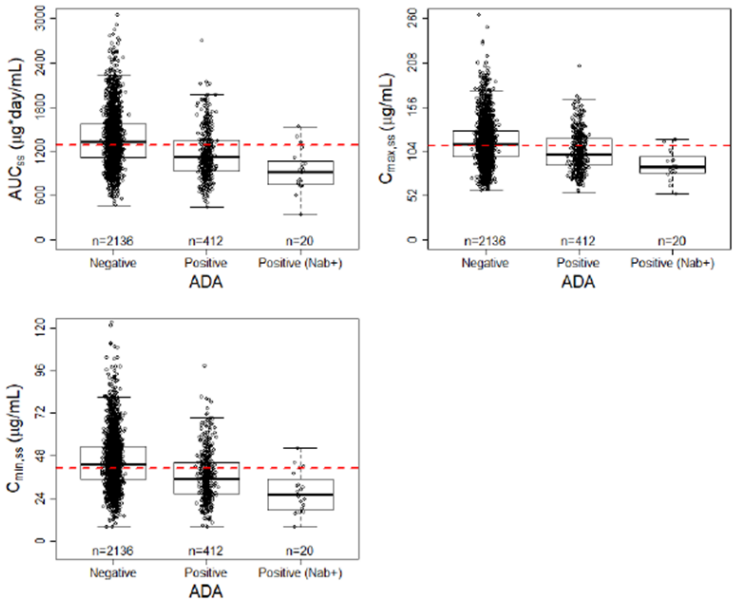
The effect of immunogenicity (ADA) on PK was further evaluated by treatment-emergent ADA status in the popPK model. The subject-level ADA status was identified as a significant covariate on the CL of tislelizumab in the final PopPK model, where ADA positive status was associated with a slightly increased CL compared with ADA negative status. The predicted steady state exposures following 200 mg Q3W dosing stratified by ADA are presented below.

The geometric mean simulated exposures (AUCss, C_{max},ss and Cmin,ss) in ADA positive subjects were up to 20.5% lower compared with those of in ADA negative subjects (Table below).

Table 12: Geometric mean (%CV) simulated steady state exposure of tislelizumab by ADA status following 200mg Q3W dosing

Characteristics		ADA		Neutralizing
		Negative	Positive	Nab+
No. of subjects (%)		2136 (83.2)	432 (16.8)	20 (0.779)
AUC_{ss} (μg*day/mL)	geometric mean (%CV)	1321 (27.7)	1114 (28.9)	895.4 (30.3)
	% difference[a]	-	-15.7	-32.2
$C_{max,ss}$ (μg/mL)	geometric mean (%CV)	112 (22)	101 (21.8)	86.7 (19.5)
	% difference[a]	-	-10.1	-22.8
$C_{min,ss}$ (μg/mL)	geometric mean (%CV)	42.6 (34.8)	33.9 (39.2)	25 (42.2)
	% difference[a]	-	-20.5	-41.3
Body weight (kg) [min, median, max]		[31.9; 65; 170]	[36.3; 65; 139]	[44.5; 65.8; 107]
Albumin (g/L) [min, median, max]		[17; 41.4; 435]	[20; 40; 53.2]	[22; 38.4; 47]
Age (year) [min, median, max]		[18; 60; 90]	[21; 61; 83]	[36; 61.5; 72]
Tumor size (mm) [min, median, max]		[10; 61.3; 380]	[10; 75; 408]	[24; 75; 271]
Sex [M/F, N(%)]		1561 (73.1)/575 (26.9)	335 (77.5)/97 (22.5)	17 (85)/3 (15)

a. %difference from the geometric mean simulated exposures of the ADA negative subjects in the overall population.



Circles are the simulated steady state tislelizumab exposure in individual subjects. The boxes represent the 25th to 75th percentiles (the interquartile range). The solid black horizontal line in the middle of each box represents the median. The whiskers represent the range of data points within 1.5 times the interquartile range. The dashed red horizontal line represents the mean of the overall population.

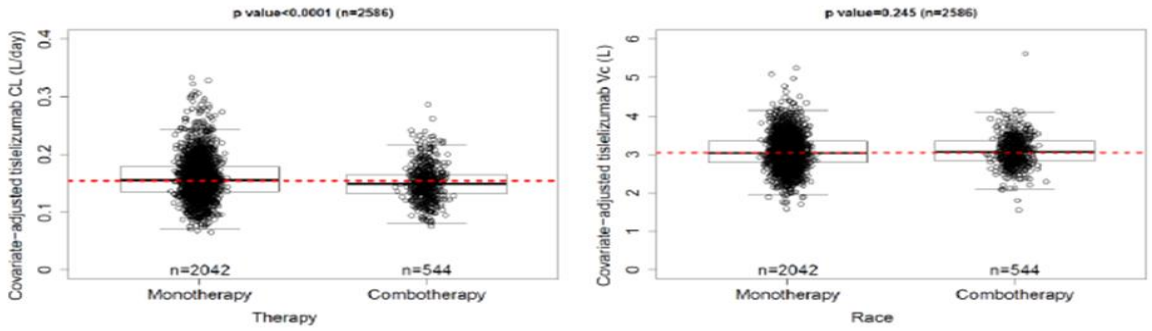
Figure 16: Simulated steady state exposure of tislelizumab by ADA following 200mg Q3W dosing

Pharmacokinetic interaction studies

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

Population PK analysis:

Single or combination therapy was not tested during the PopPK covariate model development because multiple chemotherapeutic combination regimens were included in many tumour types (i.e. NPC, GC, EC, and NSCLC) and studies (i.e. 205, 206, 304, 307, and 309). The impact of combination therapy on the covariate-adjusted tislelizumab PK parameters (CL and Vc) were evaluated in post hoc analysis based on the final model are illustrated in **Figure 17**. The result suggested a significant correlation ($p < 0.0001$) between the covariate-adjusted CL and therapy. In order to evaluate the impact of therapy on tislelizumab exposure, the predicted steady state exposures following 200 mg Q3W dosing were summarised and plotted by therapy (**Table 13** and **Figure 18**). The mean simulated exposures (AUCss, C_{max},ss and Cmin,ss) in subjects with combination therapy were up to 8.79% higher compared with those of subjects with monotherapy in the overall population. These differences were very small relative to the overall variability of exposures and are not considered clinically significant.



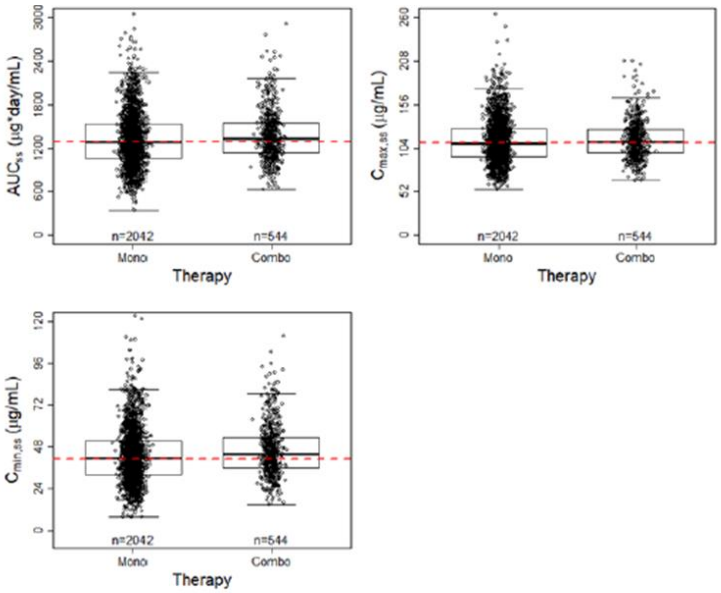
Circles are the covariate-adjusted tislelizumab CL and V_c values in individual subjects. The boxes represent the 25th to 75th percentiles (the interquartile range). The solid black horizontal line in the middle of each box represents the median. The whiskers represent the range of data points within 1.5 times the interquartile range. The dashed red horizontal line represents the mean of the entire PopPK analysis population. The p values shown on the plots are from ANOVA testing.

Figure 17: Impact of therapy on the covariate-adjusted tislelizumab CL and Vc based on the final PopPK model

Table 13: Geometric mean (%CV) simulated steady state exposure of tislelizumab by therapy following 200mg Q3W dosing

Characteristics		Therapy	
		Monotherapy	Combotherapy
No. of subjects (%)		2042 (79)	544 (21)
AUC_{ss} (μg*day/mL)	geometric mean (%CV)	1269 (29.4)	1332 (25)
	% difference [a]	-	4.97
$C_{max,ss}$ (μg/mL)	geometric mean (%CV)	110 (23.1)	112 (19.9)
	% difference [a]	-	2.07
$C_{min,ss}$ (μg/mL)	geometric mean (%CV)	40.2 (37.2)	43.8 (32.1)
	% difference [a]	-	8.79
Body weight (kg) [min, median, max]		[31.9; 65; 170]	[36; 63.5; 113]
Albumin (g/L) [min, median, max]		[17; 41; 435]	[25.4; 41.2; 61.3]
Age (year) [min, median, max]		[18; 60; 90]	[27; 61; 75]
Tumor size (mm) [min, median, max]		[10; 61.6; 408]	[10; 73; 230]
Sex [M/F, N(%)]		1462 (71.6)/580 (28.4)	450 (82.7)/94 (17.3)
ADA [Negative/Positive, N(%)]		1717 (84.8)/307 (15.2)	419 (77)/125 (23)

a. %difference from the geometric mean simulated exposures of the subjects with monotherapy in the overall population.



Circles are the simulated steady state tislelizumab exposure in individual subjects. The boxes represent the 25th to 75th percentiles (the interquartile range). The solid black horizontal line in the middle of each box represents the median. The whiskers represent the range of data points within 1.5 times the interquartile range. The dashed red horizontal line represents the mean of the overall population.

Figure 18: Simulated steady state exposure of tislelizumab by therapy following 200 mg Q3W dosing

2.6.2.2 Pharmacodynamics

Throughout the clinical studies, no specific pharmacodynamic endpoints were investigated.

Exposure-response (E-R) analyses were performed to understand the relationships between PK and efficacy, as well as safety parameters. These analyses support the proposed dosing regimen of 200 mg Q3W.

The immunogenicity profile of tislelizumab and its impact on PK, safety, and efficacy in the NSCLC population has been characterised.

Mechanism of action

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

Immunogenicity

Immunogenicity data are available from 10 clinical studies of tislelizumab administered as a monotherapy (Studies 001, 102, 203, 204, 208, 302, and 303) or in combination with chemotherapy (Studies 206, 304, and 307) in patients with different tumour types.

Monitoring of antidrug antibodies (ADA) to tislelizumab and titre determination for confirmed positive ADA samples has been performed. Neutralizing antibodies (NAbs) were evaluated in the confirmed positive ADA samples.

Tislelizumab monotherapy

Among 1424 evaluable patients treated with tislelizumab 200 mg Q3W as monotherapy, 232 (16.3%) had treatment-emergent ADA, of which 224 (15.7%) had treatment-induced ADA, and 8 (0.6%) had treatment-boosted ADA, and 11 (0.6%) had neutralizing antibodies (Table below).

Tislelizumab combination therapy

Among 492 evaluable patients treated with tislelizumab 200 mg Q3W in combination with platinum-containing chemotherapy (Studies 206, 304, and 307), 118 (24.0%) had treatment-emergent ADA, of whom 114 (23.2%) had treatment-induced ADA and 4 (0.8%) had treatment-boosted ADA, and 7 (1.4%) had NAb (Table 14). Transient ADA (14.8%) were more common than persistent ADA (8.3%), although this may reflect the limited sampling schedule in these studies (predose of Cycles 1, 2, 5, 9, and 17).

Table 14: ADA incidence by dose regimen – Studies 001, 102, 203, 204, 206, 208, 302, 303, 304 and 307 (ADA evaluable patients)

Dose Regimen	Study	Evaluable Patients N	Treatment-emergent n (%)	Treatment-boosted n (%)	Treatment-induced n (%)	Persistent n (%)	Transient n (%)	NAb Positive n (%)
0.5 mg/kgQ2W	001	3	1 (33.3)	0	1 (33.3)	0	1 (33.3)	0
2 mg/kg Q2W		21	6 (28.6)	0	6 (28.6)	2 (9.5)	4 (19.0)	0
5 mg/kg Q2W		25	5 (20.0)	0	5 (20.0)	4 (16.0)	1 (4.0)	0
10 mg/kg Q2W		6	1 (16.7)	0	1 (16.7)	1 (16.7)	0	0
2 mg/kg Q3W		19	6 (31.6)	0	6 (31.6)	3 (15.8)	3 (15.8)	0
5 mg/kg Q3W		287	44 (15.3)	1 (0.3)	43 (15.0)	21 (7.3)	22 (7.7)	0
Study 001 Weight-based dosing mono[1]		**361**	**63 (17.5)**	**1 (0.3)**	**62 (17.2)**	**31 (8.6)**	**31 (8.6)**	**0**
200 mg Q3W	001	11	3 (27.3)	0	3 (27.3)	1 (9.1)	2 (18.2)	1 (9.1)
200 mg Q3W	102	280	43 (15.4)	2 (0.7)	41 (14.6)	26 (9.3)	15 (5.4)	2 (0.7)
200 mg Q3W	203	70	6 (8.6)	0	6 (8.6)	4 (5.7)	2 (2.9)	1 (1.4)
200 mg Q3W	204	104	18 (17.3)	1 (1.0)	17 (16.3)	13 (12.5)	4 (3.8)	0
200 mg Q3W	208	231	50 (21.6)	0	50 (21.6)	33 (14.3)	17 (7.4)	4 (1.7)
200 mg Q3W	302	221	32 (14.5)	2 (0.9)	30 (13.6)	20 (9.0)	10 (4.5)	1 (0.5)
200 mg Q3W	303	507	80 (15.8)	3 (0.6)	77 (15.2)	40 (7.9)	37 (7.3)	2 (0.4)
200 mg Q3W mono[1]		**1424**	**232 (16.3)**	**8 (0.6)**	**224 (15.7)**	**137 (9.6)**	**87 (6.1)**	**11 (0.8)**
200 mg Q3W	206	51	7 (13.7)	0	7 (13.7)	1 (2.0)	6 (11.8)	0
200 mg Q3W T+PP	304	213	48 (22.5)	2 (0.9)	46 (21.6)	12 (5.6)	34 (16.0)	2 (0.9)
200 mg Q3W T+PC	307	115	43 (37.4)	2 (1.7)	41 (35.7)	18 (15.7)	23 (20.0)	1 (0.9)
200 mg Q3W T+nPC	307	113	20 (17.7)	0	20 (17.7)	10 (8.8)	10 (8.8)	4 (3.5)
200 mg Q3W combo[2]		**492**	**118 (24.0)**	**4 (0.8)**	**114 (23.2)**	**41 (8.3)**	**73 (14.8)**	**7 (1.4)**
200 mg Q3W total		**1916**	**350 (18.3)**	**12 (0.6)**	**338 (17.6)**	**178 (9.3)**	**160 (8.4)**	**18 (0.9)**
Total		**2277**	**413 (18.1)**	**13 (0.6)**	**400 (17.6)**	**209 (9.2)**	**191 (8.4)**	**18 (0.8)**

Source: [Report BGB-A317-GP-012-Table 2], [Study 208 IAR-Table 2], [Study 302 IAR-Table 2], [Study 303 IAR-Table 2], [Study 206 CSR-Table 14.3.8], [Study 304 IAR-Table 2], [Study 307 IAR-Table 2]
ADA=anti-drug antibodies; NAb=neutralizing antibody, Q2W=once every 2 weeks; Q3W=once every 3 weeks; T+PC=tislelizumab + paclitaxel + carboplatin; T+nPC=tislelizumab + *Nab*-paclitaxel + carboplatin; T+PP=tislelizumab + pemetrexed + platinum; %=n/N for each row*100
[1] Tislelizumab monotherapy administered in Studies 001, 102, 203, 204, 208, 302, and 303
[2] Tislelizumab in combination therapy: Study 206 (tislelizumab in combination with platinum-containing doublet chemotherapy), Study 304 T+PP; Study 307 T+PC and T+nPC

Higher ADA incidence rates were observed in White vs. Asian patients (21.0% vs. 14.3%) and also in Europe/North America vs. Asia (24.4% vs. 15.2%), although exposure-response analyses revealed that the difference in ADA incidence rates between White and Asian patients is not associated with altered clinical efficacy and safety.

Onset and duration

The onset and duration of treatment-induced, persistent, and transient ADA were comparable across the studies. Most patients with treatment-induced ADA, persistent or transient, developed the ADA by the second dose (Cycle 2 Day 1; Study Day 22 ± 4 days) and before the third dose of the Q3W regimen (**Table 15**).

Table 15: Onset and duration (days) of treatment induced ADA – Studies 001, 102, 203, 204, 208, 302, 303, 304 and 307 (ADA evaluable patients)

	Treatment-induced ADA		Persistent ADA		Transient ADA	
Study	Onset Median (Min, Max)	Duration Median (Min, Max)	Onset Median (Min, Max)	Duration Median (Min, Max)	Onset Median (Min, Max)	Duration Median (Range)
Tislelizumab monotherapy						
001, 102, 203, 204	42.0 (19, 338)	72.0 (19, 457)	31.0 (19, 338)	85.0 (20, 457)	43.0 (20, 337)	60.5 (19, 92)
208	23.0 (22, 170)	85.0 (9, 318)	29.5 (22, 170)	116.5 (9, 318)	22.0 (22, 85)	64.0 (63, 85)
302	23.0 (20, 343)	63.0 (5, 230)	23.0 (20, 339)	61.5 (5, 230)	23.0 (22, 343)	63*
303	23.0 (18, 255)	85.0 (22, 317)	23.0 (18, 255)	97.5 (22, 317)	22.0 (19, 174)	65.0 (60, 92)
Tislelizumab combination therapy						
304 T+PP	23.0 (20, 301)	77.0 (64, 523)	24.5 (21, 301)	132.5 (64, 523)	22.5 (20, 109)	67.0 (64, 70)
307 T+PC and T+nPC	23.0 (19, 351)	145.5 (28, 316)	25.0 (19, 351)	145.5 (28, 316)	22.0 (21, 174)	ND

Source: [Report BGB-A317-CP-012-Table 7], [Study 208 IAR Report-Section 5.2 and Table 5], [Study 302 IAR-Section 5.2 and Table 6]; [Study 303 IAR-Section 5.2 and Table 6], [Study 304 IAR-Table 5], [Study 307 IAR-Table 5]
ADA-anti-drug antibody; T+PC=tislelizumab + paclitaxel + carboplatin; T+nPC=tislelizumab + *Nab*-paclitaxel + carboplatin; T+PP=tislelizumab + pemetrexed + platinum (cisplatin or carboplatin)
For patients with a single positive ADA sample and no subsequent samples, these samples were excluded from the median calculations for duration. All min and max values are presented.
*Duration of transient ADA in Study 302 was available for only one patient
ND: the duration was marked as 'Not determined' for all patients with transient ADA in Study 307

Median titre levels

The median titre levels generally fluctuated between 10 and 100 over time. Higher titres ≥1000 were observed in some patients in Studies 304 and 307 at isolated timelines during treatment with tislelizumab in combination with chemotherapy.

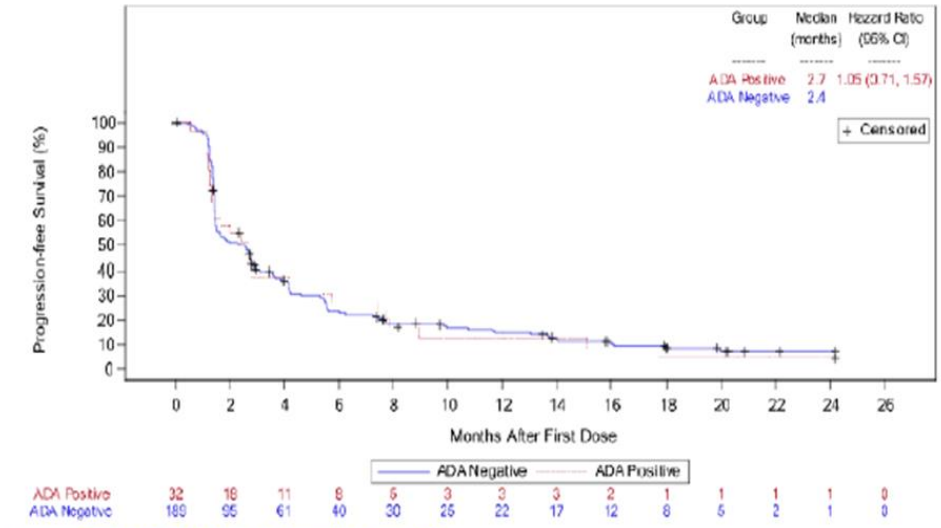
Individual titre values for most patients did not increase over the course of the studies.

Impact of ADA on clinical efficacy

Table 16: Clinical response endpoints after tislelizumab treatment by ADA status in all patients – Studies 001, 102, 203, 204, 208, 302, 303, 304 and 307 (ADA evaluable patients)

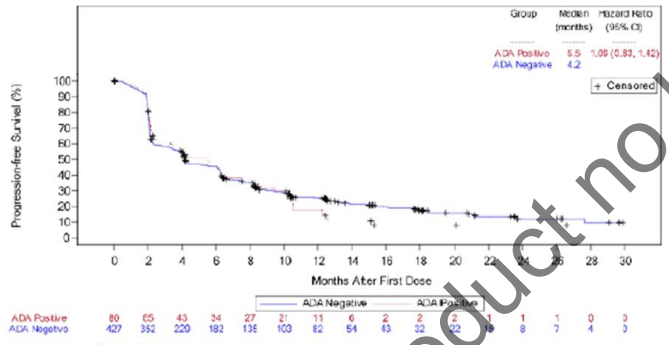
Clinical Endpoint	Treatment-emergent ADA Positive	Treatment-emergent ADA Negative
Studies 001, 102, 203 and 204 – All patients		
Objective Response - n/N (%)	25/133 (18.8)	171/693 (24.7)
Disease Control - n/N (%)	61/133 (45.9)	370/693 (53.4)
Clinical Benefit - n/N (%)	34/133 (25.6)	208/693 (30.0)
Studies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

Source: [Report BGB-A317-CP-012-Table 9 and Table 10]. [Study 208 IAR-Table 7], [Study 302 IAR-Table 7], [Study 303 IAR-Table 7], [Study 304 IAR-Table 7], [Study 307 IAR-Table 7]
ESCC=esophageal cancer; HCC=hepatocellular carcinoma; NSCLC=non-small cell lung cancer
T+PC=tislelizumab + paclitaxel + carboplatin; T+nPC=tislelizumab + *Nab*-paclitaxel + carboplatin;
T+PP=tislelizumab + pemetrexed + platinum (cisplatin or carboplatin)



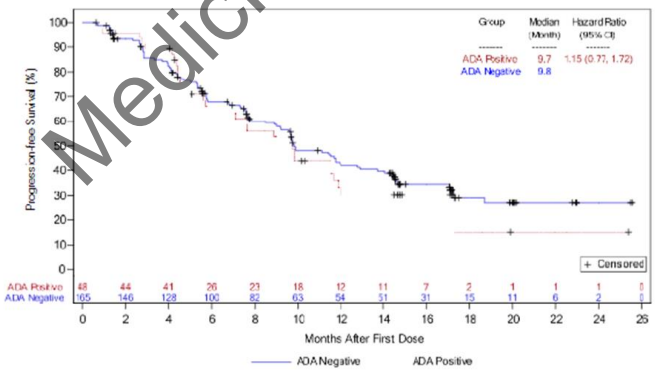
Source: [Study 302 IAR Memo-Appendix Figure 27]
ADA positive=patients with treatment-emergent ADA.

Figure 19: Progression free survival by ADA status after tislelizumab monotherapy - Study 302 (ADA evaluable patients)



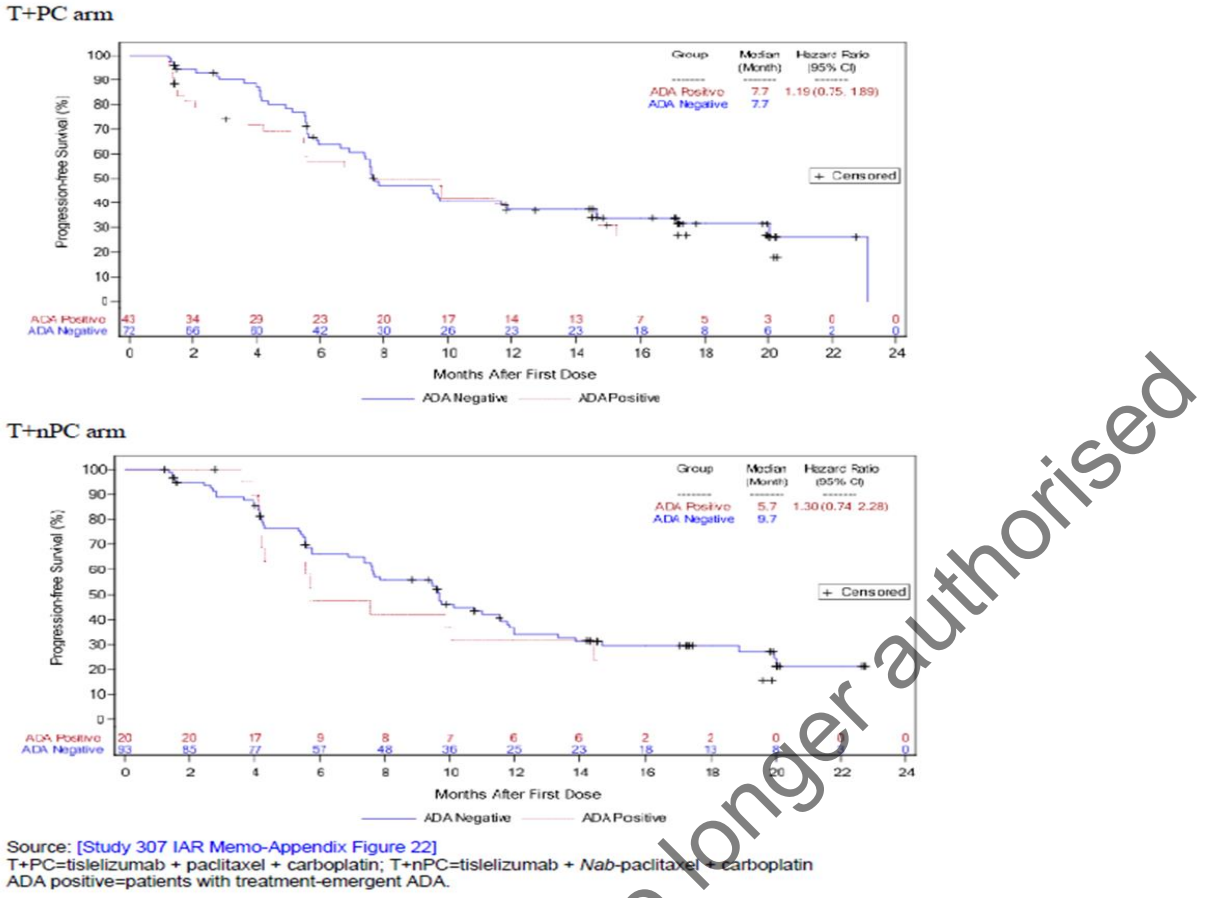
Source: [Study 303 IAR Memo-Appendix Figure 23]
ADA positive=patients with treatment-emergent ADA.

Figure 20: Progression free survival by ADA status after tislelizumab monotherapy - Study 303 (ADA evaluable patients)



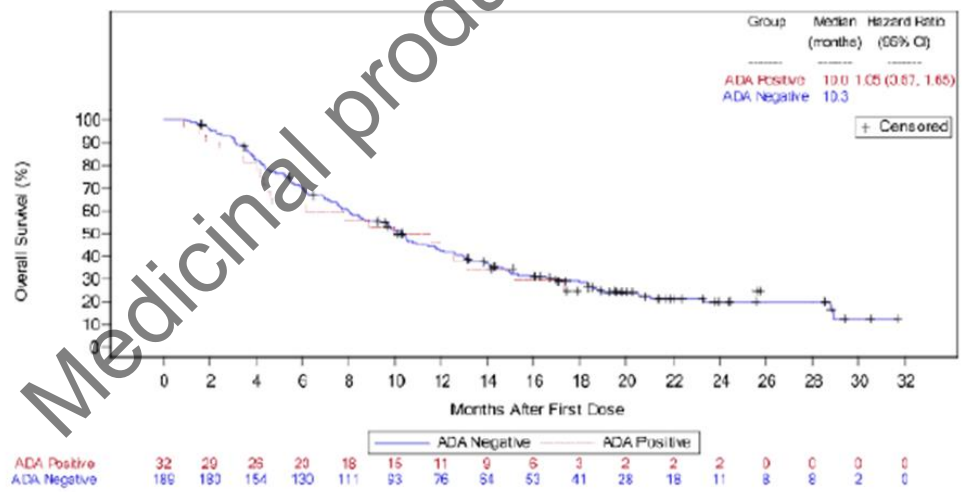
Source: [Study 304 IAR Memo-Appendix Figure 20]
ADA positive=patients with treatment-emergent ADA.

Figure 21: Progression free survival by ADA status after tislelizumab + permetrexed + cisplatin or carboplatin- Study 304 (ADA evaluable patients)



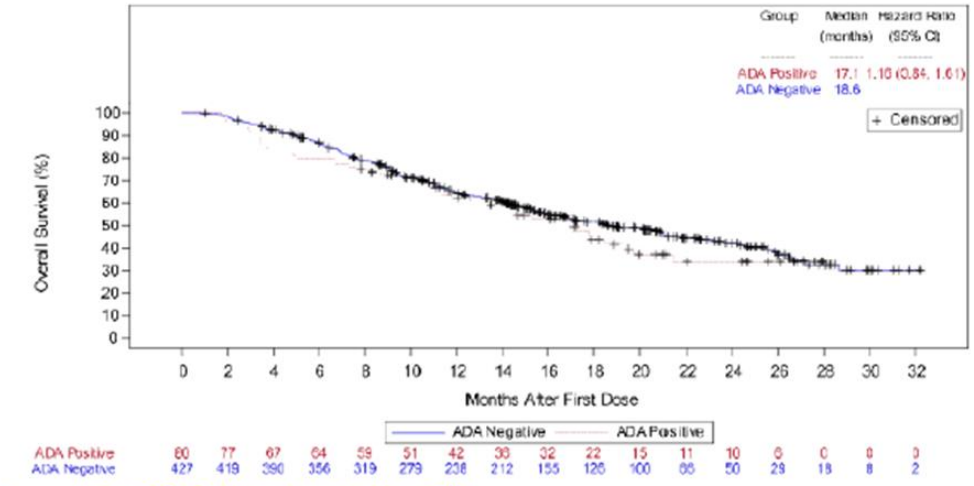
Source: [Study 307 IAR Memo-Appendix Figure 22]
T+PC=tislelizumab + paclitaxel + carboplatin; T+nPC=tislelizumab + *Nab*-paclitaxel + carboplatin
ADA positive=patients with treatment-emergent ADA.

Figure 22: Progression free survival by ADA status after tislelizumab + paclitaxel or Nab-paclitaxel + carboplatin - Study 307 (ADA evaluable patients)



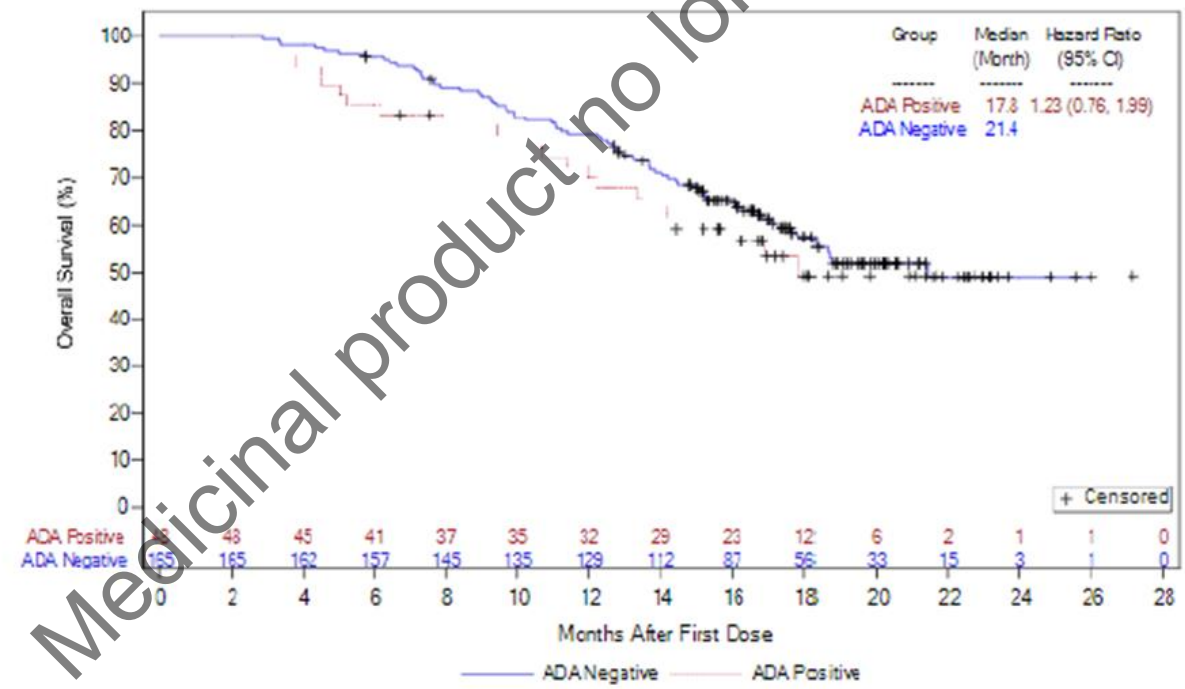
Source: [Study 302 IAR Memo-Appendix Figure 22]
ADA positive=patients with treatment-emergent ADA

Figure 23: Overall survival by ADA status after tislelizumab monotherapy - Study 302 (ADA evaluable patients)



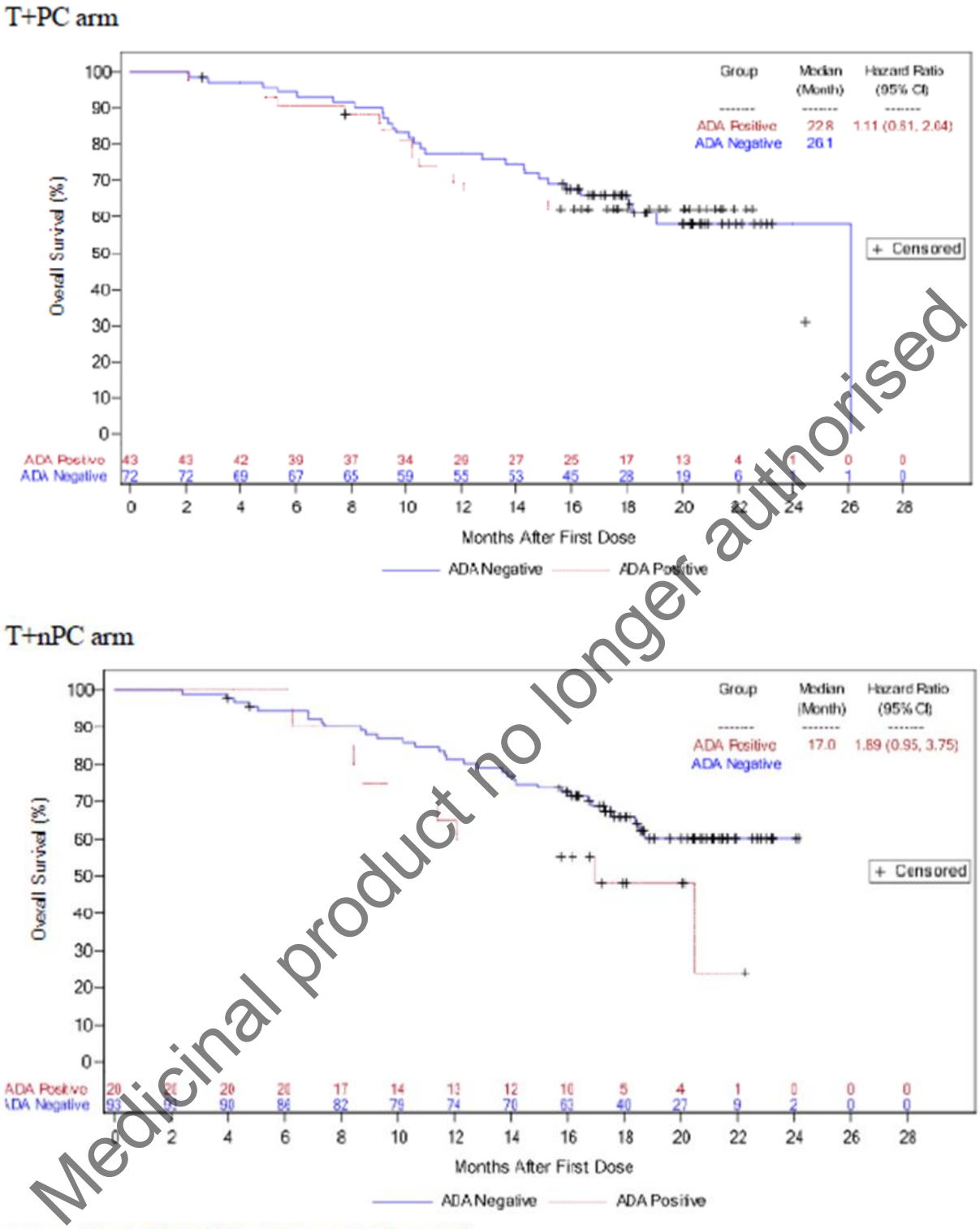
Source: [Study 303 IAR Memo-Appendix Figure 36]
ADA positive=patients with treatment-emergent ADA.

Figure 24: Overall survival by ADA status after tislelizumab monotherapy - Study 303 (ADA evaluable patients)



Source: [Study 304 IAR Memo-Appendix Figure 31]
ADA positive=patients with treatment-emergent ADA.

Figure 25: Overall survival by ADA status after tislelizumab + pemetrexed + cisplatin or carboplatin- Study 304 (ADA evaluable patients)



Source: [Study 307 IAR Memo-Appendix Figure 34]
T+PC=tislelizumab + paclitaxel + carboplatin; T+nPC=tislelizumab + *Nab*-paclitaxel + carboplatin
ADA positive=patients with treatment-emergent ADA.

Figure 26: Overall survival by ADA status after tislelizumab + paclitaxel or Nab paclitaxel + carboplatin- Study 307 (ADA evaluable patients)

To further estimate the causal treatment effects on survival in subgroups defined based on a post-baseline variable, the principal stratum strategy was applied to the primary endpoint of OS in Studies 302 and 303, and PFS in Studies 304 and 307. Comparable survival benefits favouring tislelizumab

arm compared to the adjusted control arm were observed in both ADA-positive and ADA-negative subgroups of the Phase III studies, confirming the lack of causal impact of ADA on survival (data not shown).

The impact of transient versus persistent ADA response as well as Nab positivity on evaluated efficacy parameters were investigated (data not shown).

Impact of ADA on safety

Overall, the incidence of immune-mediated AEs and AESIs (comprising immune-mediated AEs and infusion-related reactions) were comparable between patients who developed ADA and those who tested negative for ADA. AEs causing treatment discontinuation or dose modification also showed no notable differences by ADA status. There was no apparent relationship between AEs and ADA titres in ADA-positive patients, with most AEs occurring in patients with low titres <40 or <80.

A higher incidence of Grade ≥ 3 AEs in treatment-emergent ADA-positive patients compared with ADA-negative patients was observed in all studies, with the exception of Study 307 which showed similar incidence of Grade ≥ 3 AEs in the two ADA subgroups.

Table 17: Treatment-emergent adverse events by ADA status – Studies 001, 102, 203, 204, 208, 302, 303, 304 and 307 (ADA evaluable patients)

Treatment-emergent AEs	All n (%)	Treatment-emergent ADA Positive n (%)	Treatment-emergent ADA Negative n (%)
Monotherapy studies			
Studies 001, 102, 203, and 204			
N	826	133	693
Immune-mediated AEs	264 (32.0)	46 (34.6)	218 (31.5)
AESIs	296 (35.8)	49 (36.8)	247 (35.6)
AEs Grade ≥ 3	361 (43.7)	68 (51.1)	293 (42.3)
AEs causing treatment discontinuation	77 (9.3)	13 (9.8)	64 (9.2)
AEs causing dose modification	148 (17.9)	29 (21.8)	119 (17.2)
Study 208			
N	231	50	181
Immune-mediated AEs	48 (20.8)	15 (30.0)	33 (18.2)
AESIs	52 (22.5)	17 (34.0)	35 (19.3)
AEs Grade ≥ 3	106 (45.9)	27 (54.0)	79 (43.6)
AEs causing treatment discontinuation	19 (8.2)	7 (14.0)	12 (6.6)
AEs causing dose modification	72 (31.2)	18 (36.0)	54 (29.8)
Study 302			
N	221	32	189
Immune-mediated AEs	46 (20.8)	6 (18.8)	40 (21.2)
AESIs	52 (23.5)	7 (21.9)	45 (23.8)
AEs Grade ≥ 3	94 (42.5)	20 (62.5)	74 (39.2)
AEs causing treatment discontinuation	37 (16.7)	4 (12.5)	33 (17.5)
AEs causing dose modification	44 (19.9)	6 (18.8)	38 (20.1)
Study 303			
N	507	80	427
Immune-mediated AEs	70 (13.8)	14 (17.5)	56 (13.1)
AESIs	73 (14.4)	15 (18.8)	58 (13.6)
AEs Grade ≥ 3	188 (37.1)	41 (51.3)	147 (34.4)
AEs causing treatment discontinuation	46 (9.1)	9 (11.3)	37 (8.7)
AEs causing dose modification	113 (22.3)	25 (31.3)	88 (20.6)
Combination therapy studies			
Study 304: T+PP			
N	213	48	165
Immune-mediated AEs	49 (23.0)	9 (18.8)	40 (24.2)
AESIs	51 (23.9)	9 (18.8)	42 (25.5)
AEs Grade ≥ 3	148 (69.5)	39 (81.3)	109 (66.1)
SAEs	80 (37.6)	21 (43.8)	59 (35.8)
AEs causing treatment discontinuation	30 (14.1)	7 (14.6)	23 (13.9)
AEs causing dose modification	140 (65.7)	33 (68.8)	107 (64.8)
Study 307 – Combined T+PC and T+nPC			
N	228	63	165
Immune-mediated AEs	64 (28.1)	17 (27.0)	47 (28.5)
AESIs	69 (30.3)	18 (28.6)	51 (30.9)
AEs Grade ≥ 3	205 (89.9)	56 (88.9)	149 (90.3)
SAEs	97 (42.5)	30 (47.6)	67 (40.6)
AEs causing treatment discontinuation	29 (12.7)	8 (12.7)	21 (12.7)
AEs causing dose modification	151 (66.2)	35 (55.6)	116 (70.3)

Source: [Report BGB-A317-CP-012-Table 10], [Study 208 IAR-Table 12], [Study 302 IAR-Table 9], [Study 303 IAR-Table 9], [Study 304 IAR-Table 8], [Study 307 IAR-Table 8]
AESI=adverse event of special interest (immune-mediated adverse events and infusion-related reactions)
T+PC=tislelizumab + paclitaxel + carboplatin; T+nPC=tislelizumab + *Nab*-paclitaxel + carboplatin;
T+PP=tislelizumab + pemetrexed + platinum (cisplatin or carboplatin)

The imbalance in Grade ≥ 3 AEs observed between the ADA subgroups was driven mainly by Grade 3 AEs, of which the majority in both ADA subgroups were considered not related to study treatment. Across all Phase III studies, the Grade ≥ 3 events had no impact on the continuation of tislelizumab as confirmed by the comparable rates of AEs leading to discontinuation between the ADA subgroups. In general, there was no obvious temporal association between Grade ≥ 3 AEs and ADA onset (although limited by sparse ADA sampling), no correlation between toxicity grade and ADA titre, and no clinically relevant relationships between tislelizumab exposure and safety endpoints. Importantly, immune-mediated AEs and infusion-related reactions, which may be potentially attributable to ADA, showed no differences between treatment-emergent ADA positive and ADA-negative patients.

Upon request, treatment-emergent AEs by ADA status in a pooled dataset for patients treated with tislelizumab monotherapy at a dose of 200 mg Q3W and pooled for the combination therapy studies were provided separately for immune-mediated AEs, IRRs, Grade ≥3 AEs, SAEs, and AEs causing treatment discontinuation/dose modification. The ADA-positive and ADA-negative groups had comparable rates of immune-mediated AEs, IRRs, AEs causing treatment discontinuation and AEs causing dose modification, while the ADA-positive group showed higher rates of Grade ≥ 3 AEs (50.9% vs. 39.3% for monotherapy and 85.6% vs. 78.2% for combination therapy) and SAEs (37.1% vs. 29.7% for monotherapy and 45.9% vs. 38.2% for combination therapy).

Grade ≥ 3 AEs in monotherapy studies

In the pooled monotherapy studies, the following SOCs showed numerical differences >2% between the treatment-emergent ADA-positive and ADA-negative groups:

Investigations SOC (12.9% vs. 10.3%), with PTs that were generally low and comparable between the ADA-positive and ADA-negative groups.

- Metabolism and nutrition disorders (11.6% vs. 7.3%), with small differences of 1-2% between ADA-positive and ADA-negative groups in PTs of hyponatraemia (4.3% vs. 2.0%) and hypokalaemia (2.6% vs. 1.3%).
- Blood and lymphatic system disorders (9.9% vs. 5.3%), with small differences of 1-3% in anaemia (7.8% vs. 4.2%) and thrombocytopenia (1.3% vs. 0%).
- Gastrointestinal disorders (9.1% vs. 5.7%), with no single PT driving this difference.
- General disorders and administrative site conditions (6.5% vs. 3.9%), with no single PT driving this difference.
- Hepatobiliary disorders (4.7% vs. 2.1%), with PTs that occurred at very low and comparable rates (≤0.9% in either ADA group).

Grade ≥ 3 AEs in combination therapy studies

In the pooled combination therapy studies, the following SOCs showed numerical differences >2% between the treatment-emergent ADA-positive and ADA-negative:

- Blood and lymphatic system disorders (53.2% vs. 44.2%), mainly driven by anaemia (21.6% vs. 13.0%), leukopenia (18.9% vs. 14.8%) and thrombocytopenia (13.5% vs. 9.7%), and febrile neutropenia (4.5% vs. 1.8%). These haematological events are common with chemotherapy and the majority of such events were considered related to the chemotherapy rather than to tislelizumab [Study 304-Table 14.3.1.2.5.3], [Study 307- Table 14.3.1-2.5.3].
- Infections and infestations (15.3% vs. 8.2%), mainly due to pneumonia (9.0% vs. 3.9%). In the overall populations of the NSCLC studies, Grade ≥3 pneumonia occurred with comparable rates between tislelizumab + chemotherapy and chemotherapy arms [Study 304-Table 14.3.1-2.4.2], [Study 307-Table 14.3.1.2.4.2].
- Respiratory, thoracic, and mediastinal disorders (10.8% vs. 8.2%), with a small difference seen in haemoptysis (3.6% vs. 1.2%).
- Metabolism and nutrition disorders (9.9% vs. 6.7%), with small differences seen in decreased appetite (2.7% vs. 1.2%) and hypokalaemia (2.7% vs. 0.9%).
- General disorders and administration site conditions (4.5% vs. 2.4%), with a small difference seen in malaise (2.7% vs. 0.3%).

SAEs in monotherapy studies

In the pooled monotherapy studies, the following SOCs showed numerical differences >2% between the treatment-emergent ADA-positive and ADA-negative groups:

- Gastrointestinal disorders (9.1% vs. 4.5%), with differences in dysphagia (2.2% vs. 0.5%) and diarrhoea (1.3% vs. 0.1%). All other PTs occurred in ≤ 1% of patients in either group.
- Hepatobiliary disorders (3.9% vs. 1.8%), with PTs that occurred at very low and comparable rates (≤0.9% in either ADA group).

SAEs in combination therapy studies

In the pooled combination therapy studies, the following SOCs showed numerical differences >2% between the treatment-emergent ADA-positive and ADA-negative groups:

- Respiratory, thoracic, and mediastinal disorders (17.1% vs. 11.2%), driven primarily by pneumonitis (8.1% vs. 5.2%) and haemoptysis (5.4% vs. 1.2%). Pneumonitis is a known imAE of immune checkpoint inhibitors (Wu et al 2017) and was more common in the tislelizumab + chemotherapy arm vs. chemotherapy arm in the NSCLC studies: 5.9% T+PP vs. 0.9% PP [Study 304-Table 27], and 2.5% T+PC, 1.7% T+nPC vs. 0% PC [Study 307-Table 25].
- Infections and infestations (12.6% vs. 7.9%), driven by pneumonia (9.0% vs. 5.5%). In the overall populations of the NSCLC studies, the incidence of serious pneumonia was comparable between tislelizumab + chemotherapy and chemotherapy arms [Study 304- Table 27], [Study 307-Table 25].
- Blood and lymphatic system disorders (10.8% vs. 4.8%), with differences in thrombocytopenia (4.5% vs. 1.5%) and anaemia (3.6% vs. 0.3%).
- General disorders and administration site conditions (6.3% vs. 3.3%) due mainly to malaise (1.8% vs. 0%).
- Cardiac disorders (3.6% vs. 0.9%), with all PTs occurring as single events (≤0.9% in either ADA group).
- Skin and connective tissue disorders (2.7% vs. 0.6%) due mainly to rash (1.8% vs. 0%).
- Hepatobiliary disorders which were more common in the ADA-negative group (2.1%) than in the ADA-positive group (0%).

Most SOCs and PTs of SAEs listed above are not known to be mediated by ADA. On the other hand, ADA-related immune complexes have been shown to induce release of inflammatory cytokines and complement activation, leading to inflammation and breakdown of self-tolerance (Krishna and Nadler 2016). While it is unclear what role, if any, ADA may play in the pathogenesis of imAEs such as pneumonitis, the incidence of pneumonitis in tislelizumab studies in NSCLC is similar to those reported for other PD-1/PD-L1 inhibitors, including nivolumab and atezolizumab which have comparable or higher ADA incidences as tislelizumab (Wu et al 2017, Rittmeyer et al 2017).

The majority of the 18 patients with NAb (0.8% of 2277 ADA evaluable patients; Table 14) across the 10 clinical studies did not experience immune-mediated AEs or AESIs, and none had hypersensitivity AEs.

Exposure-response analyses

Exposure-efficacy analysis:

The exposure-efficacy relationship was explored for each of the pivotal studies (303, 304 and 307) using various endpoints, such as BOR, PFS, and OS.

The relationship between exposure and BOR was first illustrated descriptively for Studies 303, 304, and 307 by providing summary statistics of popPK predicted Cavg,ss and covariates of interest by response status. Logistic regression was then used to further evaluate the relationship between exposure and the probability of response (i.e., BOR being CR or PR), separately for each study, and identify significant covariates.

Similarly, OS and PFS were first illustrated by Kaplan-Meier survival curves, stratified by quartiles of tislelizumab exposure (Cavg,ss) and covariates of interest. A Cox regression model was then used to further characterise the relationship between exposure and PFS and OS and identify significant covariates.

Results

For all efficacy endpoints (BOR, PFS, and OS) analysed, there appears to be a positive trend between these efficacy endpoints and exposure within the range of exposure at 200 mg Q3W, which was the only dose evaluated in all three studies. As shown in Figure below, in general, higher exposure seems to be associated with higher probability of OS in 2/3L, and PFS in 1L SQ and NSQ NSCLC population at a given time, respectively.

Furthermore, results from Cox regression models (Table 18, Table 19 and Table 20) also suggest that the risk of death or risk of disease progression decreases with an increase in exposure for 2/3L, 1L SQ and 1L NSQ NSCLC population, respectively.

In addition, significant covariates were identified based on the covariate search. As shown in Table 18, baseline LDH, PD-L1 status, weight and disease stage were statistically significant covariates on OS in 2/3L NSCLC. Specifically, subjects with lower LDH, higher PD-L1 expression, locally advanced carcinoma and higher body weight seem to have lower risk of death. Similarly, as shown in Table 19 and Table 20, baseline weight and PD-L1 status were identified as significant covariates in 1L SQ and NSQ, respectively. Subjects with higher baseline weight, or higher PD-L1 expression tend to have lower risk of disease progression in 1L SQ and NSQ, respectively.

However, the present analysis, in which only one dose level of 200 mg Q3W was evaluated, has important limitations. For example, the positive exposure efficacy relationship in BOR observed at the 200 mg Q3W dose was not consistent with the flat exposure response relationship on BOR observed at 200 mg Q3W and 5 mg/kg Q3W, in the previous exposure response analysis based on earlier phase data on patients with NSCLC [BGB-A317-CP-009].

In fact, this inconsistency in exposure response relationship between a given dose level and across different dose levels was not uncommon in anti-PD1 drugs. For instance, in both pembrolizumab and nivolumab, within a given dose level, a similar positive relationship was observed between exposure and efficacy endpoints (Agrawal et al 2016, Feng et al 2017, Turner et al 2018), while a flat dose response relationship was observed across multiple doses. This inconsistency suggests that the within dose difference in efficacy across exposure quartile were likely due to factors other than exposure.

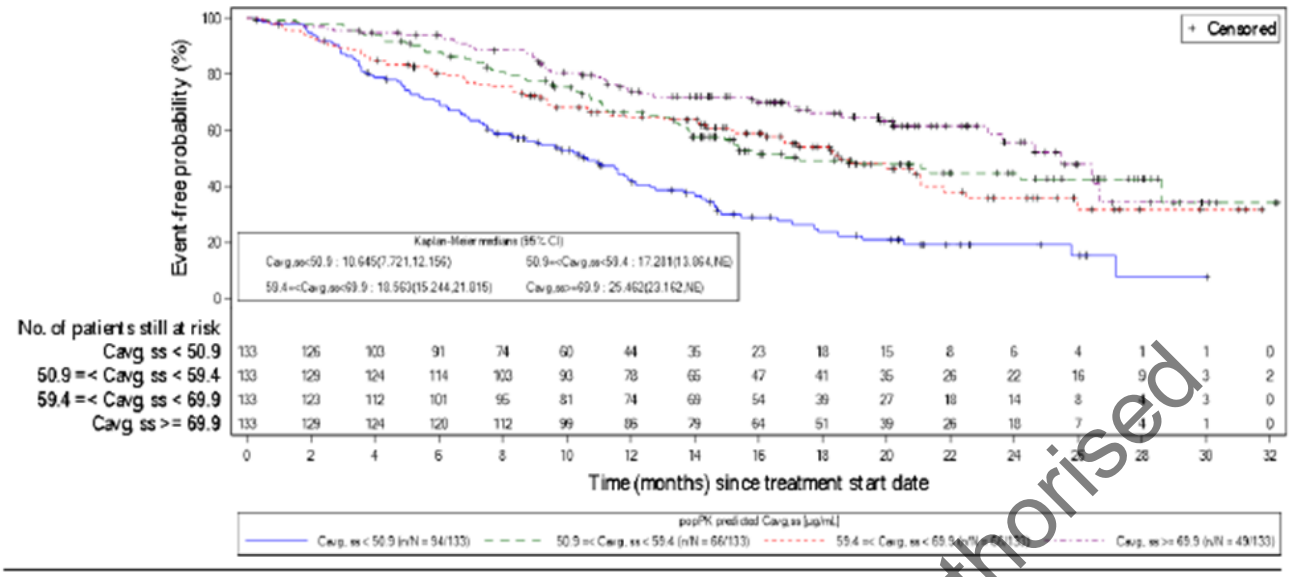


Figure 27: Kaplan-Meier curves of OS stratified by quartiles of Cavg,ss – 2L NSCLC (2LPK – Efficacy set)

Table 18: Summary of Cox model parameters for OS – 2L NSCLC (2LPK- Efficacy set)

			Hazard ratio		
				95% CI	
Parameter	**Parameter Estimate**	**Standard Error**	**Estimate**	**Lower**	**Upper**
Log of popPK predicted Cavg,ss [µg/mL]	**-2.055**	**0.241**			
30% increase in Cavg, ss			0.58	0.52	0.66
30% decrease in Cavg,ss			2.07	1.75	2.45
LDH at Baseline (kU/L)	**1.540**	**0.391**	**4.66**	**2.17**	**10.04**
0.434 vs 0.203			1.43	1.20	1.70
0.142 vs 0.203			0.91	0.87	0.95
PD-L1 Expression Group at Baseline					
<25% vs. ≥25%	0.324	0.126	1.38	1.08	1.77
Disease Stage at Baseline					
Locally Advanced vs. Metastatic	-0.463	0.178	0.63	0.44	0.89
Weight at Baseline (kg)	**-0.031**	**0.006**	**0.97**	**0.96**	**0.98**
89 vs 67			0.51	0.39	0.66
50 vs 67			1.69	1.38	2.08

For continuous covariate, odds ratios and 95% CI were generated to compare the 95th percentile vs. the median, and the 5th percentile vs. the median for this covariate.

Source: [ER Report Table 4-10]

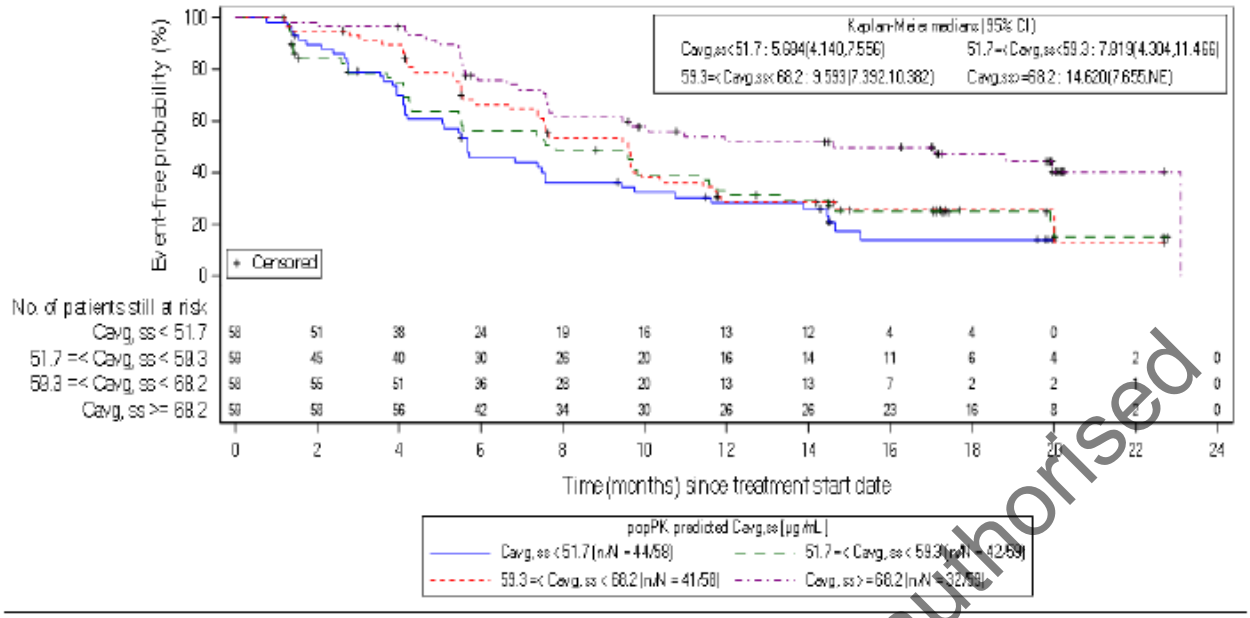


Figure 28 Kaplan-Meier curves of PSF stratified by Cavg,ss – 1L NSCLC (1LSQPK - Efficacy set)

Table 19: Summary of Cox model parameters for PFS – 1L SQ NSCLC (1LSQPK- Efficacy set)

			Hazard ratio		
				95% CI	
Parameter	**Parameter Estimate**	**Standard Error**	**Estimate**	**Lower**	**Upper**
Log of popPK predicted Cavg,ss [µg/mL]	**-2.050**	**0.399**			
30% increase in Cavg,ss			0.58	0.47	0.72
30% decrease in Cavg,ss			2.08	1.57	2.75
Weight at Baseline (kg)	**-0.026**	**0.008**	**0.97**	**0.96**	**0.99**
85 vs 62			0.55	0.38	0.80
48 vs 62			1.43	1.14	1.79

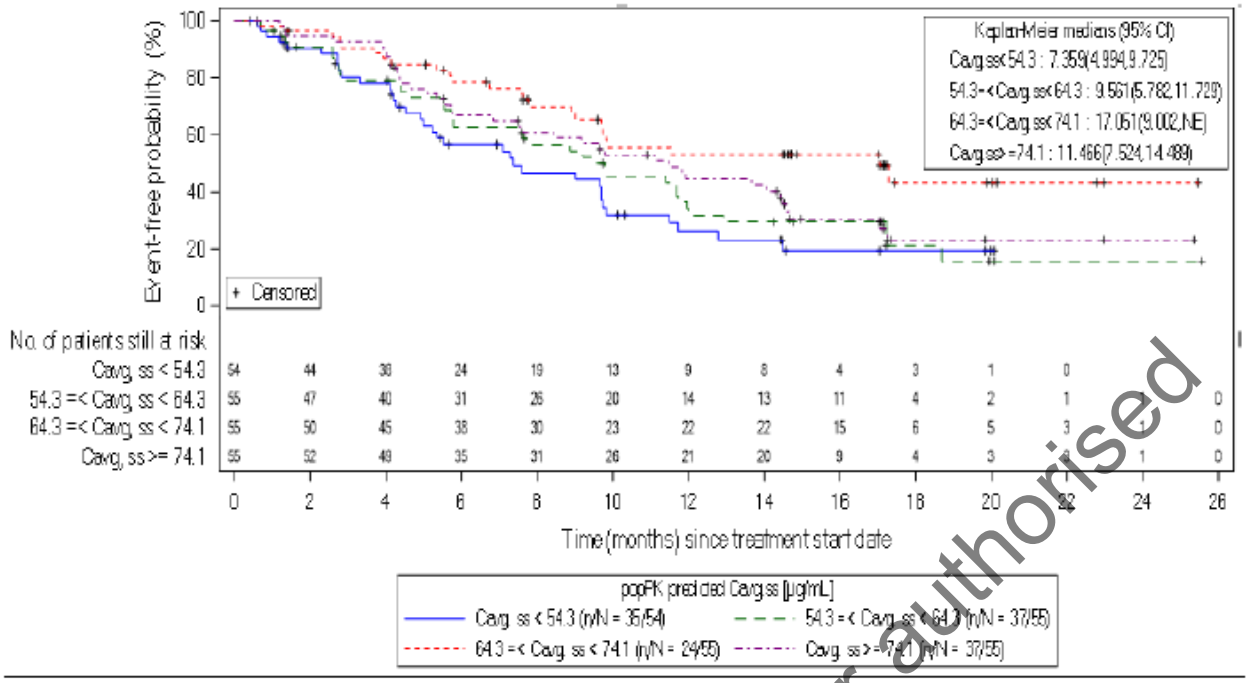


Figure 29: Kaplan-Meier curves of PFS stratified by Cavg,ss – 1L NSQ NSCLC (1LNSQPK – Efficacy set)

Table 20: Summary of Cox model parameters for PFS – 1L NSQ NSCLC (1LNSQPK- Efficacy set)

			Hazard ratio	95% CI	
Parameter	**Parameter Estimate**	**Standard Error**	**Estimate**	**Lower**	**Upper**
Log of popPK predicted Cavg,ss [µg/mL]	**-0.891**	**0.374**			
30% increase in Cavg,ss			0.79	0.65	0.96
30% decrease in Cavg,ss			1.37	1.06	1.78
PD-L1 Expression Group at Baseline					
1-49% vs. >=50%	0.640	0.249	1.90	1.16	3.09
<1% vs. >=50%	0.949	0.215	2.58	1.69	3.94

Exposure-safety analysis:

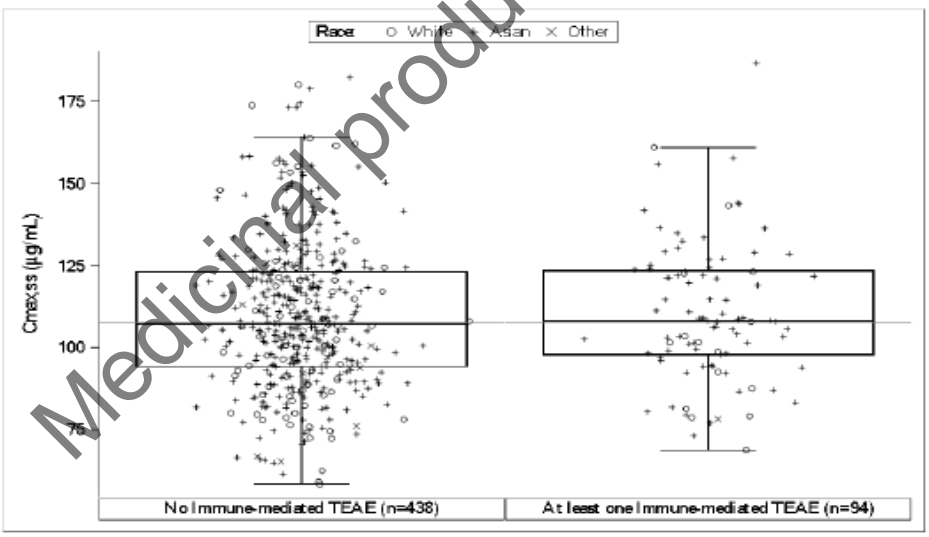
The exposure-safety relationship was explored using various endpoints, such as immune-mediated TEAEs, infusion-related reactions (IRRs), TEAEs with CTCAE Grade > 3, TEAEs leading to treatment discontinuation, and TEAEs leading to dose modification(s). The relationship between exposure and safety endpoints was first explored descriptively by providing summary statistics and boxplots of popPK predicted C_{max},ss by event status (patient experienced at least one AE, yes/no). In addition, logistic regression analysis was performed to evaluate the relationship between exposure and the probability of at least one such safety event.

While steady-state C_{max} is a common PK metric used in ER safety analysis, the conclusion would remain the same using other PK metrics, such as Cavg,ss and Cmin,ss, since all these PK metrics are highly correlated.

Results

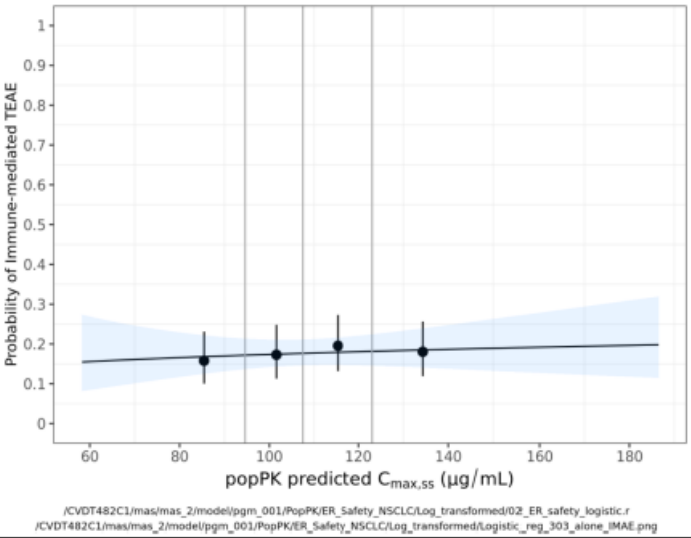
To support the indication of tislelizumab as second (or third-) line treatment for patients with locally advanced or metastatic NSCLC, the analyses were conducted separately on Study 303 and on the monotherapy pool comprising studies with various solid tumour types across a wide range of doses (0.5 – 10 mg/kg Q2W, 2-5 mg/kg Q3W including 200 mg Q3W). As shown in Figure 3-11 and Figure 3-12, the tislelizumab exposure was similar between subjects with or without any immune related TEAEs, or TEAEs with CTCAE Grade > 3, respectively, based on data from Study 303. This observation was further supported by results from logistic regression (Figures below), in which an increase in tislelizumab exposure was not associated with an increased risk of immune-mediated TEAEs or TEAEs with CTCAE Grade > 3. In fact, for all safety endpoints analysed based on data from Study 303 and the monotherapy pool, both the descriptive summary and the logistic regression suggest no clinically relevant association between exposure and increased probability of safety events. In addition, these analyses indicated that exposure metrics were comparable between Asians and Whites with or without safety events.

These same analyses and endpoints were also conducted on the combination pool to support the 1L indication in squamous and non-squamous NSCLC population. As shown in Figure 3-15 and Figure 3-16, the tislelizumab exposure was similar between subjects with or without any immune related TEAEs, or TEAEs with CTCAE grade > 3, respectively, based on data from 1L combination pool. Consistent with the observed data, logistic regression analyses also suggest that an increase in exposure does not lead to increased probability of immune-mediated TEAEs or TEAEs with CTCAE grade > 3. Moreover, for all other safety endpoints analysed based on 1L combination pool, both the descriptive statistics and the logistic regression suggest no association between tislelizumab exposure and probability of safety events.



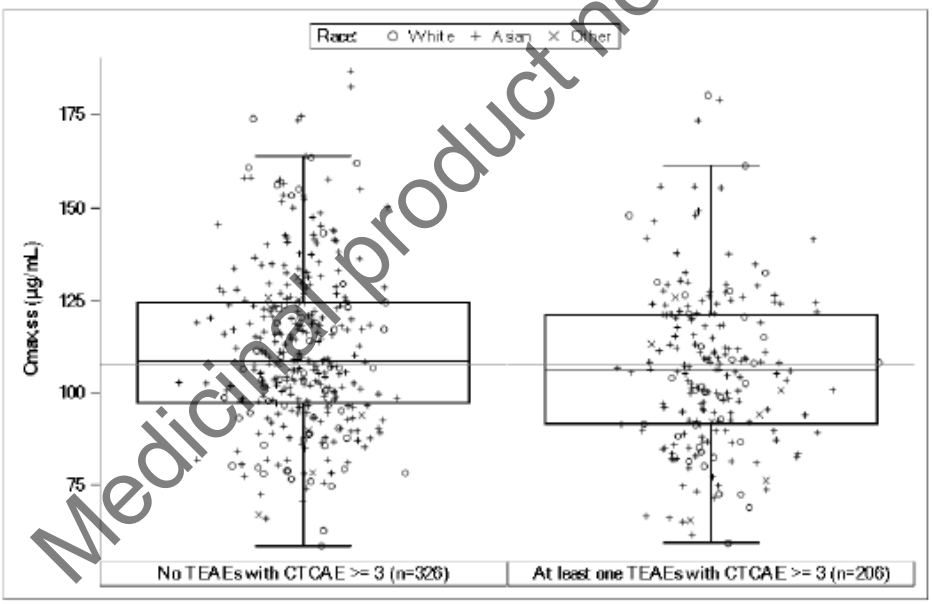
Symbols are the popPK predicted exposure matrices. The median is represented by the horizontal black line in the middle of each box. The lower and upper ends of the box plot represent the 25th and 75th percentile (the lower and upper quartiles, respectively). The bars extend to the most extreme data point which is no more than 1.5xIQR from the box. The grey horizontal line represents the median value of overall set.

Figure 30: Boxplot of popPK predicted C_{max},ss by- immune mediated TEAE status , Study 303 only 2LPK-Safety set)



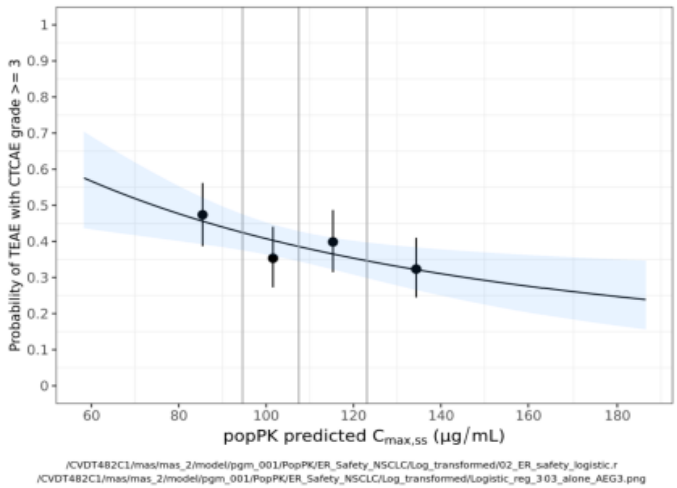
Model is log(p/(1-p)) = intercept + log popPK predicted Cmax,ss, where p is the probability of immune-mediated TEAE.
The blue shade area represents the 95% CI of the logistic regression model estimation, and the black line in the middle of the shaded area represents the median prediction
The dots are the observed proportions at the median popPK predicted Cavg,ss within each quartile, and the range represents the 95% CIs for these are based on the Clopper-Pearson method.
The three vertical grey line represents the 25th, 50th and 75th percentile of the popPK predicted Cavg,ss.

Figure 31: Probability of immune-mediated TEAE vs. exposure, Study 303 only (2LPK – safety set)



Symbols are the popPK 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 1.5xIQR from the box. The grey horizontal line represents the median value of overall set.

Figure 32: Boxplot of popPK predicted C_{max},ss by TEAEs with CTCAE grade greater than or equal to 3 status , Study 303 only (2LPK – safety set)



Model is log(p/(1-p)) = intercept + log popPK predicted Cmax,ss, where p is the probability of TEAEs with CTCAE grade ≥ 3.

The blue shade area represents the 95% CI of the logistic regression model estimation, and the black line in the middle of the shaded area represents the median prediction

The dots are the observed proportions at the median popPK predicted Cavg,ss within each quartile, and the range represents the 95% CIs for these are based on the Clopper-Pearson method.

The three vertical grey line represents the 25th, 50th and 75th percentile of the popPK predicted Cavg,ss.

Figure 33: Probability of TEAEs with CTCAE grade greater than or equal to 3 vs. exposure, Study 303 only (2LPK – safety set)

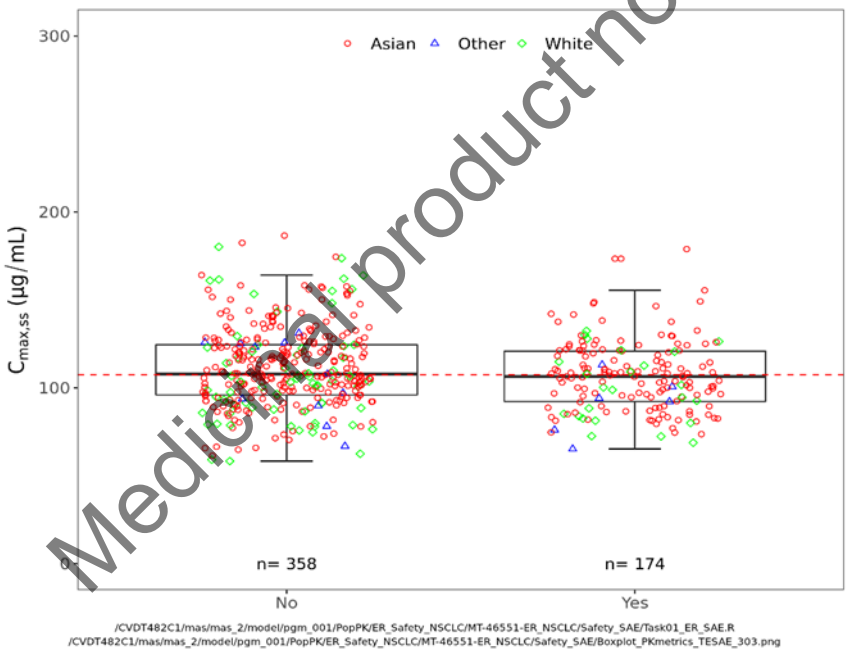


Figure 34: Boxplot of PopPK predicted C_{max},ss vs. occurrence of TESAES, Study 303

Symbols are the PopPK 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 1.5xIQR from the box. The grey horizontal line represents the median value of overall set.

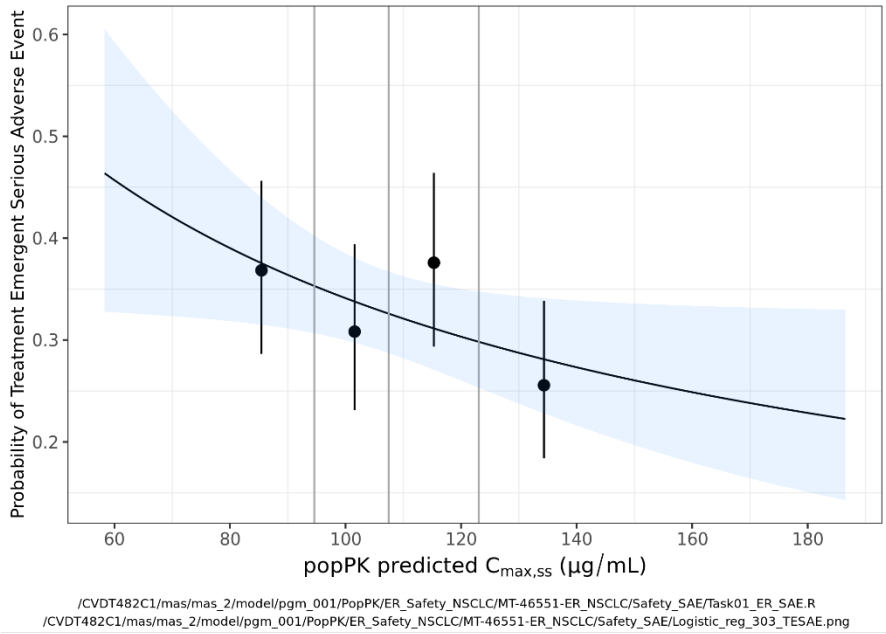
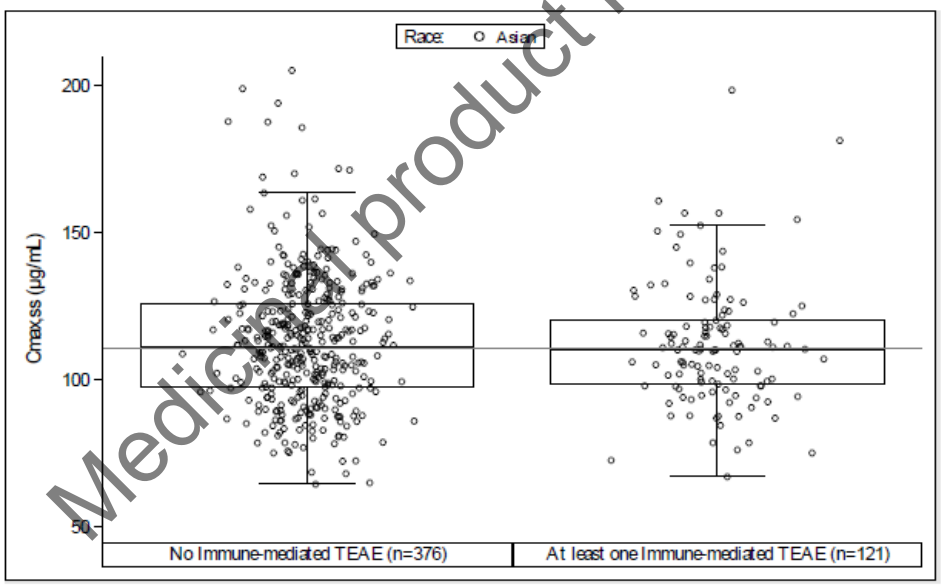


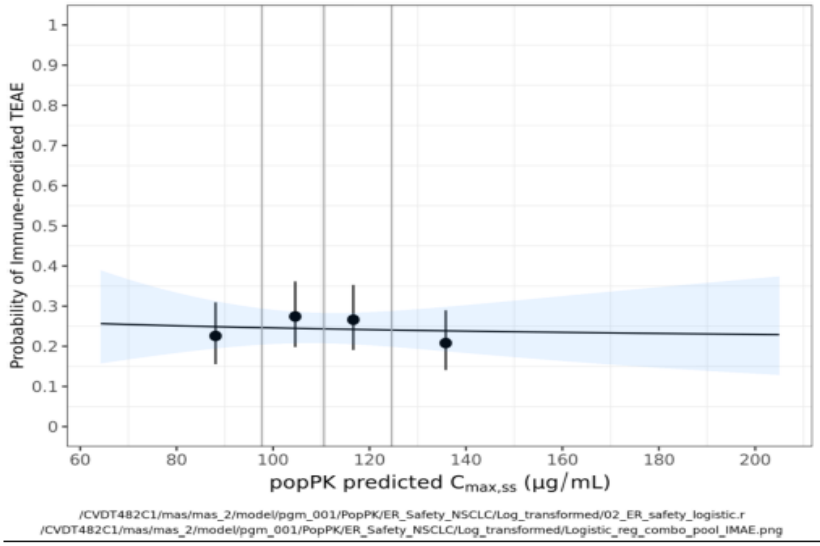
Figure 35: Probability of TESAEs vs. PopPK predicted C_{max},ss, Study 303

Model is log(p/(1-p)) = intercept + log PopPK predicted C_{max},ss, where p is the probability of TESAEs. The blue shade area represents the 95% CI of the logistic regression model estimation, and the black line in the middle of the shaded area represents the median prediction. The dots are the observed proportions at the median PopPK predicted C_{max},ss within each quartile, and the range represents the 95% CIs for these are based on the Clopper-Pearson method. The three vertical grey line represents the 25th, 50th and 75th percentile of the PopPK predicted C_{max},ss.



Symbols are the popPK 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 1.5xIQR from the box. The grey horizontal line represents the median value of overall set.

Figure 36: Boxplot of popPK predicted C_{max},ss by immune-mediated TEAE status (1LPK – Safety set)

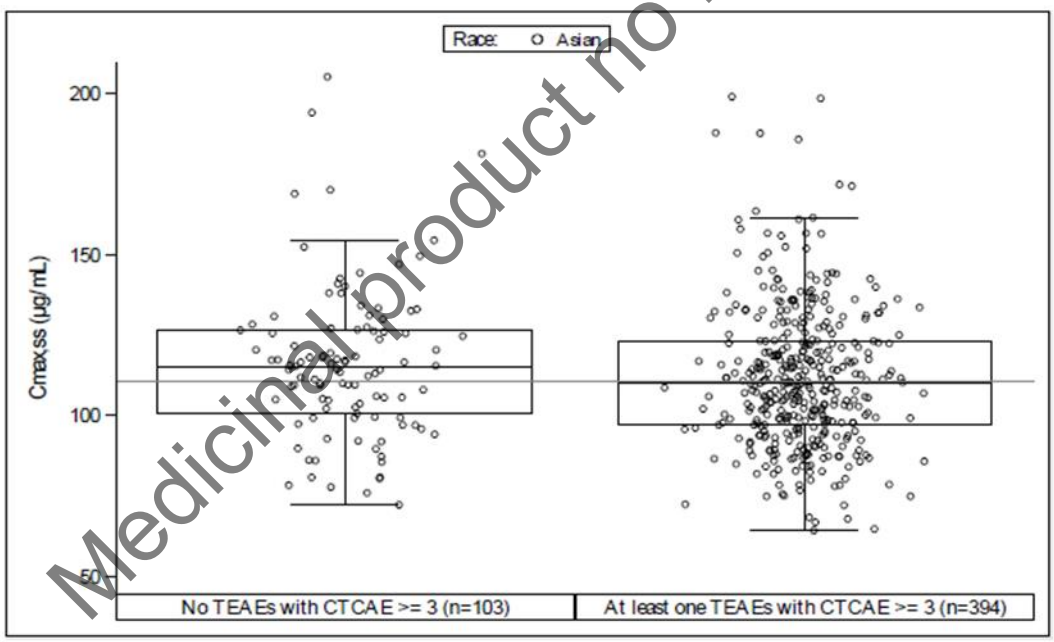


Model is log(p/(1-p)) = intercept + log popPK predicted Cmax,ss, where p is the probability of TEAEs leading to dose modification.

The blue shade area represents the 95% CI of the logistic regression model estimation, and the black line in the middle of the shaded area represents the median prediction

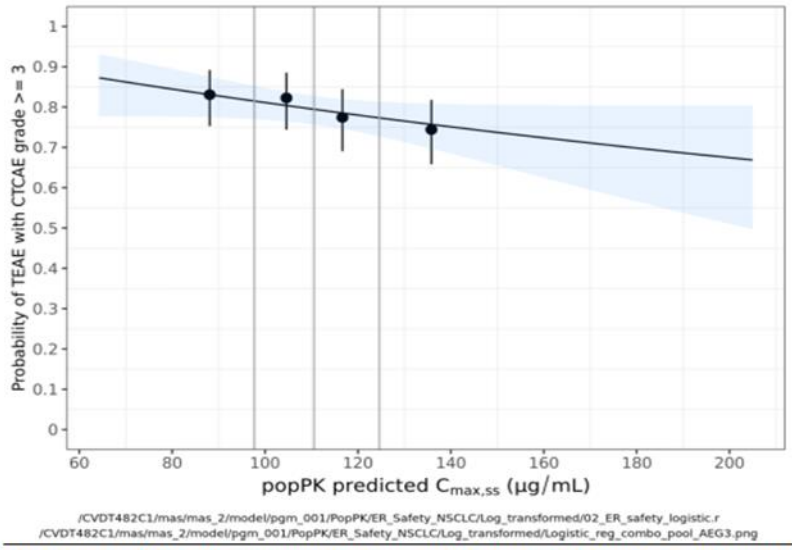
The dots are the observed proportions at the median popPK predicted Cavg,ss within each quartile, and the range represents the 95% CIs for these are based on the Clopper-Pearson method. The three vertical grey line represents the 25th, 50th and 75th percentile of the popPK predicted Cavg,ss.

Figure 37: Probability of immune-mediated TEAE vs exposure, combination therapy pool (1LPK – Safety set)



Symbols are the popPK 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 1.5xIQR from the box. The grey horizontal line represents the median value of overall set.

Figure 38: Boxplot of PopPK predicted C_{max}, ss by TEAEs with CTCAE grade greater than or equal to 3 status (1LPK safety set)



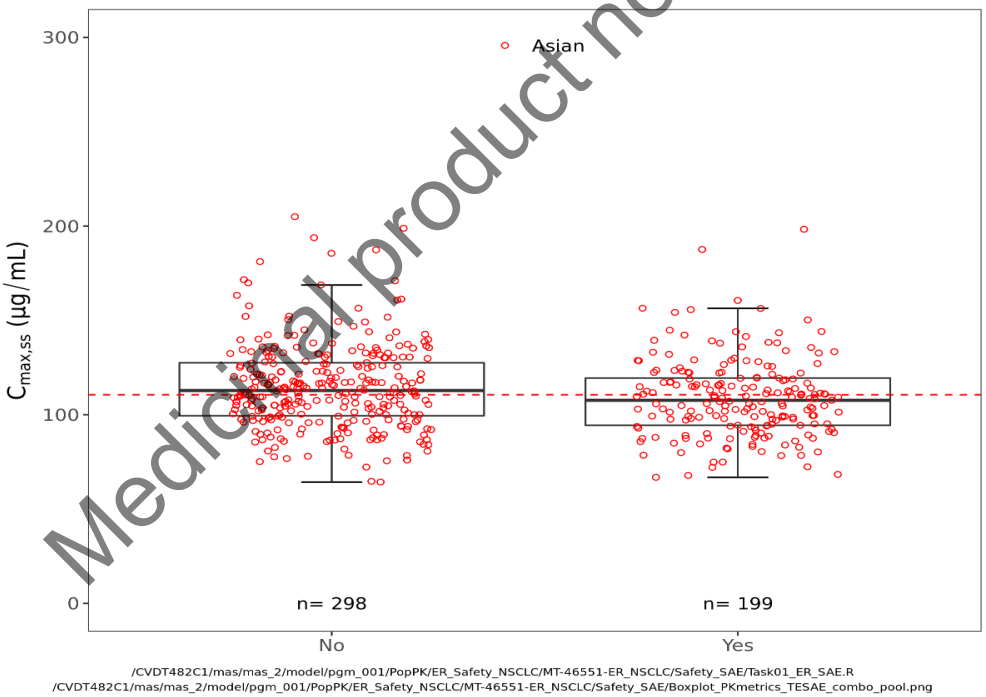
Model is log(p/(1-p)) = intercept + log popPK predicted Cmax,ss, where p is the probability of TEAEs leading to dose modification.

The blue shade area represents the 95% CI of the logistic regression model estimation, and the black line in the middle of the shaded area represents the median prediction

The dots are the observed proportions at the median popPK predicted Cavg,ss within each quartile, and the range represents the 95% CIs for these are based on the Clopper-Pearson method.

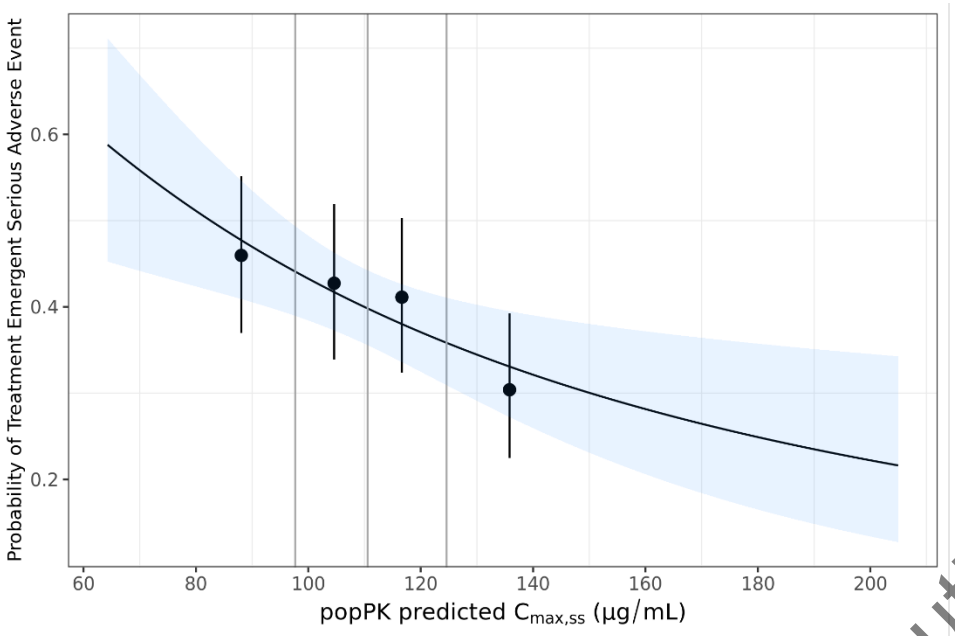
The three vertical grey line represents the 25th, 50th and 75th percentile of the popPK predicted Cavg,ss.

Figure 39. Probability of TEAEs with CTCAE grade greater than or equal to 3 vs exposure, combination therapy pool (1LPK safety set)



Symbols are the PopPK 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 1.5xIQR from the box. The grey horizontal line represents the median value of overall set.

Figure 40: Boxplot of PopPK predicted C_{max},ss vs. occurrence of TESAEs, combination therapy pool



/CVDT482C1/mas/mas_2/model/pgm_001/PopPK/ER_Safety_NSCLC/MT-46551-ER_NSCLC/Safety_SAE/Task01_ER_SAE.R
/CVDT482C1/mas/mas_2/model/pgm_001/PopPK/ER_Safety_NSCLC/MT-46551-ER_NSCLC/Safety_SAE/Logistic_reg_combo_pool_TESAE.png

Model is log(p/(1-p)) = intercept + log PopPK predicted C_{max},ss, where p is the probability of TESAEs. The blue shade area represents the 95% CI of the logistic regression model estimation, and the black line in the middle of the shaded area represents the median prediction. The dots are the observed proportions at the median PopPK predicted C_{max},ss within each quartile, and the range represents the 95% CIs for these are based on the Clopper-Pearson method. The three vertical grey line represents the 25th, 50th and 75th percentile of the PopPK predicted C_{max},ss.

Figure 41: Probability of TESAEs vs. PopPK predicted C_{max},ss, combination therapy pool

2.5.3. Discussion on clinical pharmacology

Pharmacokinetics

The clinical pharmacology package of tislelizumab comprised 12 clinical studies contributing to the characterisation of tislelizumab pharmacokinetics (2596 patients). Doses ranging from 0.5 to 10 mg/kg Q2W, 2 and 5 mg/kg Q3W, and 200 mg Q3W, all administered as intravenous infusions over 30 to 60 minutes, were investigated.

The proposed dosing regimen for tislelizumab is 200 mg administered IV once every 3 weeks.

Analytical methods

For the quantitation of tislelizumab concentrations, a quantitative indirect ELISA method was developed and validated. A formal cross-validation has been performed to verify that PK data obtained at different laboratories (method VAL136 and method 8354-363) are reliable and comparable.

For determination of anti-drug antibodies (ADA) to tislelizumab, an electro-chemiluminescent (ECL) immunoassay method using the Meso Scale Discovery (technology) was developed and validated (8354-373). A standard 3-tiered approach was applied, comprising a screening assay followed by confirmation of ADA status and determination of ADA titre. Assay sensitivity was determined to be 21.7 ng/mL relative to surrogate ADA and drug tolerance was 200 µg/mL in the presence of 100 ng/mL of surrogate ADA. Two different antibodies (mAb and pAb) were used as positive controls during the ADA assay validation in order to provide a complete characterisation of assay parameters. The mAb PC ("reference antibody 1") was used for the whole method validation (to prepare positive control samples used in the whole method validation process and validation samples, except for the drug tolerance

samples), while the pAb PC ("reference antibody 2") was used only in the drug tolerance evaluations (to prepare drug tolerance samples). This is considered to be acceptable.

A competitive ECL ligand-binding assay utilizing MSD technology to detect neutralizing antibodies (NAbs) to tislelizumab was also developed and validated (8369-215). The NAb assay sensitivity was 173 ng/mL. Drug tolerance was 100 µg/mL and 10 µg/mL in the presence of 1000 ng/mL and 500 ng/mL of surrogate NAb in the serum which is considered too low for adequate detection of NAbs in a relevant number of study samples with tislelizumab concentrations >10µg/mL. Thus, confirmed ADAs against tislelizumab might be not correctly classified as neutralizing. No Hook effect and no interference with PD-1 concentrations up to 4000 pg/mL was observed. Selectivity of the assay was not demonstrated in disease state matrix. However, to test the selectivity, additional experiments were performed in pre-dose samples from clinical studies 302 and 303. Therefore, 10 samples for each patient population were analysed in the NAb assay unspiked as well as spiked with LPC and HPC concentration of the positive control. The results of the additional experiments currently provided were in accordance with the acceptance criteria of the EU guidance and are considered acceptable. Data and information from the additional experiments to further confirm the selectivity of the NAb assay, were included in the amended bioanalytical data reports for studies BGB-A317-302 and BGB-A317-303.

Population PK model

The final population PK model was a 3-compartment model with first order elimination. The dataset consisted of 14,473 observed serum concentrations from 2,596 subjects enrolled in 12 clinical studies of tislelizumab. In the PopPK model dataset, there are 52 BLQ samples, approximately 0.36% of the total 14525 samples, which were excluded from the analysis. Due to the small percentage of BLQ data, exclusion of these data is not considered to affect the overall conclusions of the PopPK analysis and is thus considered to be acceptable. In addition, 11 PK samples, which were outside the proven stability timeframe, were included in the population PK dataset. However, these 11 PK samples are not considered to have a significant impact on the population PK modelling and parameter estimation because the number of samples (11) is very small compared to the entire dataset and only accounted for 0.076% of the total number of population PK data points. In addition, these data points do not have extreme values nor are they outside the range of samples that were within the proven stability timeframe.

In the final PopPK model, WT, age, sex, ALB, TUMSZ, TUMTP, and ADA were identified as statistically significant covariates on the PK of tislelizumab, while covariate sensitivity analysis showed that body weight was the most influential covariate on tislelizumab exposure. This is in line with what has been described for other monoclonal antibodies in the past. Goodness-of-fit (GOF) and prediction-corrected visual predictive check (VPC) plots showed good agreement between the observed and the simulated exposure supporting the structural model. However, more details on the included population regarding to BW were required to ensure that the data are representative of the EU population. Although, with the proposed 200 mg Q3W dosing regimen, the observed exposure and the simulated overall exposure (AUC) at steady state were lower in patients with BW ≥89 kg than in patients with BW < 89 kg, this difference is not considered clinically meaningful, based on the new data provided.

Referring to the presented pcVPC plots by treatment regimen, model-fit for the Q2W treatment regimen is slightly worse, as a tendency towards slight underprediction of observed values is shown. Still, the final popPK model is considered to provide acceptable estimations of tislelizumab exposure for the relevant dose of this application.

No exposure differences (simulated) were observed based on tumour subtype.

Incidence of ADAs and NAbs were low and seem to have a lowering effect on exposure. Even the mean exposure was lower than the mean for ADA negatives, all ADA/Nab positive data were within the range

of data points of ADA negatives, thus the effect is not considered clinically relevant. The submitted Pop PK model can adequately describe the PK of tislelizumab in patients with NSLC and other cancer types/subtypes included in the analysis.

ADME

Tislelizumab is presently intended to be solely administered via the IV route, which implies that the drug will be 100% bioavailable. C_{max} ranged between 89.5 µg/mL and 126 µg/mL. Central volume of distribution and clearance of tislelizumab estimated by population PK analysis was 3.05 L and be 0.153 L/day, respectively. These values correspond to typical values described for V and CL of monoclonal antibodies in the past.

No time-varying CL has been observed for tislelizumab, which was concluded from the investigation of an empirical model of time-varying clearance that did not improve model fit of the initial base model. This is considered somewhat unexpected, given that other checkpoint inhibitors currently approved which target PD-1/PD-L1 have all been described to exhibit time-varying CL (decrease in CL when tumour burden declines and disease state improves, presumably due to TMDD). In line with this, tumour size was determined to be a significant covariate affecting tislelizumab CL (lower tumour size resulted in decreased CL and higher AUC, large tumour size resulted in increased CL and decreased AUC). Although most published popPK models for other checkpoint inhibitors exhibited time varying CL, based on the currently updated information provided, it appears that the time-varying clearance of tislelizumab has no strong meaningful impact on the PK characteristics of tislelizumab. Both assessed popPK models with or without time-varying clearance appear to be largely comparable in the PK metrics (e.g. geometric mean of AUC, C_{max} and Cmin after dose 1 or at steady state (ss)). Therefore, the current approach and conclusion of a 3-compartment model without time-varying CL appears to be valid and appropriate based on the currently provided data.

The estimate for the terminal half-life of tislelizumab derived from population PK analysis (which is also stated in the SmPC) differs from the result obtained for t1/2 in noncompartmental analyses (i.e. study 001 and study 102). However, it was clarified that the terminal half-life (t1/2) of tislelizumab from the PopPK model was derived from the PK concentration time profiles for the original 2596 patients (from 12 studies), that were simulated following 200 mg Q3W IV for 17 doses. The steady state t1/2 was then estimated by non-compartmental analyses (NCA) based on the simulated concentration time profile from day 336 to day 347. However, the observed post-treatment PK concentration samples for NCA were limited (n = 5 for study 001 and n=10 for study 102 at the flat dose level of 200 mg Q3W) and the variability in study 001 for the apparent terminal half-life at a flat dose 200 mg Q3W was quite high (127%). In addition, the applicant clarified that the Q2W and Q3W dosing intervals in study 001 and Q3W intervals in Study 102 limited the sampling time windows for PK profiles after the first dose, therefore were not sufficient to robustly characterise the t1/2 of tislelizumab using NCA. The approach of using the estimated terminal half-life of tislelizumab derived from the population PK analysis based on sparse samples from a large patient population pooled from all studies with evaluable PK data, is considered acceptable.

Dose proportionality and time dependency

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.

No dose adjustment is needed for patients with mild or moderate renal impairment. Data from patients with severe renal impairment are too limited to make dosing recommendations for this population.

No dose adjustment is needed for patients with mild or moderate hepatic impairment. Data from patients with severe hepatic impairment are too limited to make dosing recommendations for this population.

Variability

Inter-individual variability with regard to PK parameters of tislelizumab was moderate, e.g. the popPK-derived estimate of inter-individual variability for tislelizumab CL was 26.3%. Higher inter-individual variability (74.7%, and 99.9%) was observed for V2 and V3.

The variability values were obtained by taking the largest differences between the 5th and 95th percentile exposures in the overall population compared to the typical individual, which are ~ 55.8%, 47.3%, and 70.8% for AUC,ss, C_{max},ss, and Cmin,ss, respectively.

Exposure in patient population

In study 001, PK of tislelizumab at dose levels ranging from 0.5 mg/kg – 10 mg/kg Q2W or Q3W was assessed by noncompartmental analysis. PK was determined after the first dose and in Cycle 4 (for Q2W regimen) or Cycle 5 (for Q3W regimen), corresponding to steady state. However, PK at steady state (Cycle 4 or Cycle 5) was derived from a rather limited number of patients (at 200 mg flat dose Q3W, 5 patients have contributed to PK results), therefore, reliability of those data is considered questionable. Geometric means of AUC0-21d, Cycle 1, and AUC0-inf, Cycle 1, were 644 and 1075 µg•day/mL, respectively. At steady state (Cycle 4 or Cycle 5), geometric mean AUC0-tau was 825 µg•day/mL.

In the Phase 1 part of study 101, further noncompartmental PK analyses were performed for tislelizumab dosed at 200 mg Q3W. The number of patients after the first dose (Cycle 1) and after multiple dosing at Cycle 5 was 20 patients and 12 patients, respectively. Overall, PK results were similar to those obtained in study 001. The geometric means of AUC0-tau in Cycle 1 and Cycle 5 were 582 and 1073 µg•day/mL, respectively.

After doses of tislelizumab at 200 mg once every 3 weeks, the geometric mean of AUCss was estimated by population PK analysis to be 1283 µg•day/mL. The estimate is similar to results for AUCtau at Cycle 4 or Cycle 5 derived by noncompartmental PK analyses in studies 001 and 102.

No meaningful discrepancies resulted from re-analysis of the population PK model as described in popPK report amendment 1.

Special populations

In the population PK model, baseline body weight, albumin level, tumour size of solid tumours, ADA status (treatment-emergent ADA), and tumour type were identified as significant covariates on CL. Baseline body weight, sex, and age were identified as significant covariates on Vc. However, simulated mean exposure differences observed in patients with impaired renal or hepatic function, different gender, different race (Asian vs. White), different body weight, and in the elderly were rather small compared to the overall variability of tislelizumab exposure and thus currently not deemed clinically relevant. Conclusively, no dose adjustment of tislelizumab is currently deemed necessary for any special populations.

The number of patients with severe renal impairment (n=5) was too low to make any valid conclusions, whether the increase in tislelizumab exposure in patients with severe renal impairment (50.5% higher as compared to subjects with normal renal function) resulted in any clinically relevant impact on efficacy or safety parameters. However, as for other mAbs, there is no mechanistic rationale for an increase in exposure with reduced renal function. Results are likely to be confounded by other baseline characteristics, such as lower body weight. Based on currently available information it is not

suggested that the observed increase in tislelizumab exposure in patients with severe renal impairment (50.5% higher as compared to subjects with normal renal function) resulted in any clinically relevant impact on efficacy or safety parameter, however no dosing recommendations can be made for these patients (see sections 4.2 and 5.2 of the SmPC).

Tislelizumab has no study conducted in paediatric subjects.

In the population PK analyses of tislelizumab, no clinically relevant differences in the clearance of tislelizumab were found between patients with mild hepatic impairment (bilirubin ≤ ULN and AST >ULN or bilirubin >1.0 to 1.5 x ULN and any AST, n = 396) or moderate hepatic impairment (bilirubin >1.5 to 3 x ULN and any AST; n = 12), compared to patients with normal hepatic function (bilirubin ≤ ULN and AST = ULN, n = 2 182) No dose adjustment is needed for patients with mild or moderate renal impairment (see sections 4.2 and 5.2 of the SmPC). Based on the limited number of patients with severe hepatic impairment (bilirubin >3 x ULN and any AST, n = 2), the effect of severe hepatic impairment on the pharmacokinetics of tislelizumab is unknown and no dosing recommendations for this population can be made.

The weight is similar in the different hepatic function groups and therefore not a potential confounder of the influence of hepatic impairment on tislelizumab PK. The use of AST, ALT, or total bilirubin as markers of metabolic liver function is questioned but will not be further pursued since tislelizumab is a monoclonal antibody for which the elimination is not expected to depend on the hepatic function.

Interactions

The impact of combination therapy on the covariate-adjusted tislelizumab PK parameters (CL and Vc) were evaluated in post hoc analysis based on the final popPK model. Again, accounting for the overall variability of exposures, differences were not considered clinically significant, which is agreed.

Pharmacodynamics

No specific pharmacodynamic parameters were investigated in the clinical development program for tislelizumab.

Immunogenicity

Immunogenicity was analysed in 10 clinical studies of tislelizumab administered either as monotherapy (Studies 001, 102, 203, 204, 208, 302, and 303) or in combination with chemotherapy (Studies 206, 304, and 307) in patients with different tumour types. Anti-drug antibodies were determined by screening and confirmatory assays, followed by the analysis of ADA titre.

Of 1 916 antidrug antibodies (ADA)-evaluable patients treated at the recommended dose of 200 mg once every 3 weeks, 18.3% of patients tested positive for treatment-emergent ADA, and neutralising antibodies (NAbs) were detected in 0.9% of patients. Population pharmacokinetic analysis showed that ADA status was a statistically significant covariate on clearance; however, the presence of treatment-emergent ADA against tislelizumab appears to have no clinically relevant impact on pharmacokinetics or efficacy.

Among ADA-evaluable patients, the following rates of adverse events (AEs) have been observed for the ADA-positive population compared to the ADA-negative population, respectively: grade ≥3 AEs 50.9% vs. 39.3%, serious adverse events (SAEs) 37.1% vs. 29.7%, AEs leading to treatment discontinuation 10.8% vs. 10.2%: (for monotherapy); grade ≥ 3 AEs 85.6% vs. 78.2%, SAEs 45.9% vs. 38.2%, AEs leading to treatment withdrawal 13.5% vs. 13.3% (for combination therapy). Patients who developed treatment-emergent ADAs tended to have overall poorer health and disease characteristics at baseline which can confound the interpretation of the safety analysis. Available data do not allow firm conclusions to be drawn on possible patterns of adverse drug reactions.

Exposure-response analyses

Exposure-efficacy analyses

In the first-line SQ NSCLC population, a positive correlation between tislelizumab exposure (Cavg,ss) and the evaluated efficacy endpoints (BOR, PFS, and OS) was observed. In addition to exposure, baseline weight was another significant covariate identified in the analyses of PFS and OS.

In the first-line NSQ NSCLC population, a positive correlation between tislelizumab exposure (Cavg,ss) and the evaluated efficacy endpoints (BOR, PFS, and OS) was observed. In addition to exposure, PD-L1 status was identified as significant covariate in the analyses of BOR and PFS.

In the overall NSCLC population (studies 001, 102, 303 including data on 5 mg/kg Q3W and 200 mg Q3W dosing groups), a positive correlation between tislelizumab exposure (Cavg,ss) and the evaluated efficacy endpoints (BOR, PFS, and OS) was observed (for results see section 3.3.2.1.1.). Several baseline characteristics were identified as significant covariates. The positive ER efficacy relationship was less pronounced when using Cavg,dose1 as compared to that with Cavg,ss.

The main limitation of these analyses is that only one dose level was tested in studies 303, 304 and 307. The phenomenon of E-R confounding has been broadly observed for monoclonal antibody cancer therapies (including immune checkpoint inhibitors) and is believed to relate to cancer cachexia and/or inflammation causing more rapid protein turnover and thus mAb catabolism in patients with poor prognosis. Hence, in the present analyses, the observed tislelizumab E-R relationship seen with 200 mg Q3W dose for BOR, OS, and PFS was likely a result of increased tislelizumab clearance in patients with poorer prognosis rather than a true exposure effect on the drug efficacy. Moreover, the flat exposure response relationship observed based on the earlier phase data of 200 mg and 5 mg/kg Q3W suggested that 200 mg Q3W might already reach the plateau, achieving maximum efficacy.

Exposure-safety analyses

The exposure-safety relationship for tislelizumab in NSCLC was explored using various endpoints, such as immune-mediated TEAEs, IRR, TEAEs with CTCAE grade > 3, TEAEs leading to treatment discontinuation and TEAEs leading to dose modification(s) and treatment-emergent SAEs. The exposure metric was based on steady-state C_{max} predicted by the population PK model. Analyses were conducted separately on Study 303 and on the monotherapy pool comprising studies with various solid tumour types. In all safety endpoints analysed (except for IRR on the monotherapy pool), logistic regression models suggest no statistically significant relationship between the probability of safety events and exposure within the range of dose levels investigated. For the analysis of IRR based on the data from the monotherapy pool, while the relationship between the probability of an event and exposure was statistically significant, the increase in the probability of having an IRR was from 3.27% at the median of the 1st exposure quartile to 5.5 % at the median of the 4th exposure quartile. Hence, this minor increase in the safety risk was not considered clinically relevant, which is agreed. In addition, the analysis based on the monotherapy pool data indicated that exposure metrics were comparable between Asians and Whites with or without safety events. Overall, based on these analyses, there was no evidence of higher tislelizumab exposure leading to increased safety risks in the population analysed.

2.5.4. Conclusions on clinical pharmacology

Overall, pharmacokinetics and pharmacodynamics, i.e. immunogenicity and exposure-response relationships, of tislelizumab have been adequately characterised.

2.5.5. Clinical efficacy

2.5.5.1. Dose response studies

The recommended dose of tislelizumab is 200 mg administered as an intravenous (IV) infusion once every 3 weeks (Q3W) until disease progression or unacceptable toxicity.

Study 001

Phase IA of Study 001 was designed to establish the recommended Phase II dose in patients with advanced tumours. Phase IA was also designed to determine the maximum tolerated dose (MTD) for tislelizumab, although no MTD was established in the study.

Four dose levels were investigated during dose escalation in Phase 1A Part 1: 0.5, 2.0, 5.0, and 10 mg/kg Q2W. After clearance of the dose-limiting toxicity (DLT) period, two dosing schedules 2 mg/kg and 5 mg/kg, Q2W and Q3W were further evaluated during schedule expansion in Phase 1A Part 2. Phase 1A Part 3 comprised the fixed dose exploration with the 200 mg Q3W dose.

Study results:

- Rates of treatment-related adverse events (AEs) and serious adverse events observed in patients receiving 2 mg/kg and 5 mg/kg either administered as Q2W or Q3W were comparable.
- Confirmed overall response rates (ORRs) in patients treated with tislelizumab 2 mg/kg and 5 mg/kg Q2W were 10% (2 of 20) and 15% (3 of 20), respectively, and ORRs were 38% (8 of 21) and 15% (3 of 20) for patients treated at 2 mg/kg and 5 mg/kg Q3W, respectively.
- Dose proportional increases in C_{max} and AUC were observed across a range of 0.5 mg/kg to 10 mg/kg. No correlation was found between clearance and body weight. The steady-state geometric mean elimination half-life was calculated to be about 23.8 days based on popPK analysis, and steady state trough concentrations were similar across the Phase 1B indication arms suggesting a lack of a disease effect on PK. .
- Pharmacokinetic data from patients who were administered 200 mg Q3W showed that tislelizumab concentrations after the first 200 mg dose were within the range of concentrations observed from the 2 mg/kg and 5 mg/kg doses .

Exposure-response analysis in patients with solid tumours

The purpose of this analysis was to analyse the exposure-response (E-R) relationships for tislelizumab efficacy and safety endpoints using data collected in the studies BGB-A317-001, BGB-A317-102, BGB-A317-203 and BGB-A317-204.

The distribution of different dose regimens used in each study is displayed in Table 21.

Table 21: Summary of dose regimens

Dose Regimen	BGB-A317-001[a] (N=450)	BGB-A317-102[b] (N=300)	BGB-A317-203 (N=70)	BGB-A317-204[c] (N=112)	Overall (N=932)
0.5 mg/kg Q2W	3 (0.7%)	-	-	-	3 (0.3%)
10 mg/kg Q2W	7 (1.6%)	-	-	-	7 (0.8%)
2 mg/kg Q2W	26 (5.8%)	-	-	-	26 (2.8%)
2 mg/kg Q3W	21 (4.7%)	-	-	-	21 (2.3%)
200 mg Q3W	13 (2.9%)	300 (100%)	70 (100%)	112 (100%)	495 (53.1%)
5 mg/kg Q2W	26 (5.8%)	-	-	-	26 (2.8%)
5 mg/kg Q3W	354 (78.7%)	-	-	-	354 (38.0%)

a. 1 subject from BGB-A317-001 ADSL without PK exposure was excluded.
b. 99 subjects from BGB-A317-102 ADSL with SAFFL="N" and no PK exposure were excluded.
c. 1 subject from BGB-A317-204 ADSL without PK exposure was excluded.

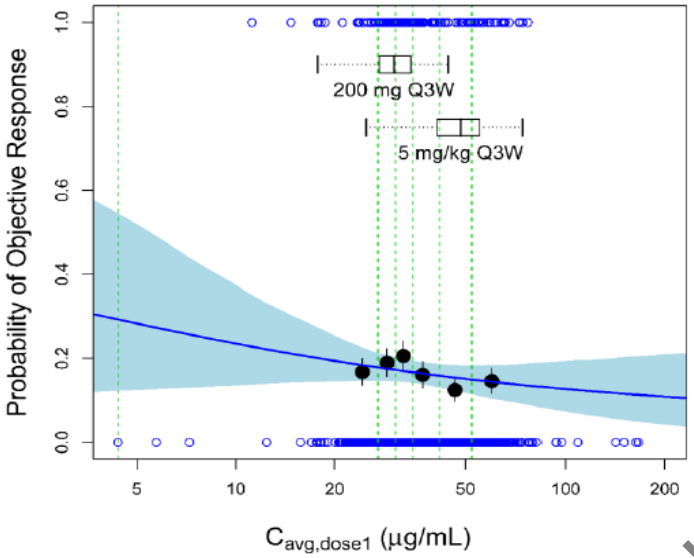
The E-R logistic regression models for ORR in patients with solid tumours against tislelizumab Cavg,dose1 were developed using combined data in all solid tumour types in studies BGB-A317-001, BGB-A317-102 and BGB-A317-204.

Table 22: The model building process for ORR

Run	Model Description	Compare to run	p-value
1	Run1 only intercept	-	-
2	Run1 + $\log(C_{avg,dose1})$	1	0.2292

Table 23: Summary of logistic model parameters for ORR in patients with solid tumours

Parameters	Estimates (SE)	p-value
Intercept	-0.495 (0.934)	0.5957
Slope of $\log(C_{avg,dose1})$	-0.313 (0.26)	0.2296



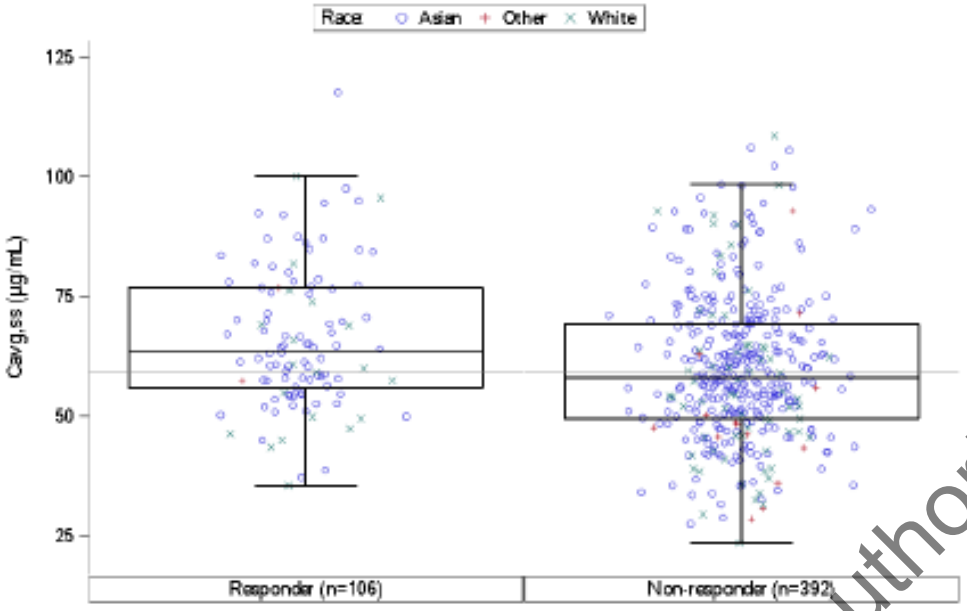
The open blue circles reflect the observed events. The filled black symbols are the observed probability of events and the error bars are SE [sqrt (P*(1-P)/N)] for quantiles (at 100x(1/6)th percentiles) of exposures (plotted at the median value within each quantile), where P is probability of event and N is the number of patients in each quantile bin. The blue line and light blue shaded area are the median and 95% prediction interval based on the 1000 bootstrap samples of the model. The horizon boxplots represent the observed exposure range of 200 mg Q3W and 5 mg/kg Q3W.

Figure 42: Logistic regression of probability of ORR versus tislelizumab exposure in patients with solid tumours

Table 24: PopPK predicted Cavg,ss by confirmed responders status – 2L NSCLC (2LPK-Efficacy set)

			Responder = No	
Parameter	Statistics	Responder = Yes	All non-responders	BOR=SD
popPK predicted Cavg,ss (µg/mL)	N	106	392	171
	Mean (SD)	66.2 (15.0)	59.9 (15.4)	60.5 (15.6)
	CV%	22.6	25.8	25.7
	Geo-mean	64.6	57.9	58.5
	Geo-CV%	22.7	26.6	26.8
	Median	63.6	58.1	59.0
	Q1-Q3	56.0-76.8	49.5-69.2	50.1-69.9
	Min-Max	35.5-118	23.5-109	27.5-106

n = number of patients
Responder = patient with a BOR of PR or CR



Symbols are the popPK predicted exposure matrices.

The median is represented by the horizontal black line in the middle of each box.

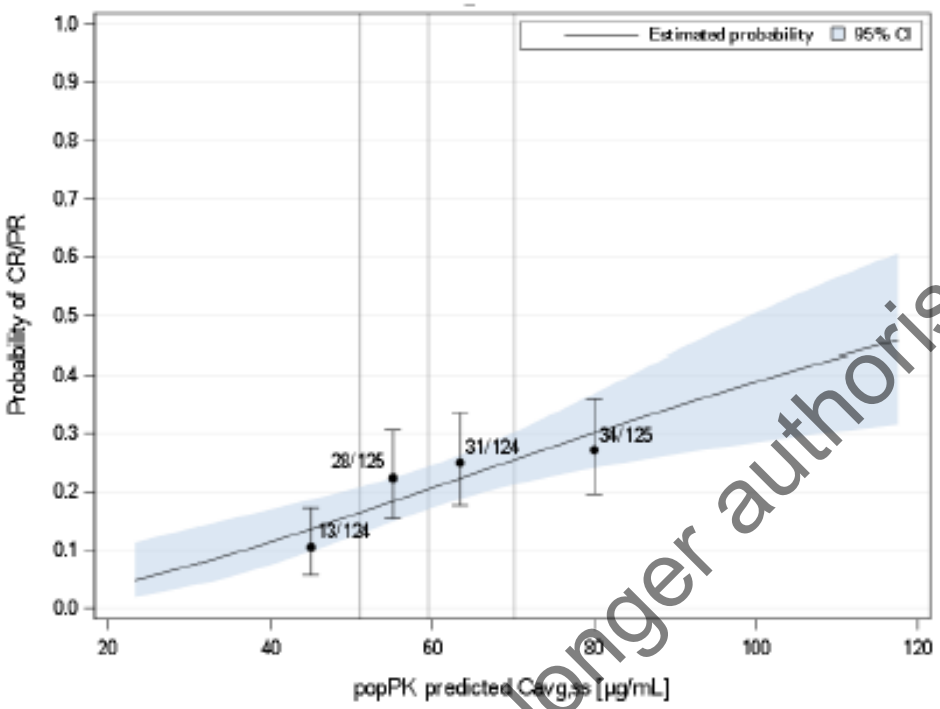
The lower and upper ends of the boxplot represent the 25th and 75th percentile (the lower and upper quartiles, respectively).

The bars extend to the most extreme data point which is no more than 1.5xIQR from the box.

The grey horizontal line represents the median value of the overall set.

Figure 43: Boxplot for popPK predicted Cavg,ss by confirmed responder status – 2L NSCLC (2LPK-Efficacy set)

Logistic regression was further used to evaluate the relationship between exposure and confirmed BOR.



Model is log(p/(1-p)) = intercept + log popPK predicted Cavg,ss, where p is the probability of BOR being CR/PR.

The blue shade area represents the 95% CI of the logistic regression model estimation, and the black line in the middle of the shaded area represents the median prediction

The dots are the observed proportions at the median popPK predicted Cavg,ss within each quartile, and the range represents the 95% CIs for these are based on the Clopper-Pearson method.

The three vertical grey line represents the 25th, 50th and 75th percentile of the popPK predicted Cavg,ss.

Figure 44: Logistic regression of probability of confirmed BOR being CR/PR vs. popPK predicted Cavg,ss – 2L NSCLC (2LPK-Efficacy set)

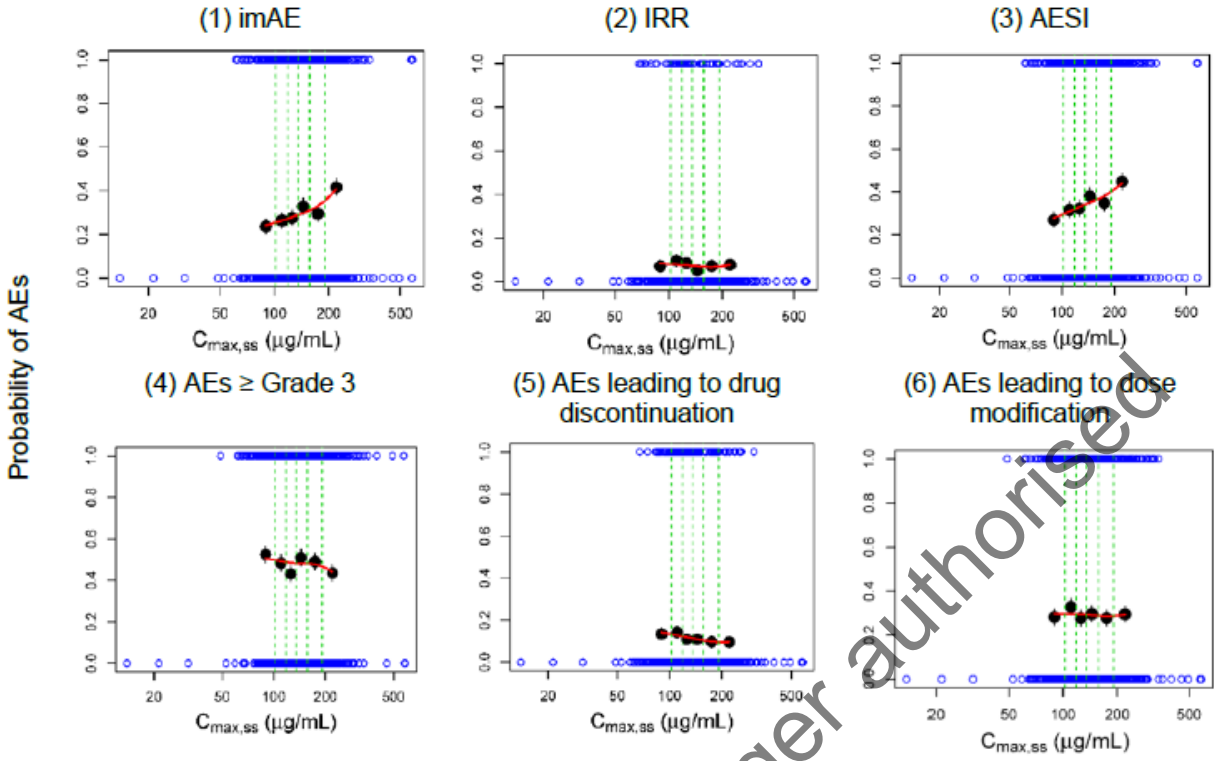
Table 25: Probability estimates of confirmed BOR being CR/PR vs. popPK predicted Cavg,ss – 2L NSCLC (2LPK-Efficacy set)

Cavg,ss category (µg/mL)	Median Cavg,ss (µg/mL)	Observed CR/PR (%) (95% CI)	Model-based probability (%) of CR/PR (95% CI)
<51.0	44.9	13/124 (10.5) (5.7, 17.3)	13.6 (9.8, 18.7)
≥51.0-<59.4	55.1	28/125 (22.4) (15.4, 30.7)	18.4 (14.9, 22.4)
≥59.4-<70.2	63.4	31/124 (25.0) (17.7, 33.6)	22.3 (18.8, 26.3)
≥70.2	80.0	34/125 (27.2) (19.6, 35.9)	30.1 (24.1, 36.9)

The slope (coefficient of log (Cavg,ss)) of the relationship between the probability of confirmed BOR being CR/PR and the log of popPK predicted Cavg,ss was positive.

Based on covariate selection analysis, "PD-L1 expression" and "sex" were identified as significant covariates and were therefore incorporated into the final model.

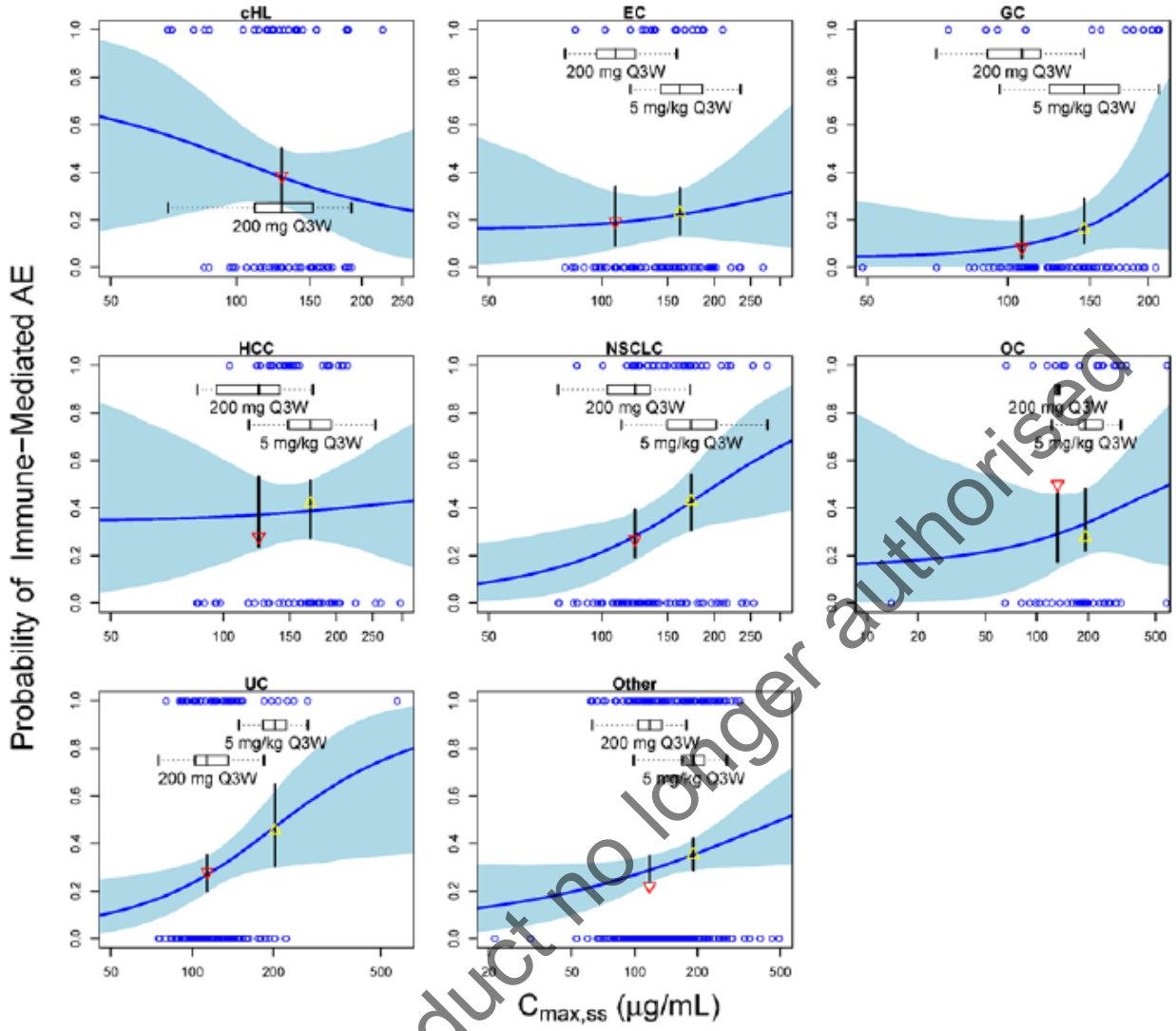
In addition, the relationship between exposure and AEs was evaluated by building logistic regression models and plotting data by tumour type for imAEs (Figure 45) and AESIs (Figure 46).



Abbreviations: AE, adverse event; AESI, adverse event of special interest; imAE, immune-mediated adverse event; IRR: infusion-related reaction; PI, prediction interval; PK, pharmacokinetics; vs, versus.

Notes: The data were collected from Studies 001, 102, 203, and 204. The 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(1/6)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 subjects in each quartile bin. The red lines are smooth curves to show the relationship between two variables.

Figure 45: Probability of selected AEs vs tislelizumab exposure in subjects with advanced tumours



Abbreviations: AE, adverse event; cHL classical Hodgkin lymphoma; EC, esophageal carcinoma; GC gastric cancer; HCC, hepatocellular cancer; imAE, NSCLC, non-small cell lung cancer; OC, ovarian cancer; UC, urothelial cancer; vs, versus.

Notes: The data were collected from Studies 001, 102, 203, and 204. The blue line and light blue shaded area are the median and 95% prediction interval based on the 1000 bootstrap samples of the model. The black solid lines are the 95% confidence interval of predicted probability at median of exposure in corresponding dose regimen based on the inverse of link function's 95% confidence interval. The horizon boxplots represent the observed exposure range of 200 mg Q3W and 5 mg/kg Q3W. The red and yellow symbols are the observed rate of AE for 200 mg Q3W and 5 mg/kg Q3W, respectively.

Figure 46: Probability of immune-mediated AEs vs tislelizumab exposure in subjects by tumour type

The safety and efficacy of the 200 mg Q3W tislelizumab dose was further verified in Study 102 in patients with multiple malignancies, and has been used in all the subsequent tislelizumab clinical studies. Thus, no additional dose selection studies or analyses were performed for the present application.

Exposure-response analyses for the overall NSCLC population

The applicant provided E-R analyses of efficacy for the overall NSCLC population by developing a model that includes studies 001, 102 and 303.

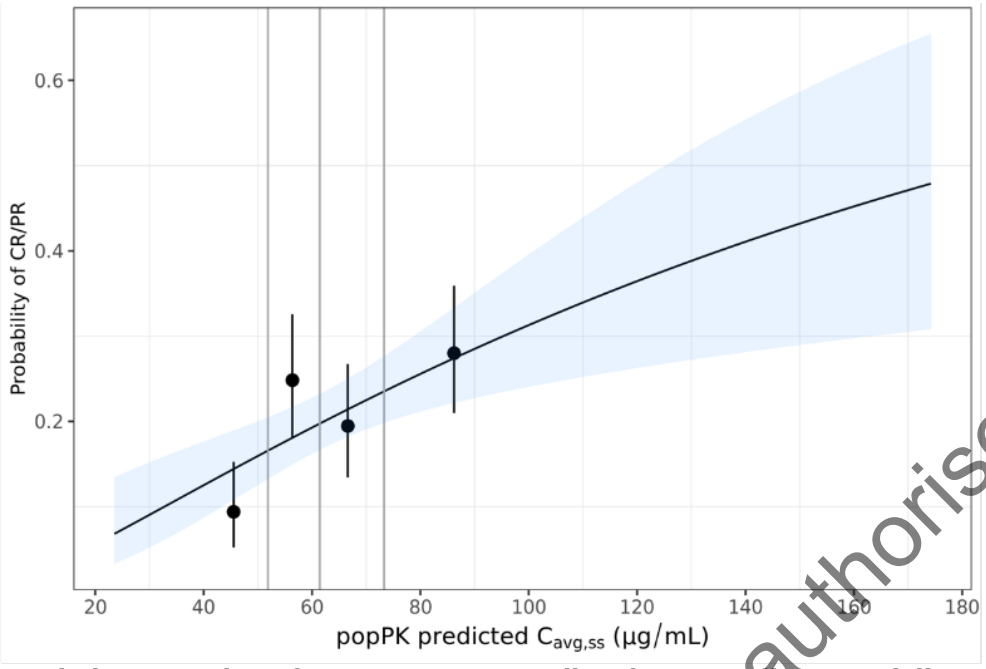


Figure 47: Logistic regression of BOR on PopPK predicted Cavg,ss (base model) – 2L NSCLC patients from studies 001, 102 and 303

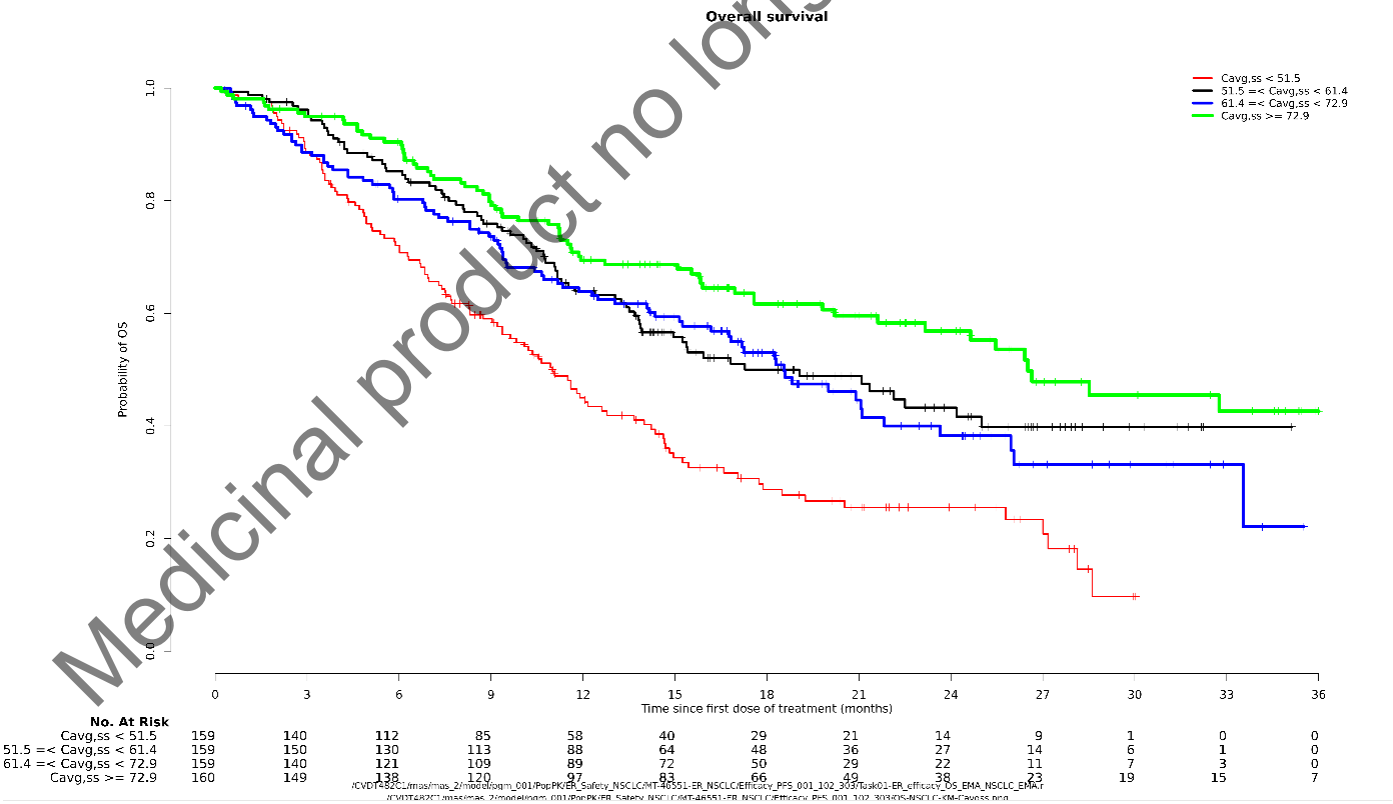


Figure 48. Kaplan-Meier OS curves stratified by Cavg,ss quartiles, 2L NSCLC patients from studies 001, 102 and 303

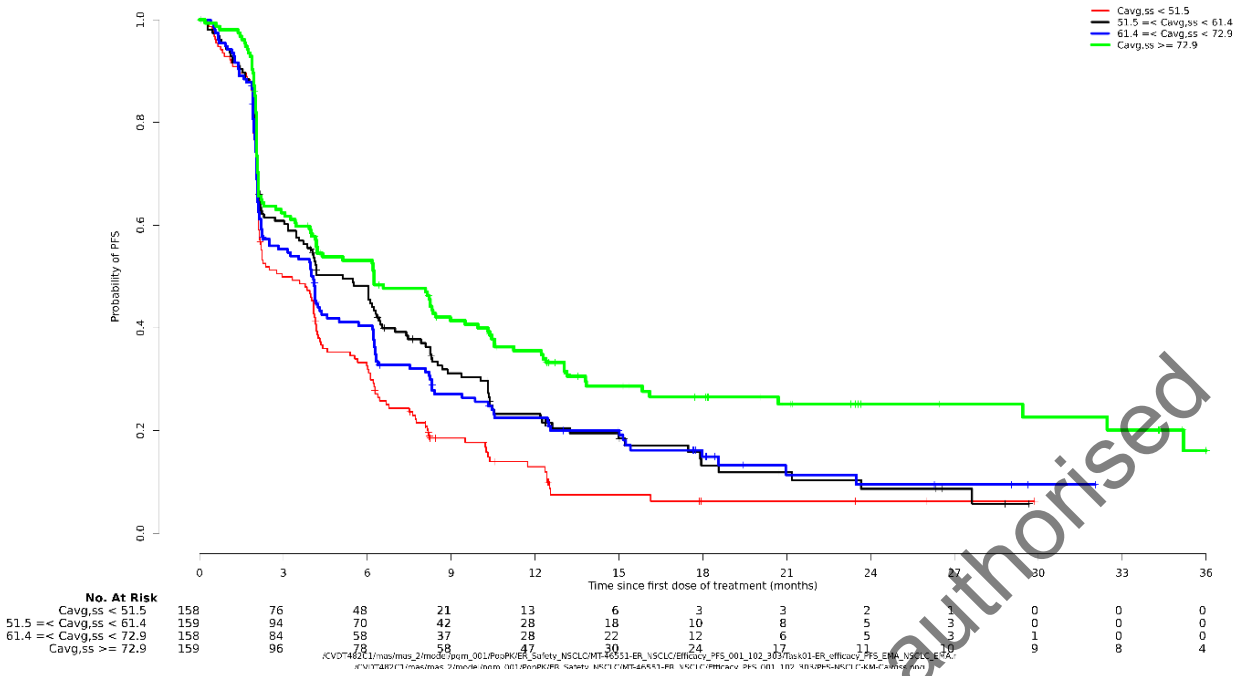


Figure 49: Kaplan-Meier PFS curves stratified by Cavg,ss, 2L NSCLC patients from studies 001, 102 and 303

With these analyses a positive relationship between exposure and efficacy response was determined. To adjust for baseline characteristics and the potential confounding effect of CL, stepwise covariate search based on AIC was conducted on baseline characteristics and the base model. As a result, in addition to CL and Cavg,dose1, several other baseline covariates were retained in the final model. While the association between Cavg,dose1 and efficacy outcomes was statistically significant in the base model, after adjusting for CL and other baseline covariates, the association between Cavg,dose1 and efficacy outcome was no longer statistically significant in the final model.

For reasons of simplifying dosing and administration, the 200 mg once every 3 weeks dose was chosen as recommended dose because this dose resulted in tislelizumab concentrations largely overlapping with concentrations observed with the 2 mg/kg and 5 mg/kg dose levels.

Ultimately, the toxicokinetic profile of tislelizumab was characterised in preceding preclinical studies in monkeys. Tislelizumab exposure in monkey serum at the NOAEL of 30 mg/kg Q2W was approximately 5- to 8-fold higher than those in patients receiving the studied human dose of 200 mg Q3W.

Main studies

Summary of the main studies supporting the 3 indications within this application, described in the sections below:

Clinical efficacy of tislelizumab monotherapy as 2L+ treatment of NSCLC	
Main study	Study 303
Supportive study(ies)	Study 001 (dose response), Study 102
Clinical efficacy of tislelizumab in combination with chemotherapy as 1L treatment of squamous NSCLC	
Main study	Study 307
Supportive study(ies)	Study 206 (squamous NSCLC cohort)
Clinical efficacy of tislelizumab in combination with chemotherapy as 1L treatment of nonsquamous NSCLC	
Main study	Study 304
Supportive study(ies)	Study 206 (nonsquamous NSCLC cohort)

2.5.5.2. Clinical efficacy of tislelizumab monotherapy as 2L+ treatment of NSCLC

Main study

<u>Study 303 (BGB-A317-303):</u> A Phase 3, Open-Label, Multicenter, Randomized Study to Investigate the Efficacy and Safety of Tislelizumab Compared With Docetaxel in Patients With Non-Small Cell Lung Cancer Who Have Progressed on a Prior Platinum-Containing Regimen

Study 303 is an ongoing Phase III, randomised, open-label, parallel-group multicentre study designed to evaluate the efficacy and safety of tislelizumab in adult patients with histologically confirmed, locally advanced or metastatic (squamous or non-squamous) NSCLC who had progressed during or after a prior platinum-containing regimen. The proportion of PD-L1-negative patients (defined as < 25% of tumour cells (TC) with PD-L1 membrane staining via the Ventana SP263 assay) was capped at ≤ 60% of patients in the study.

Patients were randomised in a 2:1 ratio to receive either tislelizumab or docetaxel treatment. Randomisation was stratified by histology (squamous vs. non-squamous), line of therapy (second- vs. third-line), and PD-L1 expression (< 25% TC vs. ≥ 25% TC).

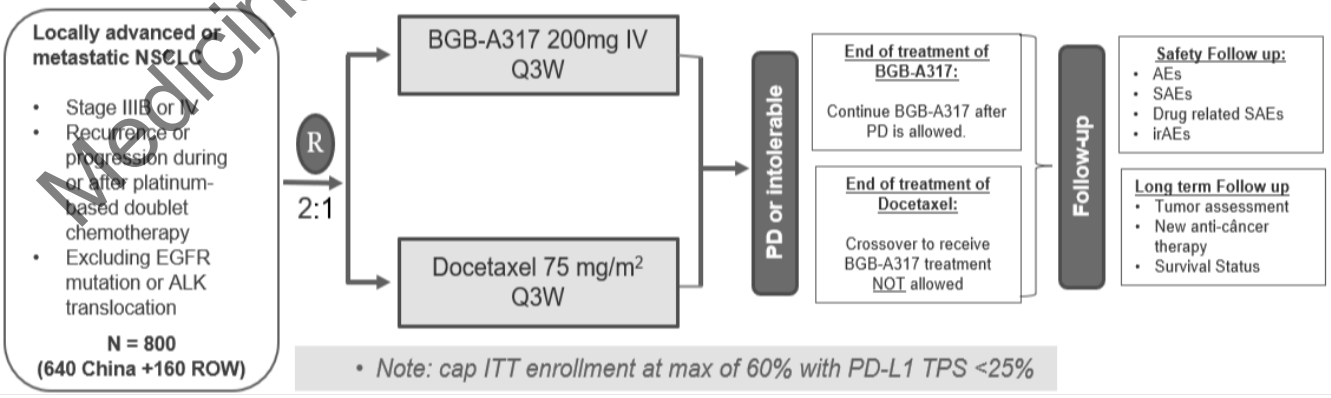


Figure 50: Study design (Study 303)

Methods

- **Study Participants**

Key inclusion criteria included:

1. Histologically confirmed disease which was currently locally advanced or metastatic NSCLC of either squamous or non-squamous histology.
2. With disease progression during or following treatment with at least one platinum-containing regimen.

    • Patients who received prior neoadjuvant or adjuvant chemotherapy but progressed within 6 months after the last dose were eligible provided the target lesion(s) had not been previously treated with local therapy (radiation) or the target lesion(s) within the field of local therapy had subsequently progressed as defined per RECIST v1.1.

    • Note: No more than 2 prior lines of systemic chemotherapy for advanced or metastatic disease

        – Chemotherapy regimens were counted on the basis of interval disease progression and not the number of agents or switches in agents (e.g., a first-line therapy that consisted of several cycles of a platinum doublet and subsequent maintenance therapy that introduced or was switched to a new chemotherapy agent without interval disease progression was all considered one chemotherapy regimen).

        – Adjuvant/neoadjuvant chemotherapy or chemoradiation counted as a prior chemotherapy regimen if ≤ 6 months had elapsed between the last dose and the date of recurrence. Combined treatment with chemotherapy and radiation constitutes a single regimen; surgery was not considered a regimen.

    • Anti-EGFR treatment with disease progression as the treatment outcome was counted as a line of therapy.

    • Anticancer agents used for pleurodesis were not counted as a line of therapy.
3. Patients were able to provide archival/fresh tumour tissues (FFPE blocks or approximately 11 [at least 5] freshly cut unstained FFPE slides) for biomarker analysis to assess PD-L1 expression and provided sufficient tissue, including TMB and GEP.
4. ECOG PS ≤ 1.

Key exclusion criteria included:

1. Received prior docetaxel treatment for metastatic disease or prior immune checkpoint inhibitor therapies targeting PD-1, PD-L1, or CTLA-4.
2. Diagnosed with NSCLC that harbours EGFR sensitizing or driver mutation or ALK gene translocation.

    • Patients with a known ALK fusion oncogene were excluded. Patients (non-squamous or squamous histology) with unknown ALK fusion oncogene status were not required to be tested at screening given that testing for ALK fusion was not considered standard in the squamous type patient population and a low frequency in non-squamous type.
3. Patients with toxicities (as a result of prior anticancer therapy including radiation) which had not recovered to baseline or stabilised, except for AEs not constituting a likely safety risk (including but not limited to alopecia, rash, pigmentation, specific laboratory abnormalities, etc). Received

chemotherapy, immunotherapy (e.g., interleukin, interferon, thymosin), or investigational agent used to control cancer ≤ 28 days (or ≤ 5 half-lives, whichever was shorter) prior to randomisation.

4. History of interstitial lung disease, non-infectious pneumonitis or uncontrolled systemic diseases, including diabetes, hypertension, pulmonary fibrosis, acute lung diseases, etc.
5. Patients with significantly impaired pulmonary function or who require supplemental oxygen at baseline.
6. Clinically significant pericardial effusion.
7. Active leptomeningeal disease or uncontrolled, untreated brain metastasis:

   • Patients with a history of treated and, at the time of screening, asymptomatic central nervous system (CNS) metastases were eligible, provided they met all the following:

   − Brain imaging at screening showed no evidence of interim progression.

   − Had measurable disease outside the CNS, only supratentorial metastases allowed.

   − No ongoing requirement for corticosteroids as therapy for CNS disease; anticonvulsants at a stable dose were allowed.

   − No stereotactic radiation or whole-brain radiation within 14 days prior to randomisation.

   • Patients with new asymptomatic CNS metastases detected at the screening scan had to receive radiation therapy and/or surgery for CNS metastases.

   − Following treatment, these patients could then be eligible, provided all other criteria, including those for patients with a history of brain metastases, were met.
8. Malignancy other than NSCLC.

   • Any active malignancy ≤ 2 years before randomisation except for the specific cancer under investigation in this study with the exception of those with a negligible risk of metastasis or death, such as localised and adequately treated malignancies (e.g., resected basal or squamous cell skin cancer, superficial bladder cancer, carcinoma in situ of the cervix or breast).
9. Requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone or equivalent) or other immunosuppressive medications within 14 days of randomisation.

   • A brief course (≤ 7 days) of corticosteroids for prophylaxis (e.g., contrast dye allergy) or for treatment of non-autoimmune conditions (e.g., delayed-type hypersensitivity reaction caused by contact allergen) was permitted.

   • Adrenal replacement steroid dose ≤ 10 mg daily prednisone equivalent was permitted in the absence of active autoimmune disease.

   • Topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption) were permitted.
10. Active autoimmune diseases or history of autoimmune diseases that may relapse were excluded. Patients with the following autoimmune diseases were allowed: controlled type 1 diabetes, hypothyroidism managed with hormone replacement therapy only, controlled celiac disease, skin diseases not requiring systemic treatment (such as vitiligo, psoriasis, or alopecia), or diseases not expected to recur in the absence of external triggering factors.
11. Any of the following cardiovascular criteria:

a. Cardiac chest pain, defined as moderate pain that limits instrumental activities of daily living, ≤ 28 days before randomisation.

b. Symptomatic pulmonary embolism ≤ 28 days before randomisation.

c. Acute myocardial infarction ≤ 6 months prior to randomisation.

d. Heart failure of New York Heart Association Classification III or IV ≤ 6 months prior to randomisation.

12. Prior allogeneic stem cell transplantation or organ transplantation.

- **Treatments**

Tislelizumab 200 mg was administered by IV infusion on Day 1 of each 21-day cycle (once every 3 weeks). The initial infusion (Cycle 1 Day 1) was delivered over 60 minutes. If this was well tolerated, then the subsequent infusions were administered over 30 minutes, which was the shortest time period permissible for infusion. Tislelizumab was not concurrently administered with any other drug. Tislelizumab was given until disease progression assessed by the investigator per RECIST v1.1, unacceptable toxicity, or withdrawal of informed consent, whichever occurs first.

Docetaxel 75 mg/m^2 was administered as an IV infusion over 1 hour once every 3 weeks until disease progression, intolerable toxicity, or withdrawal of consent. Additional premedications were administered as per standard practice.

Tumour assessments were conducted every 9 weeks for 52 weeks after randomisation and continued every 12 weeks thereafter. Survival status was followed every 3 months after discontinuation of the study treatment.

- **Objectives**

Assess the efficacy and safety of tislelizumab as monotherapy for the treatment in 2L (or 3L) of NSCLC.

- **Outcomes/endpoints**

Primary Efficacy Endpoint

Overall Survival

OS was defined as the time from the date of randomisation to the date of death due to any cause in the ITT and PD-L1-Positive Analysis Sets.

Secondary Efficacy Endpoints

Objective Response Rate

ORR was defined as the proportion of patients who had a CR or PR as assessed by the investigator per RECIST v1.1 in the ITT and PD-L1-Positive Analysis Set. Patients without any postbaseline assessment were considered non-responders. Patients without measurable disease at baseline were also considered as non-responders. The difference in ORR between arms was evaluated using the Cochran-Mantel-Haenszel (CMH) chi-square test with the actual stratification factors as strata.

The two-sided 95% CIs for the odds ratio and the difference in ORR were calculated, as well as Clopper-Pearson 95% CIs for the ORR within each arm. In addition, the number and percentage of patients for each of the BOR categories were presented. A waterfall plot of best percent change in sum of target lesion diameters from baseline was provided by treatment arm. The patients in each arm were ordered by the percentage, and patients with the largest percentage were presented on the right.

Progression-Free Survival

PFS was defined as the time from randomisation to the first objectively documented disease progression as assessed by the investigator per RECIST v1.1 or death from any cause, whichever occurred first, in the ITT and PD-L1-Positive Analysis Sets. The actual tumour assessment visit date was used to calculate PFS. The PFS censoring rules were specified in the Statistical Analysis Plan. Similar methodology except for sensitivity analyses used to evaluate OS was applied to the analysis of PFS.

Duration of Response

Duration of response (DoR) was defined for patients with an objective response as the time from the first documented objective response to documented disease progression as assessed by the investigator using RECIST v1.1, or death from any cause, whichever occurred first, in the ITT and PD-L1-Positive Analysis Sets. Only the subset of patients who showed a CR or PR were to be included in the DoR analysis. Data for patients who were alive and who had not experienced disease progression at the time of analysis were censored at the date of the last tumour assessment. If no tumour assessments were performed after the date of the first occurrence of the objective response (CR or PR), DoR was censored at the date of the first occurrence of the objective response. Median DoR and corresponding 95% CIs were estimated using the Kaplan-Meier methodology for each treatment arm. Comparisons of DoR between treatment arms was made using the log-rank test.

Health-Related Quality of Life

Analysis method: the three patient-reported outcomes used for measuring HRQoL included QLQ-C30 (measuring core cancer) and its lung cancer module QLQ-LC13. Also, EQ-5D-5L was used for measuring general health status.

Exploratory Efficacy Endpoints

Disease Control Rate per the Investigator

DCR was defined as the proportion of patients with objective response (CR or PR), non-CR/non-PD, or stable disease maintained for ≥ 9 weeks (with allowable visit window) using RECIST v1.1. DCR per the investigator was analysed. Similar methodologies for the analysis of ORR were applied.

Clinical Benefit Rate per the Investigator

CBR was defined as the proportion of patients who had CR, PR, non-CR/non-PD, and stable disease that is ≥ 24 weeks in duration per RECIST v1.1. CBR per the investigator was analysed. Similar methodologies for the analysis of ORR were applied.

Time to Response per the Investigator

Time to response per the investigator was defined for patients with an objective response as determined by the investigator as the time from randomisation to the first occurrence of a CR or PR as assessed by the investigator using RECIST v1.1. Only the subset of patients who showed a CR or PR was included in the time to response analysis. Time to response was summarised for descriptive purposes. The mean, SD, median, and range of time to response were provided.

Time to First Subsequent Anticancer Systemic Therapy

Time to first subsequent anticancer systemic therapy was defined for patients with the use of subsequent anticancer systemic therapy as the time from end of study treatment to first dose of subsequent anticancer systemic therapy. The mean, SD, median, and range of time to first subsequent anticancer systemic therapy were provided.

Subsequent Anticancer Therapy

Subsequent anticancer therapy was summarised by percentage, category and Preferred Term (PT) in the ITT and PD-L1-Positive Analysis Sets for each treatment arm.

PD-L1 Expression as a Predictive Biomarker for Response

Distribution of PD-L1 expression was examined in the ITT Analysis Set. Association between PD-L1 expression (not restricted to the prespecified cutoff level of 25%) and tislelizumab treatment effect over docetaxel (OS, ORR, PFS, DoR, DCR, CBR) was explored.

- **Sample size**

The original sample size calculation (i.e., approximately 640 patients in China and Asia Pacific region) was based on the number of events required to demonstrate the OS superiority of Arm A to Arm B in ITT-CAP and ITT-CAP patients with PD-L1 positive tumours. The sample size has been increased to include an additional 160 patients from ROW (rest of the world), hence a total of approximately 800 patients were planned to be recruited into the trial.

Six hundred and forty patients in ITT-CAP were planned to be enrolled over a 16-month period at a constant enrolment rate and randomised in a 2:1 ratio to Arms A and B. The enrolment of 160 patients in ITT-ROW was expected to start approximately 8 months after that for the ITT-CAP and to last about 12 months. The median OS was assumed as 10 months in Arm B.

An interim analysis was planned when approximately 426 deaths in the ITT Analysis Set have been observed, which represents 76% of the planned number of events (i.e. 560 events) in the ITT Analysis Set for the final analysis. There was an approximately 87% power to detect an OS HR (Arm A/Arm B) of 0.75 with a one-sided type I error of 0.02 in the ITT.

A Hwang-Shih-DeCani spending function with γ parameter of -2 based on the information fraction in the ITT Analysis Set was used in setting up the upper (efficacy) boundary. The stopping boundaries in Table 27 (below) were planned to be updated based on the actual death events observed in the ITT Analysis Set at the interim and final analyses.

The superiority test of OS in the PD-L1 positive Analysis Set were planned to be performed only in the final analysis. Two hundred and seven deaths in the ITT patients with PD-L1 positive tumours were planned to be required to have an approximately 86% power to detect an OS HR of 0.60 with a one-sided type I error of 0.007. Assuming the prevalence of PD-L1 positivity is 40% in the ITT Analysis Set, it was planned that it would take approximately 31.0 months to accumulate the required approximately 207 events in approximately 320 patients with PD-L1 positive tumours in the ITT Analysis Set.

The PD-L1 expression status was planned to be closely monitored and enrolment of patients whose tumours are PD-L1 negative was planned to be stopped as necessary through IWRT upon reaching ~60%, that is to ensure that the percentage of PD-L1 positive patients is no less than 40% of the ITT Analysis Set. The capping of PD-L1 negative patients to ~60% was planned to be implemented in both ITT-CAP and ITT-ROW independently.

The sample size and power considerations are acceptable, assumptions were well justified at the time of planning.

An interim analysis was planned when approximately 426 deaths in the ITT Analysis Set had been observed; however, the interim analysis was conducted after 441 events.

A capping of PD-L1 negative patients was planned to ensure that the percentage of PD-L1 positive patients was no less than 40% of the ITT Analysis Set. Capping was triggered for the Rest of the World

population. After triggering this cap, 33 ROW patients were randomised, among whom 31 were PD-L1 ≥25%. 131 ROW patients had been already enrolled. A total of 16 patients were screen failures due to the cap.

In amendment 1, the sample size has been increased to enrol an additional 160 patients from ROW.

- **Randomisation and Blinding (masking)**

Patients were planned to be randomised in a 2:1 ratio to receive tislelizumab or docetaxel, using the IWRT system for this study by permuted block stratified randomisation. According to the original study protocol, the randomisation was stratified according to the following factors: histology (squamous versus non-squamous), line of therapy (2 versus 3) and PD-L1 expression level on tumour cell membrane (<25% versus ≥25%). The PD-L1 expression status was planned to be measured by immunohistochemistry (IHC) assay in a central laboratory and using the Ventana PD-L1 (SP263) antibody. To mitigate the risk of obtaining skewed PD-L1 distribution toward low expression due to competing trials enrolling only patients whose tumour PD-L1 expression is high, adjustment to enrolment was planned to be made by capping the PD-L1 negative and low population to ~60% of ITT. This was planned to be accomplished through the Interactive Web Response Technology (IWRT) system, when necessary. This study was open-label.

- **Statistical methods**

Analysis Sets

The ITT population was planned to include all randomised patients and to analyse all patients according to their randomised treatment arms. It was planned to be the primary analysis population for the efficacy analysis. The ITT Analysis Sets was planned to be summarised for both the China and Asia Pacific (ITT-CAP) Analysis Set and the rest of world (ITT-ROW) Analysis Set.

According to the original protocol, the Per Protocol (PP) population was planned to include all randomised patients who received at least one dose of the assigned study drug and had no major protocol deviations. Major protocol deviations were planned to be determined and documented before the database lock for the primary analysis.

The PD-L1 positive population (>=25% TCs) was planned to include all randomised patients whose tumours were PD-L1 positive and to analyse all patients according to their randomised treatment arms. It was planned to be the dual primary analysis population for efficacy analysis.

Safety Analysis Set was planned to include all patients who received at least one dose of study drug. It was planned to be the population for the safety analyses.

The PK Analysis Set was planned to include patients who contributed at least one quantifiable post-dose PK sample.

The ADA Analysis Set was planned to include all patients who have received at least 1 dose of tislelizumab for whom non-missing baseline ADA and at least 1 non-missing postbaseline ADA results are available.

Primary and secondary endpoints

The primary endpoint of the trial was OS - defined as the time from the date of randomisation to the date of death due to any cause in the ITT and PD-L1 positive Analysis Set.

Secondary endpoints included in the multiple testing procedure were:

- ORR – defined as the proportion of patients in the ITT and PD-L1 positive Analysis Set who had a CR or PR as assessed by the investigator per RECIST v1.1.

- DoR – defined as the time from the first occurrence of a documented objective response to the time of relapse, as determined by the investigator per RECIST v1.1, or death from any cause, whichever comes first, in the ITT and PD-L1 positive Analysis Set.
- PFS – defined as the time from the date of randomisation to the date of the first objectively documented tumour progression as assessed by the investigator per RECIST v1.1 or death from any cause, whichever occurs first, in the ITT and PD-L1 positive Analysis Set.
- HRQoL – measured using European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Lung Cancer (EORTC QLQ-LC13) and Core 30 (EORTC QLQ-C30), and European Quality of Life 5-Dimensions, 5-level (EQ-5D-5L) scale.

Analysis primary endpoints

OS was planned to be compared between tislelizumab (Arm A) and docetaxel (Arm B) in the ITT analysis set in a stratified log-rank test using a significance level of 0.02 (one-sided). The null hypothesis planned to be tested was:

H0: OS in Arm A = OS in Arm B against the alternative hypothesis:

Ha: OS in Arm A ≠ OS in Arm B

This was planned to be the primary analysis once the targeted numbers of deaths would be reached in the ITT Analysis Set. The p-value from stratified log-rank test was planned to be presented using stratification factors (histology (squamous versus non-squamous), line of therapy (2 versus 3) and PD-L1 expression level on tumour cell membrane (<25% versus ≥25%)). The median OS and the cumulative probability of OS at every 6 months were planned to be calculated for each treatment arm and presented with two-sided 95% CIs. Kaplan-Meier survival probabilities for each arm were planned to be plotted over time. The hazard ratio between tislelizumab and docetaxel (HR A/B) and its 95% CI were planned to be estimated using a Cox proportional hazard model with treatment arm as a factor and stratified by the actual value of the stratification factors.

The hypothesis testing of OS in the PD-L1 positive Analysis Set was planned to be carried out at a significance level of 0.007. If the OS hypothesis in the ITT Analysis Set could be rejected, its corresponding α would be shifted to the testing in the PD-L1 positive Analysis Set (i.e., a total α of 0.025). Similar statistical methods as described above were planned to be applied with histology and line of therapy as strata in the stratified analyses.

Supplementary Analyses for Primary Endpoint

In order to evaluate the robustness of the OS results, several sensitivity analyses were planned and further described in the Statistical Analysis Plan (SAP).

The sensitivity analysis 1 was planned to be the same as the primary analysis except that it was planned to be based on the stratification factors using the values from Interactive Response Technology, by which patients were randomised.

The sensitivity analysis 2 was planned to be the same as the primary analysis except that it was planned to use Rank Preserving Structural Failure Time Model (RPSFTM) to adjust survival estimates in the presence of arm B patients receiving any subsequent immunotherapy after discontinuation of docetaxel.

The sensitivity analysis 3 was planned to be the same as the primary analysis except that a patient was planned to be censored at the date last known to be alive before his/her COVID-19 related drug administration protocol deviation.

When there are over 10% ITT patients who had critical protocol deviations, the sensitivity analysis 4 in the PP analysis set was planned to be implemented in the same way as the primary analysis.

Analysis Secondary Endpoints

The statistical significance of the difference in ORR between arms in the ITT Analysis Set was planned to be evaluated using the Cochran-Mantel-Haenszel chi-square test with the actual stratification factors as strata. The two-sided 95% CIs for the odds ratio and the difference in ORR was planned to be calculated, as well as Clopper-Pearson 95% CIs for the ORR within each arm.

Progression-free survival was planned to be compared between the 2 arms in the ITT Analysis Set using a stratified log-rank test using actual stratification factors as strata. The median PFS and the cumulative probability of PFS at every 3 months were planned be calculated for each treatment arm and presented with two-sided 95% CIs. PFS was planned be estimated using the Kaplan-Meier method. The PFS censoring rule were planned to follow the 'FDA Guidance for Industry 2007'. The actual tumour assessment visit date was planned to be used to calculate PFS. Data for patients without disease progression or death at the time of analysis were planned to be censored at the time of the last valid tumour assessment. Data for patients who start to receive new anticancer therapy or are lost to follow-up were planned to be censored at the last valid tumour assessment date prior to the introduction of new therapy or lost to follow-up. Patients who had a clinical determination of progression were planned to undergo a CT/MRI, if possible, to correlate radiographic findings with the clinical findings. If a clinical determination of progression for a patient could be confirmed, the date of the CT/MRI scan would get considered as the progression date for that patient.

The DoR was planned to be analysed similarly as the PFS. It was planned to be summarised within responders.

Efficacy outcomes (i.e., ORR, DoR, and PFS) in the PD-L1 positive Analysis Set were planned to be summarised similarly.

European Organisation for Research and Treatment of Cancer Quality of Life Cancer Questionnaire (EORTC QLQ-LC13 and EORTC QLQ-C30) and EQ-5D-5L post baseline scores were planned to be compared between the 2 treatment arms, using a mixed model with baseline score and time since the randomisation as covariates. Significant interaction between treatment and time since randomisation or quadratic term of time since randomisation (p-value<0.05) were planned to also be included in the final model.

Table 26: Censoring rules for primary analysis of PFS per RECIST version 1.1 (Study 303)

No.	Situation	Primary Analysis
1	Incomplete or no baseline tumor assessments	Censored at randomization date
2	No postbaseline tumor assessment and no death	Censored at randomization date
3	No postbaseline tumor assessment and death	Died at date of death
4	Progression documented between scheduled visits	Progressed at date of documented progression
5	No progression	Censored at date of last adequate tumor assessment with no documented progression
6	New anticancer treatment started	Censored at date of last adequate tumor assessment before date of new anticancer treatment
7	Death between adequate assessment visits	Died at date of death
8	Death or progression after ≥2 missed visit	Censored at date of last adequate tumor assessment prior to the ≥2 missed tumor assessments

Multiplicity

The overall type I error was planned to be strongly controlled at a one-sided α of 0.025 within the two dual primary hypotheses and 4 secondary efficacy hypotheses. An α of 0.02 and 0.007 was planned to be initially assigned to the primary hypothesis testing in the ITT and PD-L1 positive Analysis Sets, respectively. The α allocation accounts for the positive correlation between the test statistics in the 2 Analysis Sets (i.e., PD-L1 positive is a subset of the ITT Analysis Set). The overall type I error was controlled at 0.025 when at least 30% of the deaths in the ITT Analysis Set were from the PD-L1 positive subset. The α of 0.007 in the PD-L1 testing was planned to be adjusted downwards if the final observed percentage was lower. At the final analysis, it was planned to test the OS hypothesis first in the ITT Analysis Set. If the hypothesis in the ITT Analysis Set could be rejected, it was planned to pass the unused α on to the OS hypothesis test in PD-L1 positive Analysis Set; followed by the second efficacy hypothesis testing in the sequential order of ORR in the PD-L1 positive Analysis Set, DoR in the PD-L1 positive Analysis Set, PFS in the PD-L1 positive Analysis Set, PFS in the ITT Analysis Set, ORR in the ITT Analysis Set, DoR in the ITT Analysis Set, lung cancer symptom scale measured by QLQ-LC13 and QLQ-C30 global health status/QoL in the ITT and PD-L1 Analysis Sets. Otherwise, if the OS hypothesis in the ITT Analysis Set could not be rejected, the hypothesis testing would be carried out sequentially only in the PD-L1 positive Analysis Set for OS, ORR, DoR, PFS, lung cancer symptom scale measured by QLQ-LC13 and QLQ-C30 global health status/QoL scale at α of 0.007. The testing was planned to be continued until the first non-significant outcome occurs, following the methodology of Glimm et al (2010).

Interim Analyses

An interim analysis for OS in the ITT Analysis Set was planned to be performed by an independent statistician external to BeiGene and when approximately 426 deaths (76% of the target number of 560 deaths) among the 2 treatment arms were observed in the ITT Analysis Set. It was estimated that it would take approximately 23.1 months to observe 426 events. The final analysis of OS was planned to take place after 560 deaths were observed in the ITT Analysis Set and 207 deaths were observed in its subgroup of patients with PD-L1 positive tumours. Thus, the predefined number of deaths in the ITT Analysis Set would trigger the interim and final analyses. The information fraction used in α spending function was planned to be based on the observed number of deaths in the ITT Analysis Set at the

corresponding time points. With Protocol Amendment 3, a Hwang-Shih-DeCani (HSD) spending function with γ parameter of -2 was planned to be used in setting up the upper (efficacy) boundary. Initially, a HSD spending function with γ = -4 was defined. In Protocol Amendment 1 this was modified to a HSD with γ = -0.7. . Stopping boundaries (p-value and Z score) of superiority test for OS at the interim and final analyses in the ITT Analysis Set, as well as OS at the final analysis in the PD-L1 positive Analysis Set are shown in Table 27. The boundaries for hypothesis testing in OS were planned to be updated according to the actual numbers of death events in the interim and final analyses, using the pre-specified α spending function.

The IDMC was advised to make the recommendation of stopping the trial early for efficacy only when the early stopping boundaries for efficacy were crossed in the ITT Analysis Set.

Table 27: Stopping boundaries (p-value and Z score) and approximate HR threshold of interim and final analyses of OS (Study 303)

	Time (months)	# Deaths	p-value (Z score) for Efficacy	Approximate HR Threshold for Efficacy
Interim analysis in ITT	23.1	426	<0.0112 (>2.28)	<0.791
Final analysis in ITT	31.0	560	<0.0153 (>2.16)	<0.824
Final analysis in PD-L1 positive	31.0	207	<0.0071 (>2.46)	<0.696

Abbreviations: HR = hazard ratio; ITT = intent-to-treat (Analysis Set); PD-L1 = programmed cell death protein ligand 1

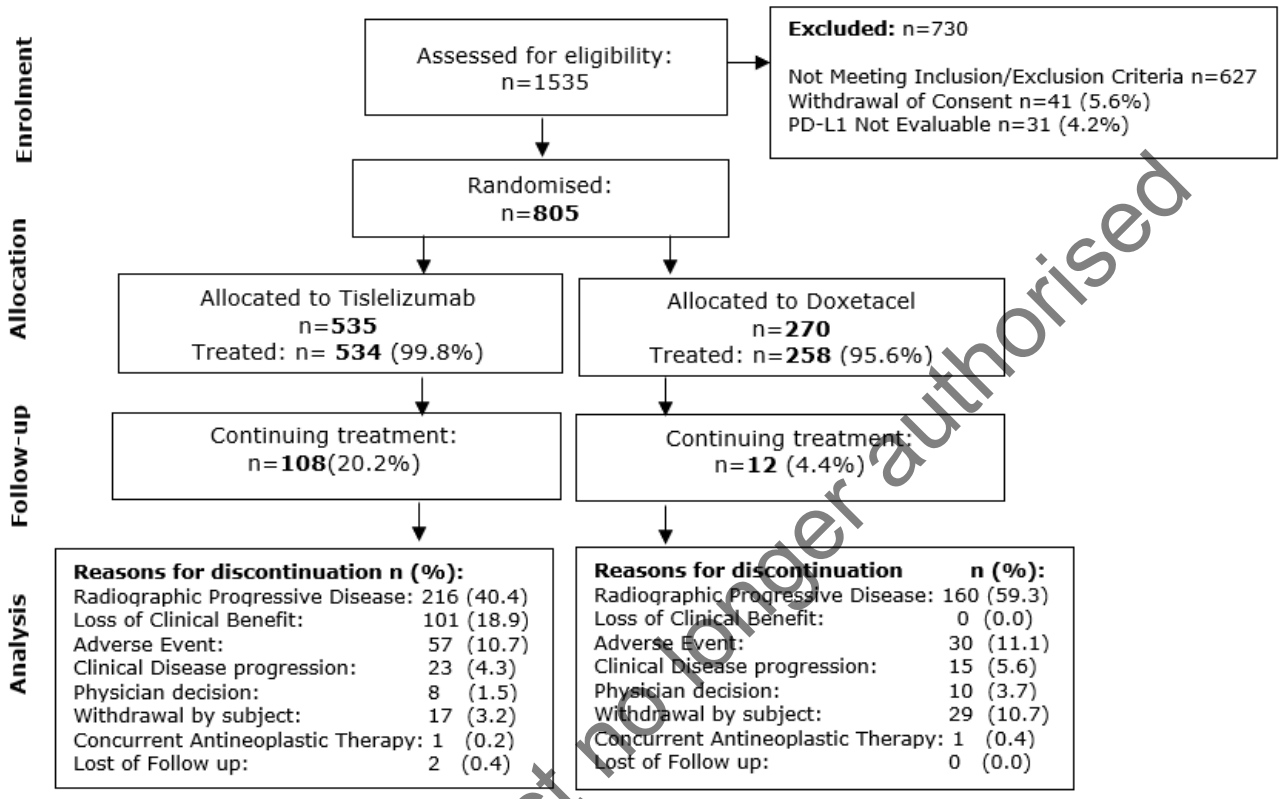
Subgroup Analyses

To determine if the treatment effect was consistent across various subgroups, the HR estimates of OS and its 95% CI were planned to be estimated and plotted within each category of the following variables: PD-L1 expression in TC (≥25% TC versus <25% TC) in the ITT Analysis Set, histology (squamous versus non-squamous), line of therapy (2 versus 3), age (≤65 versus >65 years), gender (Female versus Male), ECOG PS (0 versus 1), smoking status and region (CAP versus ROW).

Approximately 160 patients were planned to be randomised in the ITT-ROW from countries outside of China and Asia Pacific region, which consisted of the 20% of the ITT Analysis Set. With the additional region, it was possible to evaluate the treatment effect of tislelizumab in a broader population, as well as its consistency between Asian and Caucasian populations. Subgroup analysis in the ITT-ROW were planned for descriptive purpose only due to the small sample size. Selected efficacy and safety variables were planned to be summarised in the ITT-ROW as subgroup analysis using similar methodologies discussed earlier.

Results

- **Participant flow**



- **Recruitment**

This ongoing study is currently being conducted in 109 study centres. Patients were enrolled in China, Brazil, Bulgaria, Lithuania, Mexico, New Zealand, Poland, Russia, Slovakia, and Turkey. The dominating enrolling country was China with a total of 651 subjects.

The most common reasons for screen failure were Exclusion 11 (active leptomeningeal disease or uncontrolled, untreated brain metastasis/134 patients, 18.4%), Inclusion 5 (Patients must be able to provide archival/fresh tumour tissues for biomarker analysis to assess PD-L1 expression and, provided sufficient tissue, including TMB, and gene expression profiling (GEP), 132 patients, 18.1%), and Exclusion 23 (Underlying medical conditions, 84 patients, 11.5%).

- **Conduct of the study**

Table 28: Summary of protocol amendments (Study 303)

Version	Date	Key Changes
Amendment 1.0	14 February 2018	• Expanded the study to allow the enrollment of about 160 patients outside of China, including Brazil, Bulgaria, Lithuania, Mexico, New Zealand, Poland, Russia, Slovakia, and Turkey • OS in PD-L1-positive (≥ 25% TCs) population were changed to be tested at a significance level of 0.007 as the dual primary endpoint • Updated the planned timing and number of death events for interim and final analyses of OS • Removed analysis of PD-L1-positive (≥ 25% TCs) population from interim analysis • Revised to cap the PD-L1 negative (< 25% TCs) population to about 60% of ITT population • Revised the timing of collection of all imAEs and SAEs related to tislelizumab • Added ophthalmologic exams • Added questionnaire EQ-5D-5L
Amendment 1.0 Addendum 1	22 May 2018	• Added myocarditis and myositis/rhabdomyolysis as potential imAEs and provided guidelines for their diagnostic tests and management • Added monitoring of serum creatine kinase and creatine kinase cardiac muscle isoenzyme
Amendment 2.0	20 July 2018	• Revised exclusion criteria pertaining to chemotherapy and herbal medicine • Clarified inclusion/exclusion criteria including lines of prior anticancer therapy, wash out period for prior anticancer chemotherapy, herbal medicine, immunotherapy, and radiation • Added inclusion criterion of ≥ 12 weeks life expectancy • Added antibiotics wash out period of 2 weeks prior to randomization • Added guidance on the assessment of pulmonary function
Amendment 3.0	09 March 2020	• Updated the planned timing and number of death events for interim and final analyses of OS • Added symptom scale of QLQ-LC13 to HRQoL measures in statistical analysis • Clarified the definition of window of baseline tumor assessment in screening period • Added tumor-infiltrating immune cells as exploratory biomarker for efficacy

Abbreviations: AE, adverse event; EQ-5D-5L, European Quality of Life 5-Dimension, 5-Level Questionnaire; HRQoL, health-related quality of life; imAE, immune-mediated treatment-emergent adverse events; ITT, intent-to-treat; OS, overall survival; PD-L1, programmed cell death protein ligand-1; QLQ-LC13, Quality of Life Questionnaire-Lung Cancer; SAE, serious adverse event; TCs, tumor cells.

- **Baseline data**

Table 29: Demographics and baseline characteristics (ITT analysis set) (Study 303) (DCO: 15JUL2021)

	Tislelizumab (N=535) n (%)	Docetaxel (N=270) n (%)
Age (years)		
n	535	270
Mean (SD)	60.0 (8.81)	60.2 (9.02)
Median	61.0	61.0
Q1, Q3	55.0, 66.0	55.0, 66.0
Min, Max	28, 88	32, 81
Age Group, n (%)		
< 65 years	364 (68.0)	180 (66.7)
≥ 65 - < 75 years	156 (29.2)	79 (29.3)
≥ 75 - < 85 years	14 (2.6)	11 (4.1)
≥ 85 years	1 (0.2)	0 (0.0)
Sex, n (%)		
Male	416 (77.8)	206 (76.3)
Female	119 (22.2)	64 (23.7)
Race, n (%)		
American Indian or Alaska Native	12 (2.2)	1 (0.4)
Asian	424 (79.3)	219 (81.1)
Black or African American	1 (0.2)	3 (1.1)
Native Hawaiian or Other Pacific Islander	3 (0.6)	3 (1.1)
White	93 (17.4)	44 (16.3)
Other	2 (0.4)	0 (0.0)
Ethnicity, n (%)		
Hispanic	NA	NA
Non-Hispanic	NA	NA
Country, n (%)		
Brazil	17 (3.2)	8 (3.0)
Bulgaria	1 (0.2)	1 (0.4)
China	423 (79.1)	218 (80.7)
Lithuania	4 (0.7)	1 (0.4)
Mexico	12 (2.2)	2 (0.7)
New Zealand	9 (1.7)	5 (1.9)
Poland	2 (0.4)	2 (0.7)
Russia	41 (7.7)	15 (5.6)
Slovakia	2 (0.4)	3 (1.1)
Turkey	24 (4.5)	15 (5.6)
Region, n (%)		
China	423 (79.1)	218 (80.7)
ROW	112 (20.9)	52 (19.3)
Weight (kg)		
n	535	270
Mean (SD)	67.78 (11.874)	67.12 (14.034)
Median	67.00	65.00
Q1, Q3	60.00, 75.00	59.00, 73.00
Min, Max	35.0, 130.0	36.0, 129.0
BMI (kg/m^2)		
n	534	269
Mean (SD)	24.15 (3.626)	24.21 (4.466)
Median	23.86	23.46
Q1, Q3	21.78, 26.30	21.36, 26.61
Min, Max	15.1, 43.9	16.2, 48.6
ECOG Performance Status, n (%)		
0	116 (21.7)	50 (18.5)
1	419 (78.3)	220 (81.5)
Smoking Status, n (%)		
Never	162 (30.3)	82 (30.4)
Current	50 (9.3)	19 (7.0)
Former	323 (60.4)	169 (62.6)

Data Source: ADSL ADBASE ADCM ADTRSUM. Data cutoff: 15JUL2021. Data extraction: 22OCT2021.

Table 30: Disease history (ITT analysis set) (Study 303) (DCO: 15JUL2021)

	Tislelizumab (N=535) n (%)	Docetaxel (N=270) n (%)
PD-L1 Expression, n (%)		
≥ 25%	227 (42.4)	115 (42.6)
< 25%	307 (57.4)	152 (56.3)
Missing [a]	1 (0.2)	3 (1.1)
Histology, n (%)		
Squamous	248 (46.4)	122 (45.2)
Non-Squamous	287 (53.6)	148 (54.8)
EGFR Mutation, n (%)		
Wild Type	343 (64.1)	187 (69.3)
Mutant	1 (0.2)	0 (0.0)
Unknown [b]	191 (35.7)	83 (30.7)
ALK Rearrangement, n (%)		
Wild Type	241 (45.0)	130 (48.1)
Translocated	0 (0.0)	0 (0.0)
Unknown	294 (55.0)	140 (51.9)
Line of Therapy, n (%)		
Second	453 (84.7)	229 (84.8)
Third	82 (15.3)	41 (15.2)
Disease Stage at Study Entry [c], n (%)		
Locally Advanced	84 (15.7)	33 (12.2)
Metastatic	451 (84.3)	237 (87.8)
Brain Metastasis, n (%)		
Yes	39 (7.3)	18 (6.7)
No	496 (92.7)	252 (93.3)
Liver Metastasis, n (%)		
Yes	73 (13.6)	33 (12.2)
No	462 (86.4)	237 (87.8)
Baseline Target Lesions Sum of Diameters by Investigator (mm)		
n	504	258
Mean (SD)	66.80 (40.337)	71.44 (45.304)
Median	58.00	60.65
Q1, Q3	37.00, 90.00	37.00, 94.00
Min, Max	10.0, 292.7	11.0, 239.0
Time from Initial Diagnosis to Study Entry (Year)		
n	535	270
Mean (SD)	1.238 (1.2470)	1.129 (0.8922)
Median	0.887	0.839
Q1, Q3	0.632, 1.372	0.594, 1.246
Min, Max	0.05, 12.73	0.17, 5.77
Location of Distant Metastases, n (%) [d]		
Adrenal Glands	53 (9.9)	37 (13.7)
Bone	166 (31.0)	79 (29.3)
Brain	39 (7.3)	18 (6.7)
Kidney	9 (1.7)	8 (3.0)
Liver	73 (13.6)	33 (12.2)
Lung	200 (37.4)	103 (38.1)
Lymph Nodes	74 (13.8)	29 (10.7)
Pleura/Pleural Effusion	170 (31.8)	94 (34.8)
Pericardium/Pericardial Effusion	29 (5.4)	15 (5.6)
Other	53 (9.9)	32 (11.9)

	Tislelizumab (N=535) n (%)	Docetaxel (N=270) n (%)
Patients with any Prior Anticancer Systemic Therapy, n (%)	535 (100.0)	270 (100.0)
Time from End of Last Therapy to Study Entry [c] (month)		
n	535	270
Mean (SD)	4.70 (4.602)	4.20 (4.354)
Median	2.99	2.66
Q1, Q3	1.71, 6.21	1.58, 5.32
Min, Max	-0.1, 39.3	0.0, 35.5
Type of Prior Therapy, n (%) [d]		
Chemotherapy	535 (100.0)	270 (100.0)
Protein Kinase Inhibitors	16 (3.0)	9 (3.3)
Immunotherapy	0 (0.0)	0 (0.0)
Other	118 (22.1)	55 (20.4)
Setting of Prior Therapy, n (%) [d]		
Metastatic	327 (61.1)	184 (68.1)
Locally Advanced	190 (35.5)	74 (27.4)
Neoadjuvant	12 (2.2)	8 (3.0)
Adjuvant	59 (11.0)	39 (14.4)
Patients with any Prior Anticancer Surgeries, n (%)	130 (24.3)	66 (24.4)
Intention of Surgery, n (%) [d]		
Curative	103 (79.2)	52 (78.8)
Palliative	32 (24.6)	15 (22.7)
Other	1 (0.8)	1 (1.5)
Time from Last Surgery to Study Entry [c] (month)		
n	130	66
Mean (SD)	21.72 (21.723)	18.54 (12.812)
Median	14.21	13.50
Q1, Q3	8.94, 26.58	9.63, 25.30
Min, Max	0.8, 146.8	1.4, 69.3
Patients with any Prior Anticancer Radiotherapy, n (%)	199 (37.2)	101 (37.4)
Intent of Therapy, n (%) [d]		
Radical	82 (41.2)	31 (30.7)
Neoadjuvant	0 (0.0)	3 (3.0)
Adjuvant	7 (3.5)	7 (6.9)
Palliative	118 (59.3)	61 (60.4)
Missing*	1 (0.5)	1 (1.0)
Time from End of Last Radiotherapy to Study Entry [c] (month)		
n	199	101
Mean (SD)	7.65 (6.744)	8.81 (9.914)
Median	6.11	5.88
Q1, Q3	2.56, 9.92	2.50, 10.61
Min, Max	0.0, 33.8	0.0, 53.6

Data Source: ADSL ADBASE ADCM ADTRSUM. Data cutoff: 15JUL2021. Data extraction: 22OCT2021.
For patients with any prior anticancer treatment, percentages were based on N; for others, percentages were based on the number of patients with any prior anticancer treatment.

a Patients with missing baseline PD-L1 expression were the patients scored with unqualified samples

[b] Patients with unknown epidermal growth factor (EGFR) mutation included the following: Squamous (SQ) patients without EGFR testing (n=273) and nonsquamous (NSQ) patients with a non-tissue-based EGFR wild-type result (n=1). Eight NSQ patients had their EGFR mutation status updated from unknown to wild type, which was due to sites updating the EGFR wild-type result confirmed by non-tissue-based to tissue-based method. In total, there was 1 NSQ patient who did not have a tissue-based EGFR wild-type result and had only a blood-based EGFR wild-type result.
[c] Study Entry date referred to randomization date in this study.
[d] A patient was counted only once within each category, but may be counted in multiple categories.

- **Numbers analysed**

All 805 patients who were randomised to the study were included in the ITT Analysis Set.

Table 31: Analysis sets (Study 303) (DCO: 15JUL2021)

	Tislelizumab (N = 535) n (%)	Docetaxel (N = 270) n (%)	Total (N = 805) n (%)
ITT Analysis Set [a]	535 (100.0)	270 (100.0)	805 (100.0)
PD-L1+ Analysis Set [b]	227 (42.4)	115 (42.6)	342 (42.5)
Safety Analysis Set [c]	534 (99.8)	258 (95.6)	792 (98.4)
PK Analysis Set [d]	532 (99.4)	0 (0.0)	532 (66.1)
ADA Analysis Set [e]	507 (94.8)	0 (0.0)	507 (63.0)
HRQoL Analysis Set [f]	533 (99.6)	256 (94.8)	789 (98.0)
PD-L1+ HRQoL Analysis Set [g]	227 (42.4)	108 (40.0)	335 (41.6)
Per-Protocol Analysis Set [h]	489 (91.4)	253 (93.7)	742 (92.2)

Data Source: ADSL. Data cutoff: 15JUL2021. Data extraction: 22OCT2021.
[a] ITT Analysis Set included all patients randomized to the study.
[b] PD-L1+ Analysis Set included all randomized patients whose tumors were PD-L1 positive.
[c] Safety Analysis Set included all randomized patients who received at least 1 dose of any study drug.
[d] PK Analysis Set included all patients who received at least 1 dose of tislelizumab per the protocol, for whom any post-baseline PK data were available.
[e] ADA Analysis Set included 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.
[f] HRQoL Analysis Set included all randomized patients who received at least 1 dose of study drug and completed at least one HRQoL assessment.
[g] PD-L1+ HRQoL Analysis Set included all randomized patients whose tumors were PD-L1 positive and who received at least 1 dose of study drug and completed at least one HRQoL assessment.
[h] Per-Protocol Analysis Set included patients in the ITT analysis set who had no critical protocol deviations.

- **Outcomes and estimation**

Primary endpoint: dual primary (OS)

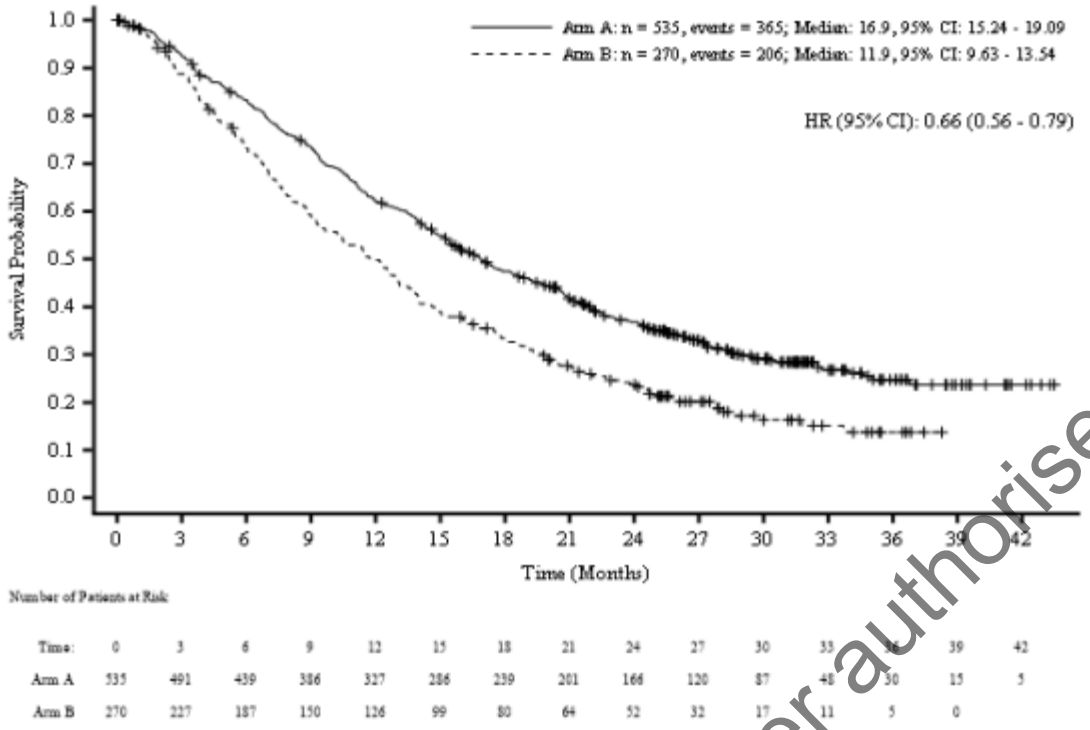
Overall Survival in the ITT analysis

The interim analysis of Study 303 (DCO 10 Aug 2020) had a median follow-up of 11.7 months (13.3 and 9.7 for Tislelizumab and Docetaxel arms, respectively). A statistically significant improvement in OS was observed in the ITT population. Results favoured the tislelizumab arm (HR = 0.64; 95% CI: 0.53, 0.78; p < 0.0001). Median OS was 17.2 months for the tislelizumab arm and 11.9 months for the docetaxel arm. The final analysis (DCO 15 July 2021) had a median follow-up of 14.2 months (16.0 and 10.7 for Tislelizumab and Docetaxel arms, respectively). Results of the final analysis are provided below:

Table 32: Analysis of overall survival (ITT analysis set) (Study 303) (DCO: 15JUL2021)

	Tislelizumab (N=535)	Docetaxel (N=270)
Overall Survival		
Death, n (%)	365 (68.2)	206 (76.3)
Censored, n (%)	170 (31.8)	64 (23.7)
Ongoing in the Study	153 (28.6)	45 (16.7)
Withdrawal by Subject	6 (1.1)	16 (5.9)
Lost to Follow-up	10 (1.9)	2 (0.7)
Study Discontinuation Due to Other Reasons	1 (0.2)	1 (0.4)
One-sided stratified log-rank test P-value [a b]	<.0001	
Stratified Hazard Ratio (95% CI) [a]	0.66 (0.559, 0.790)	
Overall Survival (month)		
Median (95% CI)	16.9 (15.24, 19.09)	11.9 (9.63, 13.54)
Q1 (95% CI)	8.4 (7.13, 9.36)	5.8 (4.53, 6.80)
Q3 (95% CI)	35.1 (30.32, NE)	22.8 (19.38, 27.56)
Event Free Rate at, %(95% CI)		
3 month (95% CI)	92.5 (89.89, 94.43)	88.7 (84.19, 92.03)
6 month (95% CI)	83.2 (79.76, 86.14)	73.8 (67.98, 78.77)
9 month (95% CI)	73.4 (69.38, 76.92)	59.2 (52.92, 64.97)
12 month (95% CI)	62.1 (57.86, 66.13)	49.7 (43.45, 55.71)
18 month (95% CI)	47.5 (43.12, 51.67)	32.6 (26.94, 38.45)
24 month (95% CI)	36.8 (32.62, 41.01)	23.7 (18.57, 29.17)
36 month (95% CI)	24.7 (20.29, 29.43)	13.8 (8.87, 19.69)
Follow-up Time (month)		
Median (95% CI)	31.1 (29.54, 31.64)	27.9 (26.38, 31.15)

Data Source: ADSL ADTTE. Data cutoff: 15JUL2021. Data extraction: 22OCT2021.
Median follow-up time was estimated by the reverse Kaplan-Meier method.
Medians and other quartiles were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley.
Event free rates were estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula.
Docetaxel arm was the reference group for hazard ratio.
[a] Stratified by stratification factors: histology (squamous versus nonsquamous), lines of therapy (second versus third), and PD-L1
[b] The primary endpoint was met, and statistical significance was achieved in the prespecified interim analysis. Formally, there is no subsequent significance testing. The p-values in this final analysis for efficacy are descriptive in nature.



Data Source: ADSL ADTTE. Data cutoff: 15JUL2021. Data extraction: 22OCT2021.
Arm A = Tislelizumab, Arm B = Docetaxel.
Abbreviations: CI, confidence interval;
Hazard ratio was estimated from stratified Cox model with docetaxel group as reference group.
Cox regression model were stratified by histology (squamous versus nonsquamous), lines of therapy (second versus third), and PD-L1 expression (≥25% TC versus <25% TC).

Figure 51: Kaplan-Meier plot of overall survival (ITT analysis set) (Study 303) (DCO: 15JUL2021)

Overall Survival in PD-L1-Positive Analysis Set (**>25% PD-L1 positivity**)

Table 33: Analysis of overall survival (PD-L1-positive analysis set, (>25% PD-L1 positivity)) (Study 303) (DCO:15JUL2021)

	Tislelizumab (N=227)	Docetaxel (N=115)
Overall Survival		
Death, n (%)	141 (62.1)	86 (74.8)
Censored, n (%)	86 (37.9)	29 (25.2)
Ongoing in the Study	80 (35.2)	19 (16.5)
Withdrawal by Subject	3 (1.3)	9 (7.8)
Lost to Follow-up	3 (1.3)	1 (0.9)
Study Discontinuation Due to Other Reasons	0 (0.0)	0 (0.0)
One-sided stratified log-rank test P-value [a]	<.0001	
Stratified Hazard Ratio (95% CI) [a]	0.53 (0.407, 0.702)	
Overall Survival (month)		
Median (95% CI)	19.3 (16.49, 22.60)	11.5 (8.15, 13.54)
Q1 (95% CI)	9.6 (8.08, 11.37)	5.1 (3.58, 6.64)
Q3 (95% CI)	NE (33.91, NE)	21.2 (16.43, 31.77)
Event Free Rate at, %(95% CI)		
3 month (95% CI)	93.8 (89.74, 96.27)	87.0 (79.04, 92.09)
6 month (95% CI)	87.1 (81.99, 90.86)	69.1 (59.40, 76.94)
9 month (95% CI)	77.7 (71.70, 82.65)	58.7 (48.73, 67.37)
12 month (95% CI)	67.4 (60.83, 73.11)	48.3 (38.51, 57.38)
18 month (95% CI)	52.8 (45.98, 59.10)	30.0 (21.49, 38.87)
24 month (95% CI)	42.3 (35.62, 48.82)	22.6 (14.98, 31.10)
36 month (95% CI)	29.6 (22.29, 37.15)	13.7 (6.72, 23.07)
Follow-up Time (month)		
Median (95% CI)	30.9 (28.48, 31.84)	27.5 (25.20, 32.30)

Data Source: ADSL ADTTE. Data cutoff: 15JUL2021. Data extraction: 22OCT2021.
Median follow-up time was estimated by the reverse Kaplan-Meier method.

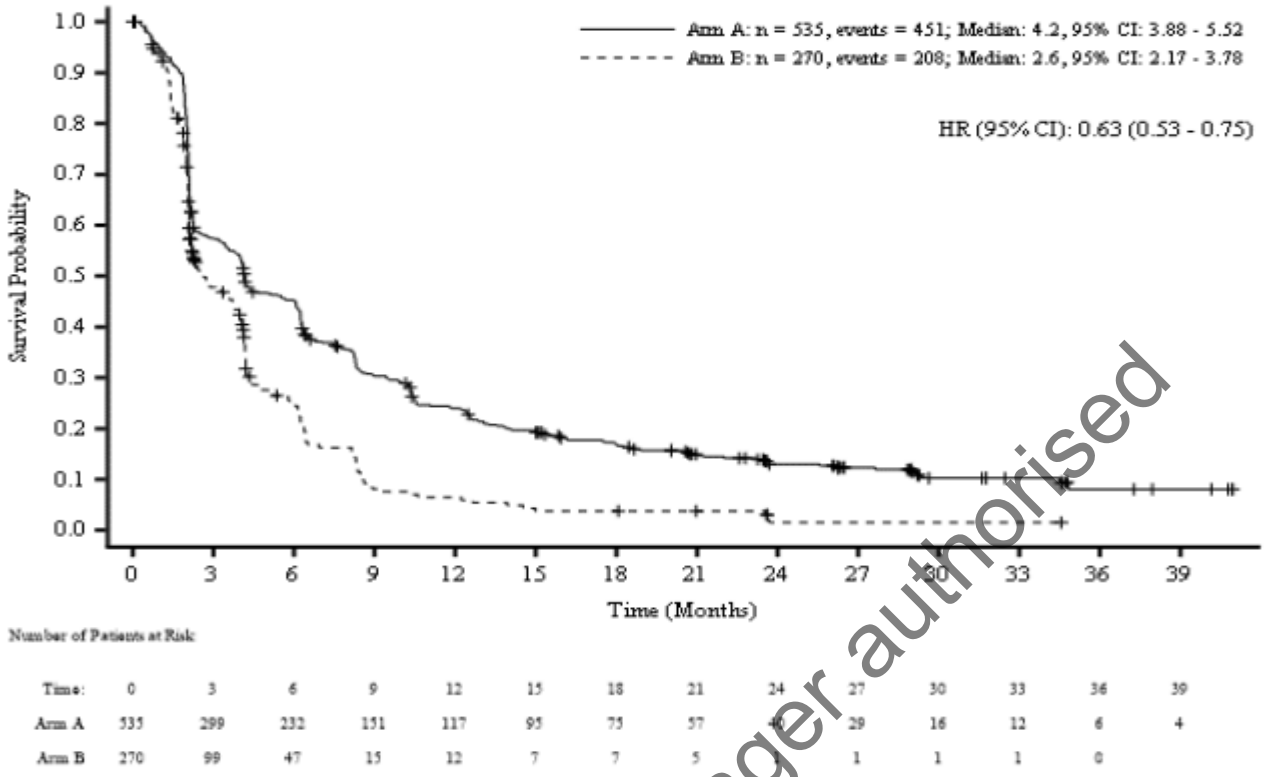
Secondary endpoints: PFS, ORR, DoR, HRQoL

Progression-Free Survival

Table 34: Analysis of progression-free survival per RECIST version 1.1 by investigator (ITT analysis set) (Study 303) (DCO: 15JUL2021)

	Tislelizumab (N=535) n (%)	Docetaxel (N=270) n (%)
Progression-Free Survival		
Events, n (%)	451 (84.3)	208 (77.0)
Progressive Disease	398 (74.4)	180 (66.7)
Death	53 (9.9)	28 (10.4)
Censored, n (%)	84 (15.7)	62 (23.0)
No Disease Progression or Death	60 (11.2)	5 (1.9)
No Baseline Assessment	0 (0.0)	0 (0.0)
No Postbaseline Assessment	7 (1.3)	24 (8.9)
New Anticancer Therapy	12 (2.2)	29 (10.7)
Death or progression after missing 2 or more consecutive tumor assessments	5 (0.9)	4 (1.5)
One-sided stratified log-rank test p-value [a]	<.0001	
Stratified Hazard Ratio (95% CI) [a]	0.63 (0.528, 0.745)	
Progression-Free Survival (month)		
Median (95% CI)	4.2 (3.88, 5.52)	2.6 (2.17, 3.78)
Q1 (95% CI)	2.0 (2.04, 2.07)	2.0 (1.84, 2.04)
Q3 (95% CI)	10.5 (10.18, 13.08)	6.0 (4.24, 6.41)
Event Free Rate at, % (95% CI)		
3 month (95% CI)	57.3 (52.92, 61.56)	47.8 (41.18, 54.09)
6 month (95% CI)	45.1 (40.83, 49.34)	25.4 (19.70, 31.54)
9 month (95% CI)	30.3 (26.39, 34.32)	8.1 (4.79, 12.55)
12 month (95% CI)	24.0 (20.39, 27.80)	6.5 (3.57, 10.61)
Follow-up Time (month)		
Median (95% CI)	26.3 (23.56, 28.94)	21.0 (18.07, 34.56)

Data Source: ADSL ADTTE. Data cutoff: 15JUL2021. Data extraction: 22OCT2021.
Median follow-up time was estimated by the reverse Kaplan-Meier method.
Medians and other quartiles were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley.
Event free rates were estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula.
Docetaxel arm was the reference group for hazard ratio.
[a] Stratified by stratification factors: histology (squamous versus nonsquamous), lines of therapy (second versus third), and PD-L1 expression (≥25% TC versus <25% TC).



Number of Patients at Risk:

Time:	0	3	6	9	12	15	18	21	24	27	30	33	36	39
Arm A	535	299	232	151	117	95	75	57	40	29	16	12	6	4
Arm B	270	99	47	15	12	7	7	5	1	1	1	1	0	

Data Source: ADSL ADTTE. Data cutoff: 15JUL2021. Data extraction: 22OCT2021.
Arm A = Tislelizumab, Arm B = Docetaxel.
Abbreviations: CI, confidence interval;
Hazard ratio was estimated from stratified Cox model with docetaxel group as reference group.
Cox regression model were stratified by histology (squamous versus nonsquamous), lines of therapy (second versus third), and PD-L1 expression (≥25% TC versus <25% TC).

Figure 52: Kaplan-Meier plot of progression-free survival per RECIST version 1.1 by investigator (ITT analysis set) (Study 303) (DCO: 15JUL2021)

In the PD-L1 Positive Analysis Set, the median PFS was 6.5 months (95% CI: 6.24, 8.28 months) and 2.5 months (95% CI: 2.10, 4.11 months) for the tislelizumab arm and Docetaxel arm, respectively, as estimated using the Kaplan-Meier method, with a stratified HR of 0.38 (95% CI: 0.285, 0.494), indicating a 62% reduction in the risk of experiencing a PFS event for patients in the Tislelizumab arm.

Objective Response Rate

Table 35: Analysis of disease response per RECIST version 1.1 by investigator (ITT analysis set), unconfirmed responses (Study 303) (DCO: 15JUL2021)

	Tislelizumab (N=535) n (%)	Docetaxel (N=270) n (%)
Best Overall Response, n (%)		
CR (Complete Response)	9 (1.7)	1 (0.4)
PR (Partial Response)	112 (20.9)	18 (6.7)
SD (Stable Disease)	157 (29.3)	91 (33.7)
non-CR/non-PD	20 (3.7)	4 (1.5)
PD (Progressive Disease)	198 (37.0)	104 (38.5)
Could Not Be Determined [a]	39 (7.3)	52 (19.3)
Objective Response Rate (ORR), n (%)	121 (22.6)	19 (7.0)
95% CI	(19.14, 26.40)	(4.29, 10.77)
CMH's p-value	<.0001	
Odds Ratio (95% CI)	3.86 (2.336, 6.393)	
ORR Difference, % (95% CI)	15.6 (10.96, 20.33)	
Disease Control Rate, n (%)	298 (55.7)	114 (42.2)
95% CI	(51.38, 59.96)	(36.26, 48.36)
Clinical Benefit Rate [b], n (%)	293 (54.8)	95 (35.2)
95% CI	(50.44, 59.04)	(29.49, 41.21)
Clinical Benefit Rate [c], n (%)	242 (45.2)	51 (18.9)
95% CI	(40.96, 49.56)	(14.40, 24.08)

Data Source: ADSL ADRS. Data cutoff: 15JUL2021. Data extraction: 22OCT2021.
Abbreviations: CI, confidence interval;
95% CI was calculated using Clopper-Pearson method.
Objective response rate differences and odds ratios between arms were calculated using the Cochran-Mantal-Haenszel Chi-square test with actual stratification factors as strata.
Docetaxel arm was the reference group.
[a] Included patients who had postbaseline tumor assessment, none of which were evaluable; or patients who had no postbaseline tumor assessments due to death, withdrawal of consent, lost to follow-up or any other reasons.
[b] Included patients with BOR in CR or PR or ≥12 weeks SD or non-CR/non-PD.
[c] Included patients with BOR in CR or PR or ≥24 weeks SD or non-CR/non-PD.

Table 36: Analysis of disease response per RECIST version 1.1 by investigator (ITT analysis set), confirmed responses (Study 303) (DCO: 15JUL2021)

	Tislelizumab (N=535) n (%)	Docetaxel (N=270) n (%)
Best Overall Response with confirmation, n (%)		
CR (Complete Response)	9 (1.7)	1 (0.4)
PR (Partial Response)	103 (19.3)	9 (3.3)
SD (Stable Disease)	166 (31.0)	100 (37.0)
non-CR/non-PD	20 (3.7)	4 (1.5)
PD (Progressive Disease)	198 (37.0)	104 (38.5)
Could Not Be Determined [a]	39 (7.3)	52 (19.3)
Objective Response Rate (ORR), n (%)	112 (20.9)	10 (3.7)
95% CI	(17.56, 24.63)	(1.79, 6.71)
CMH's p-value	<.0001	
Odds Ratio (95% CI)	6.89 (3.568, 13.292)	
ORR Difference, % (95% CI)	17.3 (13.19, 21.44)	

Data Source: ADSL ADRS. Data cutoff: 15JUL2021. Data extraction: 22OCT2021.
Abbreviations: CI, confidence interval;
95% CI was calculated using Clopper-Pearson method.
Objective response rate differences and odds ratios between arms were calculated using the Cochran-Mantal-Haenszel Chi-square test with actual stratification factors as strata.
Docetaxel arm was the reference group.
[a] Included patients who had post-baseline tumor assessment, none of which were evaluable; or patients who had no post-baseline tumor assessments due to death, withdrawal of consent, lost to follow-up or any other reasons.

In the PD-L1 Positive Analysis Set, the unconfirmed ORR in the tislelizumab arm (37.4% [95% CI: 31.13, 44.09]) was higher than the ORR in the docetaxel arm (7.0% [95% CI: 3.05, 13.25]) (with p-value < 0.0001). Meanwhile, a numerically higher ORR of 37.4% (85 patients) in the tislelizumab arm was observed in the PD-L1 Positive Analysis Set compared with 22.6% (121 patients) in the ITT Analysis Set.

Duration of Response

Table 37: Analysis of duration of response (unconfirmed) per RECIST version 1.1 by investigator (ITT analysis set) (Study 303) (DCO: 15JUL2021)

	Tislelizumab (N = 535)	Docetaxel (N = 270)
Number of Responders	121	19
Duration of Response		
Events, n (%)	75 (62.0)	16 (84.2)
Progressive Disease	66 (54.5)	15 (78.9)
Death	9 (7.4)	1 (5.3)
Censored, n (%)	46 (38.0)	3 (15.8)
One-sided log-rank test p-value	<.0001	
Hazard Ratio (95% CI)	0.31 (0.176, 0.536)	
Duration of Response (month)		
Median (95% CI)	13.5 (8.54, 19.58)	6.0 (2.10, 7.16)
Q1 (95% CI)	6.2 (4.27, 6.80)	2.3 (0.56, 4.21)
Q3 (95% CI)	30.9 (23.03, NE)	7.2 (6.05, 17.31)
Event Free Rate at, % (95% CI)		
3 month (95% CI)	90.9 (84.09, 94.83)	70.6 (43.15, 86.56)
6 month (95% CI)	78.2 (69.60, 84.57)	52.9 (27.62, 73.03)
9 month (95% CI)	58.7 (49.14, 67.05)	17.6 (4.35, 38.30)
12 month (95% CI)	52.3 (42.72, 60.96)	17.6 (4.35, 38.30)
18 month (95% CI)	42.6 (33.32, 51.63)	0.0 (NE, NE)
Follow-up Time (month)		
Median (95% CI)	24.3 (21.49, 26.97)	NE (11.89, NE)

Data Source: ADSL ADTTE. Data cutoff: 15JUL2021. Data extraction: 22OCT2021.
Percentages were based on number of responders.
Duration of response analysis included patients with objective response.
Median follow-up time was estimated by the reverse Kaplan-Meier method.
Medians and other quartiles were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley.
Event free rates were estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula.
Docetaxel arm was the reference group for hazard ratio.

In the PD-L1 Positive Analysis Set, the median DoR in the tislelizumab arm (11.9 [95% CI: 8.31, 19.85]) was higher than the median DoR in the docetaxel arm (4.2 [95% CI: 0.56, 6.05]).

Table 38: Analysis of duration of response (confirmed) per RECIST version 1.1 by investigator (ITT analysis set) (Study 303) (DCO: 15JUL2021)

	Tislelizumab (N = 535)	Docetaxel (N = 270)	Total (N = 805)
Number of Responders	112	10	122
Duration of Response			
Events, n (%)	66 (58.9)	10 (100.0)	76 (62.3)
Progressive Disease	59 (52.7)	9 (90.0)	68 (55.7)
Death	7 (6.3)	1 (10.0)	8 (6.6)
Censored, n (%)	46 (41.1)	0 (0.0)	46 (37.7)
One-sided log-rank test p-value	0.0002		
Hazard Ratio (95% CI)	0.31 (0.155, 0.607)		
Duration of Response (month)			
Median (95% CI)	14.7 (10.55, 21.78)	6.2 (4.11, 8.31)	13.5 (9.00, 19.38)
Q1 (95% CI)	6.4 (6.18, 8.31)	6.0 (4.11, 6.24)	6.2 (6.14, 6.97)
Q3 (95% CI)	NE (24.87, NE)	8.3 (6.24, 17.31)	30.9 (23.03, NE)

Data Source: ADSL ADTTE. Data cutoff: 15JUL2021. Data extraction: 22OCT2021.
Percentages were based on number of responders.
Duration of response analysis included patients with objective response.
Median follow-up time was estimated by the reverse Kaplan-Meier method.
Medians and other quartiles were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley.
Event free rates were estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula.
[a] Stratified by stratification factors: histology (squamous versus non-squamous), lines of therapy (second versus third), and PD-L1 expression (≥25% TC versus <25% TC).

Health-Related Quality of Life

Compliance rates for all the 3 questionnaires were similar in both treatment arms, with highest compliance rates of > 98% to 100% for QLQ-C30 and QLQ-LC13 and 78% to 100% for EQ-5D-5L in the HRQoL Analysis Set.

In the tislelizumab arm, there was a trend towards improvement in HRQoL as measured by QLQ-C30 GHS/QoL (LS mean difference up to Cycle 12 was 2.44 (95% CI: 4.050, 0.837), and in QLQ-LC13 coughing and dyspnoea compared to the docetaxel arm. The time to deterioration (TTD) for QLQ-C30 GHS/QoL and for the index score of the QLQ-LC13 was not reached in either treatment arm.

- **Ancillary analyses**

Sensitivity Analysis for OS

To test the robustness of the OS data, sensitivity analyses were performed as predefined in the statistical analysis plan at the interim analysis (DCO 10 Aug 2020).

Sensitivity Analysis 1

The sensitivity analysis 1 was the same as the primary analysis except that it was based on the stratification factors using the values from IRT, by which patients were randomised. Sensitivity Analysis 1 showed consistent results with those from the primary OS analysis for the ITT Analysis Set, with a stratified HR of 0.64 (95% CI: 0.529, 0.781)

Sensitivity Analysis 2

The sensitivity analysis 2 used RPSFTM to adjust survival estimates in the presence of patients in the docetaxel arm receiving any subsequent immunotherapy after discontinuation of docetaxel. As of the data cutoff date, 53 patients (19.6%) in the docetaxel arm received subsequent immunotherapy. The stratified HR was 0.58 (95% CI: 0.457, 0.736).

Sensitivity Analysis 3

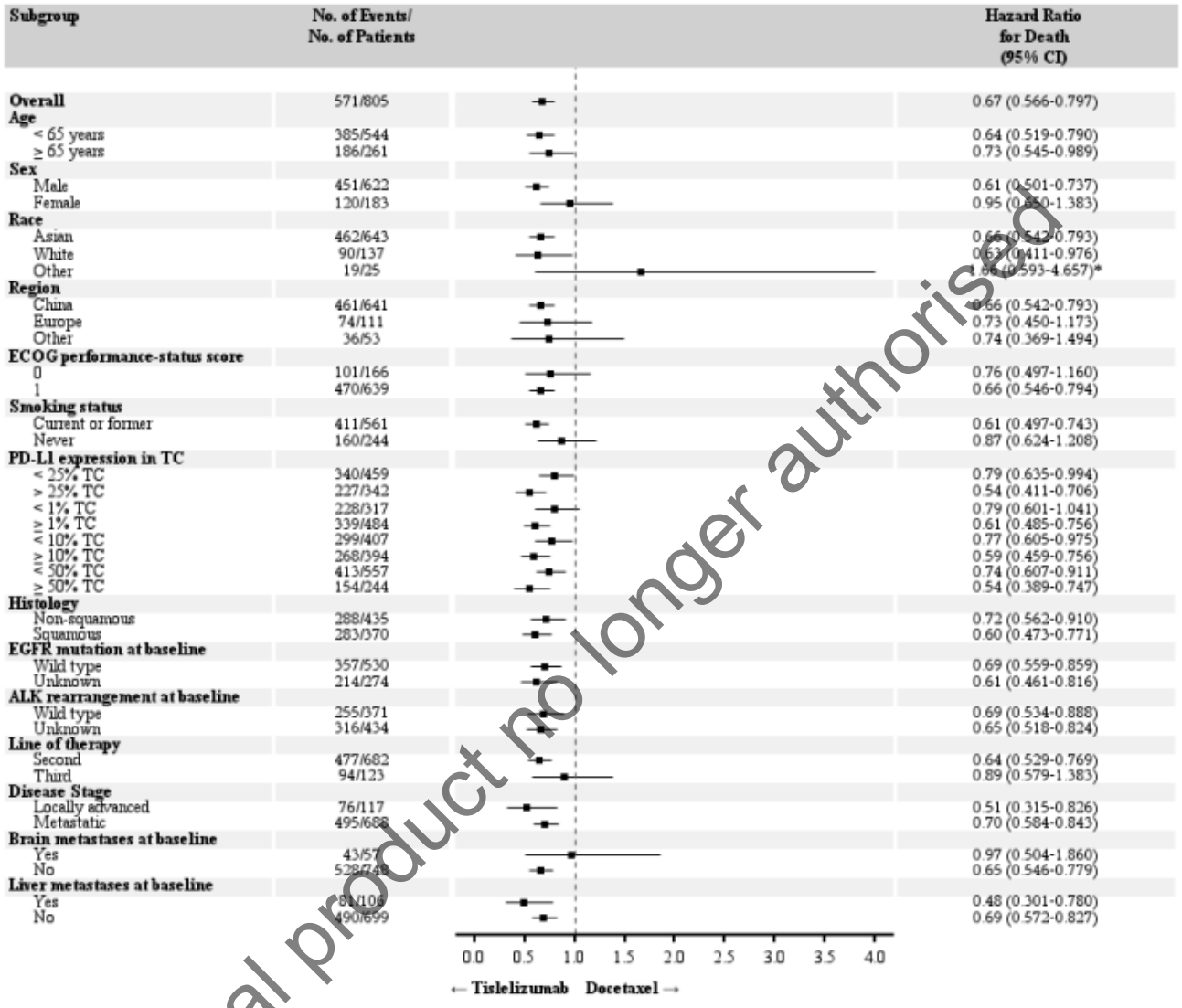
Sensitivity Analysis 3 was conducted to evaluate the impact of the COVID-19 pandemic for the primary analysis. It was the same as the primary analysis except that patients were censored at the date last known to be alive before his/her COVID-19 related drug administration protocol deviation (70 patients in total). The resulting stratified HR was 0.67 (95% CI: 0.548, 0.809)

Sensitivity Analysis 4

In total, 61 patients (7.6%) in the ITT Analysis Set had critical protocol deviations and were excluded from the PP Analysis Set. Sensitivity Analysis 4 conducted in the PP Analysis Set showed a stratified HR of 0.62 (95% CI: 0.506, 0.757).

Subgroup Analysis

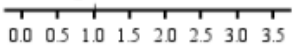
Table 39: Subgroup analysis: forest plot of OS (ITT analysis set) (Study 303) (DCO 15JUL2021)



Data source: ADSL ADTTE ADBASE. Data cutoff: 15JUL2021. Data extraction: 22OCT2021.
Abbreviations: CI, confidence interval; PD-L1, programmed death ligand-1; ECOG, Eastern Cooperative Oncology Group.
Hazard ratio and its 95% CI was estimated from unstratified Cox model with docetaxel group as reference group.
* The complete confidence interval of this subgroup is not shown due to space limitations.

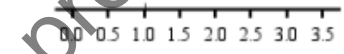
Table 40: Subgroup analysis: forest plot of PFS per RECIST 1.1 by investigator (ITT analysis set) (Study 303) (DCO 15JUL2021)

Subgroup	No. of Events/ No. of Patients	Hazard Ratio for Disease Progression (95% CI)	PFS (month) Median (95% CI)TIS	PFS (month) Median (95% CI)DOX
Overall	659/805	0.61 (0.517-0.724)	4.2 (3.88, 5.52)	2.6 (2.17, 3.78)
Age				
< 65 years	453/544	0.60 (0.493-0.740)	4.0 (2.76, 4.34)	2.3 (2.10, 3.78)
≥ 65 years	206/261	0.62 (0.456-0.835)	6.2 (4.17, 8.18)	3.7 (2.27, 4.17)
Sex				
Male	510/622	0.53 (0.440-0.648)	5.0 (4.11, 6.24)	2.4 (2.14, 3.38)
Female	149/183	0.93 (0.658-1.327)	2.3 (2.10, 4.04)	4.1 (2.10, 6.14)
Race				
Asian	529/643	0.60 (0.496-0.724)	4.1 (3.32, 4.34)	2.4 (2.14, 3.58)
White	109/137	0.59 (0.391-0.889)	7.5 (4.17, 8.41)	4.1 (2.17, 4.63)
Other	21/25	1.14 (0.414-3.157)	3.0 (2.10, 8.25)	6.2 (1.91, NE)
Region				
China	528/641	0.59 (0.492-0.719)	4.1 (3.32, 4.34)	2.3 (2.14, 3.58)
Europe	88/111	0.65 (0.413-1.018)	7.5 (4.17, 10.25)	4.1 (2.17, 5.78)
Other	43/53	0.72 (0.368-1.428)	6.1 (2.27, 8.25)	5.8 (1.91, 6.28)
ECOG performance-status score				
0	131/166	0.56 (0.375-0.822)	4.2 (2.30, 6.24)	2.2 (1.91, 4.11)
1	528/639	0.62 (0.517-0.752)	4.2 (3.58, 5.98)	2.7 (2.17, 3.98)
Smoking status				
Current or former	454/561	0.55 (0.445-0.668)	5.7 (4.14, 6.24)	2.5 (2.14, 3.78)
Never	205/244	0.78 (0.579-1.063)	2.8 (2.10, 4.14)	3.7 (2.07, 4.14)



← Tislelizumab Docetaxel →

Subgroup	No. of Events/ No. of Patients	Hazard Ratio for Disease Progression (95% CI)	PFS (month) Median (95% CI)TIS	PFS (month) Median (95% CI)DOX
PD-L1 expression in TC				
≥ 1% TC	386/459	0.86 (0.686-1.089)	2.5 (2.14, 4.04)	2.8 (2.14, 3.98)
≥ 5% TC	270/342	0.37 (0.281-0.482)	6.5 (6.24, 8.28)	2.5 (2.10, 4.11)
≥ 10% TC	268/317	0.87 (0.664-1.137)	2.3 (2.14, 4.04)	2.9 (2.14, 4.17)
≥ 25% TC	388/484	0.48 (0.381-0.595)	6.1 (4.17, 6.37)	2.4 (2.10, 4.01)
≥ 50% TC	345/407	0.85 (0.667-1.093)	2.3 (2.14, 3.98)	2.7 (2.14, 3.98)
≥ 75% TC	311/394	0.41 (0.315-0.533)	6.5 (6.05, 8.18)	2.6 (2.10, 4.11)
≥ 90% TC	470/557	0.78 (0.640-0.953)	3.4 (2.23, 4.14)	2.6 (2.30, 4.07)
< 50% TC	186/244	0.34 (0.239-0.460)	8.2 (6.24, 10.02)	2.2 (2.04, 4.01)
Histology				
Non-squamous	355/435	0.78 (0.617-0.974)	2.5 (2.14, 4.01)	3.6 (2.17, 4.14)
Squamous	304/370	0.44 (0.343-0.570)	6.2 (4.40, 6.47)	2.3 (2.10, 3.58)
EGFR mutation at baseline				
Wild type	432/530	0.66 (0.540-0.814)	4.0 (2.33, 4.24)	2.7 (2.17, 4.07)
Unknown	226/274	0.51 (0.380-0.691)	6.1 (4.17, 6.51)	2.6 (2.10, 4.17)
ALK rearrangement at baseline				
Wild type	316/371	0.62 (0.485-0.791)	2.4 (2.14, 4.01)	2.3 (2.10, 3.58)
Unknown	343/434	0.61 (0.485-0.776)	6.2 (4.21, 6.47)	3.7 (2.20, 4.17)
Line of therapy				
Second	556/682	0.58 (0.484-0.699)	4.2 (3.98, 6.08)	2.8 (2.14, 3.98)
Third	103/123	0.80 (0.517-1.226)	4.0 (2.23, 6.24)	2.4 (2.10, 4.21)
Disease Stage				
Locally advanced	80/117	0.55 (0.324-0.925)	8.3 (5.52, 13.08)	3.7 (2.10, 6.93)
Metastatic	579/688	0.63 (0.529-0.756)	4.0 (2.83, 4.21)	2.4 (2.14, 3.78)
Brain metastases at baseline				
Yes	49/57	0.76 (0.412-1.412)	2.2 (2.07, 3.45)	2.1 (1.91, 4.21)
No	610/748	0.60 (0.504-0.716)	4.2 (4.04, 6.08)	2.7 (2.17, 3.78)
Liver metastases at baseline				
Yes	89/106	0.53 (0.333-0.855)	2.1 (2.04, 4.01)	2.0 (1.84, 3.98)
No	570/699	0.62 (0.515-0.739)	4.3 (4.07, 6.18)	2.9 (2.27, 4.01)



← Tislelizumab Docetaxel →

Data source: ADSL ADTTE ADBASE. Data cutoff: 15JUL2021. Data extraction: 22OCT2021.

Overall Survival in PD-L1-Negative Analysis Set (<25% PD-L1 positivity)

Table 41: Analysis of overall survival (PD-L1-negative analysis set, (<25% PD-L1 positivity)) (Study 303) (DCO: 15JUL2021) – exploratory analysis

	Tislelizumab (N=307)	Docetaxel (N=152)
Overall Survival		
Death, n (%)	223 (72.6)	117 (77.0)
Censored, n (%)	84 (27.4)	35 (23.0)
Ongoing in the Study	73 (23.8)	26 (17.1)
Withdrawal by Subject	3 (1.0)	7 (4.6)
Lost to Follow-up	7 (2.3)	1 (0.7)
Study Discontinuation Due to Other Reasons	1 (0.3)	1 (0.7)
One-sided stratified log-rank test P-value [a]	0.0129	
Stratified Hazard Ratio (95% CI) [a]	0.77 (0.618, 0.970)	
One-sided unstratified log-rank test P-value	0.0219	
Unstratified Hazard Ratio (95% CI)	0.79 (0.635, 0.994)	
Overall Survival (month)		
Median (95% CI)	15.2 (13.44, 17.61)	12.3 (9.26, 14.26)
Q1 (95% CI)	7.2 (6.05, 8.94)	6.5 (4.63, 7.52)
Q3 (95% CI)	28.6 (24.94, NE)	24.1 (19.81, 28.62)

Data Source: ADSL ADTTE. Data cutoff: 15JUL2021. Data extraction: 22OCT2021.
Median follow-up time was estimated by the reverse Kaplan-Meier method.
Medians and other quartiles were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley.
Event free rates were estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula.
Docetaxel arm was the reference group for hazard ratio.
[a] Stratified by stratification factors: histology (squamous versus non-squamous) and lines of therapy (second versus third).

Objective Response Rate by smoking status, gender and brain metastases

Table 42: Analysis of confirmed objective response rate per RECIST version 1.1 by Investigator by smoking status, gender, and brain metastasis (ITT analysis set) (Study 303) (DCO 15JUL2021)

	Objective Response Rate n (%) (95% CI)		
	Tislelizumab	Docetaxel	Total
Smoking status			
Former (n=492)	61/323 (18.9) (14.76, 23.59)	5/169 (3.0) (0.97, 6.77)	66/492 (13.4) (10.53, 16.75)
Current (n=69)	13/50 (26.0) (14.63, 40.34)	2/19 (10.5) (1.30, 33.14)	15/69 (21.7) (12.71, 33.31)
Never (n=244)	33/162 (20.4) (14.46, 27.40)	3/82 (3.7) (0.76, 10.32)	36/244 (14.8) (10.55, 19.84)
Gender			
Male (n=622)	90/416 (21.6) (17.77, 25.91)	7/206 (3.4) (1.38, 6.88)	97/622 (15.6) (12.83, 18.69)
Female (n=183)	17/119 (14.3) (8.55, 21.88)	3/64 (4.7) (0.98, 13.09)	20/183 (10.9) (6.80, 16.37)
Brain metastasis			
Yes (n=57)	9/39 (23.1) (11.13, 39.33)	0/18 (0.0) (0.00, 18.53)	9/57 (15.8) (7.48, 27.87)
No (n=748)	98/496 (19.8) (16.34, 23.54)	10/252 (4.0) (1.92, 7.18)	108/748 (14.4) (12.00, 17.16)
PD-L1 TC <25%			
Yes	32/307 (10.4) (7.24, 14.40)	6/152 (3.9) (1.46, 8.39)	38/459 (8.3) (5.93, 11.19)

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the 2L/3L (as monotherapy) NSCLC indication of 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 43: Summary of efficacy for BGB-A317-303 (Study 303)

Title: A Phase 3, open-label, multicenter, randomized study to investigate the efficacy and safety of BGB-A317 (anti-PD1 antibody) compared with docetaxel in patients with non-small cell lung cancer who have progressed on a prior platinum-containing regimen			
Study identifier	BGB-A317-303; EudraCT number 2018-000245-39, RATIONALE 303		
Design	Phase III, multicentre, randomised (2:1), open-label study comparing tislelizumab monotherapy versus docetaxel		
	Duration of main phase:		30-Nov-2017 – Ongoing (data cut-off for interim analysis: 10-Aug-2020; final analysis: 15-July-2021) The interim and final analyses were conducted when the predefined death events had been observed for the efficacy and safety evaluations. Results for the final analysis are presented in this submission. The study will continue until the last patient has died, becomes lost to follow-up, or withdraws from study, or until Sponsor decides to terminate the study.
	Duration of Run-in phase:		Not applicable
	Duration of Extension phase:		Not applicable
Hypothesis	Superiority		
Treatments groups	Tislelizumab		200 mg IV Q3W / n = 535
	Docetaxel		75 mg/m^2 IV Q3W / n = 270
Endpoints and definitions	Primary endpoint	OS	Time from the date of randomisation to the date of death due to any cause in the ITT and PD-L1 positive analysis set (defined as ≥25% of tumour cells with PD-L1 membrane staining via Ventana SP263 assay)
	Secondary endpoint	PFS	Time from the date of randomisation to the date of the first objectively documented tumour progression as assessed by the investigator per RECIST v1.1 or death from any cause, whichever occurs first, in the ITT and PD-L1 positive analysis set
	Secondary endpoint	ORR	Proportion of patients who had a CR or PR as assessed by the investigator per RECIST v1.1 in the ITT and PD-L1-Positive Analysis
	Secondary endpoint	DOR	Time from the first occurrence of a documented objective response to the time of relapse, as determined by the investigator per RECIST v1.1, or death from any cause, whichever comes first, in the ITT and PD-L1 positive analysis set
Data cutoff	15-July-2021 (final analysis data cut-off date)		
Results and Analysis			

Analysis description	**Primary endpoint analysis – OS in ITT and PD-L1 positive subgroup**		
Analysis population and time point description	ITT and PD-L1 positive analysis set Time point: As of the data cut-off date of 15-July-2021, a total of 571 death events had occurred in the ITT Analysis Set, reaching the preplanned number of events in the final analysis for the primary endpoint.		
Descriptive statistics and estimate variability	Treatment group	Tislelizumab	Docetaxel
	ITT		
	Number of patients	535	270
	mOS (months)	16.9	11.9
	95% CI	15.24, 19.09	9.63, 13.54
	PD-L1 ≥ 25%		
	Number of patients	227	115
	mOS (months)	19.3	11.5
	95% CI	16.5, 22.6	8.2, 13.5
Effect estimate per comparison	**ITT**	Comparison groups	Tislelizumab vs. docetaxel
		HR	0.66
		95% CI	0.56, 0.79
		p-value	<0.0001
	PD-L1 ≥ 25%	Comparison groups	Tislelizumab vs. docetaxel
		HR	0.53
		95% CI	0.41, 0.70
Notes	Not applicable.		
Analysis description	**Secondary endpoint analysis - PFS in ITT and PD-L1 positive subgroup**		
Analysis population and time point description	ITT and PD-L1 positive analysis set		
Descriptive statistics and estimate variability	Treatment group	Tislelizumab	Docetaxel
	ITT		
	Number of patients	535	270
	mPFS (months)	4.2	2.6
	95% CI	3.88, 5.52	2.17, 3.78
	PD-L1 ≥ 25%		
	Number of patients	227	116
	mPFS (months)	6.5	2.5
	95% CI	6.24, 8.28	2.10, 4.11
Effect estimate per comparison	**ITT**	Comparison groups	Tislelizumab vs. docetaxel
		HR	0.63
		95% CI	0.53, 0.75

	PD-L1 ≥ 25%	Comparison groups	Tislelizumab vs. docetaxel
		HR	0.38
		95% CI	0.29, 0.49
Notes	Not applicable.		
Analysis description	**Secondary endpoint analysis - ORR in ITT and PD-L1 positive subgroup**		
Analysis population and time point description	ITT and PD-L1 positive analysis set		
Descriptive statistics and estimate variability	Treatment group	Tislelizumab	Docetaxel
	ITT		
	Number of patients	535	270
	ORR CR+PR (%)	112 (20.9)	10 (3.7)
	95% CI	17.56, 24.63	1.79, 6.71
	PD-L1 ≥ 25%		
	ORR CR+PR (%)	34.4	7.0
	95% CI	31.13, 44.09	3.05, 13.25
Notes	Not applicable.		
Analysis description	**Secondary endpoint analysis - DOR (Unconfirmed Response) in ITT and PD-L1 positive subgroup**		
Analysis population and time point description	ITT and PD-L1 positive analysis set		
Descriptive statistics and estimate variability	Treatment group	Tislelizumab	Docetaxel
	ITT		
	Number of patients	535	270
	mDOR (months)	13.5	6.0
	95% CI	8.54, 19.58	2.10, 7.16
	PD-L1 ≥ 25%		
	Number of patients	227	116
	mDOR (months)	11.9	4.2
	95% CI	8.31, 19.85	0.56, 6.05
Notes	Not applicable.		

Clinical studies in special populations

Table 44: Analysis of OS, PFS and confirmed ORR by age group (Study 303) (DCO: 15JUL2021)

	<65 years		65 - <75 years		>=75 years	
	Tislelizumab (N = 364)	Docetaxel (N = 180)	Tislelizumab (N =156)	Docetaxel (N = 79)	Tislelizumab (N =15)	Docetaxel (N = 11)
Overall survival (month)						
Median (95% CI)	17.6 (15.41, 20.57)	11.5 (9.63, 13.54)	17.2 (13.44, 23.69)	13.1 (7.49, 16.56)	7.5 (3.48, NE)	7.0 (2.73, NE)
Stratified HR (95% CI)	0.59 (0.463, 0.748)		0.67 (0.461, 0.974)		0.91 (0.289, 2.879)	
Progression-Free Survival (month)						
Median (95% CI)	4.0 (2.76, 4.24)	2.3 (2.10, 3.78)	6.0 (4.14, 7.75)	3.7 (2.23, 4.21)	3.5 (2.04, 8.31)	3.8 (2.10, 8.38)
Stratified HR (95% CI)	0.61 (0.493, 0.756)		0.55 (0.387, 0.770)		1.22 (0.371, 4.010)	
Objective response rate						
n (%)	65 (17.9)	7 (3.9)	41 (26.3)	3 (3.8)	1 (6.7)	0 (0.0)
95% CI	(14.06, 22.19)	(1.58, 7.85)	(19.57, 33.92)	(0.79, 10.70)	(0.17, 31.95)	(0.00, 28.49)

In vitro biomarker test for patient selection for efficacy

Assay used: VENTANA PD-L1 (SP263)

Analytical Performance

Cut-off TC25%

Sensitivity and Specificity

Analytical sensitivity and specificity of the VENTANA PD-L1 (SP263) CDx Assay is assessed by immunoreactivity testing on various normal and neoplastic tissues. The normal tissues were evaluated for the presence of any specific epithelial membrane staining. Neoplastic tissues were evaluated for tumour cell membrane staining and tumour-associated immune cell staining.

Repeatability and Intermediate Precision

Table 45: Repeatability and intermediate precision study of VENTANA PD-L1 (SP263) CDx assay on NSCLC tissue specimens – 25% TC cutoff

Repeatability/ Precision	Overall Percent Agreement (95%CI)
Intra-Day Repeatability (within a single day)	100.0% (96.9-100.0)*
Inter-Day Precision (5 non-consecutive days)	99.2% (97.0-99.8)*
Inter-Instrument Precision (across 3 ULTRA instruments)	98.6% (95.1-99.6)*

Lot-to-Lot Reproducibility

Table 46: Lot-to-lot reproducibility agreement rates across NSCLC tissue specimens at 25% TC cutoff

Lot to Lot Reproducibility	Positive Percent Agreement (95%CI)**	Negative Percent Agreement (95%CI)**	Overall Percent Agreement (95%CI)**
Average of all three lot-to-lot comparisons	99.2% (97.0-99.8)	97.5% (94.7-98.9)	98.4% (96.8-99.2)

** 2-sided 95% confidence intervals were calculated using the percentile bootstrap method from 2,000 bootstrap samples

Inter-and Intra-Reader Precision Studies

Table 47: Between and within reader precision of VENTANA PD-L1 (SP263) CDx Assay staining of NSCLC – 25% TC cutoff

Reader Precision (Average of all three readers)	Average Positive Agreement (95% CI)*	Average Negative Agreement (95% CI)*	Overall Percent Agreement (95% CI)*
Inter-Reader Precision	96.6% (93.8-98.8)	96.8% (93.9-98.9)	96.7% (94.2-98.9)
Intra-Reader Precision	96.2% (92.7-98.8)	96.4% (93.0-98.8)	96.3% (93.3-98.8)

* 2-sided 95% confidence intervals were calculated using the percentile bootstrap method from 2,000 bootstrap samples.

Clinical Performance

Tumour specimens from eligible patients were prospectively tested for PD-L1 expression by a central laboratory. The study enrolled all eligible patients whose tissue was evaluable for expression testing, regardless of PD-L1 expression status. The PD-L1 expression status remained blinded to BeiGene, patients, and investigators and only open to the Independent Data Monitoring Committee (IDMC).

Determination of the 25% cutoff for the PD-L1 expression level was chosen based on: (1) durvalumab studies in late-line NSCLC using the same PD-L1 kits with SP263 (Planchard et al 2016, Garassino et al 2017), and (2) NSCLC cohort data from Study 001 with tislelizumab. Both the durvalumab studies and Study 001 for tislelizumab suggest that patients with PD-L1 ≥ 25% had better clinical efficacy than PD-L1 < 25%. As such, the 25% PD L1 expression level was prespecified in the protocol to assess PD-L1 positive/negative status in Study 303. The 25% cutoff selection cannot be followed. The Applicant explained that data from published durvalumab studies (performed with the same assay) were considered. The cut-off was further validated in Study001 where PD-L1 ≥25% was determined as the most optimal cutoff based on statistical parameters relative to clinical response, as well as improved ORR and DCR.

To mitigate the risk of obtaining skewed PD-L1 distribution toward low expression due to competing studies enrolling only patients whose tumour PD-L1 expression was high, an adjustment to the enrolment was made by capping the PD-L1 negative and low population to ~60% of the ITT population. This was accomplished through the IWRT system such that the percentage of PD-L1 positive (≥ 25%) patients was no less than 40% of the ITT population (based on the reported prevalence of PD-L1 positivity of ~40% in the NSCLC population (Rebelatto et al 2016, Antonia et al

2017)). Capping was triggered towards the end of enrolment; thus, the impact could be low on the patient population selection in this study.

The percentage of PD-L1 high (60% of the study population) in the durvalumab study differs largely from the values tested in Study 303 (42%) which could be due to competing studies enrolling only patients whose tumour PD-L1 expression was high, as the applicant stated. This could, however, also indicate a low concordance between the data from durvalumab VENTANA PD-L1 (SP263) and data generated in this study. This issue is not further pursued, one should nevertheless take into consideration that PD-L1 expression data represent another uncertainty to the question of the external validity of the trial.

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

Not applicable.

Supportive study(ies)

Study 001

Study 001 was a Phase I open-label multiple dose study consisting of a Phase IA dose escalation and dose-finding component to establish the MTD, if any, and RP2D(s) followed by a Phase IB component to investigate the safety, tolerability, PK, and antitumour activity of tislelizumab in patients with advanced tumours including NSCLC.

Phase IA consisted of 3 parts. Part 1 was a multicentre, open-label, multiple-dose, dose-escalation, FIH study. Part 2 evaluated the safety and PK of 2 dosing schedules, once every 2 weeks vs. once every 3 weeks at selected doses. Part 3 evaluated the safety and PK of tislelizumab at a flat dose that did not exceed the exposure as determined in Part 1. Part 2 and Part 3 also evaluated preliminary efficacy.

Phase IB was a multicentre, open-label, multiple-dose (repeated dosing), multiple-arm, indication expansion study. The various arms of the study examined the potential efficacy, safety, and tolerability of tislelizumab in patients with cancer who had previously failed standard of care therapies.

The patients with NSCLC (n = 49) were treated at 5 mg/kg dose in Q3W dosing schedule.

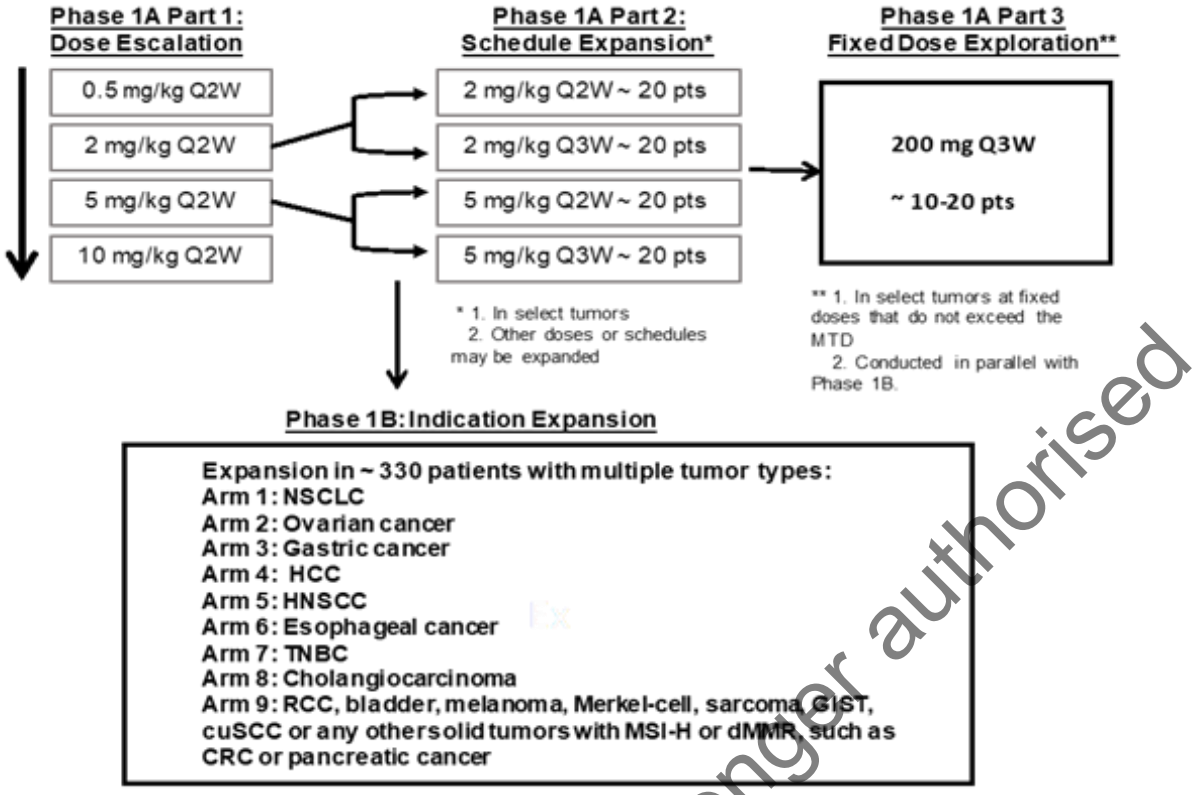


Figure 53: Study design FIH study (Study 001)

Table 48: Summary of treatment response by investigator (Study 001, phase 1B) (safety analysis set)

Overall Response Category	Arm 1 NSCLC (N = 49)
ORR (CR, PR)	
n (%)	6 (12.2)
(Exact 95% CI)	(4.63, 24.77)
Best Overall Response – Confirmed, n (%)	
CR	0 (0.0)
PR	6 (12.2)
SD	23 (46.9)
PD	13 (26.5)
Could not be determined	7 (14.3)
DCR (CR, PR, SD)	
n (%)	29 (59.2)
(Exact 95% CI)	(44.21, 73.00)
CBR (CR, PR, durable SD)	
n (%)	17 (34.7)
(Exact 95% CI)	(21.67, 49.64)
Time to Response (days)	
N	6
Mean (SD)	102.5 (51.02)
Median	91.0
Min, Max	62, 189

Table 49: Tumour response by PD-L1 expression status (Study 001) (safety analysis set)

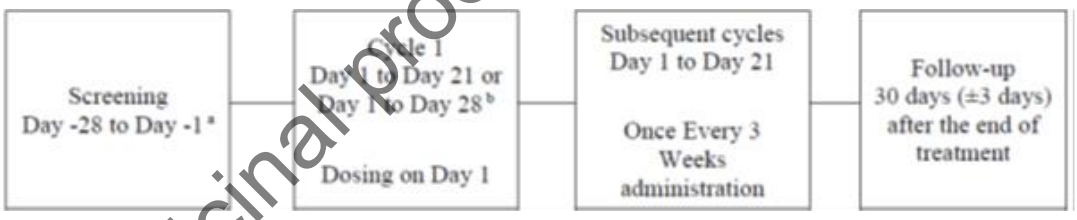
Overall Response Category	GC (N = 54)	EC (N = 54)	HCC (N = 50)	OC (N = 51)	NSCLC (N = 49)	TNBC (N = 21)	CRC (N = 21)	HNSCC (N = 20)	UBC (N = 17)	CC (N = 18)	RCC (N = 16)
Overall ORR [1] (CR, PR)											
n (%)	7 (13.0)	6 (11.1)	6 (12.0)	5 (9.8)	6 (12.2)	0 (0.0)	3 (14.3)	3 (15.0)	5 (29.4)	0 (0.0)	5 (31.3)
(Exact 95% CI)	(5.37, 24.90)	(4.19, 22.63)	(4.53, 24.31)	(3.26, 21.41)	(4.63, 24.77)	(0.00, 16.11)	(3.05, 36.34)	(3.21, 37.89)	(10.31, 55.96)	(0.00, 18.53)	(11.02, 58.66)
PD-L1 Expression Positive [2]	23	33	26	22	16	13	6	5	9	7	6
n (%) [3]	4 (17.4)	4 (12.1)	6 (23.1)	3 (13.6)	3 (18.8)	0 (0.0)	2 (33.3)	1 (20.0)	3 (33.3)	0 (0.0)	2 (33.3)
(Exact 95% CI)	(4.95, 38.78)	(3.40, 28.20)	(8.97, 43.65)	(2.91, 34.91)	(4.05, 45.65)	(0.00, 24.71)	(4.33, 77.72)	(0.51, 71.64)	(7.49, 70.07)	(0.00, 40.96)	(4.33, 77.72)
PD-L1 Expression Negative	22	16	19	22	21	6	12	13	7	5	9
n (%) [3]	1 (4.5)	1 (6.3)	0 (0.0)	2 (9.1)	2 (9.5)	0 (0.0)	1 (8.3)	1 (7.7)	1 (14.3)	0 (0.0)	3 (33.3)
(Exact 95% CI)	(0.12, 22.84)	(0.16, 30.23)	(0.00, 17.65)	(1.12, 29.16)	(1.17, 30.38)	(0.00, 45.93)	(0.21, 38.48)	(0.19, 36.03)	(0.36, 57.87)	(0.00, 52.18)	(7.49, 70.07)
PD-L1 Expression Unknown	9	5	5	7	12	2	3	2	1	6	1
n (%) [3]	2 (22.2)	1 (20.0)	0 (0.0)	0 (0.0)	1 (8.3)	0 (0.0)	0 (0.0)	1 (50.0)	1 (100.0)	0 (0.0)	0 (0.0)
(Exact 95% CI)	(2.81, 60.01)	(0.51, 71.64)	(0.00, 52.18)	(0.00, 40.96)	(0.21, 38.48)	(0.00, 84.19)	(0.00, 70.76)	(1.26, 98.74)	(2.50, 100.00)	(0.00, 45.93)	(0.00, 97.50)

Source: Table 14.2.6a, Listing 16.2.6.1
Abbreviations: CC, cholangiocarcinoma, colorectal cancer, pancreatic cancer; CI, confidence interval; CR, complete response; CRC, colorectal carcinoma; EC, esophageal cancer; GC, gastric cancer; HCC, hepatocellular cancer; HNSCC, head and neck squamous cell carcinoma; IC, immune cells; NSCLC, non-small cell lung cancer; ORR, overall response rate; OC, ovarian cancer; PD-L1, programmed death ligand 1; PR, partial response; RCC, renal cell carcinoma; TA, tumor area; TC, tumor cells; TNBC, triple negative breast cancer; UBC, urothelial bladder cancer.
[1] ORR = Objective Response Rate; Objective response (OR) is based on the confirmed CR or PR according to RECIST, Response Evaluation Criteria in Solid Tumors 1.1.
[2] GC: TC >=25% or IC>=25% ; EC: TC >=25% or IC>=25%; HCC: TC >=1%; OC: TC >=25% or IC>=25%; NSCLC: TC >=25%; TNBC: IC/TA>=1%; CRC: TC>=1%; HNSCC: TC>=25%; UBC: TC >=25% or IC>=25%; CC: TC >=1%; RCC: IC/TA>=1%.
[3] Percentages are calculated based on the total number of patients in each sub-category.
Database lock 26 August 2020.

Study 102

Study 102 was a two-phase, non-randomised, Phase 1/2 study of tislelizumab monotherapy in Chinese patients with advanced solid tumours.

The Phase 1 part of Study 102 was a multicentre and open-label study for the verification of tislelizumab dosing regimen identified in Study 001.



a Fresh tumour biopsy samples (optional) were collected within 42 days prior to the first dose of study drug if patients had no archival tumour tissue samples. Other screening assessments were completed within 28 days prior to the first dose of the study drug.

b The duration of the first cycle for the first 20 patients was 21 days, and DLT assessment was conducted in this period; the duration of the first cycle for the remaining 48 patients was 28 days, which was performed for the PK analyses of the products derived from 2 manufacturing processes and scales (500L-FMP versus 2000L-FMP).

Figure 54: Flow chart for Phase 1 (Study 102)

The Phase 2 of Study 102 was conducted as an indication-expansion study with the 200mg Q3W tislelizumab dose among the following 11 arms of indications to further assess the preliminary efficacy, safety, and PK of tislelizumab in Chinese patients with multiple malignant solid tumours. For the purpose of this submission, only data from the NSCLC arm is discussed in this report.

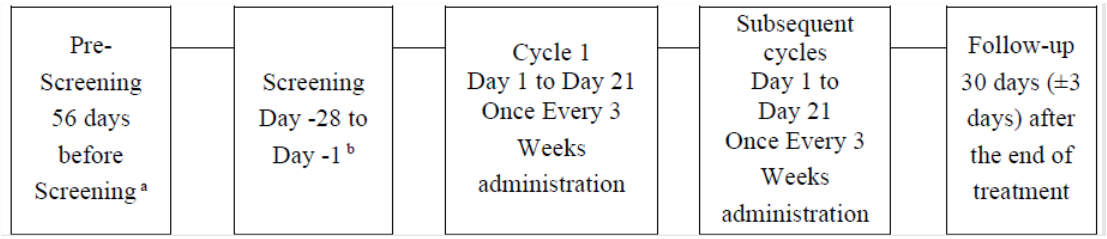


Figure 55: Flow chart for Phase 2 (Study 102)

The tumours evaluated include NSCLC; gastric cancer (GC); melanoma; oesophageal cancer; renal cell carcinoma (RCC); urothelial carcinoma (UC); microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) colorectal cancer; triple-negative breast cancer, head and neck squamous cell carcinoma, small cell neuroendocrine carcinoma or other tumours with known MSI-H or dMMR; nasopharyngeal carcinoma (NPC); and hepatocellular carcinoma including mixed hepatocellular and cholangiocellular carcinoma.

a Tumour samples and blood samples for detecting MSI or tumour samples for detecting MMR mutation status were collected during pre-screening period (≤ 8 weeks prior to screening period) from patients to be enrolled in arm 8 when their MSI/MMR mutation status was unknown.

b Fresh tumour biopsy samples were collected within 42 days prior to the first dosing if patients had no archival tumour tissue samples. Other screening assessments were completed within 28 days prior to the first dose of the study drug.

Objective response rate was a primary endpoint of the Phase 2 stage. There was no formal statistical testing for the efficacy endpoints; the efficacy analyses were descriptive only. Response was based on Investigators' judgment according to RECIST v1.1. OS was also collected.

Table 50: Baseline characteristics NSCLC population (Study 102)

Category	NSCLC (N=56)
Age(years)	
n	56
Mean (SD)	57.1 (9.88)
Median	58.0
Q1, Q3	51, 66
Min, Max	26, 72
Age Group, n (%)	
<65	40 (71.4)
≥65	16 (28.6)
Sex, n (%)	
Male	40 (71.4)
Female	16 (28.6)
ECOG Status, n (%)	
0	14 (25.0)
1	42 (75.0)
Weight (kg)	
n	56
Mean (SD)	65.25 (12.01)
Median	64.00
Q1, Q3	56.0, 72.3
Min, Max	43.0, 95.0
Alcohol Use, n (%)	
Never	36 (64.3)
Irregular	12 (21.4)
Prior regular use	8 (14.3)
Current regular use	0
Cigarettes Use, n (%)	
Never	23 (41.1)
Current	2 (3.6)
Former	31 (55.4)
Study Follow-up Duration (months) [1]	
n	56
Mean (SD)	18.29 (12.34)
Median	19.60
Q1, Q3	5.8, 28.6
Min, Max	0.2, 35.5

Table 51: Analysis of confirmed disease response per RECIST v1.1 (Study 102)

Response Category	NSCLC (N=56)	Melanoma (N=34)	ESCC (N=26)	GC (N=24)	UC (N=22)	NPC (N=21)
BOR per RECIST 1.1, n(%)						
CR (Complete Response, confirmed)	0	0	0	0	0	0
PR (Partial Response, confirmed)	10 (17.9)	6 (17.6)	2 (7.7)	4 (16.7)	4 (18.2)	10 (47.6)
SD (Stable Disease)	21 (37.5)	7 (20.6)	7 (26.9)	2 (8.3)	5 (22.7)	7 (33.3)
PD (Progressive Disease)	21 (37.5)	18 (52.9)	13 (50.0)	10 (41.7)	5 (22.7)	4 (19.0)
NE [1]	4 (7.1)	3 (8.8)	4 (15.4)	8 (33.3)	8 (36.4)	0
Objective Response Rate (ORR=CR+PR), n(%)	10 (17.9)	6 (17.6)	2 (7.7)	4 (16.7)	4 (18.2)	10 (47.6)
Exact 95% CI	(8.9, 30.4)	(6.8, 34.5)	(0.9, 25.1)	(4.7, 37.4)	(5.2, 40.3)	(25.7, 70.2)
Objective Response Rate, unconfirmed (ORR=CR+PR), n(%)	10 (17.9)	6 (17.6)	2 (7.7)	4 (16.7)	4 (18.2)	10 (47.6)
Exact 95% CI	(8.9, 30.4)	(6.8, 34.5)	(0.9, 25.1)	(4.7, 37.4)	(5.2, 40.3)	(25.7, 70.2)
Clinical Benefit Rate (CBR=CR+PR+Durable SD [2]), n(%)	30 (53.6)	12 (35.3)	7 (26.9)	6 (25.0)	8 (36.4)	17 (81.0)
Exact 95% CI	(39.7, 67.0)	(19.7, 53.5)	(11.6, 47.8)	(9.8, 46.7)	(17.2, 59.3)	(58.1, 94.6)
Clinical Benefit Rate (CBR=CR+PR+Durable SD [3]), n(%)	29 (51.8)	12 (35.3)	7 (26.9)	6 (25.0)	7 (31.8)	17 (81.0)
Exact 95% CI	(38.0, 65.3)	(19.7, 53.5)	(11.6, 47.8)	(9.8, 46.7)	(13.9, 54.9)	(58.1, 94.6)
Clinical Benefit Rate (CBR=CR+PR+Durable SD [4]), n(%)	19 (33.9)	11 (32.4)	4 (15.4)	6 (25.0)	6 (27.3)	13 (61.9)
Exact 95% CI	(21.8, 47.8)	(17.4, 50.5)	(4.4, 34.9)	(9.8, 46.7)	(10.7, 50.2)	(38.4, 81.9)
Disease Control Rate (DCR=CR+PR+SD), n(%)	31 (55.4)	13 (38.2)	9 (34.6)	6 (25.0)	9 (40.9)	17 (81.0)
Exact 95% CI	(41.5, 68.7)	(22.2, 56.4)	(17.2, 55.7)	(9.8, 46.7)	(20.7, 63.6)	(58.1, 94.6)
Time to Response (Weeks)						
n	10	6	2	4	4	10
Mean (SD)	11.87 (4.405)	18.17 (11.398)	8.86 (0.202)	11.46 (4.465)	15.54 (13.167)	18.00 (14.563)
Median	9.36	13.93	8.86	9.36	9.00	9.43
Q1, Q3	9.00, 17.14	9.14, 27.57	8.71, 9.00	9.00, 13.93	8.86, 22.21	9.00, 18.00
Min, Max	8.43, 19.29	8.43, 36.00	8.71, 9.00	9.00, 18.14	8.86, 35.29	8.86, 45.00

Among 56 patients with NSCLC, 33 (58.9%) patients had died as of the final data cutoff date. The median OS was 22.1 months (95% CI: 10.1 to 33.5). The cumulative probability of OS at 12 and 24 months was 0.6 (95% CI: 0.4 to 0.7) and 0.5 (95% CI: 0.4 to 0.6), respectively.

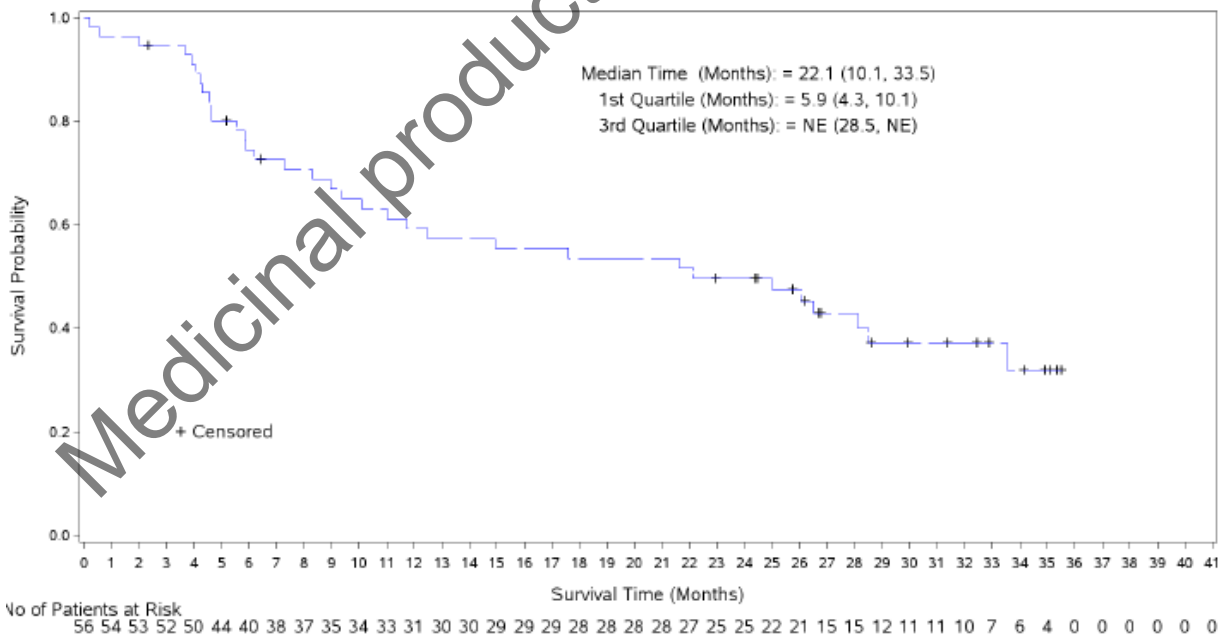


Figure 56: Kaplan-Meier plot of overall survival (Study 102) (safety analysis set)

PD-L1 expression on tumour cell membranes was assessed by the central laboratory using the VENTANA PD-L1 (SP263) assay. PD-L1 positivity was defined as ≥10% of tumour cells with PD-L1 membrane staining at any intensity. Response was observed regardless of PD-L1 expression levels. Of

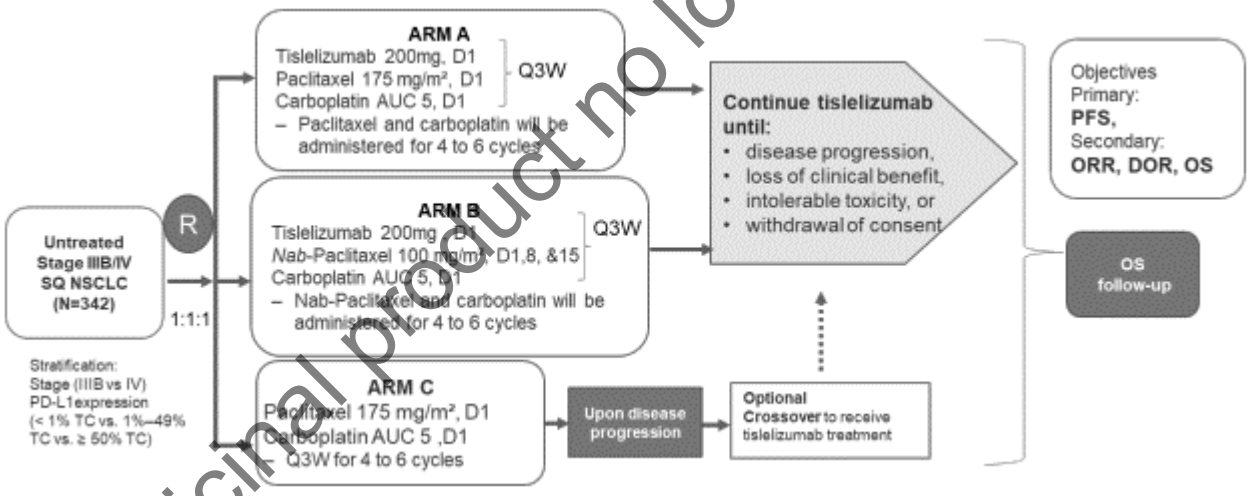
the 56 patients, there were 24 patients (42.9%) with PD-L1-positive NSCLC, 31 patients (55.4%) with PD-L1-negative NSCLC, and 1 patient (1.8%) with PD-L1 status unknown. ORR was 16.7% and 19.4% for patients with PD-L1-positive NSCLC and patients with PD-L1-negative NSCLC, respectively. The median OS was 22.1 months (95% CI: 11.0 to 28.5) for patients with PD-L1-positive NSCLC and 28.1 months (95% CI: 7.3 to NE) for patients with PD-L1-negative NSCLC, with a median survival follow-up time of 31.4 months (95% CI: 26.8 to 34.2).

2.5.5.3. Clinical efficacy of tislelizumab in combination with chemotherapy as 1L treatment of squamous NSCLC

Main study

<u>Study 307 (BGB-A317-307):</u> A Phase 3, Multicenter, Randomized Open-Label Study to Compare the Efficacy and Safety of Tislelizumab Combined With Paclitaxel Plus Carboplatin or Nab Paclitaxel Plus Carboplatin Versus Paclitaxel Plus Carboplatin Alone as First-Line Treatment for Untreated Advanced Squamous Non-small Cell Lung Cancer

Study 307 is a Phase III, 3-arm, open-label, randomised, multicentre study, conducted solely in China, designed to evaluate the efficacy and safety of tislelizumab in combination with carboplatin plus either paclitaxel (Arm T+PC) or nab-paclitaxel (Arm T+nPC) vs. paclitaxel plus carboplatin alone (Arm PC) as first-line treatment in 360 patients with Stage IIIB or IV squamous NSCLC. The study design schema is depicted below. The enrolment period was from 30-July-2018 to 13-Jun-2019.



Arm A = Arm T+PC; Arm B = Arm T+nPC; Arm C = Arm PC
Note: Patients with Stage IIIB disease were eligible for enrolment if their disease was not amenable to curative surgery or radiotherapy.

Figure 57: Study design (Study 307)

Methods

- **Study Participants**

Key inclusion criteria included:

1. 18 to 75 years old on the day of signing the informed consent form (ICF)
2. Histologically confirmed, locally advanced (Stage IIIB) not amenable to curative surgery or radiotherapy, or metastatic (Stage IV) squamous NSCLC

a. Patients with tumours of mixed non-small cell histology (squamous and non-squamous) were eligible if the major histological component appeared to be squamous.

3. Patients must have been able to provide fresh or archival tumour tissues (formalin-fixed paraffin-embedded blocks or approximately 15 [≥ 6] freshly cut unstained formalin-fixed paraffin-embedded slides) with an associated pathological report (squamous). In the absence of sufficient archival tumour tissues, a fresh biopsy of a tumour lesion at baseline was mandatory. PD-L1 expression was assessed centrally.
4. ECOG PS ≤ 1
5. Patients must have had ≥ 1 measurable lesion as defined per RECIST v1.1.
6. Must have been treatment-naive for locally advanced or metastatic squamous NSCLC.

   a. Patients who had received prior neoadjuvant, adjuvant chemotherapy, radiotherapy, or chemoradiotherapy with curative intent for nonmetastatic disease must have experienced a disease-free interval of ≥ 6 months from the last dose of chemotherapy and/or radiotherapy prior to randomisation.

Key exclusion criteria included:

1. Diagnosed with NSCLC that harbours an *EGFR*-sensitizing mutation or *ALK* gene translocation
2. Received any approved systemic anticancer therapy, including hormonal therapy within 28 days prior to initiation of study treatment
3. Treatment with systemic immune-stimulatory agents (including but not limited to interferons, interleukin 2, and tumour necrosis factor) within 4 weeks or 5 half-lives of the drug, whichever was longer, prior to randomisation (prior treatment with cancer vaccines was allowed)
4. Active leptomeningeal disease or uncontrolled, untreated brain metastasis

   a. Patients with a history of treated and, at the time of screening, asymptomatic CNS metastases were eligible, provided they met all the following:

      i. Brain imaging at screening showed no evidence of interim progression

      ii. Had measurable disease outside the CNS, only supratentorial metastases allowed

      iii. No ongoing requirement for corticosteroids as therapy for CNS disease; anticonvulsants at a stable dose allowed

      iv. No stereotactic radiation or whole-brain radiation within 14 days prior to randomisation

   b. Patients with new asymptomatic CNS metastases detected at the screening scan must have received radiation therapy and/or surgery for CNS metastases.

      i. Following treatment, these patients may have then been eligible, provided all other criteria, including those for patients with a history of brain metastases, were met.

5. Any major surgical procedure requiring general anaesthesia ≤ 28 days before randomisation
6. Any active malignancy ≤ 2 years before randomisation, except for the specific cancer under investigation in this study and any locally recurring cancer that had been treated curatively (e.g., resected basal or squamous cell skin cancer, superficial bladder cancer, carcinoma in situ of the cervix or breast)

7. Active autoimmune diseases or history of autoimmune diseases that may have relapsed Note: Patients with the following diseases were not excluded and may have proceeded to further screening:
    a. Controlled Type I diabetes
    b. Hypothyroidism (provided it was managed with hormone replacement therapy only)
    c. Controlled celiac disease
    d. Skin diseases not requiring systemic treatment (e.g., vitiligo, psoriasis, alopecia)
    e. Any other disease that was not expected to recur in the absence of external triggering factor

8. Any condition that required systemic treatment with either corticosteroids (> 10 mg daily of prednisone or equivalent) or other immunosuppressive medication ≤ 14 days before randomisation

- **Treatments**

Tislelizumab

Tislelizumab 200 mg was administered on Day 1 of each 3-week cycle, by intravenous infusion through an intravenous line containing a sterile, nonpyrogenic, low-protein-binding 0.2 or 0.22 micron in-line or add-on filter.

The initial infusion (Day 1 of Cycle 1) was delivered over 60 minutes; if it was well-tolerated, subsequent infusions were to be administered over 30 minutes, which was the shortest period permissible for infusion. Tislelizumab must not have been concurrently administered with any other drug.

As a routine precaution, after infusion of tislelizumab on Day 1 of Cycle 1 and Cycle 2, patients were monitored for ≥ 1 hour afterward in an area with resuscitation equipment and emergency agents. From Cycle 3 onward, a monitoring period of ≥ 30 minutes was required in an area with resuscitation equipment and emergency agents.

Chemotherapy

Paclitaxel 175 mg/m^2 was administered as an intravenous infusion over 3 hours on Day 1 of each cycle, **for 4 to 6 cycles**. In addition, all patients received the appropriate premedications as per the local approved label and standard practice.

Nab-paclitaxel 100 mg/m2 was administered as an intravenous infusion over 30 minutes on Day 1, Day 8, and Day 15 of each cycle **for 4 to 6 cycles**. All patients received the appropriate premedications as per the local approved label and standard practice.

Carboplatin given at AUC 5 mg/mL/min was administered as an intravenous infusion over 15 minutes on Day 1 of each cycle, **for 4 to 6 cycles** immediately after paclitaxel or nab-paclitaxel. Additional premedications were administered as per standard practice.

When clinically feasible, premedication with steroids was limited due to their immunomodulatory effects.

Table 52: Treatments (Study 307)

Study drug	Dose	Frequency of administration	Route of administration
Tislelizumab	200 mg	D1 of each cycle	Intravenous
Paclitaxel	175 mg/m^2	Day 1 of each cycle	Intravenous
Nab-paclitaxel	100 mg/m^2	D1, D8, and D15 of each cycle	Intravenous
Carboplatin	AUC 5	D1 of each cycle	Intravenous

Abbreviations: AUC, area under the plasma or serum concentration-time curve

Note: Treatment of paclitaxel or *nab*-paclitaxel was determined at randomisation. Chemotherapy was administered on a 3-week cycle.

Tumour assessments were conducted every 6 weeks for the first 6 months, then every 9 weeks for the remainder of the first year, then every 12 weeks until disease progression.

- **Objectives**

Assess the efficacy and safety of tislelizumab in combination with chemotherapy as 1L treatment of squamous NSCLC.

- **Outcomes/endpoints**

Primary Efficacy Endpoint

Progression Free Survival (per IRC)

To compare the **PFS** as assessed by the Independent Review Committee (IRC) per Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 in an Intent-to-Treat (ITT) Analysis Set between tislelizumab either combined with paclitaxel + carboplatin (Arm A) or combined with nab-paclitaxel + carboplatin (Arm B) and paclitaxel + carboplatin alone (Arm C) in patients with untreated Stage IIIB or Stage IV (as classified according to American Joint Committee Cancer 7th Edition of Cancer Staging Manual) squamous NSCLC.

Secondary Efficacy Endpoints

Overall Survival

To compare **OS** between tislelizumab combined with paclitaxel + carboplatin or nab-paclitaxel + carboplatin and paclitaxel + carboplatin alone in the ITT Analysis Set.

Progression Free Survival (per investigator)

To compare **PFS** as assessed by the investigator per RECIST v1.1 between tislelizumab combined with paclitaxel + carboplatin or nab-paclitaxel + carboplatin and paclitaxel + carboplatin alone in the ITT Analysis Set.

Objective Response Rate (per IRC and per investigator)

To compare **ORR** as assessed by the IRC and by the investigator per RECIST v1.1 between tislelizumab combined with paclitaxel + carboplatin or nab-paclitaxel + carboplatin and paclitaxel + carboplatin alone.

Duration of Response (per IRC and per investigator)

To compare **DOR** as assessed by the IRC and by the investigator per RECIST v1.1 between tislelizumab combined with paclitaxel + carboplatin or carboplatin + nab-paclitaxel and paclitaxel + carboplatin alone.

Health-related Quality of Life

To compare HRQoL between tislelizumab combined with paclitaxel + carboplatin or nab-paclitaxel + carboplatin an paclitaxel + carboplatin alone.

Others

To evaluate the safety and tolerability of tislelizumab combined with paclitaxel + carboplatin or nab-paclitaxel + carboplatin compared with paclitaxel + carboplatin alone.

To evaluate the correlation between **PD-L1 expression levels by** immunohistochemistry and antitumour activity of tislelizumab combined with paclitaxel + carboplatin or nab-paclitaxel + carboplatin.

- **Sample size**

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

1. A one-sided α of 0.025 and 80% power to detect a HR of 0.65, corresponding to an improvement in median PFS from 6 months to 9.2 months, in the PFS of A versus C comparison.

2. A one-sided α of 0.025 and 80% power to detect a HR of 0.65, corresponding to an improvement in median PFS from 6 months to 9.2 months, in the PFS of B versus C comparison.

3. One planned interim analysis for both A versus C and B versus C comparisons when ~75% of the targeted PFS events have occurred, with Lan-DeMets O'Brien-Fleming approximation spending function.

4. Dropout rate of 5% per 12 months in PFS evaluation

With these assumptions, a total of approximately 173 PFS events were planned to be required for each primary comparison of Arm A versus Arm C or Arm B versus Arm C at final analysis for PFS. Assuming 342 patients were to be enrolled and randomised at a 1:1:1 ratio over a 11.5-month period at a steady-state enrolment rate of 40 patients per month and enrolment ramp up duration of six month, i.e., enrolment rate of 10 patients per month from study Month 0 to Month 2, 20 patients per month from Month 2 to Month 4, 30 patients per month from Month 4 to Month 6, and 40 patients per month afterwards.

- **Randomisation and Blinding (masking)**

Patients were planned to be randomised at a 1:1:1 ratio in one of the three arms by using the IRT system for this study by permuted block stratified randomisation with stratification factors of Stage (IIIB versus IV) and PD-L1 expression in TC (≥ 50% TC versus 1% - 49% TC versus < 1% TC).

This study was open-label.

- **Statistical methods**

Analysis Sets

The ITT Analysis Set was planned to include all randomised patients. Patients were planned to be analysed according to their randomised treatment arms. This was planned to be the primary analysis set for efficacy analysis.

The Safety Analysis Set was planned to include all patients who received ≥ 1 dose of study drug; it was planned to be the analysis set for the safety analyses.

The PK Analysis Set was planned to include all patients who receive ≥ 1 dose of tislelizumab per the protocol, for whom any postdose PK data were available.

Primary Endpoint

The primary endpoint PFS per the IRC was defined as the time from randomisation to the first documented disease progression as assessed by the IRC with the use of RECIST v1.1, or death from any cause, whichever occurred first. The actual tumour assessment visit date was planned to be used to calculate PFS. Data for patients without disease progression or death at the time of analysis were planned to be censored at the time of the last valid tumour assessment. Data for patients without postbaseline tumour assessment were planned to be censored at the time of randomisation. Data for patients who started to receive new anticancer therapy or were lost to follow-up were planned to be censored at the last valid tumour assessment date prior to the introduction of new therapy or loss to follow-up. Patients who had a clinical determination of progression were planned to undergo a CT/MRI, if possible, to correlate radiographic findings with the clinical findings. If a clinical determination of progression for a patient was confirmed, the date of the CT/MRI scan was planned to be considered as the progression date for that patient.

PFS per the IRC was planned to be compared between tislelizumab combined with paclitaxel + carboplatin (Arm A) and paclitaxel + carboplatin (Arm C), and between tislelizumab combined with nab-paclitaxel + carboplatin (Arm B) and paclitaxel + carboplatin (Arm C), using stratified log-rank test methodology. The two primary hypothesis tests were formed as follows:

One-sided testing of PFS superiority of Arm A to Arm C:

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

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

One-sided testing of PFS superiority of Arm B to Arm C:

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

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

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

Secondary Endpoints

Overall Survival

OS was defined as the time from randomisation to death from any cause. Data for patients who were not reported as having died at the time of analysis were planned to be censored at the date last known to be alive. Data for patients without postbaseline information were planned be censored at the date of randomisation. Similar methodology used to evaluate PFS per the IRC were planned to be applied to OS analysis.

Progression-Free Survival per Investigator

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

Objective Response Rate per the IRC and per the Investigator

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

Duration of Response per the IRC and per the Investigator

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

Health-Related Quality of Life

Summary statistics (mean, standard deviation, median, and range) of the post-baseline scores and changes from baseline were planned to be reported for the EORTC questionnaires (QLQ-C30 and QLQ-LC13). Line charts depicting the mean changes (and standard errors) over time from the baseline assessment were planned to be provided for each treatment arm. The proportion of patients showing clinically meaningful changes in selected items and subscales at each assessment time point were planned to be calculated. Completion and compliance rates were planned to be summarised at each time point by treatment arm. Only patients in the ITT Analysis Set with a non-missing baseline assessment and at least one in-study non-missing post-baseline assessment were planned to be included in the analyses.

PD-L1 Expression as a Predictive Biomarker for Response

Distribution of PD-L1 expression in TC were planned to be examined in the ITT Analysis Set. Association between PD-L1 expression and tislelizumab treatment effect over control (PFS, OS, ORR, DOR, DCR) were planned to be explored.

Multiplicity

The overall Type I error for primary endpoint PFS per IRC that compared between Arm A versus Arm C or Arm B versus Arm C at the interim and final analyses was planned to be strongly controlled at an alpha of 0.025 by using sequential testing procedure. Hypothesis testing for the primary endpoint of PFS (Arm A vs C followed by Arm B vs C) was planned to be carried out sequentially, each at a one-sided alpha of 0.025, until the first non-rejection. The alpha allocation algorithm is described below:

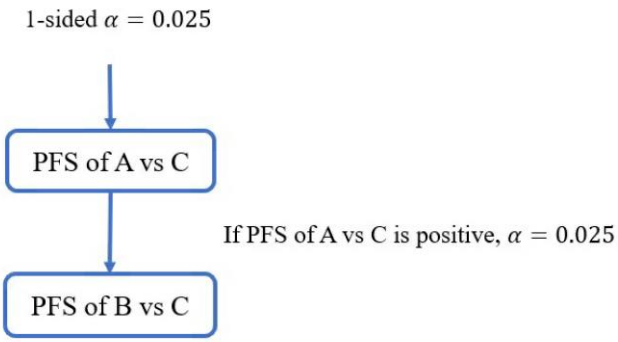


Figure 58: Type I error control scheme (Study 307)

Interim Analyses

One interim efficacy analysis of PFS was planned in each comparison performed in the ITT

Analysis Set. For the PFS endpoint, the interim efficacy analysis was planned to be performed after approximately 130 PFS events (75% of the target number of approximately 173 PFS events) would have been observed in each comparison of A versus C or B versus C. It was estimated that it would take approximately 17 months to accumulate the required number of PFS events. The final analysis for

PFS was planned to be performed after approximately 173 PFS events have been observed and it was estimated that this would occur at approximately 24 months after the first patient was randomised.

An independent statistical review was planned to be conducted to determine if the required number of events had occurred in two arms of A vs C or B vs. C. If the time of observing the targeted number of events in each comparison was different from each other, the analysis could be separate.

The interim boundary was based on Lan-DeMets O'Brien-Fleming approximation spending function.

The interim and final analyses timing and stopping boundaries for PFS are summarised in Table 53 below. The times and boundaries for the interim and final analysis were based on protocol-defined

enrolment and PFS assumptions. They were planned to be updated according to the actual PFS events included at the interim and final analyses using Lan-DeMets spending function.

Table 53: Analysis timing and stopping boundaries for PFS in each of the primary testing at one-sided α=0.025 (Study 307)

Type of analysis	Number of events	Expected time (months)	Testing boundary	
			p-value boundary	Approx. hazard ratio threshold
Interim analysis	130	16.7	0.0097	0.6637
Final analysis	173	23.8	0.0221	0.7364

Subgroup Analyses

Subgroup analysis of primary endpoint of PFS per the IRC were planned to be conducted to determine whether the treatment effect is consistent across various subgroups, and the HR estimates of PFS and its 95% CI were planned to be estimated and plotted within each category of the following variables: PD-L1 expression in TC (≥ 50% TC versus 1% to 49% TC versus < 1% TC), Stage (IIIB versus IV), age (≤ 65 versus > 65 years), gender (female versus male), ECOG PS (0 versus 1), and smoking status (former versus current versus never).

Results

- **Participant flow**

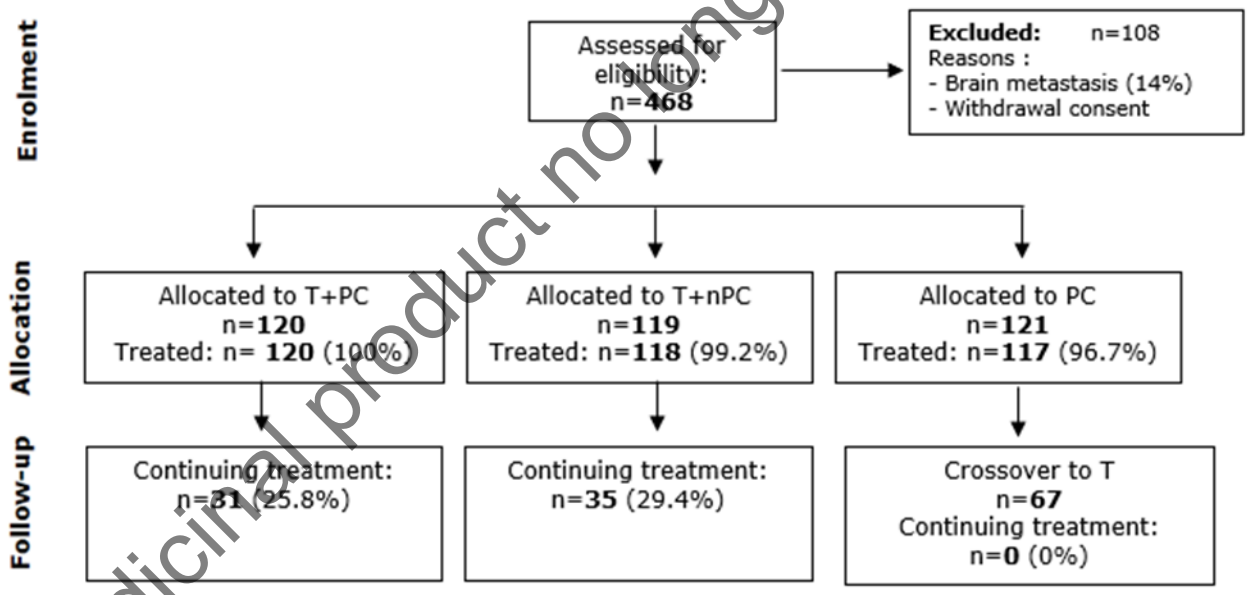


Table 54: Patient disposition and reasons for discontinuation (ITT analysis set) (Study 307) (DCO: 30SEP2020)

	T+PC (N = 120) n (%)	T+*n*PC (N = 119) n (%)	PC (N = 121) n (%)	Total (N = 360) n (%)
Number of Patients Randomized	120 (100.0)	119 (100.0)	121 (100.0)	360 (100.0)
Patients Randomized, but not Treated	0 (0.0)	1 (0.8)	4 (3.3)	5 (1.4)
Number of Patients Treated	120 (100.0)	118 (99.2)	117 (96.7)	355 (98.6)
Number of Patients Discontinued from All Study Drugs	89 (74.2)	84 (70.6)	117 (96.7)	290 (80.6)
Primary Reason for Treatment Discontinuation				
Progressive Disease	54 (45.0)	51 (42.9)	9 (7.4)	114 (31.7)
Complete Chemotherapy	1 [a] (0.8)	0 (0.0)	81 (66.9)	82 (22.8)
Adverse Event	16 (13.3)	14 (11.8)	16 (13.2)	46 (12.8)
Voluntary Withdrawal	9 (7.5)	11 (9.2)	8 (6.6)	28 (7.8)
Physician Decision	5 (4.2)	5 (4.2)	2 (1.7)	12 (3.3)
Start of a New Anticancer Therapy	1 (0.8)	1 (0.8)	0 (0.0)	2 (0.6)
Lost to Follow-Up	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.3)
Non-Compliance with Study Drug	0 (0.0)	0 (0.0)	1 (0.8)	1 (0.3)
Other	2 (1.7)	2 (1.7)	0 (0.0)	4 (1.1)
Number of Patients Remained on Treatment [b]	31 (25.8)	34 (28.6)	0 (0.0)	65 (18.1)
Number of Patients Discontinued from Study	51 (42.5)	52 (43.7)	68 (56.2)	171 (47.5)
Primary Reason for Study Discontinuation				
Death	48 (40.0)	47 (39.5)	52 (43.0)	147 (40.8)
Voluntary Withdrawal	3 (2.5)	4 (3.4)	14 (11.6)	21 (5.8)
Lost to Follow-Up	0 (0.0)	0 (0.0)	1 (0.8)	1 (0.3)
Other	0 (0.0)	1 (0.8)	1 (0.8)	2 (0.6)
Number of Patients Remained on Study	69 (57.5)	67 (56.3)	53 (43.8)	189 (52.5)
Study Follow-up Time (Months) [c]				
Median	16.97	17.15	16.13	16.66
Min, Max	1.0, 26.1	0.1, 24.2	0.1, 23.5	0.1, 26.1

Source: ADSL. Data cutoff: 30SEP2020. Data extraction: 20FEB2021.
Abbreviations: PC, Paclitaxel+Carboplatin; T+PC, Tislelizumab+Paclitaxel+Carboplatin; T+*n*PC, Tislelizumab+*nab*-Paclitaxel+Carboplatin.
Primary reason for treatment discontinuation referred to primary reason for the discontinuation of the last study drug administered.

- **Recruitment**

This study is ongoing (start date 20-Jul-2018). Patients were enrolled in 43 centres in China. Median follow up time at final analysis (DCO: 30 September 2020): 16.7 month.

- **Conduct of the study**

Amendment 1.0 (dated 27 April 2018)

• Updated NCI-CTCAE version from v4.03 to v5.0

• Updated the frequency for tumour assessments

• Updated the reasons for patients to discontinue the study treatment or discontinue study

• Clarified the guidance regarding dose modifications for tislelizumab and chemotherapy

• Added "total CK and creatine kinase cardiac muscle isoenzyme" to laboratory assessments

• Clarified the visits and the frequency to assess irAEs and concomitant medications during safety follow-up

• Updated contents of interim analysis and sample size consideration by adjusting O'Brien-Fleming boundary per Center for Drug Evaluation comments

• Changed the frequency for the data review by IDMC from "every 4 months" to "every 6 months"

• Added the diagnostic tests and treatment for myocarditis/myositis (irAE evaluation and management) according to FDA requirements

• Replaced the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation in Appendix 7 with more commonly used formula (Cockcroft-Gault Formula and Calvert Formula)

Amendment 1.0 Addendum 1 (dated 22 May 2018)

• Added details for serum CK and creatine kinase cardiac muscle isoenzyme testing

• Updated the diagnostic tests and treatment for myocarditis (irAE evaluation and management) Amendment 2.0 (dated 14 December 2018)

• Clarified the criteria for squamous NSCLC staging in the primary objective

• Updated the inclusion criteria to allow patients with unevaluable PD-L1 status to participate in this study

• Added prophylaxis antiviral therapy for patients with inactive HBsAg, treated and stable hepatitis B (HBV DNA < 500 IU/mL) to permitted concomitant medications

• Added the guidance on pulmonary function assessment

• Clarified the safety assessment schedule for patients who crossed over to tislelizumab monotherapy

• Incorporated the changes made in addendum to protocol amendment 1.0 and updated the information regarding serum CK and creatine kinase cardiac muscle isoenzyme testing

Amendment 3.0 (dated 16 August 2019)

• Updated the statistical method to control overall Type I error for hypothesis tests of PFS in each comparison of Arm A versus Arm C or Arm B versus Arm C

• Changed HR assumption of PFS from 0.6 to 0.65, and increased the number of PFS events at both interim and final analyses

• Changed the method for HRQoL analysis from model-based method to descriptive method

• Updated the tumour assessments for treatment beyond progression and for crossover

• Added biomarker sample collection procedure for patients who cross over to tislelizumab monotherapy

• Updated the definition of study termination

- **Baseline data**

Table 55: Demographics and baseline characteristics (ITT analysis set) (Study 307) (DCO: 30SEP2020)

	T+PC (N = 120) n (%)	T+*n*PC (N = 119) n (%)	PC (N = 121) n (%)	Total (N = 360) n (%)
Age (years)				
Median	60.0	63.0	62.0	62.0
Min, Max	41, 74	38, 74	34, 74	34, 74
Age Group, n (%)				
< 65 years	81 (67.5)	67 (56.3)	85 (70.2)	233 (64.7)
≥ 65 years	39 (32.5)	52 (43.7)	36 (29.8)	127 (35.3)
BMI (kg/m^2)				
Median	22.27	22.41	22.29	22.29
Min, Max	16.9, 34.9	17.4, 31.9	15.2, 29.6	15.2, 34.9
Sex, n (%)				
Male	107 (89.2)	112 (94.1)	111 (91.7)	330 (91.7)
Female	13 (10.8)	7 (5.9)	10 (8.3)	30 (8.3)
ECOG Performance Status, n (%)				
0	31 (25.8)	22 (18.5)	32 (26.4)	85 (23.6)
1	89 (74.2)	97 (81.5)	89 (73.6)	275 (76.4)
Smoking Status, n (%)				
Never	24 (20.0)	12 (10.1)	23 (19.0)	59 (16.4)
Current	24 (20.0)	21 (17.6)	27 (22.3)	72 (20.0)
Former	72 (60.0)	86 (72.3)	71 (58.7)	229 (63.6)
Baseline Target Lesions Sum of Diameters by Investigator (mm)				
Median	77.20	82.70	83.00	80.50
Min, Max	17.1, 205.3	15.0, 207.1	15.0, 196.0	15.0, 207.1
Current Disease Stage, n (%)				
IIIB	38 (31.7)	40 (33.6)	44 (36.4)	122 (33.9)
IV	82 (68.3)	79 (66.4)	77 (63.6)	238 (66.1)
PD-L1 Expression in Tumor Cell, n (%)				
<1% [a]	48 (40.0)	47 (39.5)	49 (40.5)	144 (40.0)
1%-49%	30 (25.0)	30 (25.2)	31 (25.6)	91 (25.3)
≥ 50%	42 (35.0)	42 (35.3)	41 (33.9)	125 (34.7)
Patients with any Prior Anticancer Drug Therapy, n (%)	12 (10.0)	10 (8.4)	7 (5.8)	29 (8.1)
Type of Prior Anticancer Drug Therapy, n (%) [bc]				
Adjuvant	10 (83.3)	4 (40.0)	4 (57.1)	18 (62.1)
Neoadjuvant	1 (8.3)	6 (60.0)	2 (28.6)	9 (31.0)
Locally Advanced	0 (0.0)	1 (10.0)	1 (14.3)	2 (6.9)
Metastatic	1 (8.3)	0 (0.0)	0 (0.0)	1 (3.4)
Patients with any Prior Anticancer Surgeries, n (%)	12 (10.0)	9 (7.6)	8 (6.6)	29 (8.1)
Patients with any Prior Anticancer Radiotherapy, n (%)	5 (4.2)	6 (5.0)	5 (4.1)	16 (4.4)

Source: ADSL, ADBASE. Data cutoff: 30SEP2020. Data extraction: 20FEB2021.
Abbreviations: PC, Paclitaxel+Carboplatin; T+PC, Tislelizumab+Paclitaxel+Carboplatin; T+*n*PC, Tislelizumab+*nab*-Paclitaxel+Carboplatin.
[a] There were 6 patients with not evaluable PD-L1 status in the < 1% subgroup; 1 in Arm T+PC, 1 in Arm T+*n*PC, and 4 in Arm PC.
[b] A patient was counted only once within each category, but may be counted in multiple categories.
[c] Percentages were based on the number of patients with any prior anticancer drug therapy.

Table 56: Disease characteristics (ITT analysis set) (Study 307) (DCO: 30SEP2020)

	T+PC (N = 120) n (%)	T+*n*PC (N = 119) n (%)	PC (N = 121) n (%)	Total (N = 360) n (%)
Time from Initial Diagnosis to Study Entry [a] (Day)				
Median	28.5	30.0	30.0	30.0
Min, Max	11, 1315	9, 3199	10, 1490	9, 3199
Time from Advanced/Metastatic Disease Diagnosis to Study Entry [a] (Days)				
Median	19.0	19.0	21.0	20.0
Min, Max	-7, 243	-70, 225	1, 198	-70, 243
Histology, n (%)				
Squamous Cell Carcinoma	120 (100.0)	118 (99.2)	120 (99.2)	358 (99.4)
Mixed Adeno-Squamous	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	1 (0.8)	1 (0.8)	2 (0.6)
Baseline Target Lesion Location, n (%) [b]				
Lung	111 (92.5)	110 (92.4)	112 (92.6)	333 (92.5)
Bone	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.3)
Liver	11 (9.2)	11 (9.2)	7 (5.8)	29 (8.1)
Other [c]	64 (53.3)	68 (57.1)	69 (57.0)	201 (55.8)
Location of Distant Metastases, n (%) [b]				
Bone	24 (20.0)	16 (13.4)	21 (17.4)	61 (16.9)
Liver	15 (12.5)	15 (12.6)	14 (11.6)	44 (12.2)
Brain	2 (1.7)	3 (2.5)	1 (0.8)	6 (1.7)

Source: ADSL, ADBASE. Data cutoff: 30SEP2020. Data extraction: 20FEB2021.
Abbreviations: PC, Paclitaxel+Carboplatin; T+PC, Tislelizumab+Paclitaxel+Carboplatin; T+*n*PC, Tislelizumab+*nab*-Paclitaxel+Carboplatin.
[a] Study Entry date referred to randomization date in this study.
[b] A patient was counted only once within each category, but may be counted in multiple categories.
[c] Other included brain, lymph node, muscle, peritoneum, pleura, soft tissue, and other types of lesions not specified.

- **Numbers analysed**

Table 57: Analysis sets (Study 307) (DCO: 30SEP2020)

	T+PC (N = 120) n (%)	T+*n*PC (N = 119) n (%)	PC (N = 121) n (%)	Total (N = 360) n (%)
ITT Analysis Set	120 (100.0)	119 (100.0)	121 (100.0)	360 (100.0)
Safety Analysis Set	120 (100.0)	118 (99.2)	117 (96.7)	355 (98.6)
PK Analysis Set	120 (100.0)	118 (99.2)	NA	238 (66.1)
HRQoL Analysis Set	120 (100.0)	118 (99.2)	117 (96.7)	355 (98.6)

Source: ADSL. Data cutoff: 30SEP2020. Data extraction: 20FEB2021.
Abbreviations: NA, not applicable; PC, Paclitaxel+Carboplatin; T+PC, Tislelizumab+Paclitaxel+Carboplatin; T+*n*PC, Tislelizumab+*nab*-Paclitaxel+Carboplatin.

- **Outcomes and estimation**

The efficacy results presented in this report are based on the interim analysis (**data cutoff 06 December 2019**, with a median follow-up time of 8.4 months) and final analysis of efficacy data (**data cutoff date of 30 September 2020**, with a median follow-up time of 16.7 months).

As of the data cutoff date of 30 September 2020, a total of 245 PFS events per IRC across three arms were observed (166 in the comparison of Arm T+PC versus Arm PC and 165 in the comparison of Arm T+nPC versus Arm PC in the ITT Analysis Set).

Primary Endpoint

Progression Free Survival

Table 58: Analysis of progression-free survival per RECIST version 1.1 by independent review committee (ITT analysis set) (Study 307); interim analysis (DCO: 06DEC2019)

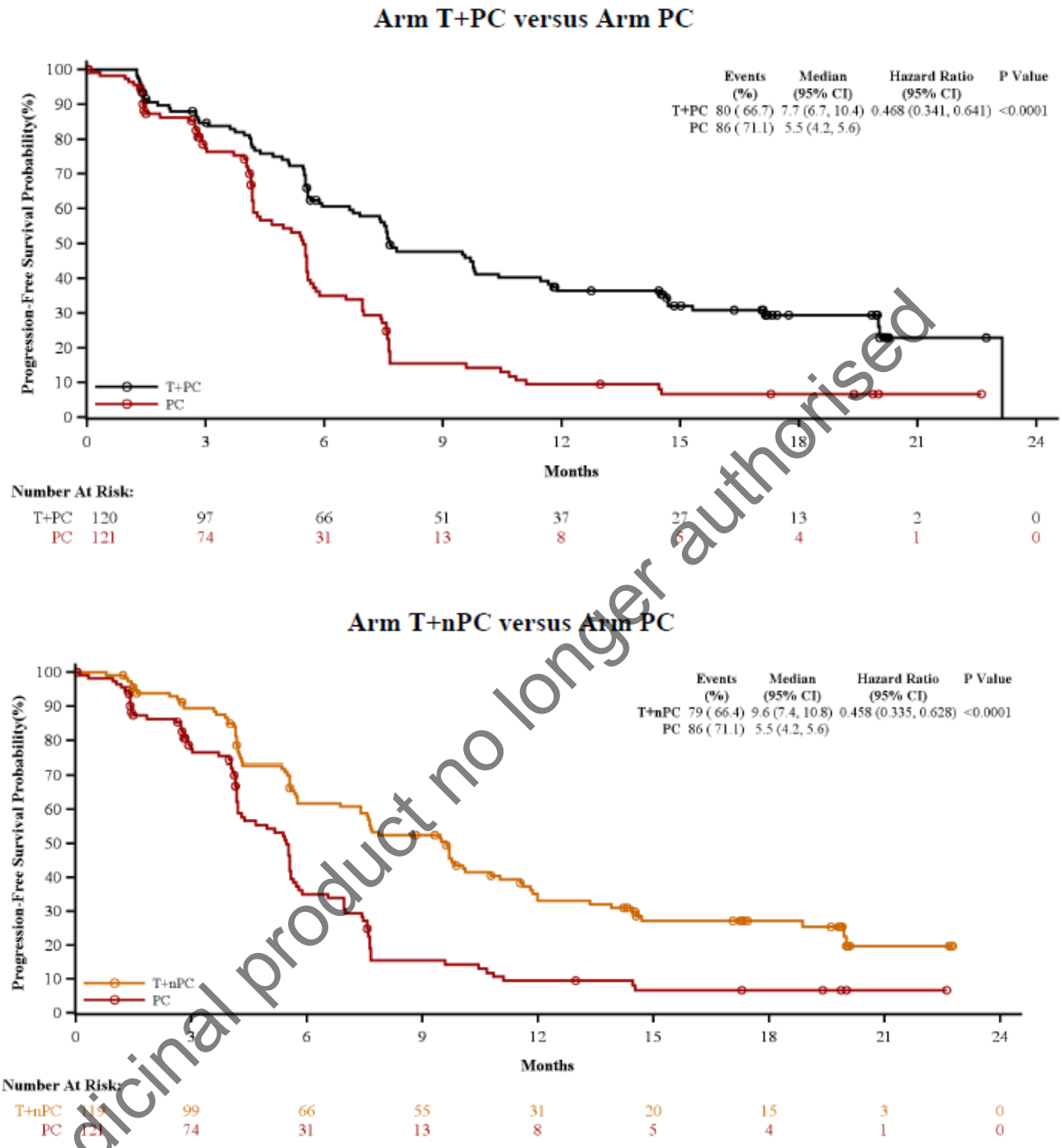
	T+PC (N = 120)	T+*n*PC (N = 119)	PC (N = 121)
Progression-Free Survival			
Events, n (%)	60 (50.0)	56 (47.1)	**75 (62.0)**
Progressive Disease	55 (45.8)	51 (42.9)	**71 (58.7)**
Death	5 (4.2)	5 (4.2)	4 (3.3)
Censored, n (%)	60 (50.0)	63 (52.9)	**46 (38.0)**
One-sided stratified log-rank test p-value [a]	**<0.0001**	<0.0001	
Stratified Hazard Ratio (95% CI) [a]	**0.483 (0.340, 0.686)**	**0.450 (0.316, 0.642)**	
Progression-Free Survival (month)			
Median (95% CI)	7.6 (5.95, 9.79)	7.6 (5.75, 11.01)	**5.4** (4.21, **5.59**)
Q1 (95% CI)	4.4 (3.06, 5.52)	4.2 (4.11, 5.55)	4.0 (2.73, 4.14)
Q3 (95% CI)	NE (10.41, NE)	NE (11.01, NE)	**7.4 (5.78, 7.66)**
Event Free Rate at, % (95% CI)			
3 month (95% CI)	83.7 (75.69, 89.31)	88.5 (80.95, 93.13)	**77.2 (67.91, 84.13)**
6 month (95% CI)	59.1 (49.16, 67.76)	58.4 (48.26, 67.27)	**32.5 (22.79, 42.58)**
9 month (95% CI)	41.7 (30.94, 52.09)	47.2 (36.46, 57.17)	**13.5 (6.66, 22.78)**
12 month (95% CI)	32.4 (19.99, 45.49)	35.7 (23.07, 48.47)	NE (NE, NE)

Source: ADSL, ADTTE. Data cutoff: 06DEC2019. Data extraction: 07JAN2020.
Abbreviations: T+PC, Tislelizumab+Paclitaxel+Carboplatin; T+*n*PC, Tislelizumab+*nab*-Paclitaxel+Carboplatin; PC, Paclitaxel+Carboplatin; NE, not estimable.
Medians and other quartiles were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley. Event free rates were estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula. Paclitaxel+Carboplatin was the reference group for hazard ratio. [a] Stratified by stratification factors: disease stage (IIIB versus IV) and PD-L1 expression in tumor cell (≥ 50% TC versus 1%-49% TC versus <1% TC).

Table 59: Analysis of progression-free survival per RECIST version 1.1 by independent review committee (ITT analysis set) (Study 307); final analysis (DCO: 30SEP2020)

	T+PC (N = 120)	T+*n*PC (N = 119)	PC (N = 121)
Progression-Free Survival			
Events, n (%)	80 (66.7)	79 (66.4)	86 (71.1)
Progressive Disease	74 (61.7)	74 (62.2)	82 (67.8)
Death	6 (5.0)	5 (4.2)	4 (3.3)
Censored, n (%)	40 (33.3)	40 (33.6)	35 (28.9)
Consent Withdrawn	1 (0.8)	0 (0.0)	4 (3.3)
Lost to Follow Up	0 (0.0)	0 (0.0)	0 (0.0)
Ongoing without Event	32 (26.7)	25 (21.0)	5 (4.1)
No Baseline Tumor Assessment	0 (0.0)	0 (0.0)	0 (0.0)
No Postbaseline Tumor Assessment	1 (0.8)	4 (3.4)	9 (7.4)
New Anticancer Therapy	5 (4.2)	8 (6.7)	13 (10.7)
Death or Progression after Missing 2 or More Consecutive Tumor Assessments	1 (0.8)	3 (2.5)	4 (3.3)
One-sided stratified log-rank test p-value [a]	<0.0001	<0.0001	
Stratified Hazard Ratio (95% CI) [a]	0.450 (0.326, 0.619)	0.428 (0.308, 0.595)	
Progression-Free Survival (months)			
Median (95% CI)	7.7 (6.74, 10.41)	9.6 (7.39, 10.78)	5.5 (4.21, 5.59)
Q1 (95% CI)	4.7 (3.61, 5.52)	4.3 (4.14, 5.55)	4.0 (2.76, 4.17)
Q3 (95% CI)	20.0 (14.69, 23.13)	19.9 (11.99, NE)	7.6 (6.54, 7.66)
Event Free Rate at, % (95% CI)			
3 months (95% CI)	84.6 (76.70, 90.02)	89.4 (82.03, 93.82)	77.5 (68.25, 84.31)
6 months (95% CI)	60.7 (51.10, 68.98)	61.8 (51.99, 70.15)	35.1 (25.51, 44.86)
9 months (95% CI)	47.8 (38.28, 56.68)	52.4 (42.64, 61.30)	15.4 (8.80, 23.76)
12 months (95% CI)	36.5 (27.58, 45.44)	33.1 (24.21, 42.26)	9.5 (4.48, 16.79)
18 months (95% CI)	29.4 (20.79, 38.42)	27.1 (18.70, 36.24)	6.8 (2.66, 13.58)
24 months (95% CI)	0.0 (NE, NE)	NE (NE, NE)	NE (NE, NE)

Source: ADSL, ADTTE. Data cutoff: 30SEP2020. Data extraction: 20FEB2021.
Abbreviations: NE, not estimable; PC, Paclitaxel+Carboplatin; T+PC, Tislelizumab+Paclitaxel+Carboplatin; T+*n*PC, Tislelizumab+*nab*-Paclitaxel+Carboplatin.
Medians and other quartiles were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley. Event-free rates were estimated by Kaplan-Meier method with 95% CIs estimated using Greenwood's formula. Paclitaxel+Carboplatin was the reference group for hazard ratio.
[a] Stratified by stratification factors: disease stage (IIIB versus IV) and PD-L1 expression in tumor cell (≥ 50% TC versus 1%-49% TC versus <1% TC).



Source: ADSL, ADTTE. Data cutoff: 30SEP2020. Data extraction: 20FEB2021.
Abbreviations: PC, Paclitaxel+Carboplatin; T+PC, Tislelizumab+Paclitaxel+Carboplatin; T+*n*PC, Tislelizumab+*nab*-Paclitaxel+Carboplatin.

Figure 59: Kaplan-Meier plots of progression-free survival per RECIST version 1.1 by independent review committee (ITT analysis set) (Study 307); final analysis (DCO: 30SEP2020)

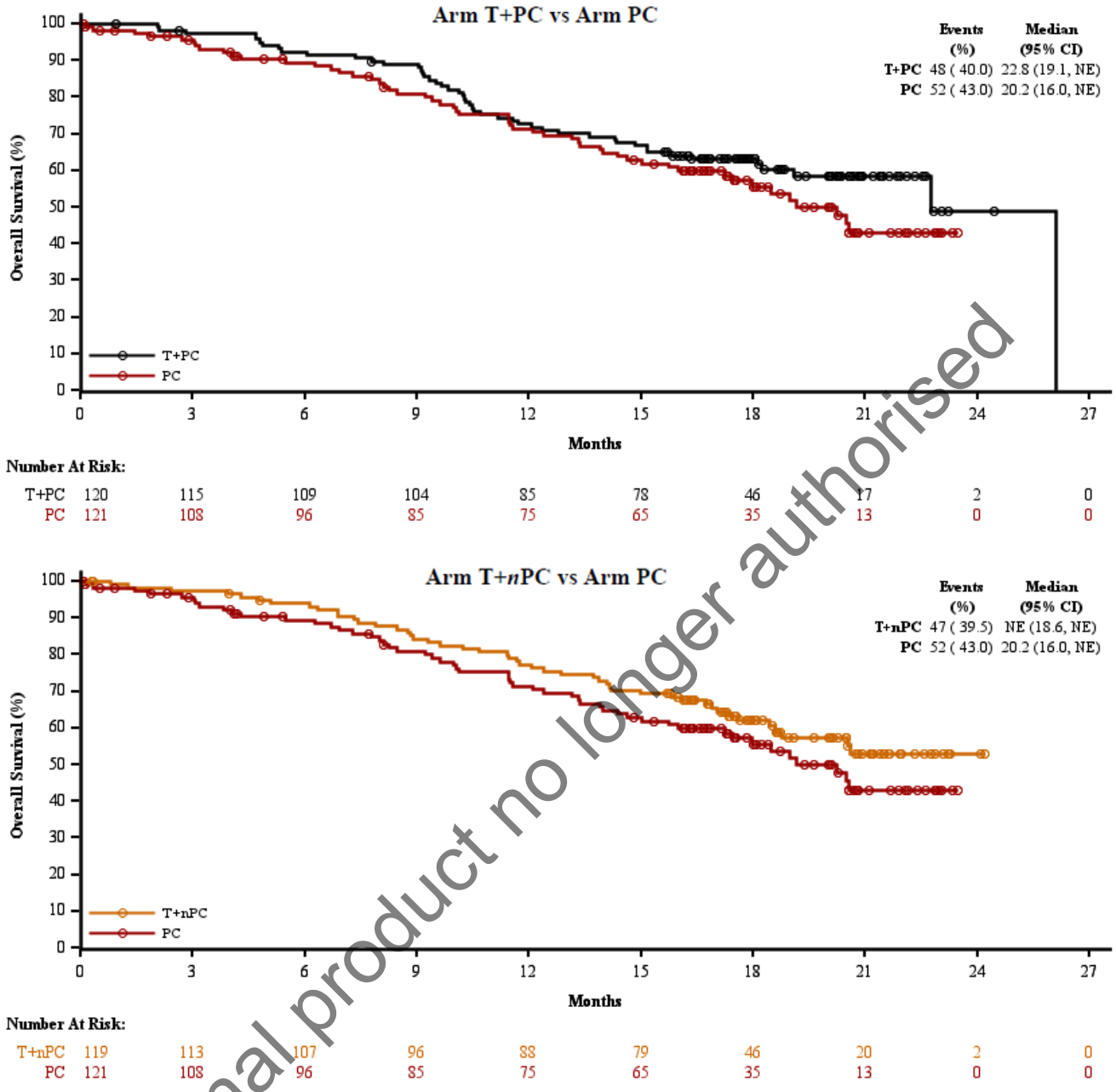
Secondary endpoints

Overall Survival

Table 60: Analysis of overall survival (ITT analysis set) (Study 307); final analysis (DCO: 30SEP2020)

	T+PC (N = 120)	T+*n*PC (N = 119)	PC (N = 121)
Overall Survival			
Death, n (%)	48 (40.0)	47 (39.5)	52 (43.0)
Censored, n (%)	72 (60.0)	72 (60.5)	69 (57.0)
Ongoing in the Study	69 (57.5)	67 (56.3)	53 (43.8)
Withdrawal by Subject	3 (2.5)	4 (3.4)	14 (11.6)
Lost to Follow-up	0 (0.0)	0 (0.0)	1 (0.8)
Study Discontinuation Due to Other Reasons	0 (0.0)	1 (0.8)	1 (0.8)
Stratified Hazard Ratio (95% CI) [a]	0.678 (0.455, 1.010)	0.752 (0.504, 1.120)	-
Overall Survival (months)			
Median (95% CI)	22.8 (19.09, NE)	NE (18.56, NE)	20.2 (15.97, NE)
Q1 (95% CI)	11.2 (9.66, 14.82)	12.8 (9.63, 16.76)	11.4 (8.11, 13.37)
Q3 (95% CI)	26.1 (NE, NE)	NE (NE, NE)	NE (NE, NE)
Event Free Rate at, % (95% CI)			
3 months (95% CI)	97.5 (92.37, 99.18)	97.4 (92.20, 99.16)	95.7 (90.01, 98.19)
6 months (95% CI)	92.4 (85.88, 95.96)	93.9 (87.70, 97.06)	89.4 (82.13, 93.86)
9 months (95% CI)	89.0 (81.79, 93.45)	84.3 (76.21, 89.79)	81.0 (72.30, 87.17)
12 months (95% CI)	72.7 (63.70, 79.87)	77.3 (68.42, 83.90)	71.4 (61.91, 79.00)
15 months (95% CI)	66.7 (57.42, 74.47)	69.4 (60.01, 76.93)	62.9 (52.98, 71.25)
18 months (95% CI)	63.2 (53.77, 71.24)	62.0 (52.10, 70.40)	55.7 (45.27, 64.83)
21 months (95% CI)	58.6 (48.46, 67.46)	52.8 (41.42, 63.03)	43.1 (31.18, 54.42)
24 months (95% CI)	48.9 (28.94, 66.11)	52.8 (41.42, 63.03)	NE (NE, NE)
Follow-up Time (months)			
Median (95% CI)	18.8 (17.94, 20.27)	18.9 (18.04, 20.50)	18.1 (17.31, 20.01)

Source: ADSL, ADTTE. Data cutoff: 30SEP2020. Data extraction: 20FEB2021.
Abbreviations: PC, Paclitaxel+Carboplatin; T+PC, Tislelizumab+Paclitaxel+Carboplatin; T+*n*PC, Tislelizumab+*nab*-Paclitaxel+Carboplatin.
Median follow-up time was estimated by the reverse Kaplan-Meier method. One-sided p-value was estimated from log rank test for descriptive purpose only. Medians and other quartiles were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley. Event free rates were estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula. Paclitaxel+Carboplatin arm was the reference group for hazard ratio.
[a] Stratified by stratification factors: disease stage (IIIB versus IV) and PD-L1 expression in tumor cell (≥ 50% TC versus 1%-49% TC versus <1% TC).



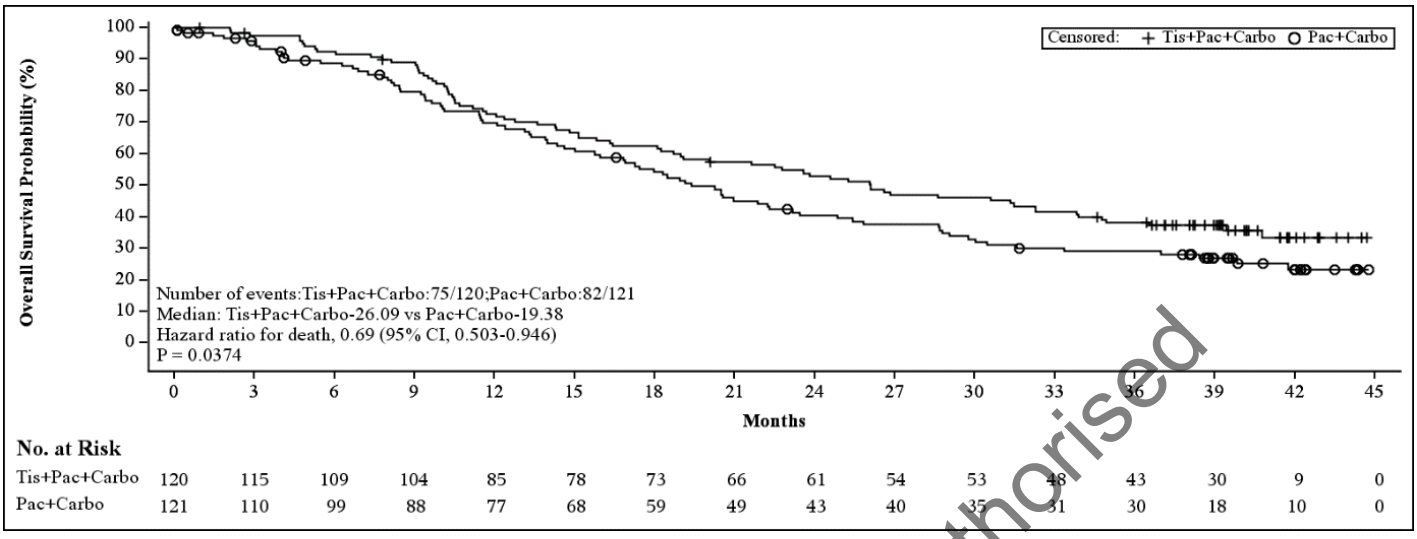
Source: ADSL, ADTTE. Data cutoff: 30SEP2020. Data extraction: 20FEB2021.
Abbreviations: PC, Paclitaxel+Carboplatin; T+PC, Tislelizumab+Paclitaxel+Carboplatin; T+*n*PC, Tislelizumab+*nab*-Paclitaxel+Carboplatin.

Figure 60: Kaplan-Meier Plot of overall survival (ITT analysis set) (Study 307); Final analysis (DCO: 30SEP2020)

Overall Survival – Updated data

As the OS data were considered not mature, OS analyses based on the most recent data extraction with a data cutoff date of **15-July-2022,** with a median study follow up of 20.5 months were provided during the assessment. At this cut-off date, the degree of maturity for OS for T+PC arm and T+nPC arm was 62.5% (75/120) and 70.6% (84/119) respectively and the fraction of cross over was app. **44 %.**

T+PC vs PC



T+nPC vs PC

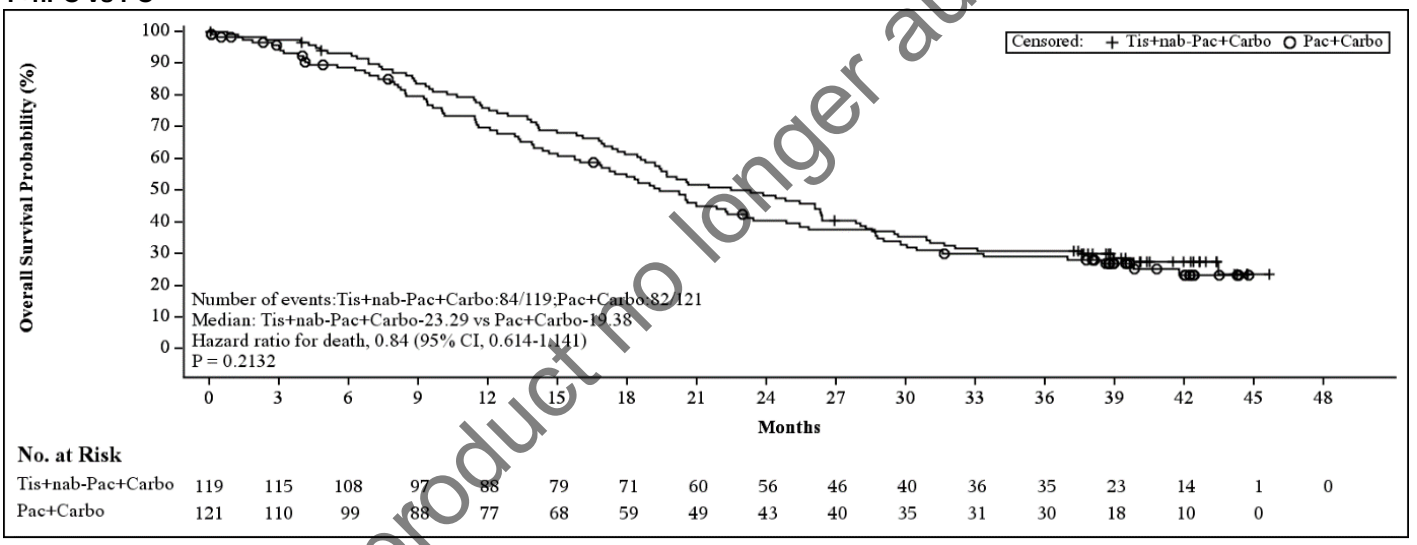


Figure 61: Kaplan-Meier plot of overall survival (ITT Analysis Set) (Study 307); Updated data (DCO: 15JUL2022)

Progression-Free Survival (per Investigator)

Table 61: Analysis of progression-free survival per RECIST version 1.1 by investigator (ITT analysis set) (Study 307); final analysis (DCO: 30SEP2020)

	T+PC (N = 120)	T+*n*PC (N = 119)	PC (N = 121)
Progression-Free Survival			
Events, n (%)	78 (65.0)	79 (66.4)	88 (72.7)
Progressive Disease	70 (58.3)	73 (61.3)	82 (67.8)
Death	8 (6.7)	6 (5.0)	6 (5.0)
Censored, n (%)	42 (35.0)	40 (33.6)	33 (27.3)
Stratified Hazard Ratio (95% CI) [a]	0.341 (0.245, 0.473)	0.403 (0.289, 0.564)	-
Progression-Free Survival (months)			
Median (95% CI)	9.6 (7.62, 11.76)	9.9 (8.57, 11.86)	5.5 (4.21, 5.65)
Q1 (95% CI)	5.7 (5.32, 7.52)	5.6 (4.30, 7.39)	4.0 (2.83, 4.14)
Q3 (95% CI)	23.2 (14.52, 23.16)	18.9 (14.36, NE)	7.6 (6.97, 7.66)
Event-Free Rate at, % (95% CI)			
3 months (95% CI)	92.1 (85.41, 95.82)	92.9 (86.22, 96.36)	80.2 (71.22, 86.62)
6 months (95% CI)	72.4 (63.18, 79.75)	69.9 (60.40, 77.59)	38.1 (28.43, 47.64)
9 months (95% CI)	54.5 (44.85, 63.19)	59.7 (49.88, 68.24)	15.2 (8.82, 23.25)
12 months (95% CI)	36.1 (27.28, 45.05)	38.9 (29.64, 47.96)	10.2 (4.95, 17.53)
18 months (95% CI)	27.8 (18.84, 37.43)	25.6 (17.40, 34.64)	7.4 (3.04, 14.37)
24 months (95% CI)	0.0 (NE, NE)	NE (NE, NE)	NE (NE, NE)

Source: ADSL, ADTTE. Data cutoff: 30SEP2020. Data extraction: 20FEB2021.
Abbreviations: NE, not estimable; PC, Paclitaxel+Carboplatin; T+PC, Tislelizumab+Paclitaxel+Carboplatin; T+*n*PC, Tislelizumab+*nab*-Paclitaxel+Carboplatin.
One-sided p-value was estimated from log rank test for descriptive purpose only. Medians and other quartiles were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley. Event free rates were estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula. Paclitaxel+Carboplatin was the reference group for hazard ratio.
[a] Stratified by stratification factors: disease stage (IIIB versus IV) and PD-L1 expression in tumor cell (≥ 50% TC versus 1%-49% TC versus <1% TC).

Objective Response Rate (per IRC)

Table 62: Analysis of unconfirmed disease response per RECIST version 1.1 by independent review committee (ITT analysis set) (Study 307); final analysis (DCO: 30SEP2020)

	T+PC (N = 120)	T+*n*PC (N = 119)	PC (N = 121)
Best Overall Response - unconfirmed, n (%)			
Complete Response	7 (5.8)	8 (6.7)	1 (0.8)
Partial Response	82 (68.3)	80 (67.2)	57 (47.1)
Stable Disease	16 (13.3)	20 (16.8)	39 (32.2)
Progressive Disease	12 (10.0)	5 (4.2)	11 (9.1)
Not Evaluable	0 (0.0)	0 (0.0)	0 (0.0)
Missing	3 (2.5)	6 (5.0)	12 (9.9)
Objective Response Rate (ORR), n (%)	89 (74.2)	88 (73.9)	58 (47.9)
95% CI	(65.4, 81.7)	(65.1, 81.6)	(38.8, 57.2)
Odds Ratio (95% CI)	3.36 (1.923, 5.881)	3.16 (1.819, 5.489)	
ORR Difference, % (95% CI)	27.0 (15.38, 38.66)	26.1 (14.33, 37.93)	
Disease Control Rate, n (%)	105 (87.5)	108 (90.8)	98 (81.0)
95% CI	(80.2, 92.8)	(84.1, 95.3)	(72.9, 87.6)

Source: ADSL, ADRS. Data cutoff: 30SEP2020. Data extraction: 20FEB2021.
Abbreviations: PC, Paclitaxel+Carboplatin; T+PC, Tislelizumab+Paclitaxel+Carboplatin; T+*n*PC, Tislelizumab+*nab*-Paclitaxel+Carboplatin.
Best overall response of missing was due to no post-baseline tumor assessment. 95% CI was calculated using Clopper-Pearson method. Objective response rate differences and odds ratios between arms were calculated using the Cochran-Mantel-Haenszel Chi-square test with actual stratification factors as strata. Paclitaxel+Carboplatin arm was the reference group.

Of note, only unconfirmed ORR results were prespecified. The Applicant provided post-hoc analysis of confirmed ORR (DCO 30 Sep 2020) results.

Table 63: Analysis of confirmed disease response per RECIST version 1.1 (efficacy analysis set) (Study 307) (DCO: 30SEP2020)

	Study 307		
	T+PC (N = 120)	T+nPC (N = 119)	PC (N = 121)
Best Overall Response [a], n (%)			
Complete Response	7 (5.8)	6 (5.0)	1 (0.8)
Partial Response	67 (55.8)	68 (57.1)	44 (36.4)
Stable Disease	31 (25.8)	34 (28.6)	52 (43.0)
Non-CR/Non-PD	0 (0.0)	0 (0.0)	1 (0.8)
Progressive Disease	12 (10.0)	5 (4.2)	11 (9.1)
Could not be Determined	3 (2.5)	6 (5.0)	12 (9.9)
Objective Response Rate (ORR), n (%)	74 (61.7)	74 (62.2)	45 (37.2)
95% CI	(52.4, 70.4)	(52.8, 70.9)	(28.6, 46.4)
Disease Control Rate, n (%)	105 (87.5)	108 (90.8)	98 (81.0)
95% CI	(80.2, 92.8)	(84.1, 95.3)	(72.9, 87.6)
Clinical Benefit Rate [b], n (%)	100 (83.3)	102 (85.7)	87 (71.9)
95% CI	(75.4, 89.5)	(78.1, 91.5)	(63.0, 79.7)
Clinical Benefit Rate [c], n (%)	86 (71.7)	86 (72.3)	57 (47.1)
95% CI	(62.7, 79.5)	(63.3, 80.1)	(38.0, 56.4)

[a] confirmed CR or PR is required in 307.

[b] Included patients with BOR in CR or PR or ≥12 weeks SD.

[c] Included patients with BOR in CR or PR or ≥24 weeks SD.

Best overall response of could not be determined include patients who had post-baseline tumour assessment, none of which were evaluable; or patients who had no post-baseline tumour assessment, and non-CR/non-PD was due to no measurable target lesion per IRC. Results were summarised based on data as assessed by independent review committee for study 307. Objective Response Rate was the proportion of Patients who achieved CR or PR using RECIST version 1.1. Disease Control Rate was the proportion of Patients who achieved CR, PR, non-CR/non-PD or SD using RECIST version 1.1.

Objective Response Rate (per Investigator)

Table 64: Analysis of unconfirmed disease response per RECIST version 1.1 by investigator (ITT analysis set) (Study 307); final analysis (DCO: 30SEP2020)

	T+PC (N = 120)	T+*n*PC (N = 119)	PC (N = 121)
Best Overall Response - unconfirmed, n (%)			
Complete Response	1 (0.8)	0 (0.0)	0 (0.0)
Partial Response	83 (69.2)	93 (78.2)	60 (49.6)
Stable Disease	27 (22.5)	17 (14.3)	45 (37.2)
Progressive Disease	4 (3.3)	2 (1.7)	5 (4.1)
Not Evaluable	2 (1.7)	1 (0.8)	0 (0.0)
Missing	3 (2.5)	6 (5.0)	11 (9.1)
Objective Response Rate (ORR), n (%)	84 (70.0)	93 (78.2)	60 (49.6)
95% CI	(61.0, 78.0)	(69.6, 85.2)	(40.4, 58.8)
Odds Ratio (95% CI)	2.56 (1.486, 4.410)	3.60 (2.052, 6.309)	--
ORR Difference, % (95% CI)	21.3 (9.47, 33.17)	28.8 (17.14, 40.50)	--
Disease Control Rate, n (%)	111 (92.5)	110 (92.4)	105 (86.8)
95% CI	(86.2, 96.5)	(86.1, 96.5)	(79.4, 92.2)

Source: ADSL, ADRS. Data cutoff: 30SEP2020. Data extraction: 20FEB2021.
Abbreviations: PC, Paclitaxel+Carboplatin; T+PC, Tislelizumab+Paclitaxel+Carboplatin; T+*n*PC, Tislelizumab+*nab*-Paclitaxel+Carboplatin.
Missing: Patients without post-baseline tumor assessment. 95% CI was calculated using Clopper-Pearson method. Objective response rate differences and odds ratios between arms were calculated using the Cochran-Mantel-Haenszel Chi-square test with actual stratification factors as strata. Paclitaxel+Carboplatin arm was the reference group.

Duration of Response (by IRC)

Table 65: Analysis of duration of response based on unconfirmed responses per RECIST version 1.1 by independent review committee (ITT analysis set) (Study 307); final analysis (DCO: 30SEP2020)

	T+PC (N = 120)	T+*n*PC (N = 119)	PC (N = 121)
Number of Responders	89	88	58
Duration of Response			
Events, n (%)	53 (59.6)	56 (63.6)	44 (75.9)
Progressive Disease	50 (56.2)	54 (61.4)	43 (74.1)
Death	3 (3.4)	2 (2.3)	1 (1.7)
Censored, n (%)	36 (40.4)	32 (36.4)	14 (24.1)
Duration of Response (months)			
Median (95% CI)	8.4 (5.03, 15.80)	8.6 (7.13, 12.48)	4.3 (2.86, 5.42)
Q1 (95% CI)	3.6 (2.79, 4.34)	4.2 (2.76, 6.28)	2.8 (1.77, 2.86)
Q3 (95% CI)	21.7 (18.69, 21.72)	NE (13.27, NE)	6.2 (5.42, 13.14)
Event Free Rate at, % (95% CI)			
6 months (95% CI)	59.8 (48.59, 69.38)	69.0 (57.86, 77.70)	30.6 (18.49, 43.55)
12 months (95% CI)	43.9 (33.04, 54.15)	39.9 (29.13, 50.41)	16.1 (7.43, 27.64)
18 months (95% CI)	38.5 (27.61, 49.36)	26.4 (16.16, 37.84)	9.6 (2.93, 21.22)
24 months (95% CI)	0.0 (NE, NE)	NE (NE, NE)	NE (NE, NE)

Source: ADSL, ADTTE. Data cutoff: 30SEP2020. Data extraction: 20FEB2021.
Abbreviations: NE, not estimable; PC, Paclitaxel+Carboplatin; T+PC, Tislelizumab+Paclitaxel+Carboplatin; T+*n*PC, Tislelizumab+*nab*-Paclitaxel+Carboplatin.
Percentages were based on number of responders. Duration of response analysis included patients with objective response. Medians and other quartiles were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley. Event free rates were estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula.

Duration of Response (per Investigator)

Table 66: Analysis of duration of response based on unconfirmed responses per RECIST version 1.1 by investigator (ITT analysis set) (Study 307); final analysis (DCO: 30SEP2020)

	T+PC (N = 120)	T+*n*PC (N = 119)	PC (N = 121)
Number of Responders	84	93	60
Duration of Response			
Events, n (%)	48 (57.1)	62 (66.7)	46 (76.7)
Progressive Disease	46 (54.8)	59 (63.4)	44 (73.3)
Death	2 (2.4)	3 (3.2)	2 (3.3)
Censored, n (%)	36 (42.9)	31 (33.3)	14 (23.3)
Duration of Response (months)			
Median (95% CI)	10.6 (7.03, 21.75)	8.8 (8.05, 11.10)	4.8 (2.86, 6.11)
Q1 (95% CI)	6.2 (4.40, 6.74)	4.8 (4.14, 6.80)	2.8 (2.66, 2.86)
Q3 (95% CI)	21.7 (NE, NE)	NE (12.71, NE)	6.3 (6.11, 13.14)
Event-Free Rate at, % (95% CI)			
6 months (95% CI)	76.8 (66.13, 84.55)	70.5 (60.03, 78.75)	39.8 (26.72, 52.58)
12 months (95% CI)	48.1 (36.88, 58.51)	37.3 (27.28, 47.30)	16.4 (7.86, 27.73)
18 months (95% CI)	38.2 (26.16, 50.10)	28.6 (19.03, 38.83)	12.3 (5.10, 22.93)
24 months (95% CI)	0.0 (NE, NE)	NE (NE, NE)	NE (NE, NE)

Source: ADSL, ADTTE. Data cutoff: 30SEP2020. Data extraction: 20FEB2021.
Abbreviations: NE, not estimable; PC, Paclitaxel+Carboplatin; T+PC, Tislelizumab+Paclitaxel+Carboplatin; T+*n*PC, Tislelizumab+*nab*-Paclitaxel+Carboplatin.
Percentages were based on number of responders. Duration of response analysis included patients with objective response. Medians and other quartiles were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley. Event free rates were estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula.

Health-Related Quality of Life

Patients in Arm T+PC and Arm T+nPC had similar HRQoL outcomes to those in Arm PC as measured by the key PRO endpoint of EORTC QLQ-C30 GHS/QoL and in lung cancer-specific symptoms of coughing, chest pain and dyspnoea. The median time to deterioration (TTD) for QLQ-C30 GHS/QoL was not reached in all treatment arms; the median TTD for the composite of cough, chest pain, and dyspnoea scores in Arm T+PC reached only in Arm T+PC of 5.7 months (95% CI: 3.06, NE).

- **Ancillary analyses**

Sensitivity analysis 1 for PFS

Sensitivity Analysis 1 evaluated the impact of censoring the primary endpoint due to new anticancer treatment. This analysis was the same as the primary analysis with regards to the censoring rules except for the handling of new anticancer treatment. The PFS was derived regardless of the new anticancer treatment.

Table 67: Censoring rules for primary and sensitivity analysis of PFS Per RECIST version 1.1 (Study 307)

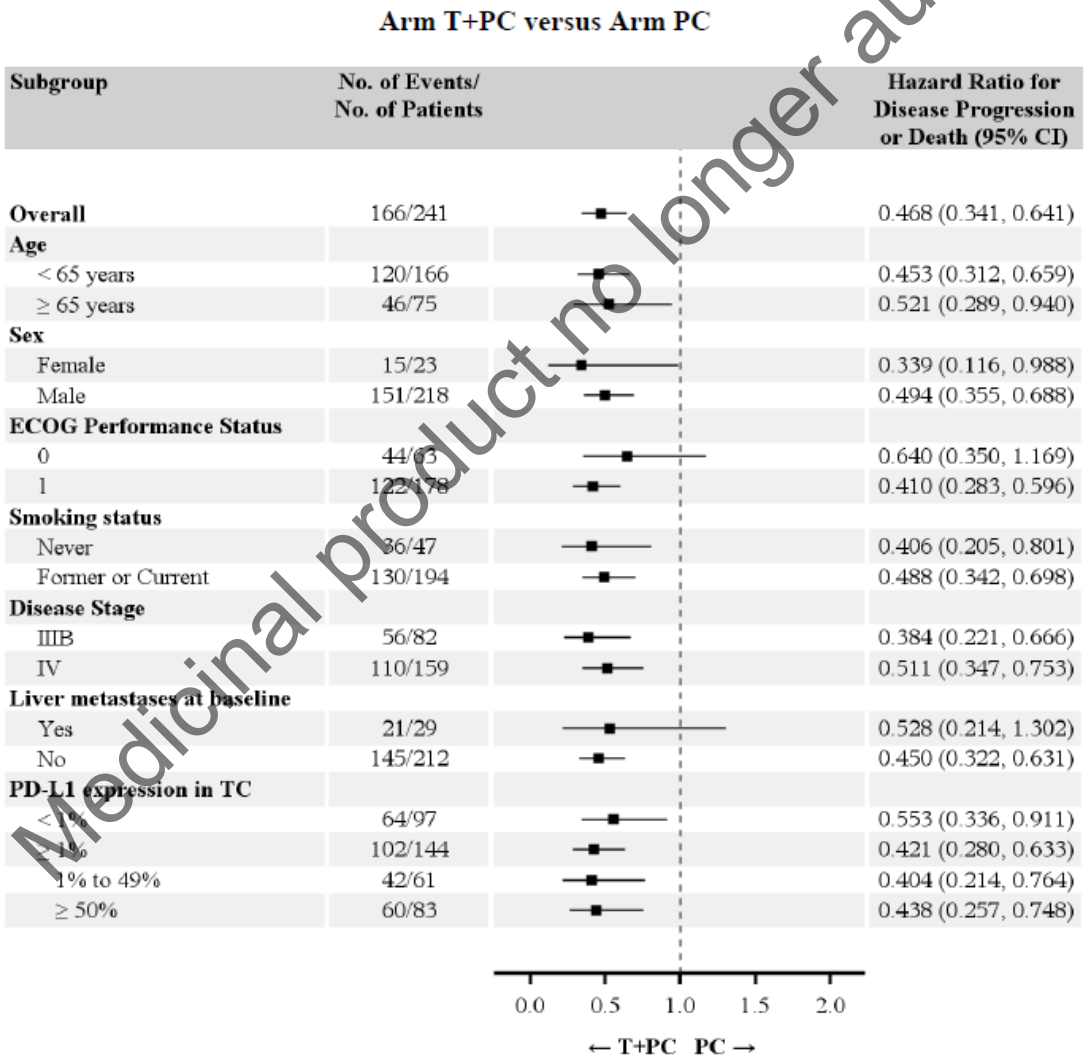
No.	Situation	Primary Analysis	Sensitivity Analysis
1	Incomplete or no baseline tumor assessments	Censored at randomization date	
2	No postbaseline tumor assessment and no death	Censored at randomization date	
3	No postbaseline tumor assessment and death	Died at date of death	
4	Progression documented between scheduled visits	Progressed at date of documented progression	
5	No progression	Censored at date of last adequate tumor assessment with no documented progression	
6	New anticancer treatment started	Censored at date of last adequate tumor assessment before date of new anticancer treatment	Progressed at Date of documented progression with protocol specified continued follow-up in all treatment arms or died at date of death whichever is earlier
7	Death between adequate assessment visits	Died at date of death	
8	Death or progression after ≥2 missed visit	Censored at date of last adequate tumor assessment prior to the ≥2 missed tumor assessments	Progressed at date of documented progression or Died at date of death whichever is earlier

Table 68: Analysis of progression-free survival per RECIST version 1.1 by independent review committee, comparison of primary analysis and sensitivity analysis (ITT Analysis Set) (Study 307); final analysis (DCO: 30SEP2020)

	Primary Analysis			Sensitivity Analysis		
	T+PC (N = 120)	T+*n*PC (N = 119)	PC (N = 121)	T+PC (N = 120)	T+*n*PC (N = 119)	PC (N = 121)
Progression-Free Survival						
Events, n (%)	80 (66.7)	79 (66.4)	86 (71.1)	81 (67.5)	81 (68.1)	88 (72.7)
Censored, n (%)	40 (33.3)	40 (33.6)	35 (28.9)	39 (32.5)	38 (31.9)	33 (27.3)
Stratified Hazard Ratio (95% CI) [a]	0.450 (0.326, 0.619)	0.428 (0.308, 0.595)		0.497 (0.362, 0.681)	0.476 (0.345, 0.658)	
Progression-Free Survival (months)						
Median (95% CI)	7.7 (6.74, 10.41)	9.6 (7.39, 10.78)	5.5 (4.21, 5.59)	7.7 (6.74, 9.82)	9.6 (7.39, 10.78)	5.5 (4.21, 5.78)

Source: ADSL, ADTTE. Data cutoff: 30SEP2020. Data extraction: 20FEB2021.

Subgroup analysis of PFS assessed by IRC



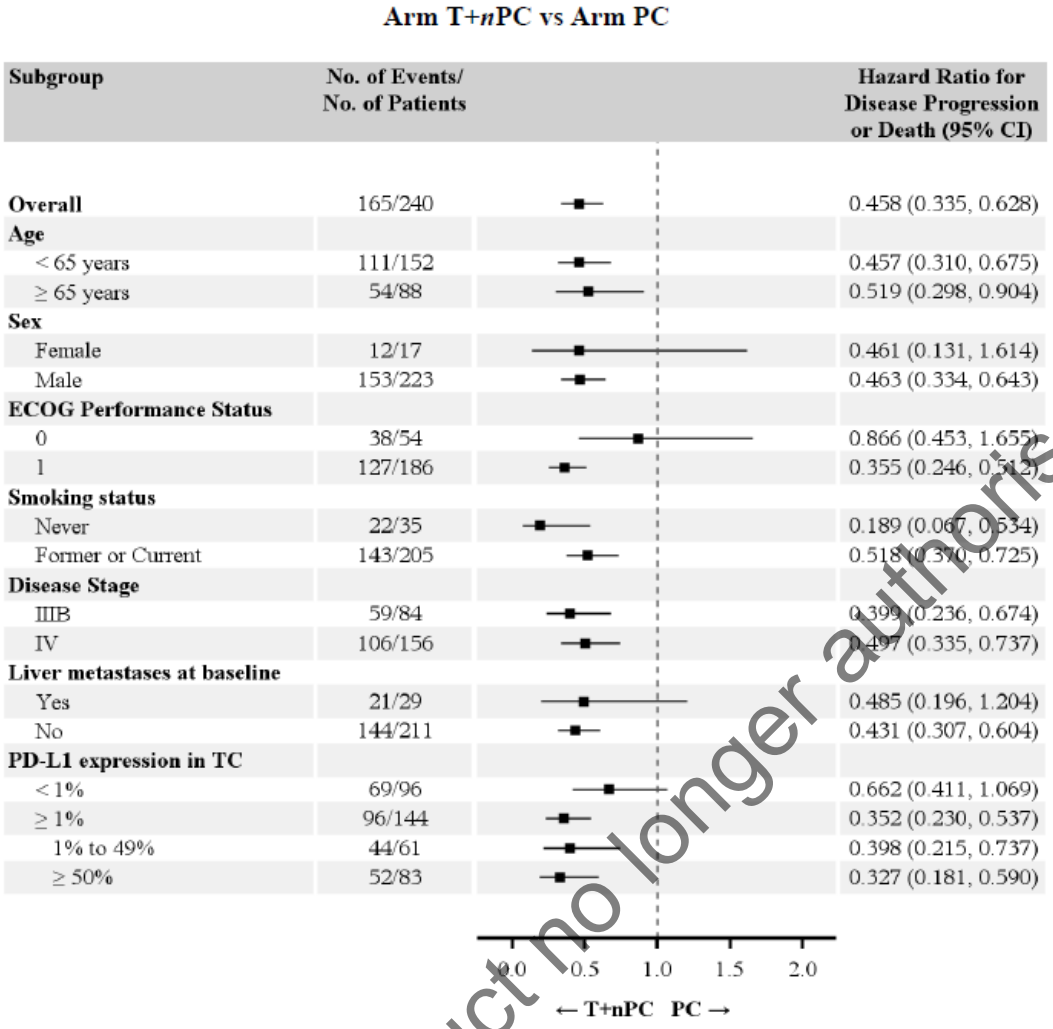


Figure 62: Subgroup analysis: forest plot of PFS per RECIST version 1.1 by independent review committee for arms T+PC and T+nPC vs PC (ITT analysis set) (Study 307); final analysis (DCO: 30SEP2020)

Subgroup Analysis of OS

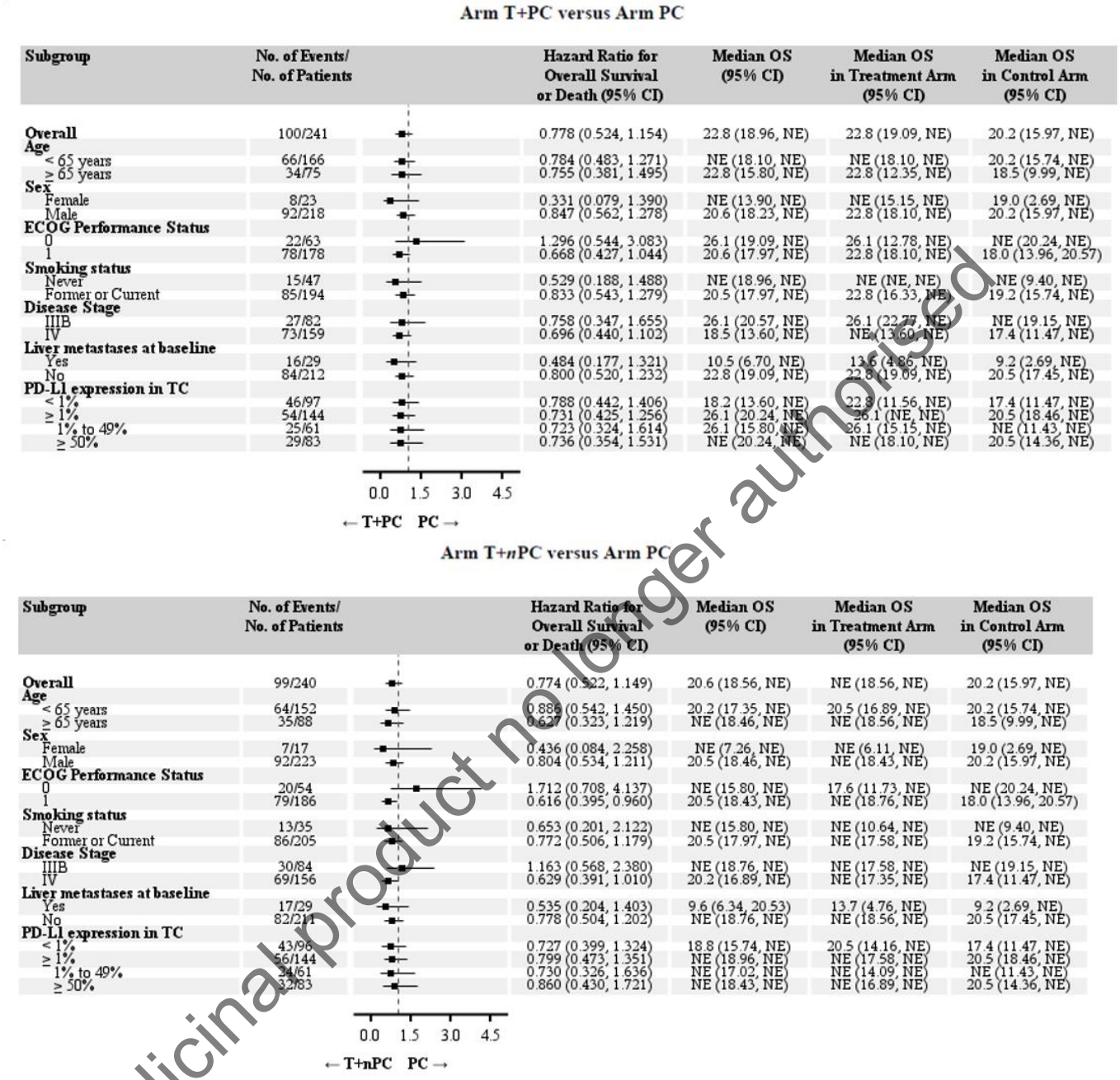


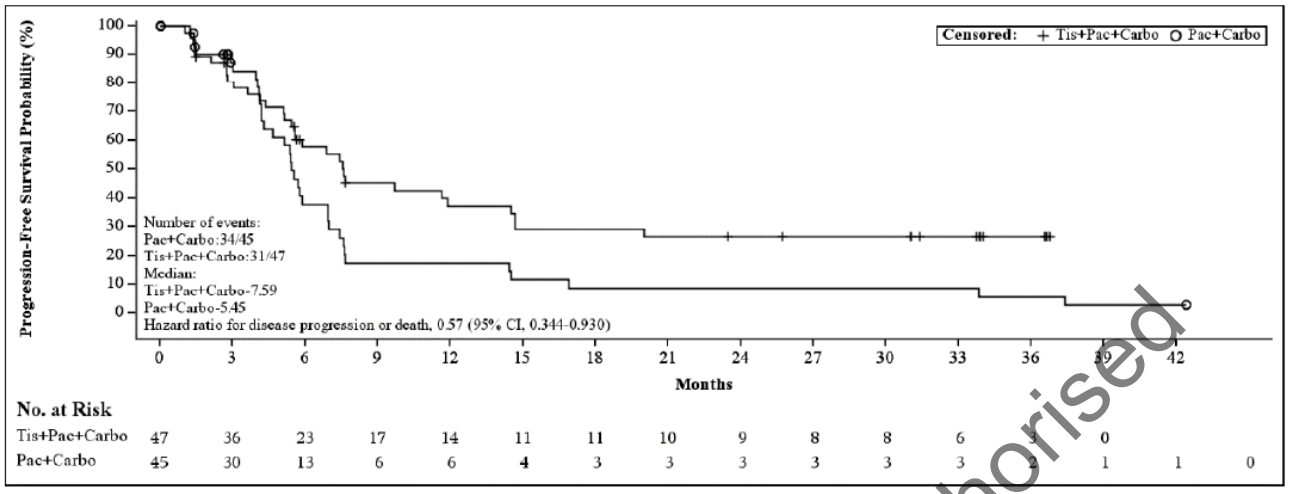
Figure 63: Subgroup analysis: forest plot of OS (ITT Analysis Set) (Study 307); final analysis (DCO: 30SEP2020)

Efficacy by PD-L1 Expression

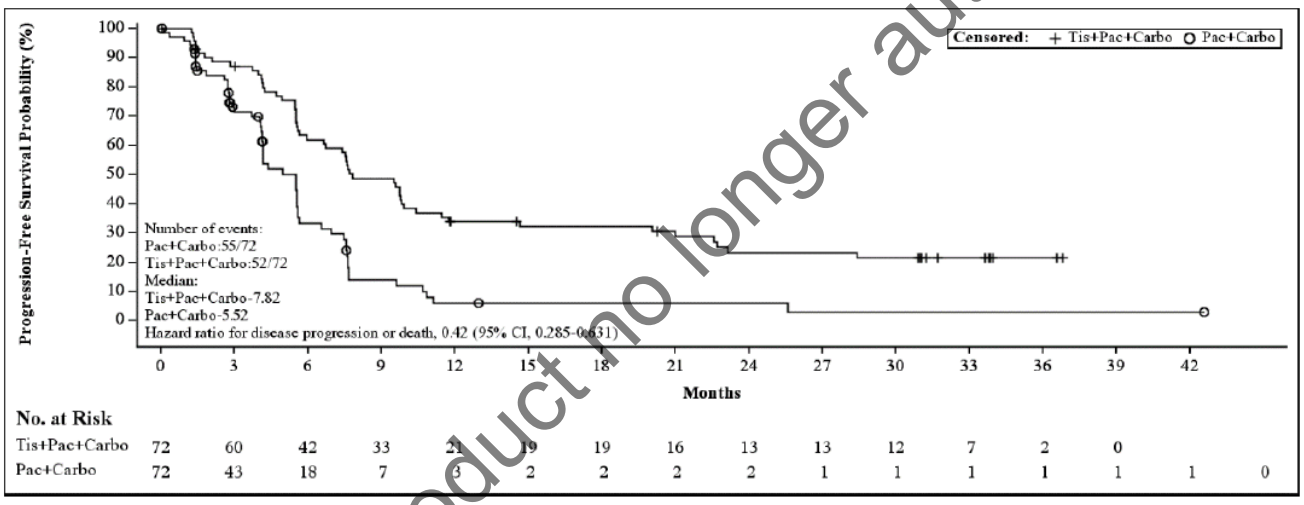
- **PFS by PD-L1 Expression**

Data cutoff date **15-July-2022,** median study follow-up of 20.5 months. At this cut-off date, the maturity of the PFS data was 70.0% (84/120) and 72.3% (86/119) for the T+PC arm and T+nPC arm respectively.

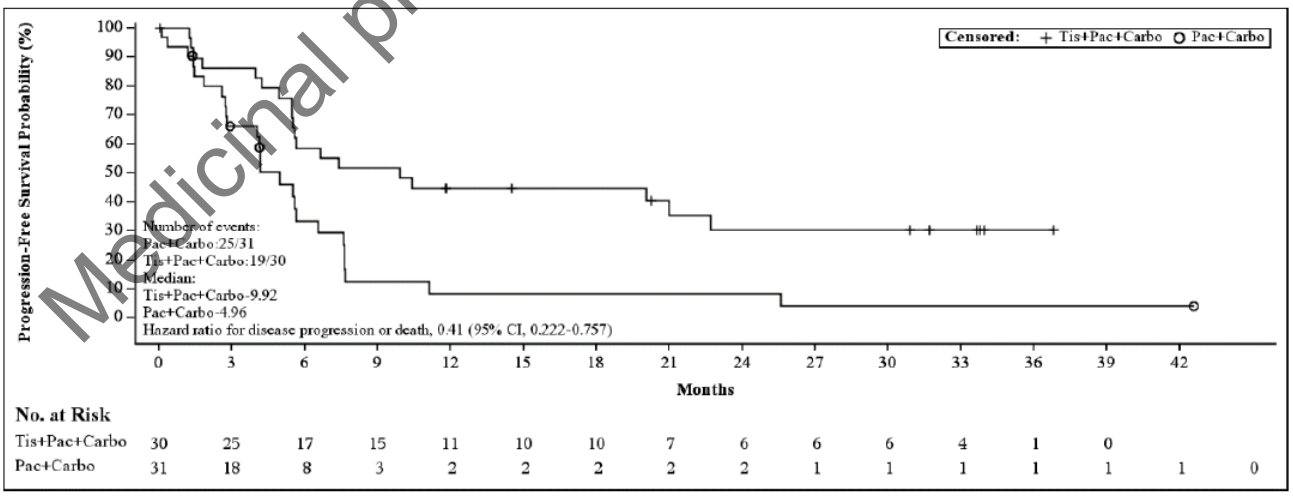
T+PC vs PC: TC < 1%



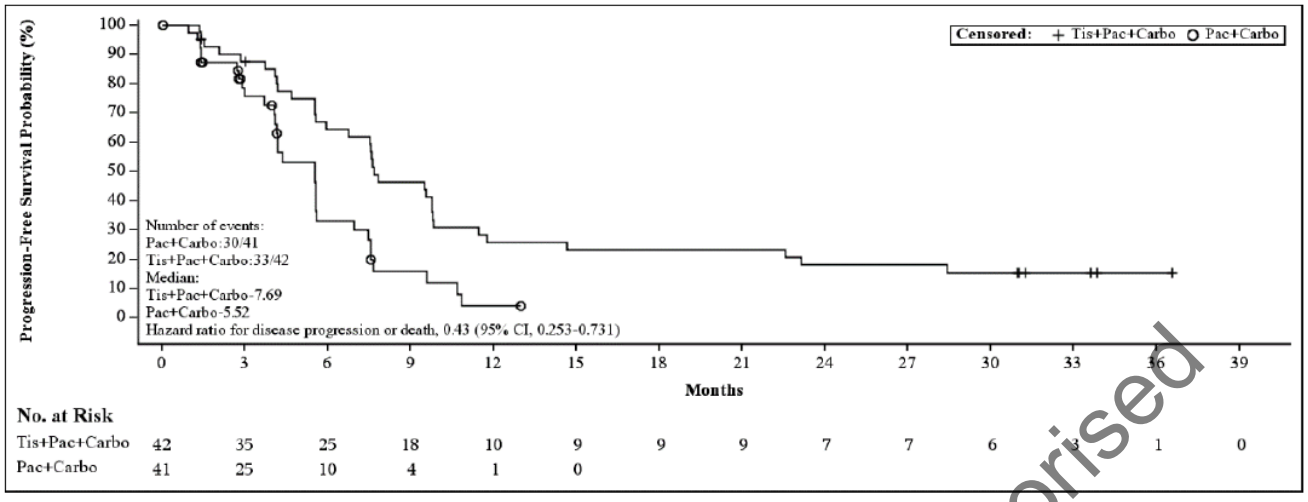
T+PC vs PC: TC >= 1%



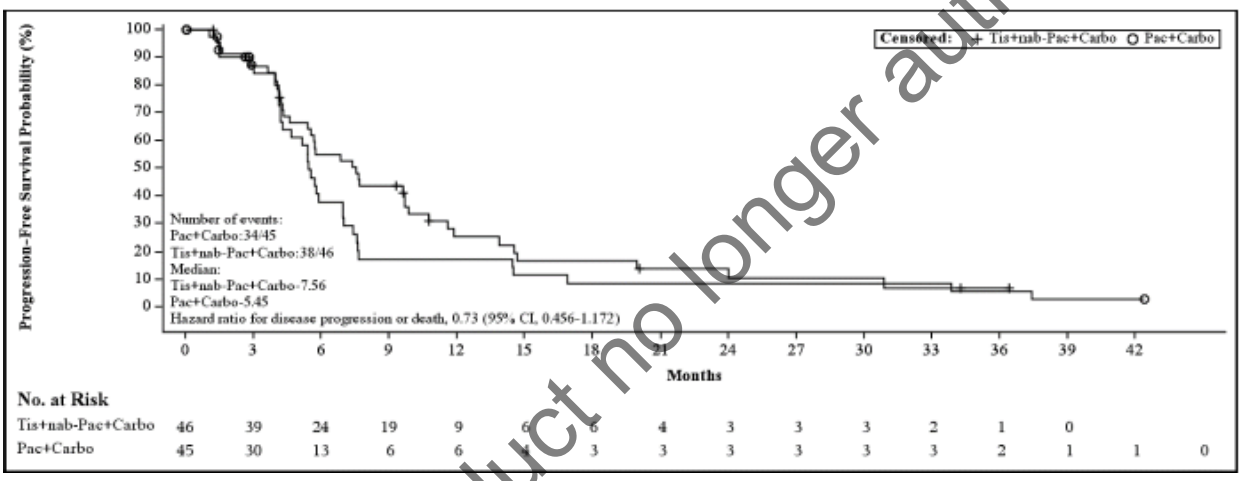
T+PC vs PC: TC 1%-49%



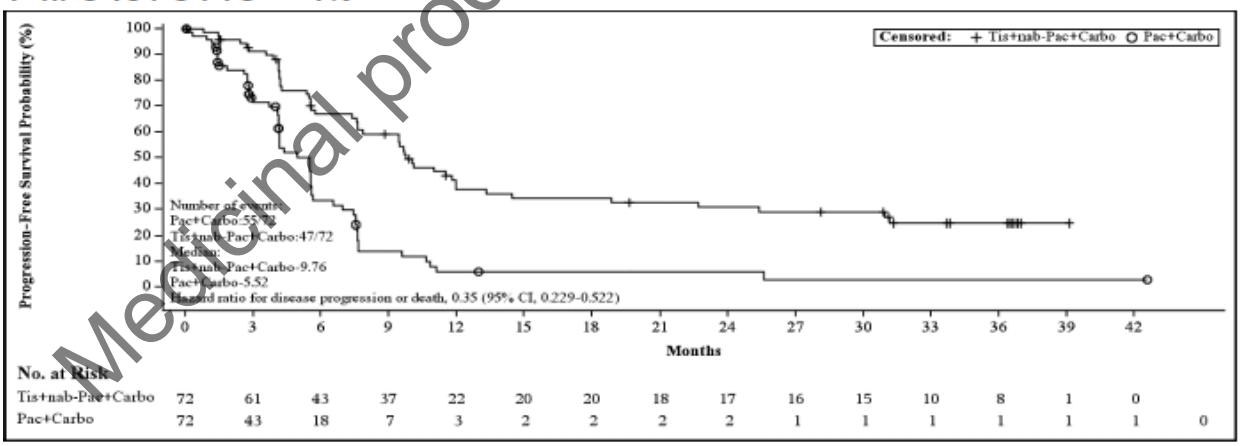
T+PC vs PC: TC >= 50%

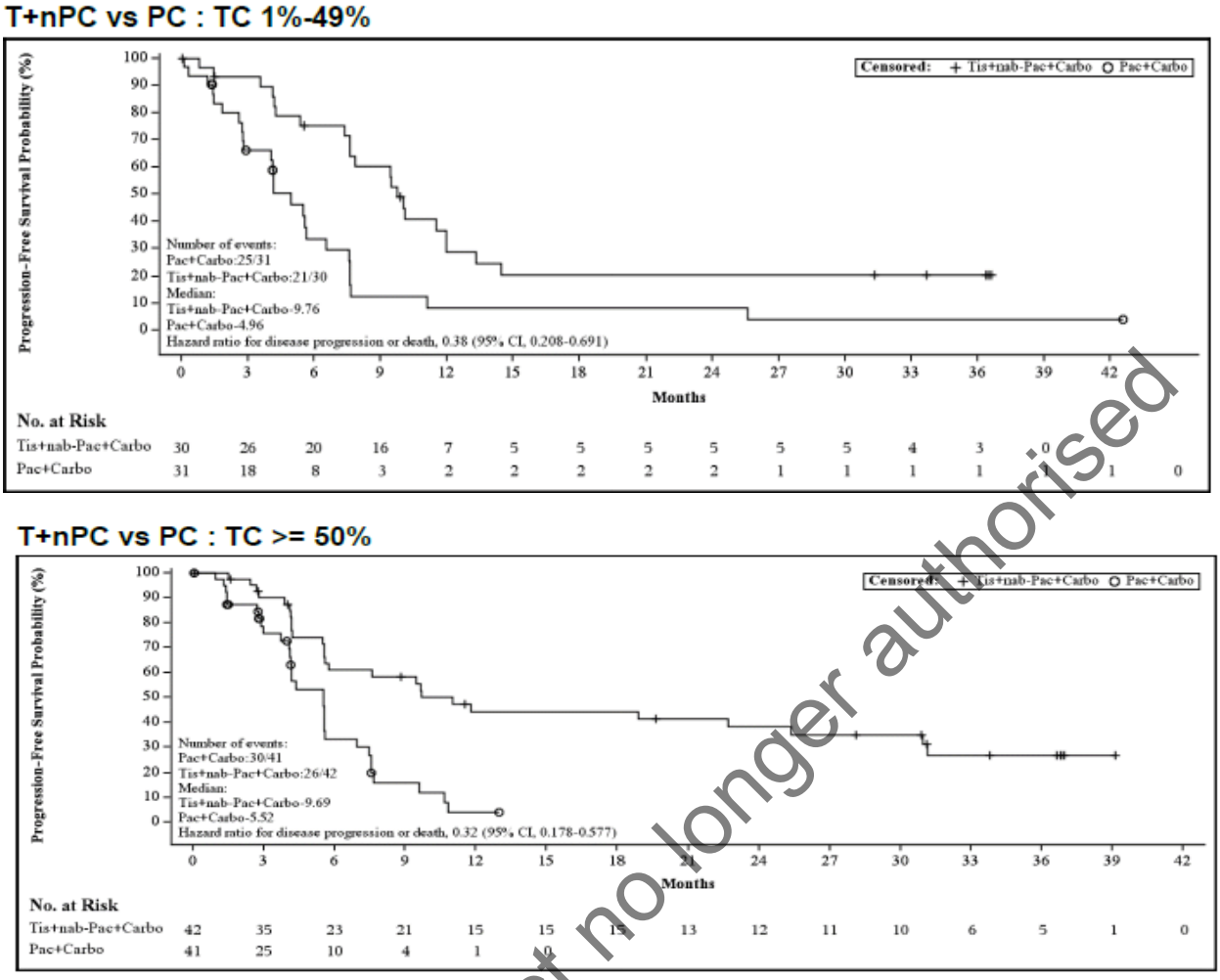


T+nPC vs PC : TC < 1%



T+nPC vs PC : TC >= 1%





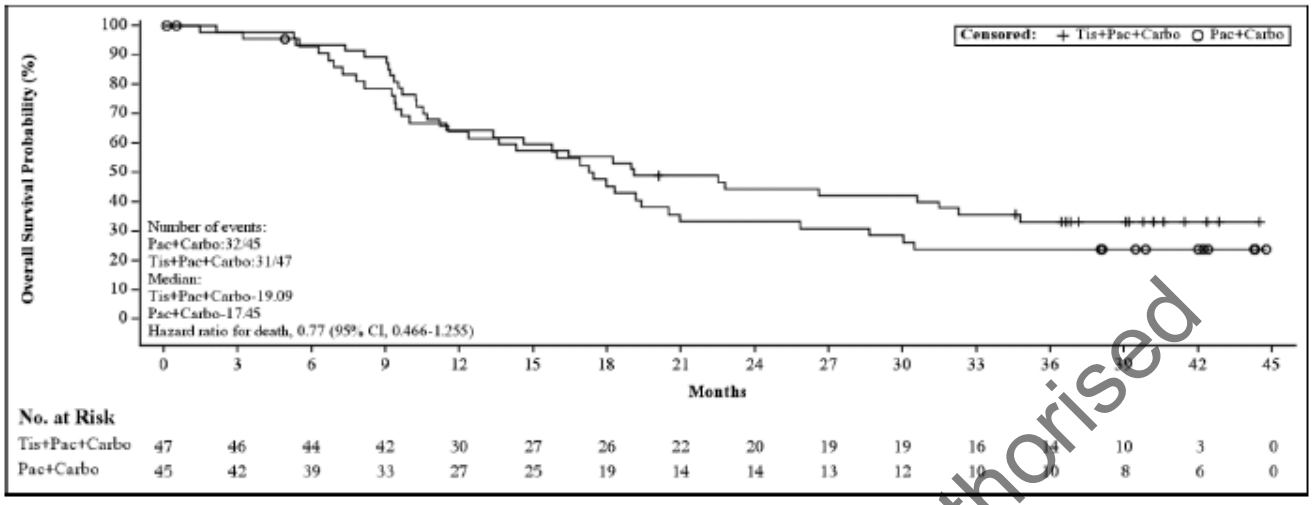
Source: 1L/2L NSCLC Response to CHMP Day 180 LoOIs Appendix 1-EU_D180_Figure 1-2

Figure 64: Kaplan-Meier plot of progression-free survival per RECIST version 1.1 by independent review committee by PD-L1 Expression (ITT analysis set) (Study 307); updated data (DCO: 15JUL2022)

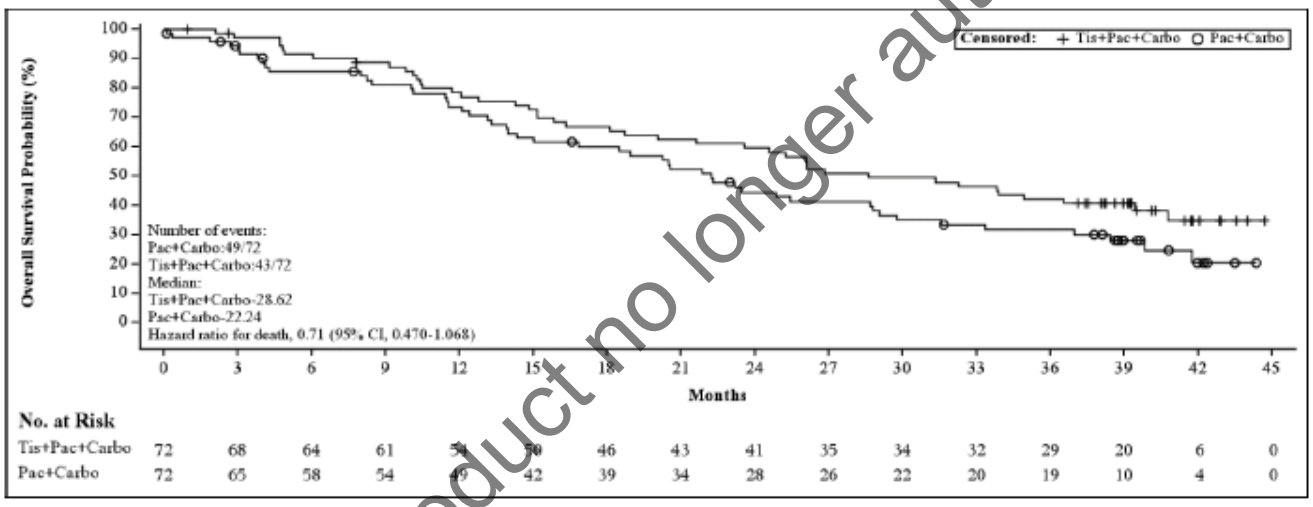
- **OS by PD-L1 Expression**

Data cutoff date **15-July-2022,** median study follow-up of 20.5 months. At this cut-off date, the maturity of the OS data for T+PC arm and T+nPC arm was 62.5% (75/120) and 70.6% (84/119) respectively and the fraction of cross over was 58.7%.

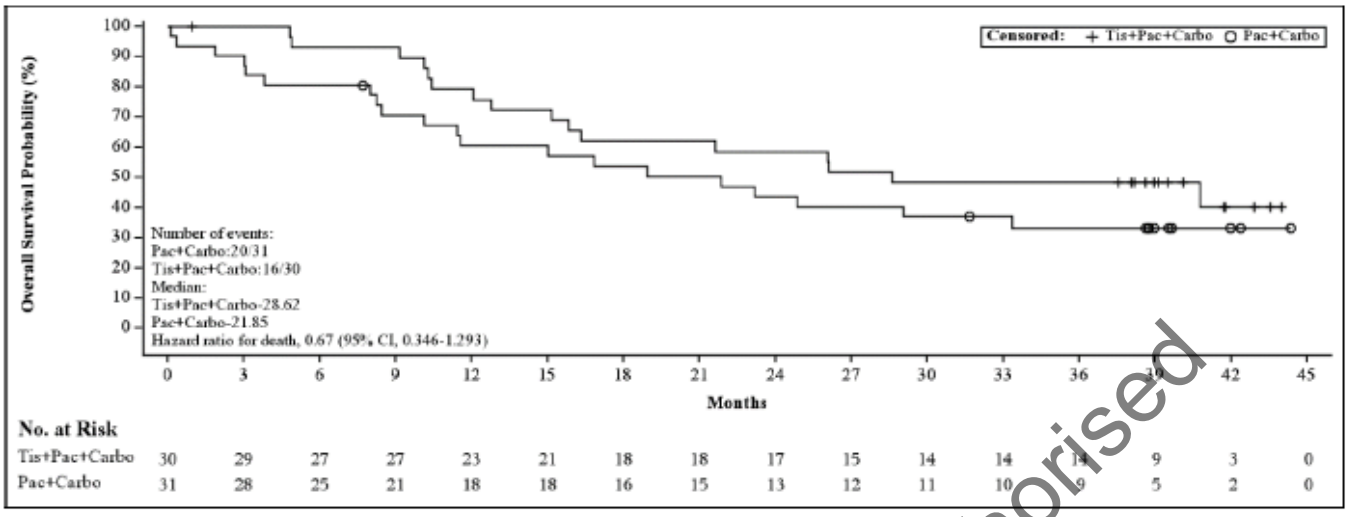
T+PC vs PC: TC < 1%



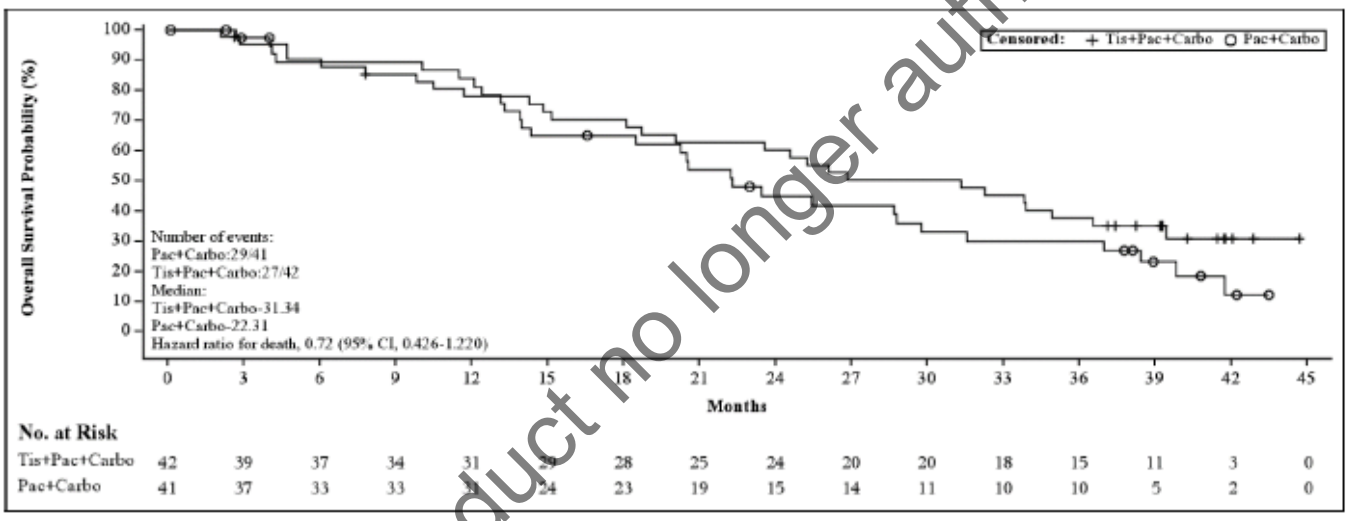
T+PC vs PC: TC >= 1%



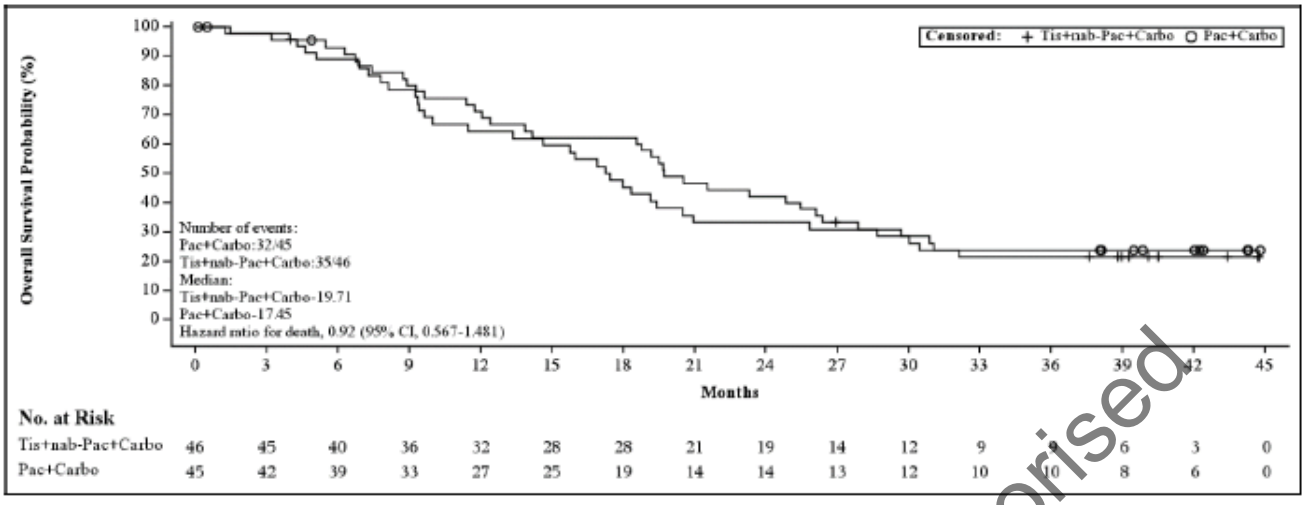
T+PC vs PC: TC 1%-49%



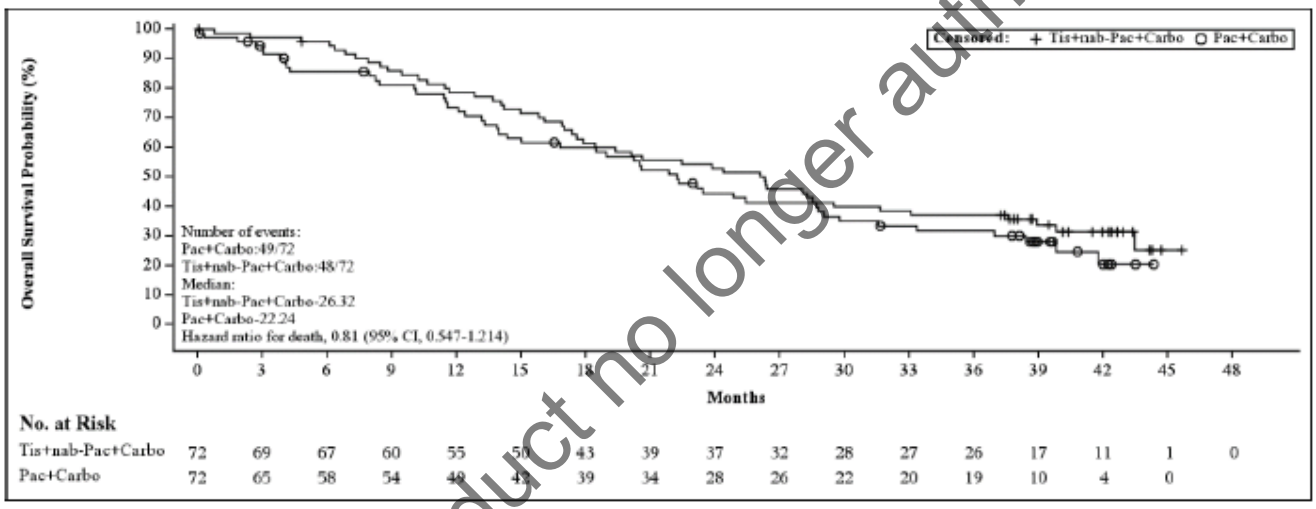
T+PC vs PC: TC >= 50%



T+nPC vs PC : TC < 1%



T+nPC vs PC : TC >= 1%



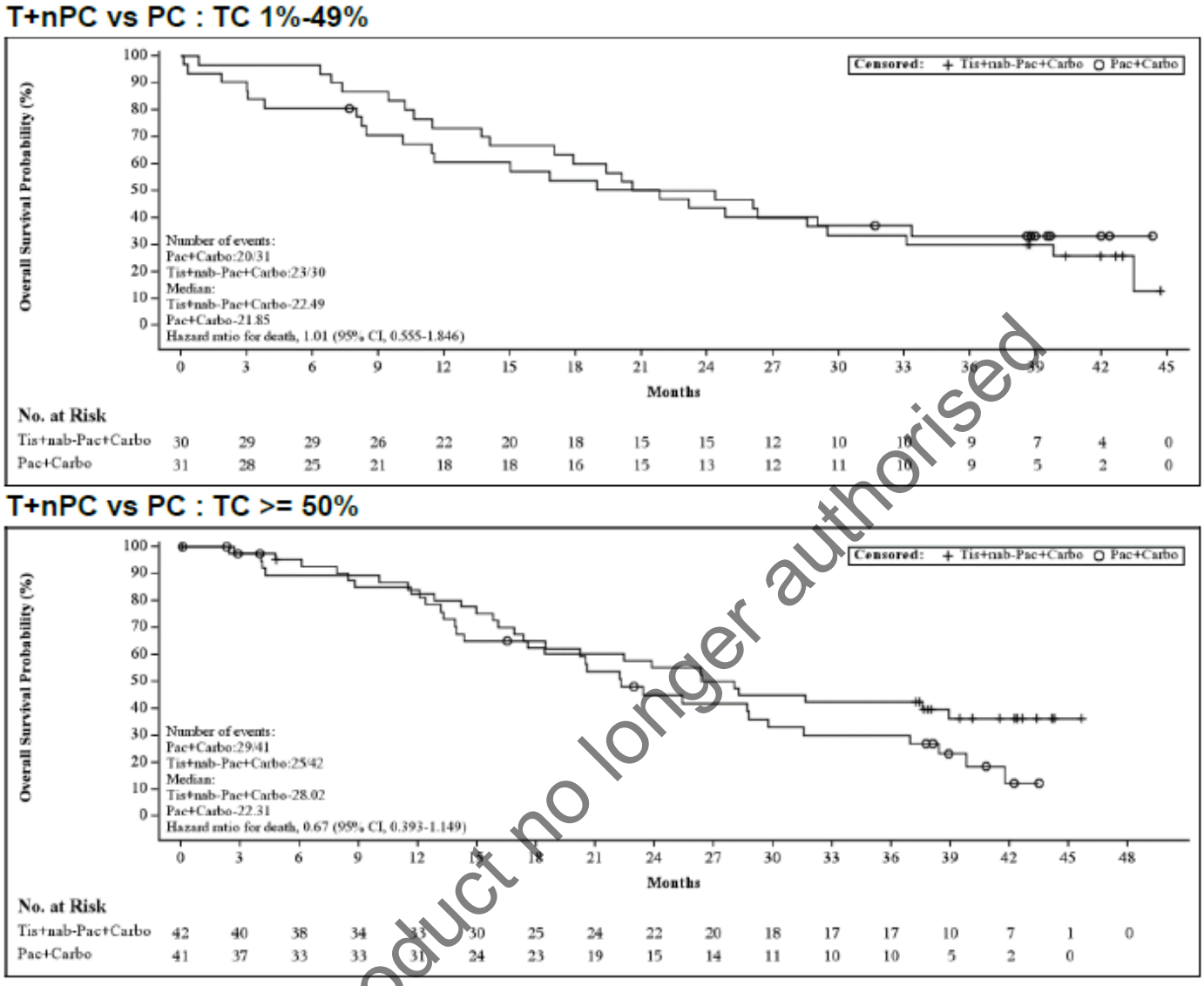
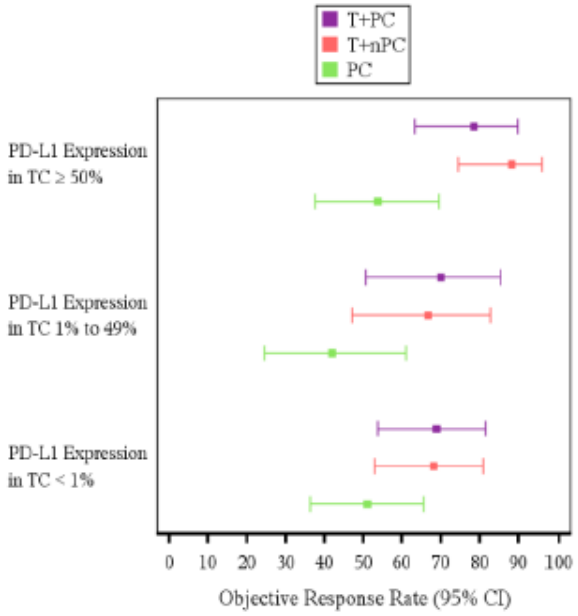


Figure 65: Kaplan-Meier plot of overall survival by PD-L1 expression (ITT analysis set) (Study 307); updated data (DCO: 15JUL2022)

- **ORR by PD-L1 Expression**



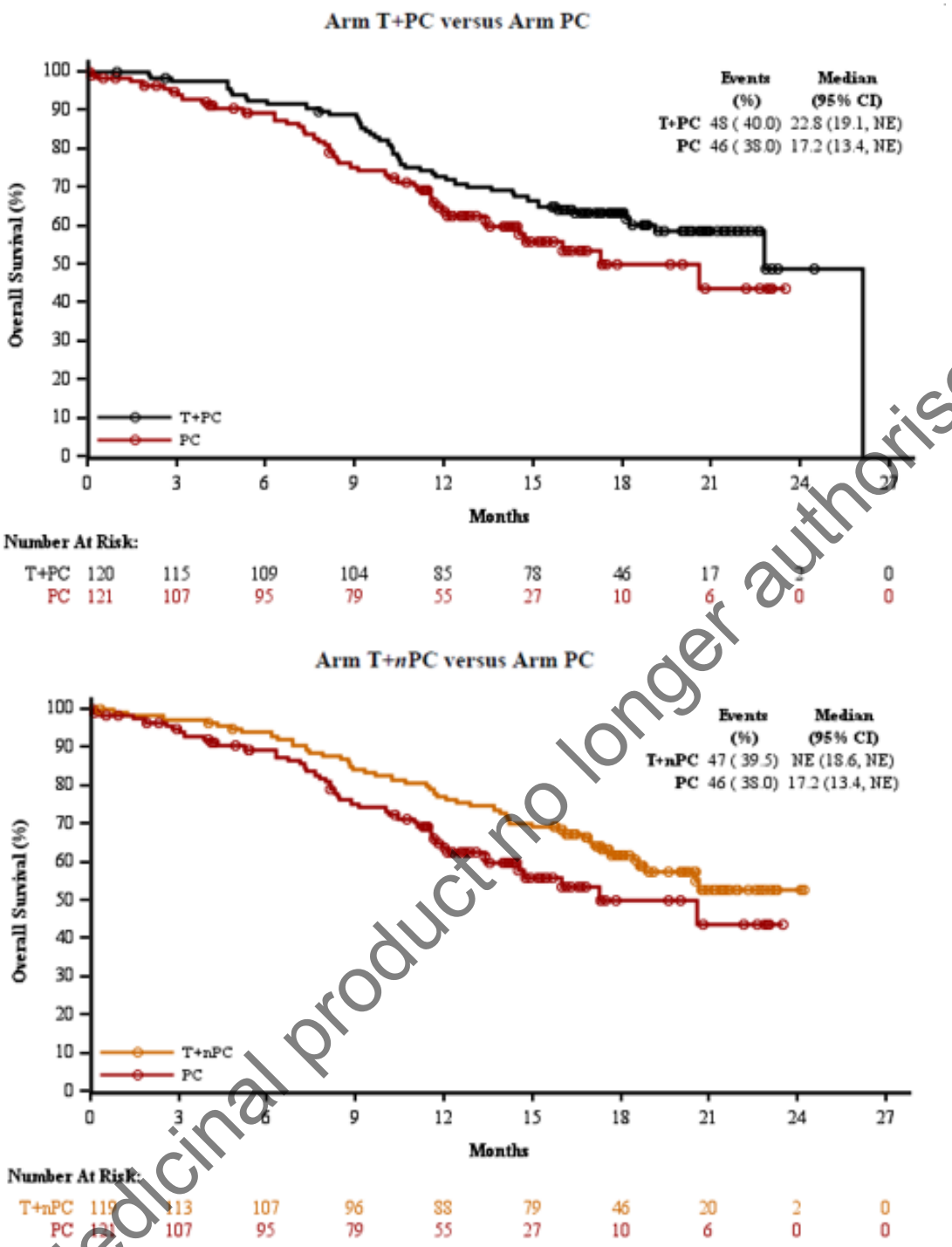
No. of Response/ No. of Patients	ORR (95% CI)	Estimated Treatment Difference (95% CI)
33/42	78.6 (63.2, 89.7)	24.9 (5.2, 44.6)
37/42	88.1 (74.4, 96.0)	34.4 (16.3, 52.6)
22/41	53.7 (37.4, 69.3)	
21/30	70.0 (50.6, 85.3)	28.1 (4.2, 52.0)
20/30	66.7 (47.2, 82.7)	24.7 (0.5, 48.9)
13/31	41.9 (24.5, 60.9)	
33/48	68.8 (53.7, 81.4)	17.7 (-1.4, 36.9)
32/47	68.1 (52.9, 80.9)	17.1 (-2.3, 36.4)
25/49	51.0 (36.3, 65.6)	

Figure 66: Objective response per RECIST version 1.1 by IRC by PD-L1 expression (ITT analysis set) (Study 307); final analysis (DCO: 30SEP2020)

OS Supportive Analyses

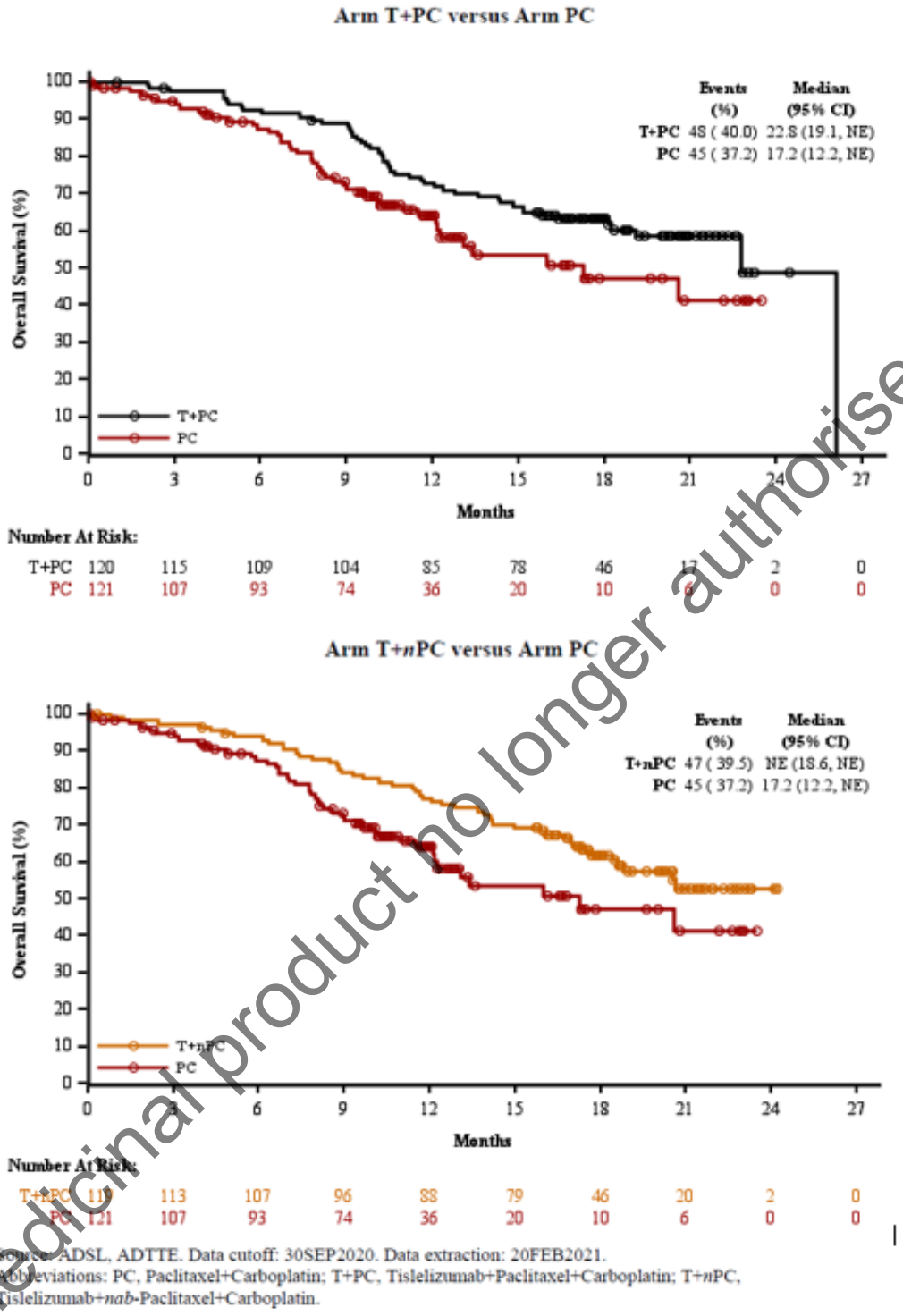
To assess the impact of in-study crossover on OS, a supportive analysis was conducted using Rank-Preserving Structural Failure Time Model (RPSFTM, Robins et al 1991). The stratified HRs were 0.630 (95% CI: 0.312, 1.272) for the comparison between Arm T+PC and Arm PC and 0.624 (95% CI: 0.196, 1.981) for the comparison between Arm T+nPC and Arm PC.

In addition, a supportive analysis using a two-stage method (Latimer et al 2014) was also performed to estimate the in-study crossover effect on the post-progression survival (PPS) using data from patients who progressed per IRC assessment before any subsequent anticancer therapy in the control arm only. The stratified HRs based on the counterfactual survival time of patients in Arm PC who had crossed over to receive tislelizumab and the observed survival times in the rest of the patients were estimated as 0.572 (95% CI: 0.350, 0.934) for Arm T+PC versus Arm PC and 0.572 (95% CI: 0.344, 0.951) for Arm T+nPC versus Arm PC.



Source: ADSL, ADTTE. Data cutoff: 30SEP2020. Data extraction: 20FEB2021.
Abbreviations: PC, Paclitaxel+Carboplatin; T+PC, Tislelizumab+Paclitaxel+Carboplatin; T+*n*PC, Tislelizumab+*nab*-Paclitaxel+Carboplatin.

Figure 67: Kaplan-Meier Plot of OVERALL SURVIVAL – Sensitivity ANALYSIS USING RANK-PRESERVING STRUCTURAL FAILURE TIME MODEL (ITT ANALYSIS SET) (Study 307); FINAL ANALYSIS (DCO: 30SEP2020)



Source: ADSL, ADTTE. Data cutoff: 30SEP2020. Data extraction: 20FEB2021.
Abbreviations: PC, Paclitaxel+Carboplatin; T+PC, Tislelizumab+Paclitaxel+Carboplatin; T+*n*PC, Tislelizumab+*nab*-Paclitaxel+Carboplatin.

Figure 68: Kaplan-Meier plot of overall survival – sensitivity analysis using two-stage model (ITT analysis set) (Study 307); final analysis (DCO: 30SEP2020)

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the 1L (in combination with chemotherapy) squamous NSCLC indication of 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 69: Summary of efficacy for trial BGB-A317-307 (Study 307)

Title: A Phase 3, multicenter, randomized open-label study to compare the efficacy and safety of tislelizumab (BGB A317, anti-PD1 antibody) combined with paclitaxel plus carboplatin or *nab*-paclitaxel plus carboplatin versus paclitaxel plus carboplatin alone as first-line treatment for untreated advanced squamous non-small cell lung cancer		
Study identifier	BGB-A317-307, RATIONALE 307	
Design	Phase III, multicentre, randomised (1:1:1), open-label study comparing tislelizumab + paclitaxel + carboplatin or tislelizumab + nab-paclitaxel + carboplatin versus paclitaxel + carboplatin alone	
	Duration of main phase:	30-Jul-2018 – Ongoing (**data cut-off for final analysis: 30-Sep-2020**) The interim and final analyses were conducted when the predefined PFS events had been observed for the efficacy and safety evaluations. The study met its primary objective of PFS at the interim analysis. Results for the final analysis are presented in this report. The study will continue until the last patient has disease progression, is lost to follow-up, or withdraws from study, or until study completion by Sponsor.
	Duration of Run-in phase:	Not applicable
	Duration of Extension phase:	Not applicable
Hypothesis	Superiority	
Treatments groups	Arm T+PC: Tislelizumab Paclitaxel Carboplatin	n = 120 Tislelizumab 200 mg i.v. D1 + paclitaxel 175 mg/m^2 D1 + carboplatin AUC 5 D1 for 4-6 cycles followed by tislelizumab 200 mg Q3W
	Arm T+nPC: Tislelizumab Nab-Paclitaxel Carboplatin	n = 119 Tislelizumab 200 mg D1 +nab-paclitaxel 100 mg/m^2 D1, D8, and D15 + carboplatin AUC 5 D1 for 4-6 cycles followed by tislelizumab 200 mg Q3W
	Arm PC: Paclitaxel Carboplatin	n = 121 Paclitaxel 175 mg/m^2 D1 and carboplatin AUC 5 D1 for 4-6 cycles

Endpoints and definitions	Primary endpoint	PFS as assessed by the IRC	Time from randomisation to the first objectively documented disease progression, or death from any cause, whichever occurs first, as assessed by the IRC per RECIST v1.1 in the ITT analysis set
	Secondary endpoint	OS	Time from the date of randomisation to the date of death due to any cause in the ITT analysis set
	Secondary endpoint	PFS as assessed by the investigator	Time from randomisation to the first objectively documented disease progression, or death from any cause, whichever occurs first, as determined by the investigator per RECIST v1.1 in the ITT analysis set
	Secondary endpoint	ORR as assessed by the IRC	Proportion of patients who had complete response (CR) or partial response (PR) as assessed by the IRC per RECIST v1.1 in all randomised patients with measurable disease at baseline
	Secondary endpoint	ORR as assessed by the investigator	Proportion of patients who had CR or PR as determined by the investigator per RECIST v1.1 in all randomised patients with measurable disease at baseline
	Secondary endpoint	DOR as assessed by the IRC	Time from the first occurrence of a documented objective response to the time of relapse, or death from any cause, whichever comes first, as assessed by the IRC per RECIST v1.1 in all randomised patients with documented objective responses
	Secondary endpoint	DOR as assessed by the investigator	Time from the first occurrence of a documented objective response to the time of relapse, or death from any cause, whichever comes first, as determined by the investigator per RECIST v1.1 in all randomised patients with documented objective responses
Database lock	30-Sep-2020 (data cut-off date)		

Results and Analysis

Analysis description	**Primary endpoint analysis – PFS by IRC**			
Analysis population and time point description	ITT analysis set Time point: after 245 PFS by IRC events			
Descriptive statistics and estimate variability	Treatment group	Arm T+PC	Arm T+nPC	Arm PC
	Number of patients	120	119	121
	mPFS (months)	7.7	9.6	5.5
	95% CI	6.74, 10.41	7.39, 10.78	4.21, 5.59
Effect estimate per comparison	Comparison groups	Arm T+PC vs Arm PC	Arm T+nPC vs Arm PC	
	HR	0.450	0.428	
	95% CI	0.326, 0.619	0.308, 0.595	

	p-value	<0.0001	<0.0001	
Notes	The primary endpoint was met, and statistical significance was achieved for the prespecified interim analysis (06-Dec-2019 data cut-off) in both PFS comparisons of Arm T+PC versus Arm PC and Arm T+nPC versus Arm PC. The P-value for 30-Sep-2020 data cut-off was descriptive.			
Analysis description	**Secondary endpoint analysis – OS**			
Analysis population and time point description	ITT analysis set			
Descriptive statistics and estimate variability	Treatment group	Arm T+PC	Arm T+nPC	Arm PC
	Number of patients	120	119	121
	mOS (months)	22.8	NE	20.2
	95% CI	19.09, NE	18.56, NE	15.97, NE
Effect estimate per comparison	Comparison groups	Arm T+PC vs Arm PC	Arm T+nPC vs Arm PC	
	HR	0.678	0.752	
	95% CI	0.455, 1.010	0.504, 1.120	
Notes				
Analysis description	**Secondary endpoint analysis – PFS by investigator**			
Analysis population and time point description	ITT analysis set			
Descriptive statistics and estimate variability	Treatment group	Arm T+PC	Arm T+nPC	Arm PC
	Number of patients	120	119	121
	mPFS (months)	9.6	9.9	5.5
	95% CI	7.62, 11.76	8.57, 11.86	4.21, 5.65
Effect estimate per comparison		Arm T+PC vs Arm PC	Arm T+nPC vs Arm PC	
	HR	0.341	0.403	
	95% CI	0.245, 0.473	0.289, 0.564	
Notes	Not applicable			
Analysis description	**Secondary endpoint analysis – ORR by IRC**			
Analysis population and time point description	ITT analysis set			
Descriptive statistics and estimate variability	Treatment group	Arm T+PC	Arm T+nPC	Arm PC
	Number of patients	120	119	121
	OOR, n (%)	89 (74.2)	88 (73.9)	58 (47.9)
	95% CI	65.4, 81.7	65.1, 81.6	38.8, 57.2
Effect estimate per comparison		Arm T+PC vs Arm PC	Arm T+nPC vs Arm PC	
	Odds ratio	3.36	3.16	

	95% CI	1.923, 5.881	1.819, 5.489	
Notes	Not applicable			
Analysis description	**Secondary endpoint analysis – ORR by investigator**			
Analysis population and time point description	ITT analysis set			
Descriptive statistics and estimate variability	Treatment group	Arm T+PC	Arm T+nPC	Arm PC
	Number of patients	120	119	121
	OOR, n (%)	84 (70.0)	93 (78.2)	60 (49.6)
	95% CI	61.0, 78.0	69.6, 85.2	40.4, 58.8
Effect estimate per comparison		Arm T+PC vs Arm PC	Arm T+nPC vs Arm PC	
	Odds ratio	2.56	3.60	
	95% CI	1.486, 4.410	2.052, 6.309	
Notes	Not applicable			
Analysis description	**Secondary endpoint analysis – DOR by IRC**			
Analysis population and time point description	ITT analysis set			
Descriptive statistics and estimate variability	Treatment group	Arm T+PC	Arm T+nPC	Arm PC
	Number of patients	120	119	121
	mDoR (months)	8.4	8.6	4.3
	95% CI	5.03, 15.80	7.13, 12.48	2.86, 5.42
Notes				
Analysis description	**Secondary endpoint analysis – DOR by investigator**			
Analysis population and time point description	ITT analysis set			
Descriptive statistics and estimate variability	Treatment group	Arm T+PC	Arm T+nPC	Arm PC
	Number of patients	120	119	121
	mDoR (months)	10.6	8.8	4.8
	95% CI	7.03, 21.75	8.05, 11.10	2.86, 6.11
Notes				

Clinical studies in special populations

Only patients under 75 years were included, therefore no analysis on special populations were performed for Study 307.

In vitro biomarker test for patient selection for efficacy

Clinical Performance

Archival tumour tissue (formalin-fixed paraffin-embedded or approximately 15 [≥ 6] unstained slides) was sent to central laboratory for central immunohistochemistry assessment of PD-L1 status. PD-L1

status was characterised as PD-L1 membrane staining on TC via the Ventana SP263 assay. If the submitted tumour tissue was unevaluable for PD-L1 expression status, patients were included in the < 1% TC group. Other exploratory predictive biomarkers, such as tumour mutation load, immune-related gene expression profiling, and tumour-infiltrating immune cells that are related to response or clinical benefit of tislelizumab may also have been evaluated. If no archival samples were available, a fresh tumour biopsy at baseline was required.

Rationale cut-off selection:

PD-L1 expression was tested centrally, and results remained blinded to the investigators, the patients, and the Applicant. The 3 cutoff levels employed (< 1% TC vs. 1%- 49% TC vs. ≥ 50% TC) were selected based on prevalence data from previous NSCLC studies with ICIs. For the 3 cutoff levels employed (< 1% TC vs. 1%- 49% TC vs. ≥ 50% TC) that were also chosen for stratification, no analytical validation report was provided. Data provided so far only support the 25% cutoff.

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

Not applicable.

Supportive study(ies)

Study 206

Study 206 was a multi-cohort, open label Phase II study of tislelizumab in combination with standard platinum-containing doublet chemotherapy as first-line treatment in Chinese patients with locally advanced or metastatic lung cancer. Patients were enrolled into 1 of 4 cohorts according to their pathological/histological diagnosis of the primary disease. These include a non-squamous NSCLC cohort, 2 squamous NSCLC cohorts (A and B), and a SCLC cohort. The study includes a safety run-in stage and a dose-expansion stage. Tislelizumab was continually dosed Q3W for all cohorts until the patients were deemed not to be benefiting from therapy under investigators' discretion, intolerable toxicity, or withdrawal of consent. Doublet chemotherapy was given until the completion of 4 to 6 cycles (4 cycles for the non-squamous NSCLC cohort), disease progression assessed by RECIST v1.1, intolerable toxicity, or withdrawal of consent.

At the cutoff date of 31-Dec-2019, end of study was reached with the database closed as the final data point of interest had been collected from the last patient.

The median age of all patients was 61.0 years (range: 36 to 75 years), most patients were male (74.1%); 83.3% had a baseline ECOG performance status of 1. All of 16 patients (100%) in the non-squamous cohort were negative for EGFR and ALK mutations. More than half of the patients (55.6%) had <10% PD-L1 expression on tumour cells.

Study 307 and Study 206 (squamous NSCLC cohort)

The applicant presented a critical analysis of the clinical data from squamous NSCLC patients in Study 307 and squamous NSCLC cohort in Study 206. The results from the two studies were presented side by side.

All analyses were based on the efficacy set from Study 307 (T+PC; N = 120) (T+nPC; N = 119) (PC; N=121) and from Study 206 including 21 patients (squamous NSCLC cohorts; T+PC; N=15 and T+GC*; N=6). [*GC = cis/carboplatin + gemcitabine].

Efficacy endpoints include PFS, ORR, DCR, DOR, CBR, and OS. There were differences between Study 307 and 206 regarding the definition of these efficacy endpoints. In Study 307, efficacy endpoints were assessed by IRC, and CR/PR confirmation was not required, whereas in Study 206, efficacy endpoints

are assessed by investigator and confirmed CR/PR was required. For completeness, confirmed CR/PR were also included for Study 307. Confirmation CR/PR is defined as two determinations of CR/PR at least four weeks apart before progression as per RECIST 1.1.

Table 70: Demographics and baseline characteristics – Studies 307 and 206 (Efficacy Analysis Set)

	Study 307			Study 206	
	T+PC (N = 120)	T+*n*PC (N = 119)	PC (N = 121)	T+PC (N = 15)	T+GC (N = 6)
Age (Years)					
Median	60.0	63.0	62.0	59.0	63.0
Min, Max	41, 74	38, 74	34, 74	40, 74	42, 72
Age Group, n (%)					
< 65 years	81 (67.5)	67 (56.3)	85 (70.2)	12 (80.0)	4 (66.7)
≥ 65 years	39 (32.5)	52 (43.7)	36 (29.8)	3 (20.0)	2 (33.3)
Sex, n (%)					
Male	107 (89.2)	112 (94.1)	111 (91.7)	12 (80.0)	6 (100.0)
Female	13 (10.8)	7 (5.9)	10 (8.3)	3 (20.0)	0 (0.0)
BMI (kg/m^2)					
Median	22.27	22.41	22.29	24.46	19.55
Min, Max	16.9, 34.9	17.4, 31.9	15.2, 29.6	14.8, 35.2	16.7, 26.5
ECOG Performance Status at Baseline, n (%)					
0	31 (25.8)	22 (18.5)	32 (26.4)	4 (26.7)	1 (16.7)
1	89 (74.2)	97 (81.5)	89 (73.6)	11 (73.3)	5 (83.3)
Smoking Status, n (%)					
Never	24 (20.0)	12 (10.1)	23 (19.0)	2 (13.3)	0 (0.0)
Current	24 (20.0)	21 (17.6)	27 (22.3)	3 (20.0)	2 (33.3)
Former	72 (60.0)	86 (72.3)	71 (58.7)	10 (66.7)	4 (66.7)
PD-L1 Expression in Tumor Cell, n (%) [a]					
< 1%	48 (40.0)	47 (39.5)	49 (40.5)	3 (20.0)	2 (33.3)
1% - 49%	30 (25.0)	30 (25.2)	31 (25.6)	7 (46.7)	1 (16.7)
≥ 50%	42 (35.0)	42 (35.3)	41 (33.9)	5 (33.3)	3 (50.0)
Baseline Target Lesions Sum of Diameters by Investigator (mm)					
Median	77.20	82.70	83.00	62.00	83.00
Min, Max	17.1, 205.3	15.0, 207.1	15.0, 196.0	30.0, 164.0	22.0, 161.0
Time from Initial Diagnosis to Study Entry [b] (Days)					
Median	28.5	30.1	30.1	9.1	24.0
Min, Max	11, 1315	9, 3199	10, 1490	1, 2128	0, 622
Current Disease Stage, n (%)					
IIIB	38 (31.7)	40 (33.6)	44 (36.4)	6 (40.0)	0 (0.0)
IV	82 (68.3)	79 (66.4)	77 (63.6)	9 (60.0)	6 (100.0)
Histology, n (%)					
Squamous Cell Carcinoma	120 (100.0)	119 (100.0)	120 (99.2)	14 (93.3)	6 (100.0)

Efficacy analysis: PFS

Table 71: Analysis of progression-free survival per RECIST v1.1 (Studies 307 and 206) (Efficacy Analysis Set)

	Study 307			Study 206	
	T+PC (N = 120)	T+*n*PC (N = 119)	PC (N = 121)	T+PC (N = 15)	T+GC (N = 6)
Progression-Free Survival Events, n (%)	80 (66.7)	79 (66.4)	86 (71.1)	10 (66.7)	2 (33.3)
Progressive Disease	74 (61.7)	74 (62.2)	82 (67.8)	8 (53.3)	2 (33.3)
Death	6 (5.0)	5 (4.2)	4 (3.3)	2 (13.3)	0 (0.0)
Censored	40 (33.3)	40 (33.6)	35 (28.9)	5 (33.3)	4 (66.7)
Progression-Free Survival (Months) Median (95% CI)	7.7 (6.74, 10.41)	9.6 (7.39, 10.78)	5.5 (4.21, 5.59)	7.0 (5.52, 18.63)	NE (4.27, NE)
Q1 (95% CI)	4.7 (3.61, 5.52)	4.3 (4.14, 5.55)	4.0 (2.76, 4.17)	6.0 (0.66, 7.03)	4.7 (4.27, NE)
Q3 (95% CI)	20.0 (14.69, 23.13)	19.9 (11.99, NE)	7.6 (6.54, 7.66)	18.6 (7.03, NE)	NE (4.27, NE)
Stratified Hazard Ratio (95% CI) [a]	0.450 (0.326, 0.619)	0.428 (0.308, 0.595)			
Event Free Rate at, % (95% CI)					
6 month (95% CI)	60.7 (51.10, 68.98)	61.8 (51.99, 70.15)	35.1 (25.51, 44.86)	71.1 (39.83, 88.11)	75.0 (12.79, 96.05)
12 month (95% CI)	36.5 (27.58, 45.44)	33.1 (24.21, 42.26)	9.5 (4.48, 16.79)	39.5 (14.63, 63.81)	50.0 (5.78, 84.49)
18 month (95% CI)	29.4 (20.79, 38.42)	27.1 (18.70, 36.24)	6.8 (2.66, 13.58)	29.6 (8.13, 55.44)	50.0 (5.78, 84.49)
24 month (95% CI)	0.0 (NE, NE)	NE (NE, NE)	NE (NE, NE)	19.7 (3.41, 45.89)	50.0 (5.78, 84.49)

Efficacy analysis: Disease response

Table 72: Analysis of confirmed disease response per RECIST v1.1 (Studies 307 and 206) (Efficacy Analysis Set)

	Study 307			Study 206	
	T+PC (N = 120)	T+*n*PC (N = 119)	PC (N = 121)	T+PC (N = 15)	T+GC (N = 6)
Best Overall Response, n (%)[a]					
Complete Response	7 (5.8)	6 (5.0)	1 (0.8)	0 (0.0)	0 (0.0)
Partial Response	67 (55.8)	68 (57.1)	44 (36.4)	12 (80.0)	4 (66.7)
Stable Disease	31 (25.8)	34 (28.6)	52 (43.0)	2 (13.3)	1 (16.7)
Non-CR/Non-PD	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)
Progressive Disease	12 (10.0)	5 (4.2)	11 (9.1)	0 (0.0)	0 (0.0)
Could not be Determined	3 (2.5)	6 (5.0)	12 (9.9)	1 (6.7)	1 (16.7)
Objective Response Rate (ORR), n (%)	**74 (61.7)**	**74 (62.2)**	**45 (37.2)**	**12 (80.0)**	**4 (66.7)**
95% CI	(52.4, 70.4)	(52.8, 70.9)	(28.6, 46.4)	(51.9, 95.7)	(22.3, 95.7)
Disease Control Rate, n (%)	**105 (87.5)**	**108 (90.8)**	**98 (81.0)**	**14 (93.3)**	**5 (83.3)**
95% CI	(80.2, 92.8)	(84.1, 95.3)	(72.9, 87.6)	(68.1, 99.8)	(35.9, 99.6)
Clinical Benefit Rate [b], n (%)	100 (83.3)	102 (85.7)	87 (71.9)	14 (93.3)	5 (83.3)
95% CI	(75.4, 89.5)	(78.1, 91.5)	(63.0, 79.7)	(68.1, 99.8)	(35.9, 99.6)
Clinical Benefit Rate[c] n (%)	86 (71.7)	86 (72.3)	57 (47.1)	14 (93.3)	4 (66.7)
95% CI	(62.7, 79.5)	(63.3, 80.1)	(38.0, 56.4)	(68.1, 99.8)	(22.3, 95.7)

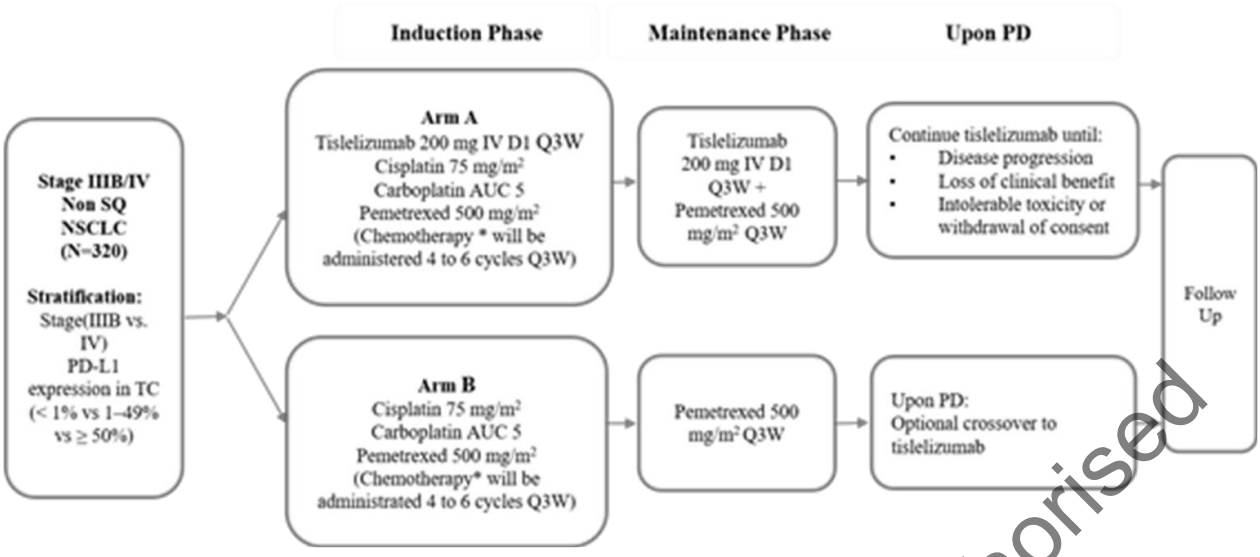
a Best overall response of could not be determined include patients who had post-baseline tumour assessment, none of which were evaluable; or patients who had no post-baseline tumour assessment, and non-CR/non-PD was due to no measurable target lesion per IRC. Results were summarised based on data as assessed by independent review committee for Study 307 and as assessed by investigator for study 206. Objective Response Rate was the proportion of Patients who achieved CR or PR using RECIST version 1.1. Disease Control Rate was the proportion of patients who achieved CR, PR, non-CR/non-PD or SD using RECIST version 1.1.
b Included patients with BOR in CR or PR or ≥12 weeks SD
c including those patients with BOR in CR or PR or SD ≥ 24 weeks SD

2.5.5.4. Clinical efficacy of tislelizumab in combination with chemotherapy as 1L treatment of non-squamous NSCLC

Main study

Study 304 (BGB-A317-304): Phase III Open Label First Line Therapy Study of Tislelizumab With Chemotherapy Versus Chemotherapy in Untreated Advanced Non-Squamous Non-Small Cell Lung Cancer (NSCLC)

Study 304 is a Phase III, open-label, multicentre, randomised study, conducted solely in China, and designed to evaluate the efficacy and safety of tislelizumab in combination with platinum and pemetrexed vs. platinum and pemetrexed alone in chemotherapy-naive patients with Stage IIIB or IV non-squamous NSCLC.



AJCC staging system v7

Arm A = Arm T+PP; Arm B = Arm PP
Patients were randomised in a 2:1 ratio to treatment with Arm T+PP or Arm PP
Patients with Stage IIIB disease were eligible for enrolment if their disease was not amenable to curative surgery or radiotherapy

Figure 69: Study design (Study 304)

Methods

- **Study Participants**

Key inclusion criteria included:

1. 18 to 75 years old on the day of signing the ICF
2. Histologically confirmed, locally advanced (Stage IIIB) not amenable to curative surgery or radiotherapy, or metastatic (Stage IV) non-squamous NSCLC. Patients with tumours of mixed non-small cell histology (squamous and non-squamous) were eligible if the major histological component appears to be non-squamous.
3. Patients must have been able to provide fresh or archival tumour tissues (FFPE blocks or approximately 15 [at least 6] freshly cut unstained FFPE slides) with an associated pathological report (non-squamous). Patients must have been able to provide documentation of wild-type EGFR reported by a tissue-based test. For patients without documented EGFR status, archival or fresh tumour tissues were required for EGFR mutation assessment prior to enrolment. In the absence of archival tumour tissues, a fresh biopsy of a tumour lesion at baseline was mandatory. PD-L1 expression was to be assessed centrally, and patients who had evaluable PD-L1 results are eligible.
4. ECOG performance status ≤ 1
5. Patients must had at least one measurable lesion as defined per RECIST v1.1.
6. Have had no prior systemic chemotherapy for advanced or metastatic NSCLC. Patients who had received prior neo-adjuvant, adjuvant chemotherapy, radiotherapy, or chemoradiotherapy with curative intent for non-metastatic disease must had experienced a treatment-free interval of at least 6 months from the last dose of chemotherapy and/or radiotherapy prior to randomisation.

7. Life expectancy ≥ 12 weeks

Key exclusion criteria included:

1. Diagnosed with NSCLC that harbours an *EGFR*-sensitizing mutation or *ALK* gene translocation
2. Any approved systemic anti-cancer therapy, including hormonal therapy, within 28 days prior to initiation of study treatment
3. Received prior treatment with EGFR inhibitors or ALK inhibitors
4. Received prior therapies targeting PD-1 or PD-L1
5. Treatment with systemic immune-stimulatory agents (including but not limited to interferons, interleukin IL-2, and tumour necrosis factor) within 4 weeks or 5 half-lives of the drug, whichever is longer, prior to randomisation (prior treatment with cancer vaccines is allowed)
6. Had received any Chinese herbal medicine or Chinese patent medicines used to control cancer within 14 days of randomisation
7. With history of interstitial lung disease, non-infectious pneumonitis, or uncontrolled systemic diseases, including diabetes, hypertension, pulmonary fibrosis, acute lung diseases, etc
8. Active leptomeningeal disease or uncontrolled, untreated brain metastasis

   • Patients with a history of treated and, at the time of screening, asymptomatic CNS metastases are eligible, provided they meet all the following:

   - Brain imaging at screening shows no evidence of interim progression
   - Have measurable disease outside the CNS, only supratentorial metastases allowed
   - No ongoing requirement for corticosteroids as therapy for CNS disease; anticonvulsants at a stable dose allowed
   - No stereotactic radiation or whole-brain radiation within 14 days prior to randomisation

   • Patients with new asymptomatic CNS metastases detected at the screening scan must receive radiation therapy and/or surgery for CNS metastases.

   - Following treatment, these patients may then be eligible, provided all other criteria, including those for patients with a history of brain metastases, are met.
9. Any major surgical procedure ≤ 28 days before randomisation
10. Any condition that required systemic treatment with either corticosteroids (> 10 mg daily of prednisone or equivalent) or other immunosuppressive medication ≤ 14 days before randomisation
11. Active autoimmune diseases that may have relapsed. Patients with the following diseases were not excluded and may have proceeded to further screening:
    a. controlled type I diabetes;
    b. hypothyroidism (provided that it was managed with hormone replacement therapy only);
    c. controlled celiac disease;
    d. skin diseases not requiring systemic treatment (e.g., vitiligo, psoriasis, alopecia); and e) any other disease that was not expected to recur in the absence of external triggering factors.

- **Treatments**

Tislelizumab

Tislelizumab 200 mg was administered on Day 1 of each 21-day cycle (every 3 weeks) by IV infusion through an IV line containing a sterile, nonpyrogenic, low-protein-binding 0.2 or 0.22 micron in-line or add-on filter.

The initial infusion (Cycle 1 Day 1) was delivered over 60 minutes; if it was well-tolerated, the subsequent infusions were administered over 30 minutes, which was the shortest period permissible for infusion. Tislelizumab was not to be concurrently administered with any other drug.

As a routine precaution, after infusion of tislelizumab on Day 1 of Cycle 1 and Cycle 2, patients were monitored for ≥ 1 hour afterward in an area with resuscitation equipment and emergency agents. From Cycle 3 onwards, a ≥ 30-minute monitoring period was required in an area with resuscitation equipment and emergency agents.

Chemotherapy

Pemetrexed administration was performed before cisplatin or carboplatin during the induction phase. Pemetrexed 500 mg/m2 was administered as an IV infusion over 10 minutes once every 3 weeks until disease progression or unacceptable toxicity. All patients received the appropriate supplementation of vitamin B12 and folic acid according to the approved product label and/or standard practice. In addition, all patients received the appropriate corticosteroid pre-medications as per the local approved label. Additional pre-medications were to be administered as per standard practice.

Carboplatin area under the curve (AUC) 5 was administered as an IV infusion over 15 minutes once every 3 weeks for 4 to 6 cycles immediately after pemetrexed. Additional premedications were to be administered as per standard practice.

Cisplatin 75 mg/m2 was administered as an IV infusion over 2 hours once every 3 weeks for 4 to 6 cycles. All patients received adequate hydration (including pre-treatment hydration) and diuretics. Urinary output >2000 mL was maintained for 24 hours after the infusion.

Table 73: Treatments (Study 304)

Study Drug	Dose	Frequency of Administration	Route of Administration
Tislelizumab	200 mg	Every 3 weeks	Intravenous
Pemetrexed	500 mg/m^2	Every 3 weeks	Intravenous
Cisplatin	75 mg/m^2	Every 3 weeks	Intravenous
Carboplatin	AUC 5	Every 3 weeks	Intravenous

Abbreviation: AUC, area under curve.

Tumour assessments were conducted every 6 weeks for the first 6 months, then every 9 weeks for the second 6 months, then every 12 weeks.

- **Objectives**

Assess the efficacy and safety of tislelizumab in combination with chemotherapy as 1L treatment of non-squamous NSCLC.

Primary Objective

• To compare the progression-free survival (PFS) as assessed by the Independent Review Committee (IRC) per Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 in the Intent-to-Treat (ITT)

Analysis Set between tislelizumab combined with platinum-pemetrexed and platinum-pemetrexed alone in chemotherapy-naive patients with Stage IIIB or Stage IV (as classified according to the American Joint Committee Cancer 7th Edition of Cancer Staging Manual) non-small cell lung cancer (NSCLC).

Secondary Objectives

• To compare the overall response rate (ORR) as assessed by the IRC and by the investigator per RECIST v1.1 between tislelizumab combined with platinum-pemetrexed and platinum-pemetrexed alone.

• To compare the duration of response (DOR) as assessed by the IRC and by the investigator per RECIST v1.1 between tislelizumab combined with platinum-pemetrexed and platinum-pemetrexed alone.

• To compare overall survival (OS) between tislelizumab combined with platinum-pemetrexed and platinum-pemetrexed alone in the ITT Analysis Set.

• To compare PFS as assessed by the investigator per RECIST v1.1 between tislelizumab combined with platinum-pemetrexed and platinum-pemetrexed alone in the ITT Analysis Set.

• To compare health-related quality of life (HRQoL) between tislelizumab combined with platinum-pemetrexed and platinum-pemetrexed alone.

• To evaluate the safety and tolerability of tislelizumab combined with platinum -pemetrexed compared with platinum-pemetrexed alone.

• To evaluate the correlation between programmed death-ligand 1 (PD-L1) expression levels by immunohistochemistry (IHC) and antitumour activity of tislelizumab combined with platinum-pemetrexed.

Exploratory Objectives

• To compare tumour assessment outcomes (e.g., disease control rate [DCR], time to response [TTR]) between tislelizumab combined with platinum-pemetrexed and platinum-pemetrexed alone as assessed by the investigator per RECIST v1.1.

• To assess tumour and blood biomarkers of tislelizumab response, resistance, and patient prognosis.

• To characterise the pharmacokinetics (PK) of tislelizumab when given in combination with platinum-pemetrexed.

• To assess host immunogenicity to tislelizumab.

- **Outcomes/endpoints**

<u>Primary Efficacy Endpoint</u>

•PFS as assessed by the IRC

the time from randomisation to the first objectively documented disease progression, or death from any cause, whichever occurs first, as determined by the IRC per RECIST v1.1 in an ***ITT*** Population.

<u>Secondary Efficacy Endpoints</u>

• **OS** – the time from the date of randomisation to the date of death due to any cause in an ITT Population.

• ***PFS as assessed by the investigator*** – the time from randomisation to the first objectively documented disease progression, or death from any cause, whichever occurs first, as determined by the investigator per RECIST v1.1 in an ITT Population.

• ***ORR as assessed by the IRC*** – the proportion of patients who had complete response (CR) or partial response (PR) as determined by the IRC per RECIST v1.1 in all randomised patients with measurable disease at baseline.

• ***ORR as assessed by the investigator*** – the proportion of patients who had CR or PR as determined by the investigator per RECIST v1.1 in all randomised patients with measurable disease at baseline.

• ***DOR as assessed by the IRC*** – the time from the first occurrence of a documented objective response to the time of relapse, or death from any cause, whichever comes first, as determined by the IRC per RECIST v1.1 in all randomised patients with documented objective responses.

• ***DOR as assessed by the investigator*** – the time from the first occurrence of a documented objective response to the time of relapse, or death from any cause, whichever comes first, as determined by the investigator per RECIST v1.1 in all randomised patients with documented objective responses.

• ***HRQoL***–measured using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Lung Cancer (EORTC QLQ LC13) and Core 30 (EORTC QLQ-C30) as presented in patient-reported outcomes

• Incidence and severity of treatment-emergent AEs (TEAEs) graded according to National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE), v4.03.

• ***PD-L1 expression by IHC as a predictive biomarker for response.***

Exploratory Endpoints

• DCR – the proportion of patients who had a complete response (CR), partial response (PR), or stable disease (SD) as assessed by the investigator per RECIST v1.1.

• TTR –the time from randomisation to the first occurrence of a documented objective response as assessed by the investigator per RECIST v1.1.

• Status of exploratory biomarkers, including but not limited to: PD-L1, tumour mutation burden (TMB), and immune-related gene expression profiling (GEP) in archival and/or freshly obtained tumour tissues and blood (or blood derivatives) obtained before, during, or after treatment with tislelizumab or at progression and the association with disease status and/or response to tislelizumab in combination with chemotherapy.

• Summary of serum concentrations of tislelizumab.

• Assessments of immunogenicity of tislelizumab by determining the incidence of antidrug antibodies (ADAs).

- **Sample size**

The sample size calculation was based on the number of events required to demonstrate the PFS superiority of Arm A to Arm B in the ITT analysis set. The estimates of the number of events required to demonstrate efficacy about PFS in the primary comparisons were based on the following assumptions:

1. Median PFS of 7 months in Arm B with exponential distribution assumption.

2. At a one-sided α of 0.025, 85% power to detect an HR of 0.65, corresponding to an improvement in median PFS from 7 months to 10.8 months, in the ITT analysis set.

3. Randomisation ratio of 2:1.

4. One interim analysis of PFS planned in the ITT analysis set when approximately 71% of total PFS events occurred, with Lan-DeMets' approximation to O'Brien-Fleming boundary (O'Brien et al, 1979).

With these assumptions, a total of 215 PFS events were planned to be required for the ITT analysis set for the PFS final analysis. Assuming 320 patients were planned to be enrolled over an 8-month period at a constant enrolment rate, the PFS final analysis was planned to occur approximately 19.2 months after the first patient was randomised.

- **Randomisation and Blinding (masking)**

Patients were planned to be randomised in a 2:1 ratio to either Arm A or Arm B using the IRT system for this study by permuted block stratified randomisation with stratification factors of Stage (IIIB versus IV) and PD-L1 expression in TC (≥ 50% TC versus 1%-49% TC versus < 1% TC). The stratified randomisation was planned to be produced, reviewed, and approved by an independent statistician.

The trial is an open-label study. Due to the open-label design, access to the patient level clinical data in the EDC system was planned to be assigned to predefined study personnel only. Functions/persons with access to the EDC system were planned to be prohibited from using the EDC system to generate unnecessary listings/summaries that may introduce unwanted bias, or share such outputs from the EDC system with other functions/persons who do not have access to the EDC. In addition, the central imaging vendor was planned to perform the central imaging review without knowledge of treatment arm assignment. Although the study is open label, analyses or summaries generated by randomised treatment assignment and actual treatment received were planned to be limited and documented.

To minimise the potential for assessment bias in the open-label Study 304 when comparing tislelizumab combined with platinum-pemetrexed versus platinum-pemetrexed alone, PFS evaluated by a blinded IRC per RECIST v1.1 was used as the primary endpoint of the study.

- **Statistical methods**

Analysis Sets

The ITT Analysis Set was planned to include all randomised patients. Patients were planned to be analysed according to their randomised treatment arms. This was planned to be the primary analysis set for efficacy analysis.

The Per-Protocol (PP) Analysis Set was planned to include randomised patients who received at least 1 dose of the assigned study drug and had no major protocol deviations. Major protocol deviations were planned to be determined and documented before the database lock for the primary analysis.

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

The PK Analysis Set was planned to include all patients who received at least 1 dose of tislelizumab per the protocol, for whom any post-dose PK data were available.

The immunogenicity (ADA) Analysis Set was planned to include all patients who received at least 1 dose of tislelizumab for whom both baseline ADA and at least 1 post-baseline ADA results were available.

Primary Endpoint

The primary endpoint PFS per the IRC was defined as the time from randomisation to the first documented disease progression as assessed by the IRC with the use of RECIST v1.1, or death from any cause, whichever occurred first. The actual tumour assessment visit date was planned to be used to calculate PFS. Data for patients without disease progression or death at the time of analysis were planned to be censored at the time of the last valid tumour assessment. Data for patients without post-baseline tumour assessment were planned to be censored at the time of randomisation. Data for patients who started to receive new anticancer therapy or were lost to follow-up were planned to be censored at the last valid tumour assessment date prior to the introduction of new therapy or loss to follow-up. Patients who had a clinical determination of progression were planned to undergo a CT/MRI, if possible, to correlate radiographic findings with the clinical findings. If a clinical determination of progression for a patient was confirmed, the date of the CT/MRI scan was planned to be considered as the progression date for that patient.

PFS per the IRC was planned to be compared between tislelizumab with platinum-pemetrexed (Arm A) and platinum-pemetrexed alone (Arm B) in a stratified log-rank test at one-sided significance level α=0.025.

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

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

The p-value from a stratified log-rank test was planned to be presented using stratification factors. The median PFS was planned to be calculated for each treatment arm and presented with two-sided 95% CIs. Kaplan-Meier survival probabilities for each arm were planned to be plotted over time. The hazard ratio (HR) between Arm A and Arm B and its 95% CI were planned to be estimated using a Cox proportional hazard model with treatment arm as a factor and stratified by the actual value of the stratification factors as recorded in the eCRF.

Secondary Endpoints

Overall Survival

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

Progression-Free Survival per Investigator

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

Objective Response Rate per the IRC and per the Investigator

ORR per the IRC or per the Investigator, resp. (confirmation not required according to RECIST v1.1) was defined as the proportion of patients who had a CR or PR as assessed by the IRC per RECIST v1.1 resp. as determined by the investigator per RECIST v1.1 in ITT analysis set. Patients without any post-baseline assessment were planned to be considered non-responders. The difference in ORR per the IRC and in ORR per the Investigator between arms in the ITT analysis set were planned to be evaluated using the Cochran-Mantel-Haenszel (CMH) chi-square test with the actual stratification factors as

strata. The two-sided 95% CIs for the odds ratio and the difference in ORR per the IRC as well as in ORR per the Investigator were planned to be calculated, as well as Clopper-Pearson 95% CIs for the ORR within each arm.

Duration of Response per the IRC and per the Investigator

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

Health-Related Quality of Life

Summary statistics (mean, SD, median, and range) of the post-baseline scores were planned to be reported for the EORTC Quality of Life Cancer Questionnaire (EORTC QLQ-LC13 and EORTC QLQC30). The mean change of the scores from baseline (and 95% CI with use of the normal approximation) were also planned to be assessed. Line charts depicting the mean changes (and standard errors) over time from the baseline assessment were planned to be provided for each treatment arm. The proportion of patients showing clinically meaningful change in selected items and subscales at each assessment time point were planned to be calculated. Completion and compliance rates were planned to be summarised at each time point by treatment arm. Only patients with a non-missing baseline assessment and at least one in-study non-missing post-baseline assessment were planned to be included in the analyses. Summaries were planned be performed for the ITT analysis set only.

PD-L1 Expression as a Predictive Biomarker for Response

Distribution of PD-L1 expression in TC was planned to be examined in the ITT analysis set. Association between PD-L1 expression and tislelizumab treatment effect over control (PFS, OS, ORR, DOR, DCR) were planned to be explored.

Restricted Mean survival times

Upon request, the applicant provided restricted mean survival times to address potentially non-proportional hazards. PD-L1 was included for as a continuous variable. Results (RMST(Arm T+PP) - RMST(Arm PP): 3.19 months (95% CI: 1.23, 5.15, p= 0.001)) provide reassurance.

Interim Analyses

One interim efficacy analysis of PFS performed in the ITT analysis set was planned. The interim efficacy analysis of PFS was planned to be performed when approximately 153 PFS events (71% of the targeted number of 215 PFS events) were observed in the ITT analysis set. It was estimated that it would take approximately 12.8 months to observe 153 PFS events. The interim boundary for PFS was based on the Lan-DeMets approximation to O'Brien-Fleming boundary. The interim and final analysis timing and stopping boundaries were summarised in Table 74, and the exact time of each analysis was planned to depend on actual number of events occurred.

Table 74: Analysis timing and stopping boundary for PFS in the ITT analysis set (overall one-sided hypothesis testing at α = 0.025) (Study 304)

Type of Analysis	Time (Months)	Number of Events	Testing Boundary	
			P-value Boundary	Approx. HR Threshold
Interim analysis	12.8	153	0.0078	0.660
Final analysis	19.2	215	0.0226	0.748

Subgroup Analyses

Subgroup analysis of primary endpoint of PFS per the IRC were planned to be conducted to determine if the treatment effect is consistent across various subgroups, the HR estimates of PFS and its 95% CI were planned to be estimated and plotted within each category of the following variables: PD-L1 expression in TC (≥ 50% TC versus 1%-49% TC versus < 1% TC), Stage (IIIB versus IV), age (≤ 65 versus > 65 years), gender (female versus male), ECOG PS (0 versus 1), and smoking status (Former versus Current versus Never).

Results

- **Participant flow**

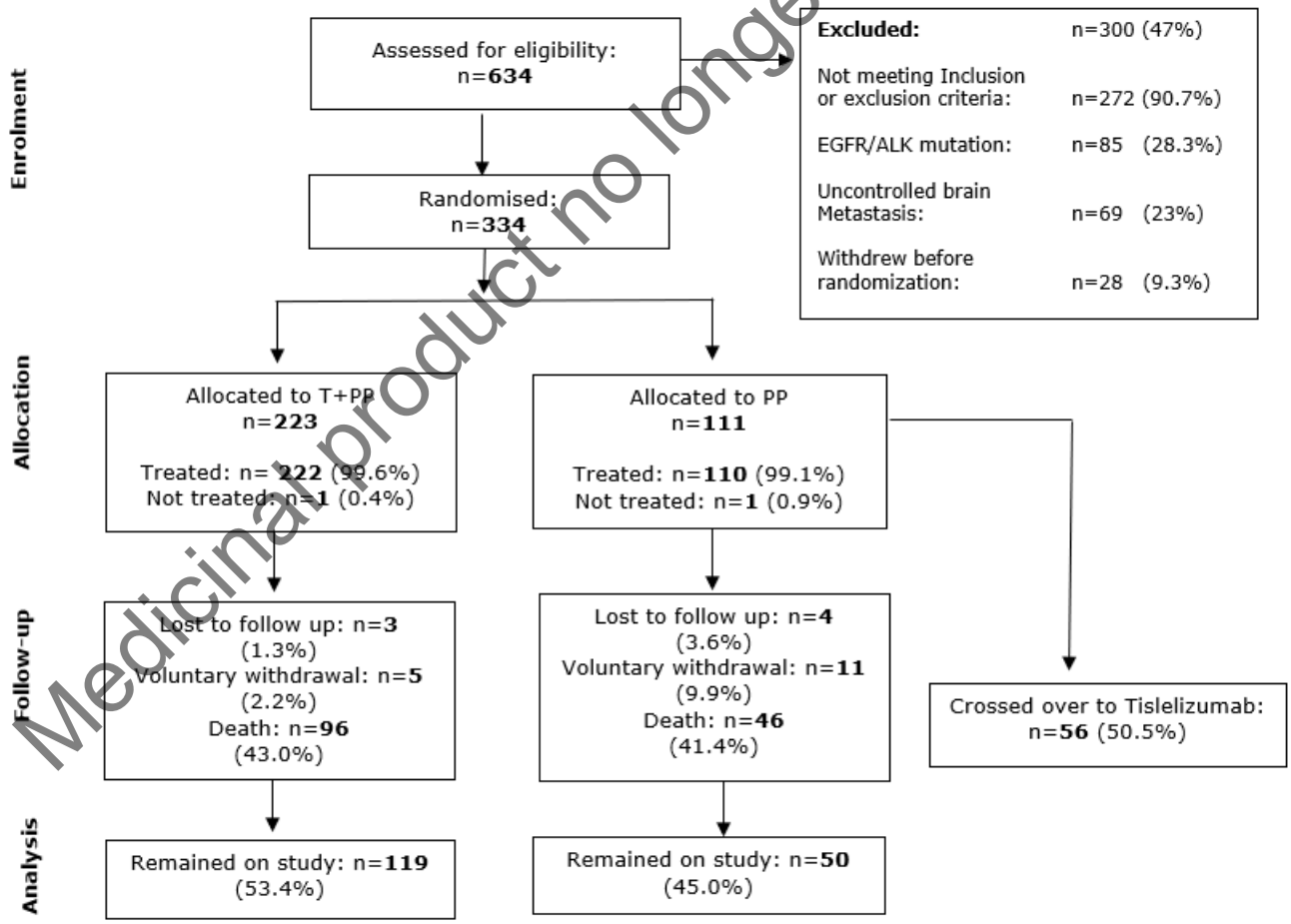


Table 75: Patient disposition and reasons for discontinuation (ITT analysis) (Study 304) (DCO: 26OCT2020)

	Arm T+PP (N = 223) n (%)	Arm PP (N = 111) n (%)
Number of Patients Treated	**222 (99.6)**	**110 (99.1)**
Number of Patients Discontinued from all Study drugs	**168 (75.3)**	**104 (93.7)**
Primary Reason for Treatment Discontinuation [a]		
Radiographic Progression	111 (49.8)	72 (64.9)
Patient Withdrawal of Consent	20 (9.0)	14 (12.6)
Adverse Event	24 (10.8)	8 (7.2)
Clinical Progression	5 (2.2)	3 (2.7)
Physician Decision	2 (0.9)	4 (3.6)
Non-Compliance with Study Drug	2 (0.9)	2 (1.8)
Other	4 (1.8)	1 (0.9)
Number of Patients Remained on Treatment	**54 (24.2)**	**6 (5.4)**
Number of Patients Discontinued from Study	**104 (46.6)**	**61 (55.0)**
Primary Reason for Study Discontinuation		
Death	96 (43.0)	46 (41.4)
Voluntary Withdrawal	5 (2.2)	11 (9.9)
Lost to Follow-Up	3 (1.3)	4 (3.6)
Other[c]	0 (0.0)	0 (0.0)
Number of Patients Remained on Study	**119 (53.4)**	**50 (45.0)**
Study Follow-up Time (Months) [c]		
Median	16.49	15.15
Min, Max	0.0, 27.2	0.0, 25.8

Data cutoff: 26Oct2020
Abbreviations: 304, A317-304; T+PP, Tislelizumab+Pemetrexed+Platinum; PP, Pemetrexed+Platinum.
a Primary reason for treatment discontinuation referred to primary reason of study drug which discontinued last.
c Study follow-up time was defined as the time from the randomisation date to date of death or end of study date (whichever occurs first) for patient discontinued from the study or the database cutoff date for ongoing patients.

- **Recruitment**

This ongoing study is being conducted in 47 study centres in China. Start date was 24-Jul-2018. Median follow-up time at final analysis (DCO: 26 October 2020): 16.1 months.

- **Conduct of the study**

Amendment 1.0 (dated 07 June 2018)

The main purpose of this protocol amendment was:

• To update the safety data and clinical PK data according to the latest tislelizumab IB 5.0 and protocol template.

• To update statistical analysis parts by adjusting O'Brien-Fleming boundary per CDE comments, and PFS interim analysis timing per PFS delayed effect.

• To update protocol language to align with the latest protocol template, including updates to risk and management of myocarditis/myositis

Amendment 2.0 (dated 24 January 2019)

The main purpose of this protocol amendment was:

• To clarify the operational details of serum creatinine kinase (CK) and creatinine kinase cardiac muscle isoenzyme (CK-MB) testing for close monitoring of myocarditis/myositis;

• To update myocarditis/myositis language (immune-related adverse event evaluation and management) according to FDA requirements;

• To update to allow subjects with PD-L1 unevaluated results to be included in this study;

• To update the procedures for select study assessments to allow for greater flexibility in keeping with clinical practice;

• To revise the content for clarity and consistency to align with the latest updates to the tislelizumab protocol template, including updates to safety assessment.

Note: Patients with PD-L1 unevaluated results were allowed to be included in this study with protocol amendment V2

- **Baseline data**

Table 76: Demographics and baseline characteristics (ITT analysis set) (Study 304) (DCO: 26OCT2020)

	T+PP (N = 223) n (%)	PP (N = 111) n (%)	Total (N = 334) n (%)
Age (years)			
Median	60.0	61.0	61.0
Min, Max	27, 75	25, 74	25, 75
Age Group, n (%)			
< 65 years	163 (73.1)	74 (66.7)	237 (71.0)
≥ 65 years	60 (26.9)	37 (33.3)	97 (29.0)
Sex, n (%)			
Male	168 (75.3)	79 (71.2)	247 (74.0)
Female	55 (24.7)	32 (28.8)	87 (26.0)
BMI (kg/m^2)			
Median	23.41	22.49	23.08
Min, Max	16.0, 33.8	15.6, 29.7	15.6, 33.8
ECOG Performance Status, n (%)			
0	54 (24.2)	24 (21.6)	78 (23.4)
1	169 (75.8)	87 (78.4)	256 (76.6)
Smoking Status, n (%)			
Never	76 (34.1)	45 (40.5)	121 (36.2)
Current	32 (14.3)	13 (11.7)	45 (13.5)
Former	115 (51.6)	53 (47.7)	168 (50.3)
Baseline Target Lesions Sum of Diameters by Investigator (mm)			
Median	66.60	63.00	65.50
Min, Max	10.0, 230.0	10.4, 219.0	10.0, 230.0
PD-L1 Expression in Tumor Cell, n (%)			
<1%[a]	96 (43.0)	48 (43.2)	144 (43.1)
1% - 49%	53 (23.8)	27 (24.3)	80 (24.0)
≥ 50%	74 (33.2)	36 (32.4)	110 (32.9)
Patients with any Prior Anticancer Drug Therapy, n (%)	16 (7.2)	8 (7.2)	24 (7.2)
Type of Prior Anticancer Drug Therapy, n (%)[b,c]			
Adjuvant	11 (68.8)	7 (87.5)	18 (75.0)
NeoAdjuvant	2 (12.5)	0 (0.0)	2 (8.3)
Curative Radiochemotherapy	1 (6.3)	0 (0.0)	1 (4.2)
Other[d]	3 (18.8)	1 (12.5)	4 (16.7)
Patients with any Prior Anticancer Surgeries, n (%)	21 (9.4)	15 (13.5)	36 (10.8)
Patients with any Prior Anticancer Radiotherapy, n (%)	19 (8.5)	8 (7.2)	27 (8.1)

Source: ADSL, ADBASE. Data cutoff: 26Oct2020. Data extraction: 23Feb2021.

Table 77: Disease characteristics (ITT analysis set) (Study 304) (DCO: 26OCT2020)

	T+PP (N = 223) n (%)	PP (N = 111) n (%)	Total (N = 334) n (%)
Time from Initial Diagnosis to Study Entry [a] (Months)			
Median	1.02	1.05	1.02
Min, Max	0.3, 46.1	0.3, 151.7	0.3, 151.7
Time from Advanced/Metastatic Disease Diagnosis to Study Entry [a] (Months)			
Median	0.89	0.89	0.89
Min, Max	0.0, 18.5	0.1, 52.5	0.0, 52.5
Current Disease Stage, n (%)			
IIIB	40 (17.9)	21 (18.9)	61 (18.3)
IV	183 (82.1)	90 (81.1)	273 (81.7)
Histology, n (%)			
Adenocarcinoma	215 (96.4)	107 (96.4)	322 (96.4)
Mixed Adeno-Squamous	1 (0.4)	2 (1.8)	3 (0.9)
Other	7 (3.1)	2 (1.8)	9 (2.7)
EGFR Mutation Status, n (%) [b]			
Negative	218 (97.8)	109 (98.2)	327 (97.9)
Missing	5 (2.2)	2 (1.8)	7 (2.1)
ALK Rearrangement, n (%)			
Negative	166 (74.4)	79 (71.2)	245 (73.4)
Unknown	57 (25.6)	32 (28.8)	89 (26.6)
Location of Baseline Target Lesion, n (%) [c]			
Lung	200 (89.7)	107 (96.4)	307 (91.9)
Liver	12 (5.4)	12 (10.8)	24 (7.2)
Other [d]	128 (57.4)	54 (48.6)	182 (54.5)
Location of Distant Metastases, n (%) [c]			
Bone	75 (33.6)	41 (36.9)	116 (34.7)
Liver	20 (9.0)	17 (15.3)	37 (11.1)
Brain	11 (4.9)	7 (6.3)	18 (5.4)

Source: ADSL, ADBASE. Data cutoff: 26Oct2020. Data extraction: 23Feb2021.
Abbreviations: T+PP, Tislelizumab+Pemetrexed+Platinum; PP, Pemetrexed+Platinum.

- **Numbers analysed**

Table 78: Analysis sets (Study 304) (DCO: 26OCT2020)

	T+PP (N = 223) n (%)	PP (N = 111) n (%)	Total (N = 334) n (%)
ITT Analysis Set	223 (100.0)	111 (100.0)	334 (100.0)
Safety Analysis Set	222 (99.6)	110 (99.1)	332 (99.4)
PK Analysis Set	222 (99.6)	NA	222 (66.5)
HRQoL Analysis Set	222 (99.6)	110 (99.1)	332 (99.4)

Source: ADSL. Data cutoff: 26Oct2020. Data extraction: 23Feb2021.
Abbreviations: T+PP, Tislelizumab+Pemetrexed+Platinum; PP, Pemetrexed+Platinum; NA, Not applicable.

- **Outcomes and estimation**

Primary Endpoint

Progression free survival (by IRC)

At **Interim Analysis** (data cut-off date 23 Jan 2020), a total of 104 (46.6%) PFS events in Arm A and 54 (48.6%) in Arm B had occurred, with a median follow-up time of 9.8 months in the ITT Analysis Set.

Table 79: Analysis of progression-free survival per RECIST version 1.1 by independent review committee (ITT analysis set) (Study 304); interim analysis (DCO: 23JAN2020)

	T+PP (N = 223)	PP (N = 111)
Progression-Free Survival		
Events, n (%)	104 (46.6)	**54 (48.6)**
Progressive Disease	96 (43.0)	**49 (44.1)**
Death	8 (3.6)	5 (4.5)
Censored, n (%)	119 (53.4)	**57 (51.4)**
One-sided stratified log-rank test p-value [a]	**0.0054**	
Stratified Hazard Ratio (95% CI) [ab]	**0.651 (0.465, 0.912)**	
Progression-Free Survival (month)		
Median (95% CI)	9.7 (7.72, 11.53)	7.6 (5.55, 8.02)
Q1 (95% CI)	5.0 (4.17, 5.62)	3.9 (2.69, 4.30)
Q3 (95% CI)	12.9 (11.76, NE)	9.8 (8.02, NE)
Event-free Rate at, % (95% CI)		
3 months (95% CI)	85.7 (80.24, 89.81)	77.4 (67.97, 84.40)
6 months (95% CI)	64.8 (57.59, 71.03)	56.3 (45.01, 66.06)
9 months (95% CI)	54.3 (46.45, 61.57)	**35.4 (22.90, 48.16)**
12 months (95% CI)	31.3 (21.67, 41.44)	**17.7 (7.26, 31.90)**

Source: ADSL, ADTTE. Data cutoff: 23Jan2020. Data extraction: 31Mar2020.

The **final efficacy analysis** was performed by the IRC after 201 PFS events (60.2% of 334 patients in the ITT Analysis Set) were observed on 26 October 2020, the data cutoff date. The median follow-up time at the final analysis was 16.1 months.

In the following, efficacy results from the data cutoff 26 Oct 2020 at the final analysis are presented.

Table 80: Analysis of progression-free survival per RECIST version 1.1 by independent review committee (ITT analysis set) (Study 304); final analysis (CO: 26OCT2020)

	T+PP (N = 223)	PP (N = 111)
Progression-Free Survival		
Events, n (%)	133 (59.6)	68 (61.3)
Progressive Disease	122 (54.7)	63 (56.8)
Death	11 (4.9)	5 (4.5)
Censored, n (%)	90 (40.4)	43 (38.7)
Consent Withdrawn	1 (0.4)	3 (2.7)
Lost to Follow Up	1 (0.4)	1 (0.9)
Ongoing without Event	54 (24.2)	9 (8.1)
No Baseline Tumor Assessment	0 (0.0)	0 (0.0)
No Postbaseline Tumor Assessment	4 (1.8)	4 (3.6)
New Anticancer Therapy	27 (12.1)	25 (22.5)
Death or Progression after Missing 2 or More Consecutive Tumor Assessments	3 (1.3)	1 (0.9)
One-sided stratified log-rank test p-value [a]	0.0013	
Stratified Hazard Ratio (95% CI) [a,b]	0.632 (0.467, 0.855)	
Progression-Free Survival (month)		
Median (95% CI)	9.8 (8.94, 11.70)	7.6 (5.55, 8.02)
Q1 (95% CI)	5.0 (4.17, 5.75)	3.9 (2.69, 4.30)
Q3 (95% CI)	NE (17.08, NE)	9.9 (9.69, 16.82)
Event Free Rate at, % (95% CI)		
3 month (95% CI)	85.8 (80.29, 89.84)	77.4 (67.97, 84.40)
6 month (95% CI)	66.3 (59.32, 72.33)	57.0 (46.09, 66.58)
9 month (95% CI)	57.2 (49.93, 63.72)	38.6 (27.59, 49.42)
12 month (95% CI)	39.9 (33.76, 46.84)	20.1 (11.56, 30.22)
18 month (95% CI)	26.6 (19.49, 34.32)	11.3 (4.64, 21.21)
24 month (95% CI)	25.1 (17.83, 32.97)	NE (NE, NE)

Source: ADSL, ADTTE. Data cutoff: 26Oct2020. Data extraction: 23Feb2021.
Abbreviations: T+PP, Tislelizumab+Pemetrexed+Platinum; PP, Pemetrexed+Platinum; NE, Not Estimable.
Medians and other quartiles were estimated by Kaplan-Meier methodology with 95% CIs estimated using the method of Brookmeyer and Crowley. Event-free rates were estimated by Kaplan-Meier methodology with 95% CIs estimated using Greenwood's formula.
[a] Stratified by stratification factors: disease stage (IIIB versus IV) and PD-L1 expression in tumor cell (≥50% TC versus 1%-49% TC versus <1% TC).
[b] Hazard ratio was estimated from Cox model with pemetrexed+platinum group as reference group.

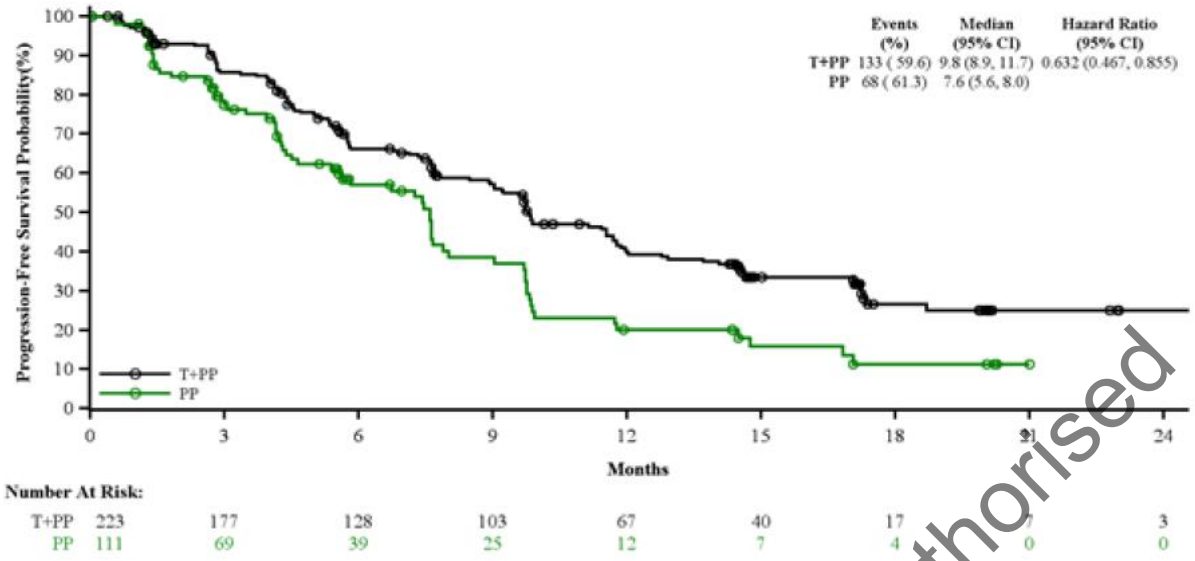


Figure 70: Kaplan-Meier plot of progression-free survival per RECIST v1.1 by independent review committee (ITT analysis set) (Study 304); final analysis (DCO: 26OCT2020)

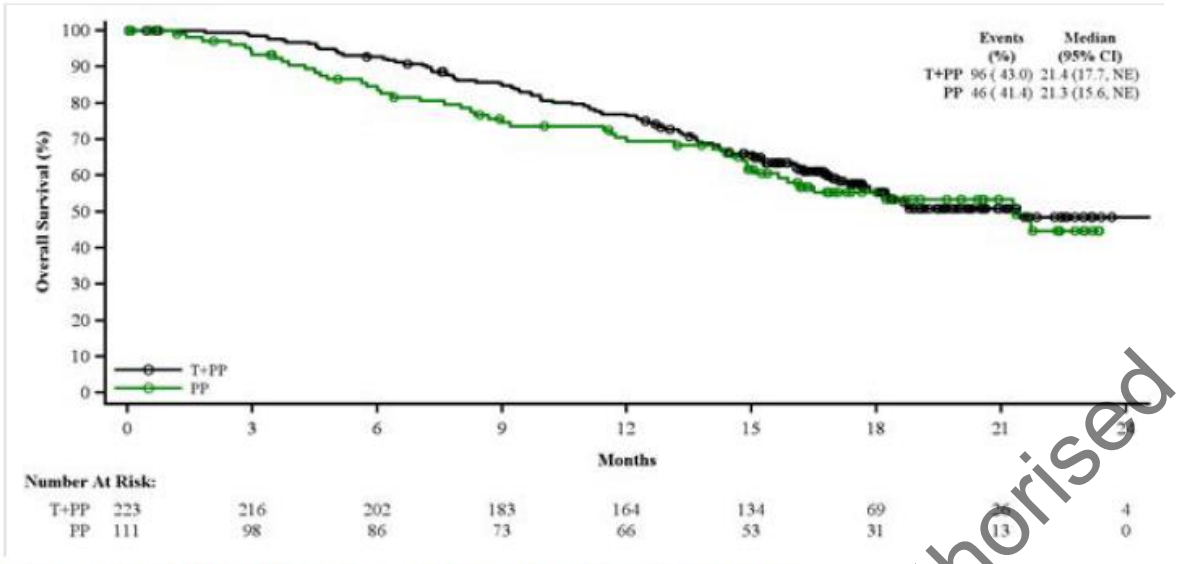
Secondary Endpoints

Overall Survival

Table 81: Analysis of overall survival (ITT analysis set) (Study 304); final analysis (DCO: 26OCT2020)

	T+PP (N = 223)	PP (N = 111)
Overall Survival		
Death, n (%)	96 (43.0)	46 (41.4)
Censored, n (%)	127 (57.0)	65 (58.6)
Ongoing in the Study	119 (53.4)	50 (45.0)
Withdrawal by Subject	5 (2.2)	11 (9.9)
Lost to Follow-up	3 (1.3)	4 (3.6)
Stratified Hazard Ratio (95% CI) [a]	0.900 (0.631, 1.283)	–
Overall Survival (months)		
Median (95% CI)	21.4 (17.68, NE)	21.3 (15.64, NE)
Q1 (95% CI)	12.5 (9.95, 13.83)	9.0 (6.01, 14.36)
Q3 (95% CI) [b]	NE (NE, NE)	NE (NE, NE)
Event-Free Rate at; % (95% CI)		
3 months (95% CI)	98.6 (95.81, 99.56)	93.4 (86.59, 96.78)
6 months (95% CI)	92.7 (88.35, 95.46)	84.6 (76.08, 90.27)
9 months (95% CI)	85.3 (79.84, 89.36)	74.6 (65.01, 81.97)
12 months (95% CI)	76.4 (70.19, 81.54)	69.4 (59.41, 77.42)
18 months (95% CI)	55.4 (47.98, 62.17)	55.3 (44.59, 64.77)
24 months (95% CI)	48.4 (39.66, 56.67)	NE (NE, NE)
Follow-up Time (month)		
Median (95% CI)	18.4 (17.54, 19.45)	18.0 (16.79, 18.86)

Source: ADSL, ADTTE. Data cutoff: 26Oct2020. Data extraction: 23Feb2021.



Source: ADSL, ADTTE. Data cutoff: 26Oct2020. Data extraction: 23Feb2021.
Abbreviations: T+PP, Tislelizumab+Pemetrexed+Platinum;PP, Pemetrexed+Platinum;NE, Not Estimable.

Figure 71: Kaplan-Meier plot of overall survival (ITT analysis set) (Study 304); final analysis (DCO: 26OCT2020)

Overall Survival – Updated data

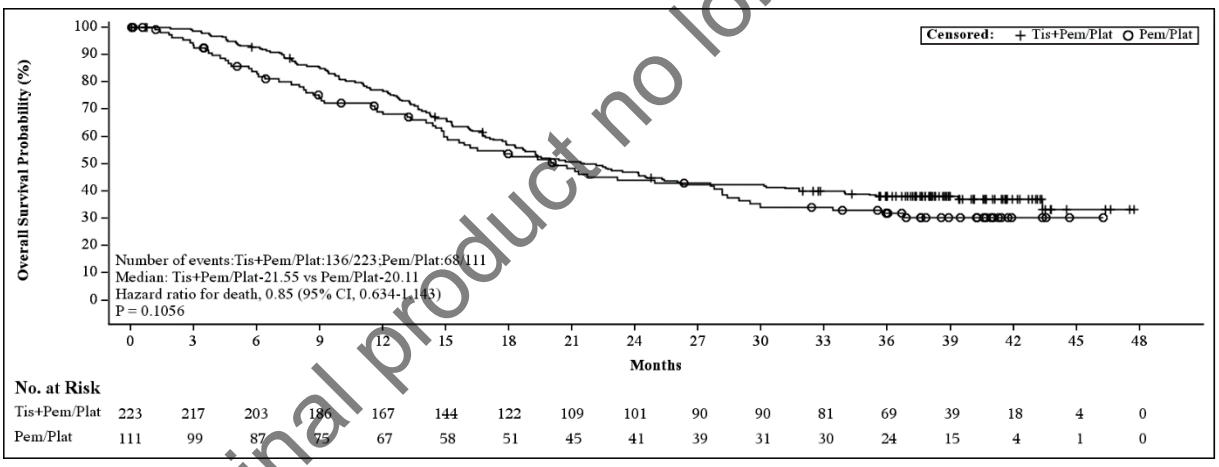


Figure 72: Kaplan-Meier plot of overall survival (ITT analysis set) (Study 304); updated data (DCO: 15JUL2022)

Progression-Free Survival (by Investigator)

Table 82: Analysis of progression-free survival per RECIST version 1.1 by investigator (ITT analysis set) (Study 304); final analysis (DCO: 26OCT2020)

	T+PP (N = 223)	PP (N = 111)
Progression-Free Survival		
Events, n (%)	143 (64.1)	81 (73.0)
Progressive Disease	134 (60.1)	77 (69.4)
Death	9 (4.0)	4 (3.6)
Stratified Hazard Ratio (95% CI) [a,b]	0.550 (0.415, 0.729)	–
Progression-Free Survival (month)		
Median (95% CI)	9.7 (7.66, 11.70)	5.6 (4.80, 7.89)
Q1 (95% CI)	5.0 (4.17, 5.78)	4.0 (2.53, 4.30)
Q3 (95% CI)	19.2 (17.25, NE)	9.9 (9.69, 12.68)
Event-Free Rate at, % (95% CI)		
3 months (95% CI)	85.8 (80.35, 89.87)	76.1 (66.66, 83.16)
6 months (95% CI)	68.8 (62.02, 74.63)	47.9 (37.55, 57.50)
9 months (95% CI)	52.4 (45.34, 58.99)	35.0 (25.14, 44.96)
12 months (95% CI)	40.0 (33.14, 46.67)	17.5 (10.07, 26.60)
18 months (95% CI)	25.1 (18.38, 32.89)	6.8 (2.39, 14.52)
24 months (95% CI)	23.8 (17.03, 31.20)	NE (NE, NE)

Source: ADSL, ADTTE. Data cutoff: 26Oct2020. Data extraction: 23Feb2021.

Objective Response Rate (by IRC)

Table 83: Analysis of confirmed disease response per RECIST v1.1 by independent review committee (ITT analysis set) (Study 304); final analysis (DCO: 26OCT2020)

	Study 304	
	T+PP (N = 223)	**PP (N = 111)**
Best Overall Response [a], n (%)		
Complete Response	9 (4.0)	2 (1.8)
Partial Response	104 (46.6)	29 (26.1)
Stable Disease	83 (37.2)	56 (50.5)
Non-CR/Non-PD	3 (1.3)	3 (2.7)
Progressive Disease	15 (6.7)	14 (12.6)
Could not be Determined	9 (4.0)	7 (6.3)
Objective Response Rate (ORR), n (%)	113 (50.7)	31 (27.9)
95% CI	(43.9, 57.4)	(19.8, 37.2)
Disease Control Rate, n (%)	199 (89.2)	90 (81.1)
95% CI	(84.4, 93.0)	(72.5, 87.9)
Clinical Benefit Rate [b], n (%)	184 (82.5)	80 (72.1)
95% CI	(76.9, 87.3)	(62.8, 80.2)
Clinical Benefit Rate [c], n (%)	149 (66.8)	54 (48.6)
95% CI	(60.2, 73.0)	(39.0, 58.3)

DCO: 26Oct2020
Abbreviations: T+PP, Tislelizumab+Pemetrexed+Platinum; PP, Pemetrexed+Platinum.
Best overall response of could not be determined included patients who had post-baseline tumour assessment, none of which were evaluable; or patients who had no post-baseline tumour assessments due to death, withdrawal of consent, lost to follow-up or any other reasons, and non-CR/non-PD was due to no measurable target lesion per IRC. Results were summarised based on data as assessed by independent review committee. Objective Response Rate was the proportion of Patients who achieved CR or PR using RECIST version 1.1. Disease Control Rate was the proportion of Patients who achieved CR, PR, non-CR/non-PD or SD using RECIST v1.1.
a Confirmed CR or PR is required.
b Included patients with BOR in CR or PR or ≥12 weeks SD.
c Included patients with BOR in CR or PR or ≥24 weeks SD.

Duration of Response (by IRC)

Table 84: Analysis of duration of response confirmed per RECIST v1.1 by independent review committee (ITT analysis set) (Study 304); final analysis (DCO: 26OCT2020)

	Study 304	
	T+PP (N = 223)	**PP (N = 111)**
Number of Responders[a]	**113**	**31**
Duration of Response		
Events, n (%)	**53 (46.9)**	**17 (54.8)**
Progressive Disease	48 (42.5)	16 (51.6)
Death	5 (4.4)	1 (3.2)
Censored	60 (53.1)	14 (45.2)
Duration of Response (Months)		
Median (95% CI)	14.5 (10.09, NE)	8.4 (5.95, 15.47)
Q1 (95% CI)	6.5 (4.99, 8.31)	5.9 (3.25, 7.00)
Q3 (95% CI)	NE (NE, NE)	15.5 (8.48, NE)
Event Free Rate at, % (95% CI)		
6 months	78.5 (69.47, 85.19)	63.8 (41.78, 79.35)
12 months	53.9 (43.63, 63.11)	37.2 (18.32, 56.24)
18 months	42.0 (30.35, 53.17)	20.7 (4.86, 43.97)
24 months	42.0 (30.35, 53.17)	NE (NE, NE)

DCO: 26Oct2020 for 304.
Abbreviations:T+PP, Tislelizumab+Pemetrexed+Platinum; PP, Pemetrexed+Platinum; NE, not estimable.
a Responders are defined as patients who achieved best overall response of confirmed CR or PR using RECIST version 1.1.Percentages were based on number of responders.
Results were summarised based on data as assessed by independent review committee. Medians and other quartiles were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley. Event free rates were estimated by Kaplan-Meier method with 95% CI estimated using the Greenwood's formula.

Health-related Quality of Life

The addition of tislelizumab to platinum-pemetrexed trended towards improvements in HRQoL compared to platinum-pemetrexed alone in patients with previously untreated stage IIIB or IV non-squamous NSCLC. The difference in LS mean change scores at Cycle 5 for QLQ-C30 GHS/QoL was 3.9 (95% CI: -0.9, 8.7); however, the difference at Cycle 7 (5.7 [95% CI: 1.0, 10.5]) showed a trend towards higher scores for Arm T+PP. The difference in LS mean change scores at Cycle 5 for QLQ-LC13 chest pain was -3.2 (95% CI: -7.6, 1.2); however, the difference at Cycle 7 (-6.2 [95% CI: -10.8, -1.6]) showed a trend towards lower scores for Arm T+PP. The difference in LS mean change scores at Cycle 5 for QLQ-LC13 coughing was -2.2 (95% CI: - 7.4, 3.1); however, the difference at Cycle 7 (-5.9 [95% CI: -11.6, -0.1]) showed a trend towards lower scores for Arm T+PP. The median TTD for QLQ-C30 GHS/QoL was not reached in either treatment arms; the median TTD for the composite of cough, chest pain, and dyspnoea in the QLQ LC13 was 5.8 months (95% CI: 4.40, NE) in Arm T+PP and 4.3 months (95 %CI: 3.09, NE) in Arm PP.

- **Ancillary analyses**

Sensitivity Analyses for PFS

Sensitivity Analysis 1 evaluated the impact of censoring the primary endpoint due to new anticancer treatment. This analysis was the same as the primary analysis with regards to the censoring rules except for the handling of new anticancer treatment. The PFS was derived regardless of the new anticancer treatment.

Table 85: Analysis of progression-free survival per RECIST version 1.1 by independent review committee - comparison of primary analysis and sensitivity analysis (ITT analysis set) (Study 304); final analysis (DCO: 26OCT2020)

	Primary Analysis		Sensitivity Analysis 1	
	T+PP (N = 223)	PP (N = 111)	T+PP (N = 223)	PP (N = 111)
Stratified Hazard Ratio (95% CI) [a,b]	0.632 (0.467, 0.855)	–	0.625 (0.467, 0.837)	–
Progression-Free Survival (months)				
Median (95% CI)	9.8 (8.94, 11.70)	7.6 (5.55, 8.02)	9.7 (8.90, 11.70)	7.5 (5.39, 7.89)

Source: ADSL, ADTTE. Data cutoff: 26Oct2020. Data extraction: 23Feb2021. Abbreviations: T+PP, Tislelizumab+Pemetrexed+Platinum; PP, Pemetrexed+Platinum.

An additional analysis was conducted to evaluate the impact of never smoking and baseline liver metastasis on the primary analysis. The stratified HR as estimated from the Cox model adjusted for never-smoking and baseline liver metastasis was 0.636 (95% CI: 0.468, 0.863).

Table 86: Analysis of progression-free survival per RECIST version 1.1 by independent review committee – adjusting for smoking status and baseline liver metastasis (ITT analysis set) (Study 304); final analysis (DCO: 26OCT2020)

	T+PP (N = 223)	PP (N = 111)
Progression-Free Survival		
Events, n (%)	133 (59.6)	68 (61.3)
Progressive Disease	122 (54.7)	63 (56.8)
Death	11 (4.9)	5 (4.5)
Censored, n (%)	90 (40.4)	43 (38.7)
Consent Withdrawn	1 (0.4)	3 (2.7)
Lost to Follow Up	1 (0.4)	1 (0.9)
Ongoing without Event	54 (24.2)	9 (8.1)
No Postbaseline Tumor Assessment	4 (1.8)	4 (3.6)
New Anticancer Therapy	27 (12.1)	25 (22.5)
Death or Progression after Missing 2 or More Consecutive Tumor Assessments	3 (1.3)	1 (0.9)
One-sided stratified log-rank test p-value [a]	0.0013	
Stratified Hazard Ratio (95% CI) [ab]	0.636 (0.468, 0.863)	
One-sided unstratified log-rank test p-value	0.0003	
Unstratified Hazard Ratio (95% CI) [b]	0.601 (0.445, 0.810)	
Progression-Free Survival (month)		
Median (95% CI)	9.8 (8.94, 11.70)	7.6 (5.55, 8.02)
Q1 (95% CI)	5.0 (4.17, 5.75)	3.9 (2.69, 4.30)
Q3 (95% CI)	NE (17.08, NE)	9.9 (9.69, 16.82)
Event Free Rate at, % (95% CI)		
3 month (95% CI)	85.8 (80.29, 89.84)	77.4 (67.97, 84.40)
6 month (95% CI)	66.3 (59.32, 72.33)	57.0 (46.09, 66.58)
9 month (95% CI)	57.2 (49.93, 63.72)	38.6 (27.59, 49.42)
12 month (95% CI)	39.9 (32.76, 46.84)	20.1 (11.56, 30.22)
24 month (95% CI)	25.1 (17.83, 32.97)	NE (NE, NE)
Follow-up Time (month)		
Median (95% CI)	17.1 (14.75, 17.18)	14.4 (5.78, 20.04)

Source: ADSL, ADTTE. Data cutoff: 26Oct2020. Data extraction: 23Feb2021.

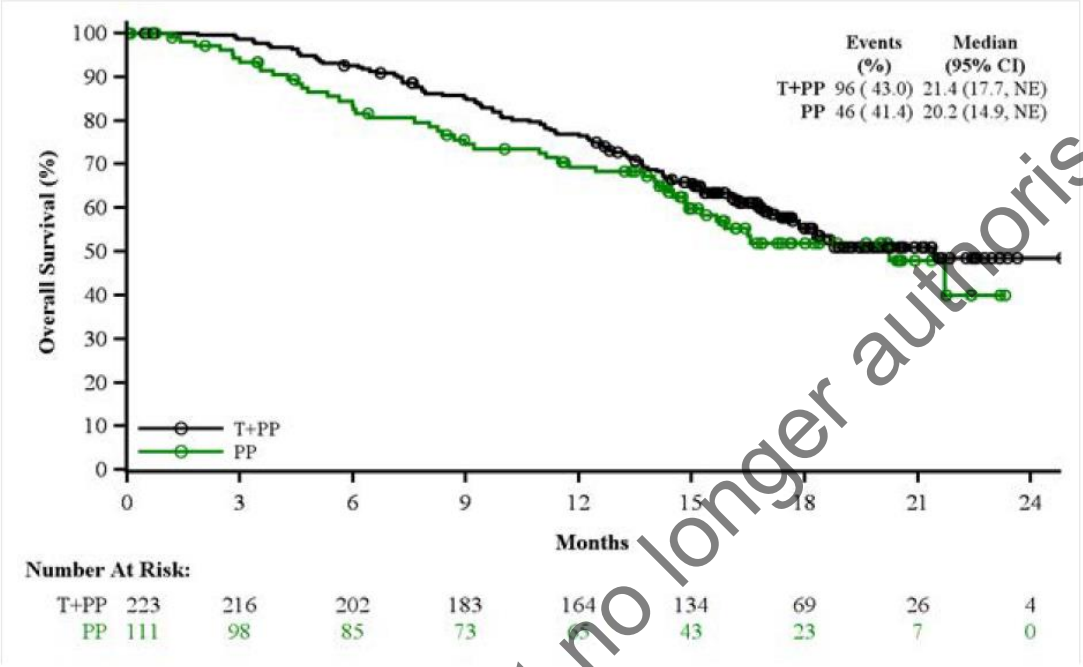
Sensitivity Analyses for OS

As of the data cutoff date of 26 October 2020, 16 patients (7.2%) in Arm T+PP, and 56 patients (50.5%) in Arm PP had received subsequent immunotherapy, including 40 patients (36.0%) with in-study crossover. The median time from randomisation to crossover was 35.1 weeks and from end of study treatment to crossover was 2.6 weeks (minimum: 0.1 week).

To assess the impact of in-study crossover on OS, a supportive analysis was conducted using Rank-

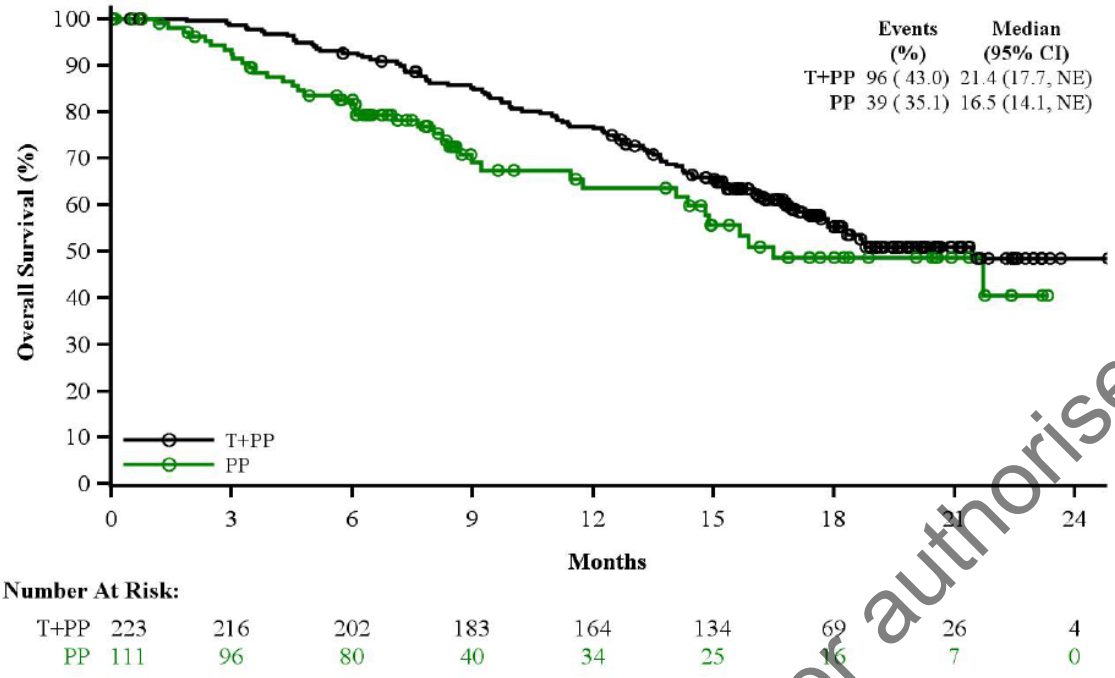
Preserving Structural Failure Time Model (RPSFTM, Robins, et al. 1991). The stratified HR from this analysis was 0.844 (95% CI: 0.479, 1.488).

In addition, a supportive analysis using two-stage method (Latimer, et al. 2014) was also performed to estimate the in-study crossover effect on post-progression survival (PPS) using data from patients who progressed per IRC assessment before any subsequent anti-cancer therapy in the control arm only. The stratified HR based on the counterfactual survival time in arm PP crossed-over patients and the observed survival times in the rest of the patients was estimated as 0.707 (95% CI: 0.468, 1.070).



Source: ADSL, ADTTE. Data cutoff: 26Oct2020. Data extraction: 23Feb2021.
Abbreviations: T+PP, Tislelizumab+Pemetrexed+Platinum; PP, Pemetrexed+Platinum.

Figure 73: Kaplan-Meier Plot of overall survival - sensitivity analysis using rank- preserving structural failure time model (ITT analysis set) (Study 304); final analysis (DCO: 26OCT2020)



Source: ADSL, ADTTE. Data cutoff: 26Oct2020. Data extraction: 23Feb2021.

Figure 74: Kaplan-Meier plot of overall survival - sensitivity analysis using two stage method (ITT analysis set) (Study 304); final analysis (DCO: 26OCT2020)

Subgroup Analyses

Subgroup Analysis of PFS Assessed by IRC

Subgroup	No. of Events/ No. of Patients	Hazard Ratio for Disease Progression or Death (95% CI)	Median PFS (95% CI)	Median PFS in Treatment Arm (95% CI)	Median PFS in Control Arm (95% CI)
Overall	202/334	0.594 (0.443, 0.798)	9.2 (7.66, 9.79)	9.8 (8.94, 11.70)	7.6 (5.55, 8.02)
Age					
< 65 years	141/237	0.598 (0.416, 0.860)	9.0 (7.62, 9.86)	9.8 (8.90, 11.76)	7.5 (4.37, 7.89)
≥ 65 years	61/97	0.593 (0.355, 0.991)	9.7 (6.87, 9.89)	9.7 (6.87, 12.02)	7.7 (4.21, 9.76)
Sex					
Female	57/87	0.846 (0.485, 1.476)	8.5 (7.13, 11.14)	9.2 (5.75, 11.86)	7.7 (5.82, 9.92)
Male	145/247	0.516 (0.364, 0.730)	9.7 (7.62, 9.82)	9.9 (9.03, 11.99)	7.5 (4.21, 8.18)
ECOG Performance Status					
0	46/78	0.860 (0.452, 1.638)	9.7 (7.66, 13.70)	9.7 (7.56, 14.62)	9.7 (4.14, 14.49)
1	156/256	0.535 (0.383, 0.748)	8.9 (7.62, 9.82)	9.9 (7.82, 11.76)	7.3 (4.37, 7.62)
Smoking status					
Never	77/121	0.849 (0.523, 1.380)	8.5 (7.43, 11.14)	9.0 (5.75, 11.86)	7.7 (6.74, 9.92)
Former or Current	125/213	0.470 (0.324, 0.682)	9.7 (7.62, 9.86)	9.9 (9.20, 13.02)	4.6 (4.11, 8.02)
Disease Stage					
IIIB	36/61	0.594 (0.301, 1.171)	9.7 (5.82, 16.82)	11.8 (5.78, NE)	8.2 (3.48, 9.86)
IV	166/273	0.590 (0.425, 0.818)	9.2 (7.62, 9.79)	9.7 (8.94, 11.53)	7.5 (4.37, 7.89)
Liver metastases at baseline					
Yes	26/37	0.267 (0.112, 0.639)	6.7 (2.83, 9.69)	10.7 (4.04, NE)	4.1 (1.38, 7.43)
No	176/297	0.675 (0.490, 0.931)	9.7 (7.72, 9.86)	9.8 (8.94, 11.70)	7.6 (5.82, 9.72)
PD-L1 expression in TC					
< 1%	98/144	0.787 (0.511, 1.212)	7.6 (5.59, 8.94)	7.6 (5.36, 9.72)	7.6 (4.27, 8.18)
≥ 1%	104/190	0.481 (0.322, 0.721)	9.9 (9.69, 11.86)	11.9 (9.86, 17.25)	7.4 (4.50, 9.76)
1% to 49%	49/80	0.897 (0.494, 1.631)	9.7 (7.62, 11.53)	9.7 (6.87, 11.70)	9.7 (5.62, 16.82)
≥ 50%	55/110	0.286 (0.164, 0.500)	11.7 (9.03, 14.75)	14.6 (11.53, NE)	4.6 (3.48, 9.69)
ALK rearrangement					
Negative	155/245	0.592 (0.422, 0.829)	9.2 (7.66, 9.82)	9.8 (8.94, 11.70)	7.6 (4.63, 8.18)
Unknown	47/89	0.612 (0.334, 1.121)	9.7 (5.75, 14.55)	9.7 (5.75, 14.65)	6.7 (2.92, 14.75)

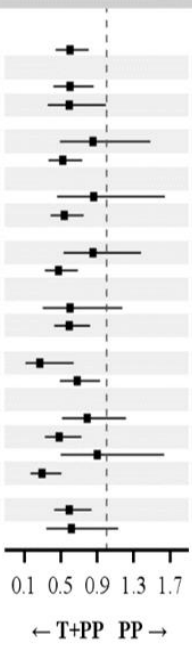
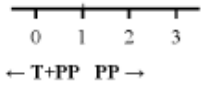


Figure 75: Subgroup analysis: forest plot of PFS per RECIST version 1.1 by independent review committee (ITT analysis set) (Study 304); final analysis (DCO: 26OCT2020)

Subgroup Analysis of OS

Subgroup	No. of Events/ No. of Patients	Hazard Ratio for OS (95% CI)	Median OS (95% CI)	Median OS in Treatment Arm (95% CI)	Median OS in Control Arm (95% CI)
Overall	142/334	0.891 (0.627, 1.266)	21.4 (17.84, NE)	21.4 (17.68, NE)	21.3 (15.64, NE)
Age					
< 65 years	96/237	0.878 (0.568, 1.357)	NE (18.14, NE)	NE (17.68, NE)	NE (15.08, NE)
≥ 65 years	46/97	0.974 (0.534, 1.779)	17.8 (14.26, NE)	17.8 (14.06, NE)	21.3 (11.73, NE)
Sex					
Female	30/87	1.020 (0.477, 2.182)	NE (18.66, NE)	NE (16.82, NE)	21.3 (15.08, NE)
Male	112/247	0.842 (0.566, 1.253)	18.7 (16.76, NE)	18.7 (16.89, NE)	21.7 (14.06, NE)
ECOG Performance Status					
0	30/78	0.832 (0.389, 1.779)	NE (16.76, NE)	NE (16.82, NE)	NE (14.78, NE)
1	112/256	0.896 (0.603, 1.333)	21.3 (17.08, NE)	21.4 (16.89, NE)	21.3 (14.88, NE)
Smoking status					
Never	41/121	1.306 (0.665, 2.561)	NE (21.29, NE)	NE (18.27, NE)	NE (18.14, NE)
Former or Current	101/213	0.703 (0.465, 1.062)	17.8 (15.64, NE)	18.3 (16.76, NE)	15.9 (9.20, NE)
Disease Stage					
IIIB	26/61	1.208 (0.525, 2.779)	NE (14.78, NE)	NE (11.50, NE)	NE (14.52, NE)
IV	116/273	0.836 (0.567, 1.233)	21.3 (17.68, NE)	21.4 (17.68, NE)	21.3 (14.88, NE)
Liver metastases at baseline					
Yes	24/37	0.386 (0.171, 0.871)	15.0 (9.40, 18.14)	17.8 (11.10, NE)	8.0 (2.83, 15.87)
No	118/297	1.098 (0.735, 1.642)	NE (18.66, NE)	21.4 (17.68, NE)	NE (16.49, NE)
PD-L1 expression in TC					
< 1%	68/144	1.441 (0.832, 2.499)	17.8 (15.31, NE)	17.1 (15.05, 18.76)	21.7 (14.88, NE)
≥ 1%	74/190	0.599 (0.376, 0.956)	NE (18.30, NE)	NE (21.42, NE)	18.1 (11.99, NE)
1% to 49%	30/80	1.170 (0.535, 2.554)	21.4 (16.89, NE)	21.4 (16.89, NE)	NE (15.64, NE)
≥ 50%	44/110	0.388 (0.214, 0.703)	NE (17.25, NE)	NE (NE, NE)	13.1 (5.62, NE)
ALK rearrangement					
Negative	104/245	0.873 (0.580, 1.316)	21.3 (17.25, NE)	NE (16.89, NE)	21.3 (15.08, NE)
Unknown	38/89	0.934 (0.471, 1.854)	21.4 (15.64, NE)	18.8 (15.28, NE)	NE (8.97, NE)



Source: ADSL, ADTTE. Data cutoff: 26Oct2020. Data extraction: 23Feb2021.

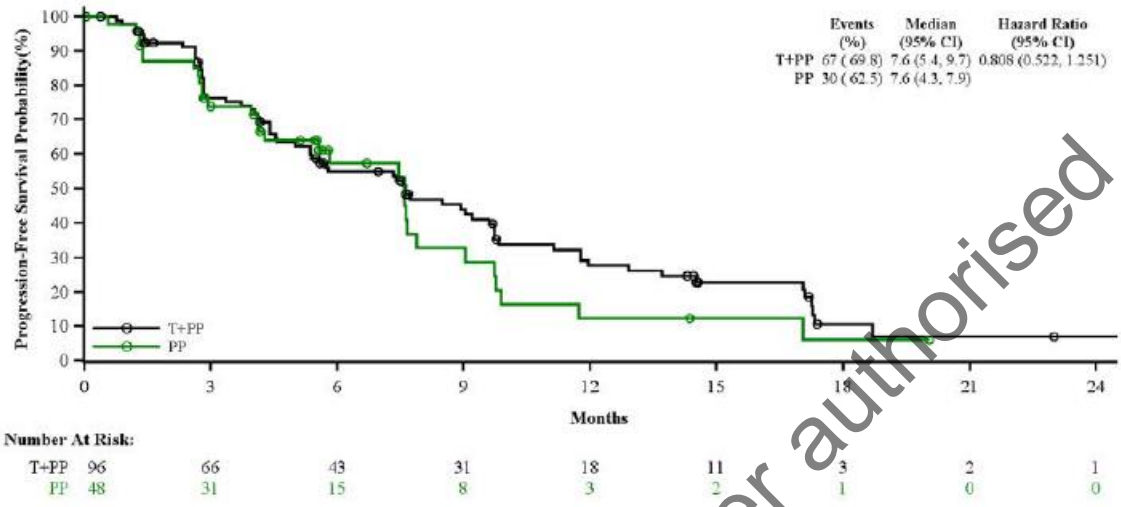
Figure 76: Subgroup analysis: forest plot of overall survival (ITT analysis set) (Study 304); final analysis (DCO: 26OCT2020)

Efficacy by PD-L1 Expression

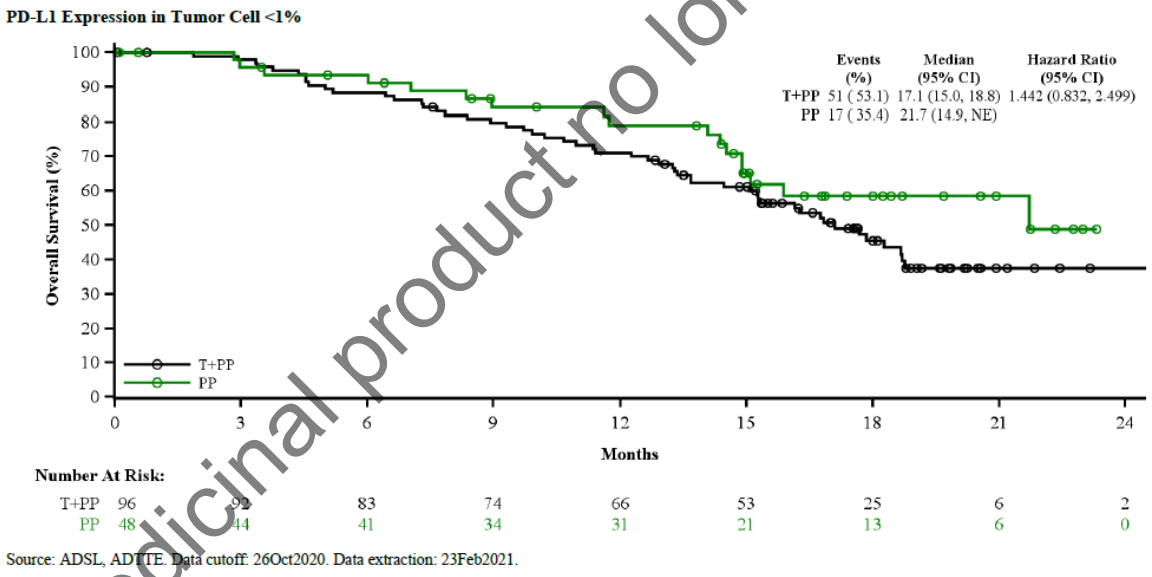
PD-L1 <1%

PFS

A. PD-L1 Expression in Tumor Cell <1%



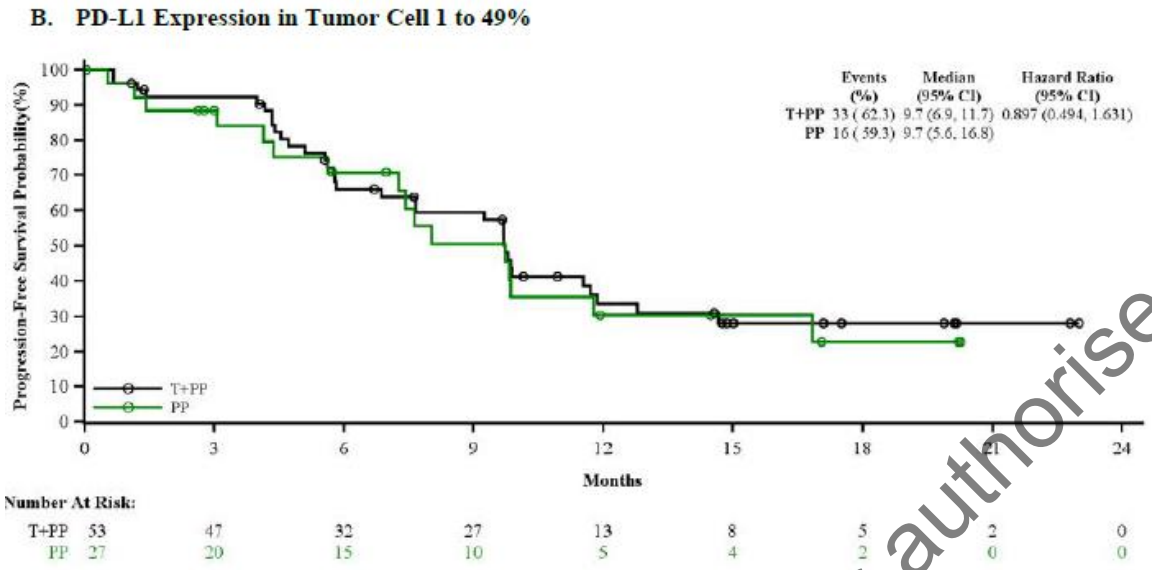
OS



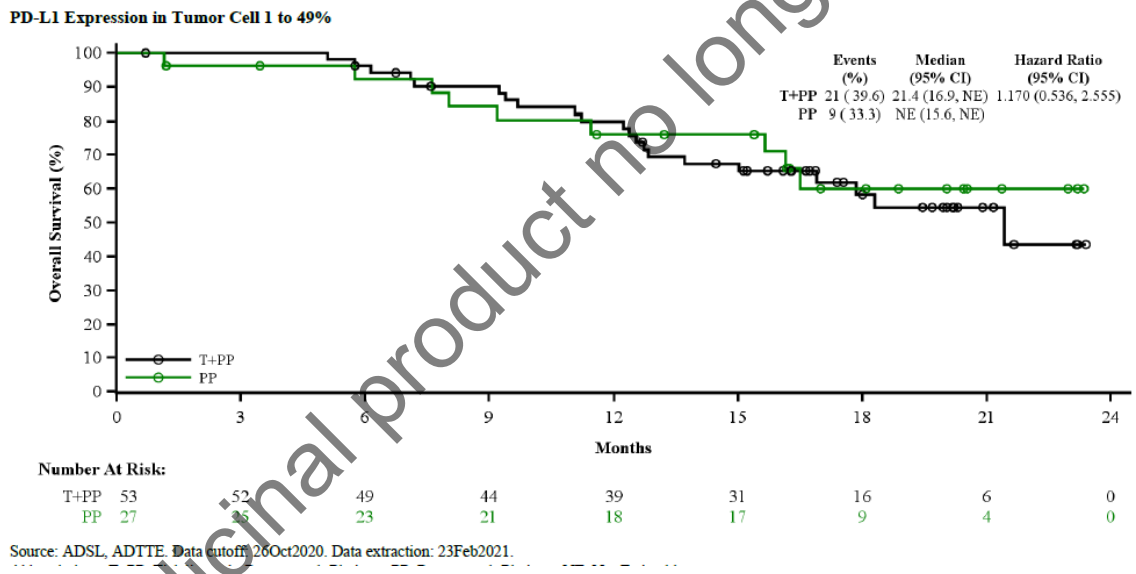
Source: ADSL, ADTTE. Data cutoff: 26Oct2020. Data extraction: 23Feb2021.

PD-L1 1%-49%

PFS



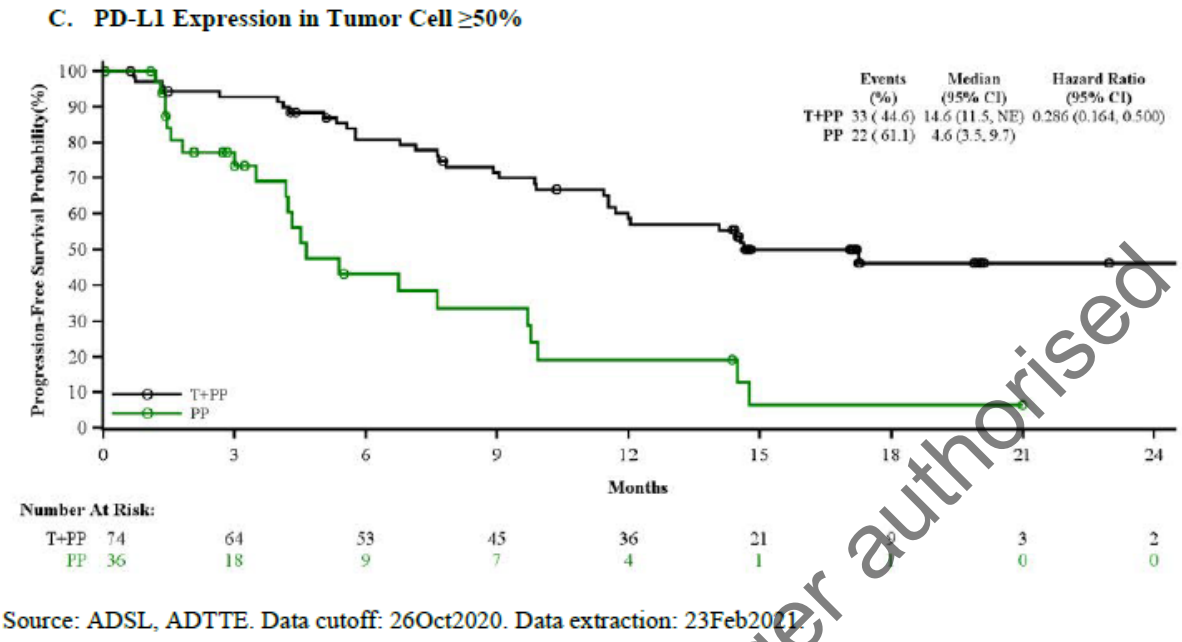
OS



Source: ADSL, ADTTE. Data cutoff: 26Oct2020. Data extraction: 23Feb2021.

PD-L1 ⩾ 50%

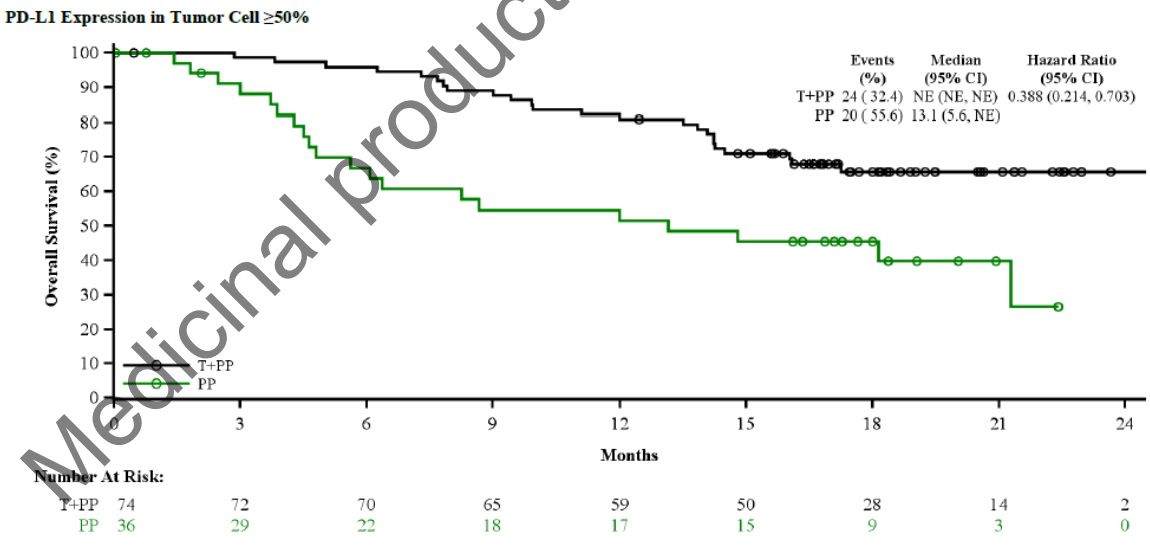
PFS



Source: ADSL, ADTTE. Data cutoff: 26Oct2020. Data extraction: 23Feb2021.

Stratified Hazard Ratio (95% CI): 0.31 (0.18, 0.55)

OS

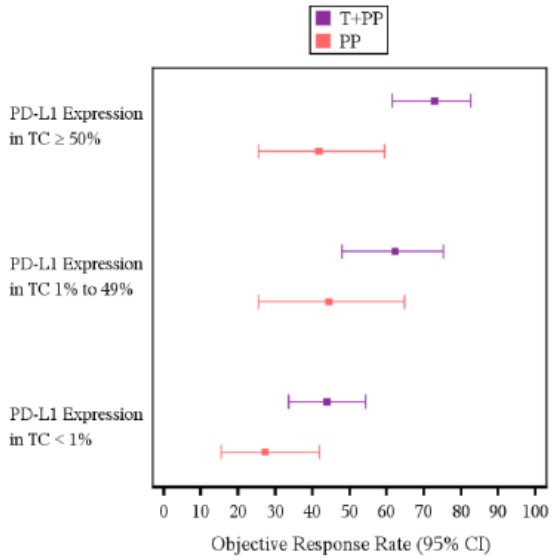


Source: ADSL, ADTTE. Data cutoff: 26Oct2020. Data extraction: 23Feb2021.

Stratified Hazard Ratio (95% CI): 0.39 (0.22, 0.71)

Figure 77: Kaplan-Meier plot of PFS per RECIST version 1.1 by independent review committee and OS by PD-L1 expression (ITT analysis set) (Study 304); final analysis (DCO: 26OCT2020)

ORR by PD-L1 expression



Number of Response/ Number of Patients	ORR (95% CI)	Estimated Treatment Difference (95% CI)
54/74	73.0 (61.4, 82.6)	31.3 (12.3, 50.3)
15/36	41.7 (25.5, 59.2)	
33/53	62.3 (47.9, 75.2)	17.8 (-5.0, 40.7)
12/27	44.4 (25.5, 64.7)	
42/96	43.8 (33.6, 54.3)	16.7 (0.7, 32.7)
13/48	27.1 (15.3, 41.8)	

Figure 78: Objective response per RECIST version 1.1 by IRC by PD-L1 expression (ITT analysis set) (Study 304); final analysis (DCO: 26OCT2020)

Table 87: Confirmed objective response, PD-L1 positive population (PD-L1 expression ≥50%) (Study 304); final analysis (DCO: 26OCT2020)

Endpoint	Tislelizumab + Pemetrexed + Platinum (n = 74)	Pemetrexed + Platinum (n = 36)
ORR, n (%)	52 (70.3)	11 (30.6)
95% CI	(58.5, 80.3)	(16.3, 48.1)
CR, n (%)	7 (9.5)	0 (0.0)
PR, n (%)	45 (60.8)	11 (30.6)

DoR by PD-L1 expression

Table 88: Duration of Response, PD-L1 positive population (PD-L1 expression ≥50%) (Study 304) Final Analysis (DCO: 26OCT2020)

Endpoint	Tislelizumab + Pemetrexed + Platinum (n = 74)	Pemetrexed + Platinum (n = 36)
DoR		
Median DoR (months) (95% CI)	NE (13.2, NE)	8.5 (3.3, NE)

OS Supportive Analyses

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the 1L (in combination with chemotherapy) nonsquamous NSCLC indication of 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 89: Summary of efficacy for trial BGB-A317-304 (Study 304)

Title: A Phase 3, open-label, multicenter, randomized study to investigate the efficacy and safety of tislelizumab (BGB-A317) (anti-PD1 antibody) combined with platinum-pemetrexed versus platinum-pemetrexed alone as first-line treatment for patients with stage IIIB or IV non-squamous non-small cell lung cancer		
Study identifier	BGB-A317-304, RATIONALE 304	
Design	Phase III, multicentre, randomised (2:1), open-label study comparing tislelizumab + platinum-pemetrexed versus platinum-pemetrexed alone	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	24-Jul-2018 – Ongoing (**data cut-off for final analysis: 26-Oct-2020**) The interim and final analyses were conducted when the predefined PFS events had been observed for the efficacy and safety evaluations. The study met its primary objective of PFS at the interim analysis. Results for the final analysis are presented in this submission. The study will continue until the last patient has disease progression, is lost to follow-up, or withdraws from study, or until study completion by Sponsor. Not applicable Not applicable
Hypothesis	Superiority	
Treatments groups	Arm T+PP Tislelizumab Pemetrexed Carboplatin or cisplatin	n = 223 Tislelizumab 200 mg i.v. + carboplatin AUC 5 OR cisplatin 75 mg/m^2 + pemetrexed 500 mg/m^2 Q3W for 4-6 cycles followed by tislelizumab 200 mg + pemetrexed 500 mg/m^2 Q3W
	Arm PP Pemetrexed Carboplatin or cisplatin	n = 111 Carboplatin AUC 5 OR cisplatin 75 mg/m^2 + pemetrexed 500 mg/m^2 Q3W for 4-6 cycles followed by pemetrexed 500 mg/m^2 Q3W

Endpoints and definitions	Primary endpoint	PFS as assessed by the IRC	Time from randomisation to the first objectively documented disease progression, or death from any cause, whichever occurs first, as assessed by the IRC per RECIST v1.1 in ITT analysis set
	Secondary endpoint	OS	Time from the date of randomisation to the date of death due to any cause in ITT analysis set
	Secondary endpoint	PFS as assessed by the investigator	Time from randomisation to the first objectively documented disease progression, or death from any cause, whichever occurs first, as determined by the investigator per RECIST v1.1 in ITT analysis set
	Secondary endpoint	ORR as assessed by the IRC	Proportion of patients who had complete response (CR) or partial response (PR) as assessed by the IRC per RECIST v1.1 in ITT analysis
	Secondary endpoint	DOR as assessed by the IRC	Time from the first occurrence of a documented objective response to the time of relapse, or death from any cause, whichever comes first, as assessed by the IRC per RECIST v1.1 in ITT analysis set with documented objective responses
Database lock	26-Oct-2020 (data cut-off date)		
Results and Analysis			
Analysis description	**Primary endpoint analysis – PFS by IRC**		
Analysis population and time point	ITT analysis set Time point: after 201 PFS by IRC events		
Descriptive statistics and	Treatment group	Arm T+PP	Arm PP
	Number of patients	223	111

estimate variability	mPFS (months)	9.8	7.6
	95% CI	8.94, 11.70	5.55, 8.02
Effect estimate per comparison		Comparison groups	Arm T+PP vs. Arm PP
		HR	0.632
		95% CI	0.467, 0.855
		p-value	0.0013
Notes	The primary endpoint was met, and statistical significance was achieved in the pre-specified interim analysis (23-Jan-2020 data cut-off), the p-value is descriptive for 26-Oct-2020 data cut-off.		
Analysis description	**Secondary endpoint analysis - OS**		
Analysis population and time point	ITT		
Descriptive statistics and estimate variability	Treatment group	Arm T+PP	Arm PP
	Number of patients	223	111
	mOS (months)	21.4	21.3
	95% CI	17.68, NE	15.64, NE
Effect estimate per comparison		Comparison groups	Arm T+PP vs. Arm PP
		HR	0.900
		95% CI	0.631, 1.283
Notes			
Analysis description	**Secondary endpoint analysis – PFS by investigator**		
Analysis population and time point description	ITT		
Descriptive statistics and estimate variability	Treatment group	Arm T+PP	Arm PP
	Number of patients	223	111
	mPFS (months)	9.7	5.6
	95% CI	7.66, 11.70	4.80, 7.89
Effect estimate per comparison		Comparison groups	Arm T+PP vs. Arm PP
		HR	0.550
		95% CI	0.415, 0.729
Notes			

Analysis description	**Secondary endpoint analysis – ORR by IRC**		
Analysis population and time point description	ITT		
Descriptive statistics and estimate variability	Treatment group	Arm T+PP	Arm PP
	Number of patients	223	111
	ORR, n (%)	113 (50.7)	31 (27.9)
	95% CI	43.9, 57.4	19.8, 37.2
Notes			
Analysis description	**Secondary endpoint analysis – DOR by IRC**		
Analysis population and time point description	ITT		
Descriptive statistics and estimate variability	Treatment group	Arm T+PP	Arm PP
	Number of patients	223	111
	mDoR (months)	14.5	8.4
	95% CI	10.09, NE	5.9 (3.25, 7.00)
Analysis description	**Subgroup analysis – PFS by IRC (PD-L1 ≥ 50%)**		
Analysis population and time point description	PD-L1 ≥ 50%		
Descriptive statistics and estimate variability	Treatment group	Arm T+PP	Arm PP
	Number of patients	74	36
	mPFS (months)	14.6	4.6
	95% CI	11.5, NE	3.5, 9.7
		Comparison groups	Arm T+PP vs. Arm PP
		HR	0.31
		95% CI	0.18, 0.55
Notes			
Analysis description	**Subgroup analysis – OS by IRC (PD-L1 ≥ 50%)**		
Analysis population and time point description	PD-L1 ≥ 50%		
	Treatment group	Arm T+PP	Arm PP

	Number of patients	74	36
	mOS (months)	NE	13.1
	95% CI	NE, NE	5.6, NE
		Comparison groups	Arm T+PP vs. Arm PP
		HR	0.39
		95% CI	0.22, 0.71
Notes			

Clinical studies in special populations

Not applicable.

In vitro biomarker test for patient selection for efficacy

Clinical Performance

Archival tumour tissue (formalin-fixed paraffin-embedded or approximately 15 [≥ 6] unstained slides) was sent to central laboratory for central immunohistochemistry assessment of PD-L1 status. PD-L1 status was characterised as PD-L1 membrane staining on TC via the Ventana SP263 assay. If the submitted tumour tissue was unevaluable for PD-L1 expression status, patients were included in the < 1% TC group. Other exploratory predictive biomarkers, such as tumour mutation load, immune-related gene expression profiling, and tumour-infiltrating immune cells that are related to response or clinical benefit of tislelizumab may also have been evaluated. If no archival samples were available, a fresh tumour biopsy at baseline was required.

Rationale cut-off selection:

PD-L1 expression was tested centrally, and results remained blinded to the investigators, the patients, and the Applicant. The 3 cutoff levels employed (< 1% TC vs. 1%- 49% TC vs. ≥ 50% TC) were selected based on prevalence data from previous NSCLC studies with ICIs. For the 3 cutoff levels employed (< 1% TC vs. 1%- 49% TC vs. ≥ 50% TC) that were also chosen for stratification, no analytical validation report was provided. Data provided so far only support the 25% cutoff.

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

Not applicable.

Supportive study(ies)

Study 206

Study 206 was a multi-cohort, open label Phase II study of tislelizumab in combination with standard platinum-containing doublet chemotherapy as first-line treatment in Chinese patients with locally advanced or metastatic lung cancer. Patients were enrolled into 1 of 4 cohorts according to their pathological/histological diagnosis of the primary disease. These include a nonsquamous NSCLC cohort, 2 squamous NSCLC cohorts (A and B), and a SCLC cohort. The study includes a safety run-in stage and a dose-expansion stage. Tislelizumab was continually dosed Q3W for all cohorts until the patients were deemed not to be benefiting from therapy under investigators' discretion, intolerable toxicity, or withdrawal of consent. Doublet chemotherapy was given until the completion of 4 to 6 cycles (4 cycles

for the nonsquamous NSCLC cohort), disease progression assessed by RECIST v1.1, intolerable toxicity, or withdrawal of consent.

At the cutoff date of 31-Dec-2019, end of study was reached with the database closed as the final data point of interest had been collected from the last patient.

Table 90: Efficacy of tislelizumab combination therapy in patients with lung cancer (Study 206)

Treatment	Nonsquamous N = 16 Tislelizumab+ cis/carboplatin+ paclitaxel	Squamous A N = 15 Tislelizumab+ cis/carboplatin+ paclitaxel	Squamous B N = 6 Tislelizumab+ cis/carboplatin+ gemcitabine
Median OS (mo) (95% CI)	NE (13.31, NE)	NE (15.44, NE)	NE (8.25, NE)
Median PFS (mo) (95% CI)	9.0 (4.27, 21.36)	7.0 (5.52, 18.63)	NE (4.27, NE)
ORR (%) (95% CI)	43.8 (19.8, 70.1)	80.0 (51.9, 95.7)	66.7 (22.3, 95.7)
DCR (%) (95% CI)	93.8 (69.8, 99.8)	93.3 (68.1, 99.8)	83.3 (35.9, 99.6)

NE=not estimable

2.5.6. Discussion on clinical efficacy

Tislelizumab monotherapy as 2L+ treatment of NSCLC

Design and conduct of clinical studies

The application for approval of tislelizumab for the treatment of 2L+ NSCLC is based on the single open-label, randomised, controlled, pivotal Phase 3 study BGB-A317-303 (Study 303). The study was conducted in adult patients with histologically confirmed, locally advanced or metastatic (squamous or nonsquamous) NSCLC who had progressed during or after a prior platinum-containing regimen. Overall, the study design is endorsed. Stratification factors histology (squamous versus non-squamous), line of therapy (2 versus 3) and PD-L1 expression level on tumour cell membrane (<25% versus ≥25%) are endorsed.

In general, the applied inclusion and exclusion criteria selected an adequate population of patients with advanced or metastatic NSCLC eligible for 2nd line treatment, although the population may be considered somewhat selected due to exclusion of patients with ECOG PS ≥ 2, which could raise concerns about the external validity of the trial. Considering that patients included were required to have ECOG PS ≤1, the population represents a rather selected population accounting for the fact that there is evidence from literature that approx. 20% of NSCLC patients have ECOG PS 2-4 (Kawaguchi et al. Journal of Thoracic Oncology, 2010). Patients were enrolled regardless of their tumour PD-L1 expression level, which is considered acceptable.

Overall survival was selected as primary endpoint and is endorsed, as OS represents the most persuasive outcome – both from a clinical and methodological point of view – and is adequate, especially considering the prognosis of NSCLC patients having failed prior therapy. Other secondary efficacy endpoints (PFS, ORR, DOR, HRQoL) are standard in oncology trials and generally acceptable,

although an independent central review of PFS, ORR and DOR instead of the sole assessment by investigator would have been more persuasive and thus preferred. Nevertheless, since OS was selected as primary endpoint, the lack of independent central assessment of imaging endpoints can be considered acceptable.

The methods are overall acceptable. The sample size and power considerations are acceptable, assumptions were well justified at the time of planning. The primary analysis by means of a stratified log-rank test is in principle supported. An interim analysis was planned when approximately 426 deaths in the ITT Analysis Set had been observed and was conducted after 441 events. This is incorporated in the alpha-spending approach and had no relevant impact on study conduct or results.

A 2:1 randomisation ratio is acceptable. The choice and number of strata are considered feasible and reasonable.

The primary analysis set, comprising all randomised subjects, is endorsed. Adherence to the ITT principle is endorsed. However, no estimand was defined. The primary analysis by means of a stratified log-rank test is in principle supported. The hazard ratio was calculated using a Cox proportional hazard model with treatment arm as factor and stratified by the actual value of the stratification factors. The primary analysis was stratified for strata as recorded in the eCRF rather than the strata used for randomisation, which is not considered optimal. A sensitivity analysis based on the randomisation stratification factors showed consistent results.

A sensitivity analysis was planned using a Rank Preserving Structural Failure Time Model (RPSFTM) to adjust survival estimates in the presence of arm B patients receiving any subsequent immunotherapy after discontinuation of docetaxel. The model should be interpreted with care because the adjustment is based on an intercurrent event. Nonetheless results are overall consistent with the primary analysis, which provides reassurance.

A one-sided significance level of α=0.025 is acceptable, and the use of the proposed alpha spending approach to account for multiple analyses as well as the use of a hierarchical testing approach for sequential testing of the secondary endpoints in the final analysis in the ITT as well as the PD-L1 population is acceptable. The timing (and populations) for interim analyses and the alpha-spending approach was updated multiple times. Initially, a Hwang-Shih-DeCani (HSD) spending function with γ = -4 was defined. In Protocol Amendment 1 this was modified to a HSD with γ = -0.7. Only in Protocol Amendment 3 (09 Mar 2020) the final HSD spending function with γ = -2 was defined. Given that the study was an open-label study this is considered potentially problematic. The rationale for these changes provided by the Applicant upon request (delayed treatment effect became apparent from results of other studies) was considered acceptable. Sensitivity analyses provided reassurance that there was no meaningful impact on the obtained results.

The alpha was split for the two dual primary hypotheses to control the overall type I error strongly at a one-sided alpha of 0.025. To account for the positive correlation between the test statistics in the 2 Analysis Sets (since the PD-L1 positive set is a subset of the ITT Analysis Set), it was planned to assign an alpha of 0.02 and 0.007 to the primary hypothesis testing (in contrast to a conservative 0.02 and 0.005 split) in the ITT and PD-L1 analysis set. The applicant provided a justification that under the global null hypothesis of no effect this approach would control type I error at the level of 0.025. It is not obvious how the properties would be in case an interaction between PD-L1 and treatment (i.e. null hypothesis in one subgroup and effect in the complementary subgroup), however given the results the assessors do not see any value in further discussion.

Censoring rules for OS are acceptable. However, for PFS the censoring rules warrant further discussion. Data for patients who start to receive new anticancer therapy or died/progressed after two or more missed visits were planned to be censored at the last valid tumour assessment date prior to

the introduction of new anticancer therapy or were planned to censored at date of last adequate tumour assessment prior to the >=2 missed tumour assessments. This is not in line with the (Appendix 1 to the) EMA guideline on the evaluation of anticancer medicinal products in man (EMA/CHMP/27994/2008/Rev.1). Upon request, the applicant has conducted the analysis applying the censoring strategy requested with respect to missing observation, treatment discontinuation and rescue medication preceding the death. The results of the requested analyses agree with those previously provided.

Recruitment and conduct of the study

Study 303 recruited patients from 10 countries, including Asia and Europe. In the ITT Analysis Set, a total of 805 patients were randomised 2:1 to receive tislelizumab or docetaxel. More patients in the docetaxel arm as compared to the tislelizumab arm were randomised but not treated (4.4% vs. 0.2%) or withdrew from the study. The higher proportion of patients in the control group who were not treated at all or discontinued treatment early could have had an impact on the performance of the control arm. The proportion of patients with uncontrolled, untreated brain metastasis excluded could be reasonable, this refers also to the incidence of EGFR mutation. The applicant provided conservative sensitivity analyses addressing this imbalance which were supporting.

At the data cutoff date of 15 July 2021, the median follow-up time was 16.0 months for the tislelizumab arm and 10.7 months for the docetaxel arm in the ITT Analysis Set.

Baseline characteristics

The study population included in Study 303 was predominantly male (77%) and had a median age of 61.0 years. The majority of patients were recruited at sites in Asia and thus, 80% of patients were Asian versus 17% being of White or Caucasian race. Tumour tissue (either archival tissue or fresh biopsy) was required for enrolment in this study. Patients with known EGFR/ALK mutations were excluded.

Overall, there are no meaningful imbalances in patients' baseline characteristics among treatment arms. However, several points could question whether the enrolled population is representative of real-life EU patients (i.e. 55% male, 45% female, 10% never smoker, 70% non-squamous, Simeone et al. 2019). In Study 303, 30% of patients were never smokers, 54% non-squamous and only 22% were female, which is not considered representative. 80% of the patients were enrolled in China, which means the ethnicity, the standard of care and the histology differs largely from a Western European population.

It is noted that most patients (85%) included in Study 303 had received 1 prior anticancer therapy. Only 2nd and 3rd line patients are included. The indication statement did not include a restriction of administration of tislelizumab to patients having received 1 or 2 prior therapy in the past. As such, patients may also be treated with tislelizumab in even further lines of therapy. Although no data are available for patients with advanced or metastatic NSCLC in later lines of therapy, the extrapolation of study results is considered acceptable. 15% of patients included in Study 303 had locally advanced disease, the remaining patients had been diagnosed with metastatic disease at study entry. Conclusively, the inclusion of locally advanced disease stage in the indication wording is agreed.

Efficacy data and additional analyses

The primary efficacy analysis demonstrated a statistically significant difference in **OS** with tislelizumab versus docetaxel. The stratified HR was 0.66 (95% CI: 0.56, 0.79). The median OS was 16.9 months (95% CI: 15.24, 19.09 months) and 11.9 months (95% CI: 9.63, 13.54 months) for the tislelizumab arm and docetaxel arm, respectively. The median follow-up time estimated by the reverse Kaplan-

Meier method was 31.1 months (95% CI: 29.54, 31.64 months) for the tislelizumab arm and 27.9 months (95% CI: 26.38, 31.15 months) for the docetaxel arm in the ITT Analysis Set.

Benefit could be shown for investigator-assessed **PFS** in the ITT population (stratified HR = 0.63; 95% CI: 0.53, 0.75). The secondary endpoint of unconfirmed **ORR**, as assessed by the investigator per RECIST v1.1, showed a higher response rate for tislelizumab; 22.6 % vs. 7% of patients in the tislelizumab vs. docetaxel arm presented with objective response. A relatively high percentage of patients in the docetaxel arm (52 patients; 19.3%) with BOR "could not be determined" is noted. Per definition, this included patients with no post-baseline tumour assessment by the data cutoff due to discontinuation (for any reason) or death without having any post-baseline tumour assessment. The number of patients with indeterminable response in the docetaxel arm is in line and can be explained by the number of patients randomised but not treated or withdrawn from study treatment (N = 41). The high proportion of missing values in the control arm is considered unfortunate. DOR analysis demonstrated that among patients with objective response (CR or PR, as assessed by the investigator per RECIST v1.1), responses were of longer duration for tislelizumab as compared to control (median DOR 13.5 months vs. 6.0 months). These results were consistent with the interim analysis results (DCO 10 Aug 2020).

A median OS of 17 months for the tislelizumab arm in study 303 is considered outstanding, when compared with other PD-(L)-1 inhibitors in the 2L NSCLC indications. Median OS ranged from 9.23 months (Opdivo CA209017(squamous)) to 13.8 months (Tecentriq OAK). A longer median OS is also reported in the control arm. Difference in OS could be explained by a selected patient population with a more favourable prognosis as the effect of tislelizumab on the other endpoints does not seem to differ from the effect of other PD-(L)1 inhibitors (e.g. ORR).

Efficacy in subgroups

A statistically significant improvement in OS was observed in the PD-L1 ≥25% analysis set favouring the tislelizumab arm (HR = 0.54; 95% CI: 0.41, 0.71) with median OS being 19.3 months for the tislelizumab arm and 11.7 months for the docetaxel arm. A notably lower OS advantage was observed for tislelizumab relative to docetaxel in the PD-L1 negative subset (PD-L1 <25%), with a stratified HR of 0.79 (95% CI; 0.64, 0.99), and median OS estimates of 15.2 months (95% CI: 13.4, 17.6) for the tislelizumab arm vs. 12.3 months (95% CI: 9.3, 14.3) for the docetaxel arm.

OS subgroup analyses showed a lower effect for never smokers, female patients and subjects with brain metastasis when compared to the effect of tislelizumab on the ITT population. Acknowledging the wide confidence intervals due to the limited number of events, the evidence does not allow to conclude on the lower benefit in these subgroups. No meaningful differences are observed based on histology.

Subgroup analyses in subjects ≤65 and >65 years suggest a similar efficacy for both age groups with slightly lower values for the higher age group (HR for OS 0.64 [95% CI 0.519, 0.790] vs. 0.73 [95%CI 0.545, 0.989]). Data in patients ≥75 year old were too limited to draw any conclusion, this is reflected in section 4.8 of the SmPC.

Wording of the indication

As tislelizumab would be the 4th PD-(L)1 inhibitor in this setting, the following statement was added to the indication in line with Tecentriq and Keytruda: *Patients with EGFR mutant or ALK positive NSCLC should also have received targeted therapies before receiving Tizveni.*

It is acknowledged that the pivotal Study 303 only excluded patients with known EGFR and ALK mutations. However, since the initiation of Study 303, the treatment landscape has changed and several ROS-targeted therapies have been approved for patients with ROS1 rearrangements that are recommended prior to treatment with immune- or chemotherapy (please refer to ESMO clinical

practice guidelines). Therefore, the indication wording could lack reference to patients with mutations (as proposed by the applicant and as done for Opdivo). Nevertheless, for consistency reasons and to adequately reflect the inclusion criteria of study 303, a statement regarding EGFR and ALK mutations was added.

In consideration of heterogeneity of patients with locally advanced disease, which could be treated with Tizveni after progression to (neo)adjuvant chemotherapy, chemoradiation therapy or 1L metastatic chemotherapy –platinum-based in all four scenarios–, deleting "chemo" is endorsed to encompass both chemoradiation and chemotherapy.

Final indication statement:

Tizveni as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer after prior platinum-based therapy. Patients with EGFR mutant or ALK positive NSCLC should also have received targeted therapies before receiving tislelizumab.

Tislelizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel for the 1L treatment of squamous NSCLC

Design and conduct of clinical studies

The pivotal study supporting the sought indication is the ongoing Study 307, a phase III randomised, open-label trial with tislelizumab in combination with carboplatin-paclitaxel/nab-paclitaxel (T+(n)PC) compared to carboplatin-paclitaxel (PC) in first line locally advanced (stage IIIB) or metastatic (stage IV) squamous NSCLC. No Scientific Advice to CHMP was requested on this study.

Tislelizumab 200 mg Q3W was administered in combination with carboplatin AUC5 + paclitaxel 175 mg/m^2 or nab-paclitaxel 100 mg/m^2 for a total of 4 to 6 cycles, followed by tislelizumab until progression. Carboplatin with either paclitaxel or nab-paclitaxel is one of the accepted standard treatment options for 1st line squamous cell lung cancer. Cisplatin, although indicated and used in squamous disease, was not included in this study. Therefore, no data are available for tislelizumab in combination with cisplatin-based chemotherapy in squamous histology, contrary to non-squamous NSCLC (Study 304) where both cisplatin and carboplatin (with pemetrexed) have been tested (see section 2.6.6.4 below). The sought indication for tislelizumab in squamous NSCLC is ultimately in combination with carboplatin and either paclitaxel or nab-paclitaxel. International guidelines recommend the use of 4 to 6 cycles of treatment for chemotherapy, Investigators choice of number of cycles (up to six) is therefore supported. Of note, lower doses for paclitaxel and carboplatin were applied in Study 307 compared to the recommended standard doses in European guidelines. However, literature data suggested that the dose reductions would likely not have a relevant impact on the efficacy results.

Statistical methods

The sample size, power considerations and randomisation methods are acceptable. The primary PFS analysis for Study 307 by means of a stratified log-rank test using stratification factors with actual values as recorded in the EDC at randomisation is in principle supported. The hazard ratio was calculated using a Cox proportional hazard model with treatment arm as factor and stratified by the actual value of the stratification factors. This is endorsed. No estimand was defined. A one-sided significance level of α=0.025 is acceptable, and the use of the proposed sequential hypothesis testing procedure (Arm A vs C followed by Arm B vs C) as well as the use of the spending function approach to account for multiple analyses is also endorsed. The prespecified p-value boundaries per Lan-DeMets O Brien-Fleming approximation spending function were updated as 0.0115 for 136 events and 0.0103 for

132 events, this is supported. Censoring rules for OS are acceptable. However, for PFS the censoring rules were not in line with the relevant EMA guideline (EMA/CHMP/27994/2008/Rev.1) but reflected FDA censoring rules. A sensitivity analysis based on EMA censoring rules was provided. Overall, this is acceptable.

Originally, it was planned to assign an alpha of 0.0125 and 0.0125 to the primary hypothesis testing of PFS of A versus C and PFS of B versus C, combined with an alpha passing to the other comparison in case any of the two comparisons would be statistically significant at the initial assigned alpha of 0.0125. In Amendment 3 this was changed to a hierarchical approach: Hypothesis testing for the primary endpoint of PFS was planned to be carried out sequentially (Arm A vs C followed by Arm B vs C), each at a one-sided alpha of 0.025, until the first non-rejection. Additionally, it was originally planned to perform the interim analysis when approximately 109 PFS events (67% of the targeted number of events, slightly corrected to 103 PFS events in Amendment 1) would have been observed. In Amendment 3 this was changed to 130 PFS events (75% of the now targeted number of 173 PFS events, based on an updated sample size calculation with a now assumed HR of 0.65 in Arm A as well as Arm B). Since this is an open-label trial, such late changes in the timing of the interim analysis (4 months before data cut-off) raise uncertainties.

Upon request, the Applicant clarified that a delayed treatment effect was not expected during the initial planning but was suggested by results from other studies that were finalised during the conduct of this study. This led to the changes of the study. Although some uncertainty remains, e.g. due to the open-label study design, this explanation seems reasonable. Further, results based on the original plan with 103 events in Arms T+PC and PC and Arms T+nPC and PC provide reassurance.

Recruitment and conduct of the study

In the ITT Analysis Set, a total of 360 patients were randomised 1:1:1 to receive T+PC, T+nPC or PC. More patients in the control arm as compared to the T+(n)PC arms were randomised but not treated or withdrew from the study (14.9% vs. 4.2%).

Baseline characteristics

The 307 study population was predominantly male (91.7%), had a median age of 62.0 years and 16% never smoker were included. Patients were enrolled in 43 centres in China. Some imbalances could be detected in the T+nPC arm compared to control (and T+PC). There are only 6% female and 10% never smoker in this arm. Overall, only Asian patients were included, the median age of 62 years is considered low (expected 69 years) and 8% female patients only are not considered representative for a European patient population, this raises concerns about the external validity of the trial.

Both intrinsic and extrinsic ethnic factors are of influence in the presented data for both trials. The magnitude of the differences in the intrinsic factors of age and gender distribution and the extrinsic factor of smoking status distribution between the 2 cohorts of study 304 and 307 and a European corresponding patient population, is notable and of importance. In studies 304/307, the median age was 61/62 years, the female fraction was 26%/8.3% and the never-smoker fraction was 36.2%/16.4%. In the European population of patients with mNSCLC, the median age at diagnosis is ~70 years, the distribution of females /males is ~35-50%/50-65% and the fraction of never-smokers is ~5-10%. However, this fraction of never-smokers is lower when patients with driver mutations are excluded, which is the situation in the cohorts of study 304 and 307. This fact makes the high frequency of never-smokers in study 304 and 307 even more striking.

It is reasonable to believe, that the efficacy and safety profile of a population of relatively younger patients, primarily male and far more frequent never-smokers, not impacted by the comorbidity that comes with smoking, could differ significantly from that of a population of older patients, a different gender distribution, and with the far majority being smoker/previous smokers (with the concomitant

comorbidities smoking entails). Conversely, it is not justifiable to assume that there are no or only neglectable differences in the outcome of efficacy and toxicity profile between two patient populations with such distinct differences in characteristics.

The pattern of distribution of these intrinsic and extrinsic factors is consistent across the 2 trials; 304 and 307, verifying the fact, that the Chinese mNSCLC patient population presents inherent and distinct differences from that of the European population.

To generate reliable data –upon which an assessment of benefits and risks can be based– in a patient population that differs markedly from the one the medication was investigated in, a clinical trial, e.g., a bridging study, in the population of the new region (in this case Europe) is needed. This is clearly reflected in the ICH E5 guideline on Ethnic factors in the acceptability of foreign clinical data. External validity of the outcome data from study 304 and 307 was questioned, however considering that results could be regarded as comparable to other studies with PD-L1 inhibitors in NSCLC this issue was not further pursued.

Inclusion was limited to ECOG PS 0-1 and the inclusion was restricted to participants younger than 75 years which cannot be followed and is suboptimal, as it hampers the comparability with the real-world setting. Patients with sensitizing *EGFR* mutation or *ALK* translocation were not eligible. As consequence, this could result in exclusion of patients with *EGFR* and *ALK* mutations in the indication wording. However, compared with lung adenocarcinoma, evidence about the efficacy of EGFR TKIs and treatment progress in patients with lung squamous cell carcinoma (SCC) is limited and controversial. Activation of EGFR mutations are rare in patients with SCC (<3%); the lack of reported mutations may limit the use of EGFR-TKIs in lung cancer patients with SCC. In addition, *ALK* and *ROS1* rearrangements in lung squamous cell carcinoma are very rare (Zhao et al. Lung cancer 2016), so not considered relevant in real world setting.

Overall, there are no meaningful imbalances in patients' baseline characteristics between the treatment arms T+PC and PC.

Efficacy data and additional analyses

A statistically significant and clinically meaningful improvement in **PFS** assessed by the IRC per RECIST v1.1 was shown for both treatment arms (T+PC and T+nPC vs PC alone) at the interim analysis. With a total of 191 PFS events (53% of the overall population), the stratified HR was 0.48 (95% CI: 0.34, 0.69) for T+PC vs PC and 0.45 (95% CI: 0.32, 0.64) for T+nPC vs PC. The median PFS was 7.6 months (95% CI: 5.9, 9.8) in Arm T+PC and 7.6 months (95% CI: 5.8, 11.0) in Arm T+nPC vs 5.4 months (95% CI: 4.2, 5.6) in Arm PC.

In the final analysis, the stratified PFS HR was 0.45 (95% CI: 0.32, 0.62) for T+PC vs PC and 0.43 (95% CI: 0.31, 0.62) for T+nPC vs PC. At the data cutoff date for the final analysis (30 September 2020), the median follow-up time was 16.7 months in the ITT. Results from PFS sensitivity analysis 1, representing the preferred PFS analysis by EMA, and PFS based on investigator assessment were consistent with the primary analysis.

OS results showed a beneficial trend at the final PFS analysis with OS HRs of 0.68 (95% CI 0.46, 1.01) and 0.75 (95% CI 0.50, 1.12) in favour of T+PC and T+nPC vs PC, respectively. Median OS was 22.8 months in Arm T+PC, not reached in Arm T+nPC, and 20.2 months in Arm PC. However, taking the KM curves into consideration, the clinical relevance of the OS improvement appears less obvious. The maturity level of OS is only 41% at this analysis and OS KM curves are hardly interpretable after month 9 due to the high rate of censoring.

In Study 307, statistical testing was only planned for PFS, but not for OS which is seen as a shortcoming in the study design. Overall survival is considered the clinically most relevant endpoint and generally also the preferred endpoint in oncology clinical trials when it can be reasonably assessed.

Since crossover to tislelizumab treatment (in 55% of patients in the control arm) could have hampered the chance to show meaningful OS results, two supplementary OS analyses (both not pre-specified) were performed to adjust for the crossover effect of tislelizumab. Both analyses suggested potentially more favourable OS benefit in Arm T+PC and Arm T+nPC compared with Arm PC, but the 95% confidence intervals for the HR's for both comparisons in both sensitivity analyses still include 1 and especially the difference between the point estimates based on the classical analysis and compared to the RPSFT model-based estimate is small. Furthermore, the differences in the results of the two sensitivity analyses raise uncertainties about the robustness of these analyses.

An advantage of T+(n)PC over PC alone is seen regarding **response** rates (confirmed ORR assessed by the IRC: 61.7% and 62.2% vs 37.2%). Median DOR (for unconfirmed responses) was also longer for T+PC and T+nPC vs PC (8.4 and 8.6 vs 4.3 months).

Overall, the PFS advantage of T+(n)PC appears to be maintained in most of the **subgroups** analysed. It has been noted, that no meaningful benefit was observed for patients with ECOG-PS 0, however, numbers are too small and no biological rationale could support this finding. Only 1.7% of patients with brain metastasis were included, therefore the evidence does not allow to conclude on the treatment effect in patients with brain metastasis.

During the procedure, updated PFS and OS data were provided based on a data cutoff date of 15-July-2022, with a median follow up of 20.5 months. In literature, a trend for a better outcome with checkpoint inhibitor chemo combination with higher **PD-L1 score** has been observed also in squamous NSCLC. This trend was also evident in the updated PFS and OS data provided for Study 307. However, PFS and OS data indicate a meaningful benefit in the PD-L1 negative subgroup (T+PC vs PC: TC<1% (HR: 0.57, 95% CI: 0.34, 0.93); and T+nPC vs PC: TC<1% (HR: 0.73, 95% CI: 0.46, 1.17)) supporting an indication regardless of PD-L1 expression.

Wording of the indication

Overall, patients' selection criteria are considered reflective of the target population in the indication. The inclusion of patients with locally advanced stage in the indication wording for the first line treatment of both squamous NSCLC is accepted with the clarification that these patients were not candidates to platinum-based chemoradiation. Therefore, the indication was updated as follows:

Tizveni in combination with carboplatin and either paclitaxel or nab-paclitaxel is indicated for the first-line treatment of adult patients with squamous NSCLC who have:

- *locally advanced NSCLC* ***and are not candidates for surgical resection or platinum-based chemoradiation, or***
- *metastatic NSCLC.*

Tislelizumab in combination with platinum and pemetrexed for the first line treatment of metastatic nonsquamous NSCLC

Design and conduct of clinical studies

The pivotal study supporting the sought indication is the ongoing Study 304, a phase III randomised, open-label trial with tislelizumab in combination with cisplatin or carboplatin and pemetrexed (T+PP) compared to cisplatin or carboplatin and pemetrexed (PP) in first line metastatic (stage IIIB/ IV AJCC 7th edition) non-squamous NSCLC. No Scientific Advice to CHMP was requested on this study.

Tislelizumab 200 mg Q3W was administered in combination with cisplatin 75 mg/m^2 or carboplatin AUC5 and pemetrexed 500 mg/m^2 for a total of 4 to 6 cycles, followed by tislelizumab in combination with pemetrexed 500 mg/m^2 Q3W until progression. A meta-analysis has supported the interchangeable use of carboplatin and cisplatin in combination with SOC antineoplastic agents and this is also reflected in the NCCN recommendations, nevertheless this is neither reflected in the ESMO-Guideline for metastatic NSCLC (Ann Oncol (2016) 27 (suppl 5): v1-v27) nor it is clinical practice in Europe. Cisplatin doublets are currently recommended as the preferred choice and used in clinical practice in patients with no contraindications. Investigators choice for the platinum component is however considered acceptable. This refers also to the investigators' choice of number of cycles (up to six).

Statistical methods

Please refer to the section above, discussion on Study 307.

Recruitment and conduct of the study

In the ITT Analysis Set, a total of 334 patients were randomised 2:1 to receive T+PP or PP. More patients in the control arm as compared to the T+PP arms withdrew from the study or treatment (22.5% vs. 11.2%) (see Table 75). At the data cutoff date of 26 October 2020, the median follow-up time was 16.1 months for the ITT Analysis Set.

Baseline characteristics

The study population included in Study 304 was predominantly male (74.0%) and had a median age of 61.0 years. 36.2% of patients were never smoker. Patients were enrolled in 47 centres solely in China. Tumour tissue (either archival tissue or fresh biopsy) was required for enrolment in this study.

Overall, patients' selection criteria are considered reflective of the target population in the indication; however, several limitations due to the inclusion of Chinese patients only should be taken into consideration. The median age of 61 years is considered low (expected 69 years) and the percentage of never smokers is significantly higher (36.2% vs. 10% in the European patient population). The percentage of female patients (26%) is rather low, but much more comparable to a European patient population than the proportion of women in Study 307 (10%). In addition, the considerably low percentage of patients with brain metastasis (ca. 5%) or liver metastasis (11%) indicates a highly selected patient population. 33% of the patients had tumour cell PD-L1 expression ≥50%. The baseline characteristics for this study population were: median age 61 years (range: 25 to 75), 29% age 65 years or older; 74% male; 23.4% with ECOG PS of 0 and 76.6% with ECOG PS of 1; 18.3% with disease stage IIIB; 26.6% with unknown status for ALK rearrangement and 73.4% with negative ALK rearrangement; 36.2% never-smokers. The characteristics of age, sex, ECOG PS, stage, smoking status, PD-L1 TC score expression and prior anticancer treatments were balanced between the treatment arms. There were several imbalances in patients baseline characteristics between the treatment arms, e.g. patients ≥ 65 years (26.9% vs. 33.3%) and distant metastasis (including liver metastasis) (9.0% vs. 15.3% for T+PP vs. PP, respectively). Imbalances could also be detected regarding smoking status and sex.

The relatively young Asian patient population raised concerns regarding the external validity of the trial. However, the favourable OS could be regarded to be relevant to outweigh these uncertainties.

Inclusion was limited to ECOG PS 0-1. The inclusion was restricted to participants younger than 75 years which is not supported, as it hampers the comparability with the real-world setting. A statement was added in section 4.8 of the SmPC to highlight that data in patients aged 75 years and above are too limited to draw conclusions on this population.

Patients with ROS rearrangements were not considered to be excluded in the indication wording, as they were not excluded in Study 304. At the time of study initiation the inclusion of these patients was acceptable. However, it is worth mentioning that in the meantime effective TKIs were approved for patients with ROS rearrangements. Crizotinib and entrectinib are both highly effective first line treatments for patients with ROS1 rearranged tumours, being entrectinib a preferred option in those patients with brain metastases.

Efficacy data and additional analyses

A statistically significant improvement in **PFS** assessed by the IRC per RECIST v1.1 was observed in the overall patient population. The stratified HR of PFS was 0.632, indicating a 37% reduction in the risk of experiencing a PFS event of PD or death. The median PFS was 9.8 months (95% CI: 8.94, 11.70) in Arm T+PP and 7.6 months (95% CI: 5.55, 8.02) in Arm PP. The estimated 12-month PFS event-free rate was 39.9% (95% CI: 32.76, 46.84) in Arm T+PP and 20.1% (95% CI: 11.56, 30.22) in Arm PP.

The median **OS** in Arm T+PP was 21.4 months (95% CI: 17.68, NE) compared to 21.3 months in Arm PP (95% CI: 15.64, NE) with a stratified HR of 0.90 (95% CI: 0.63, 1.28), being the OS comparable in the two arms. Taking the KM curves into consideration, the OS data is considered to be inconclusive. Maturity level of OS was 42% at this analysis and, due to the high rate of censoring, a late crossing of the curves cannot be excluded. The allowance of cross-over from the chemo arm (PP) to tislelizumab is presumably the reason for the unusually high OS in the chemo arm, what is confounding the OS data.

In Study 304 statistical testing was only planned for PFS, but not for OS which is seen as a shortcoming in the study design. Overall survival is considered the clinically most relevant endpoint and generally also the preferred endpoint in oncology clinical trials when it can be reasonably assessed.

As of the data cutoff date of 26 October 2020, 16 patients (7.2%) in Arm T+PP, 56 patients (50.5%) in Arm PP had received subsequent immunotherapy including 40 patients (36.0%) with in-study crossover. Since crossing over to tislelizumab treatment could have hampered the OS results, two supplementary OS analyses (both not pre-specified) were performed to adjust for the crossover effect of tislelizumab. Both analyses suggested a potentially more favourable OS benefit in Arm T+PP compared with Arm PP, but the 95% confidence intervals for the HR's for both comparisons in both sensitivity analyses still include 1 and especially the difference between the point estimates based on the classical analysis and compared to the RPSFT model-based estimate is small. Furthermore, the differences in the results of the two sensitivity analyses raise uncertainties about the robustness of these analyses.

More mature OS results were provided (DCO 15 July 2022). In this updated analysis, the stratified HR for OS was 0.85 (95% CI: 0.63, 1.14) for Arm T+PP vs. Arm PP. Median OS was 21.6 months in Arm T+PP and 20.1 months in Arm PP.

An advantage of T+PP over PP alone is seen in the response rate (confirmed ORR assessed by the IRC: 50.7% vs 27.9%). Median DOR was also longer for T+PP (14.5 vs 8.4 months).

Overall, it appears that the PFS results are consistent in most subgroups analysed. Subgroups which had an unstratified PFS HR with 95% CI including 1.0 were females, ECOG PS 0, never smoker, and disease stage IIIB, which could be due to smaller sample size.

A strong benefit was demonstrated for patients with PD-L1 expression on ≥50% of the tumour cells, The unstratified PFS HR was 0.28 (95% CI: 0.16, 0.50) and OS HR 0.38 (95% CI: 0.21, 0.70). For patients with PD-L1 expression on < 1% of TC, the unstratified PFS HR was 0.79 (95% CI: 0.51, 1.21) for T+PP vs PP, for patients with 1% - 49% TC the unstratified PFS HR was 0.90 (95% CI: 0.49, 1.63).

OS data indicate a potential detrimental effect in these subgroups with HR 1.44 (95% CI: 0.83, 2.50) and HR 1.17 (95% CI: 0.54, 2.55), respectively.

Updated data for the 3 prespecified subgroups of PD-L1 expression negative, low and high (PD-L1 expression <1%, 1-49%, ≥50%) substantiated the strong effect in PD-L1 highly positive patients but not in PD-L1 negative and low patients (<1%, 1-49%) where the median PFS was the same for the tislelizumab+chemo combination as for chemotherapy alone. A shorter median OS was reported for the PD-L1 negative patients with PD-L1 <1%: 17.1 months for the combination treatment vs 21.7 months for chemotherapy alone with a HR of 1.44(95% CI: 0.82, 2.50). A shorter median OS was also observed for patients with PD-L1 1-49%: 21.4 months vs NE, respectively with a HR of 1.17 (95% CI 0.54, 2.55). Patients with missing PD-L1 status were wrongly included in the PD-L1 negative subgroup. When analyses were performed after excluding patients with missing PD-L1 status, the point estimate of the OS HR increased to 1.526 (95% CI 0.880, 2.645) in the PD-L1 <1% population.

In both subgroups (PD-L1 negative and PD-L1 low), a small ORR treatment difference (16.7% and 17.9% respectively), a borderline PFS benefit (HR 0.78; 95% CI 0.51, 1.2 and HR 0.90; 95% CI 0.49, 1.63, respectively) and a detrimental OS could be observed. It is acknowledged that crossover to tislelizumab was almost 40% within the trial and 14.5% of the patients received IO outside the trial; however, similarly high crossover rates to IO were observed in KEYNOTE-189 (41.3%) and in IMpower130 (59.2%). Demonstration of benefit for the addition of tislelizumab to chemotherapy in 1L nsq NSCLC is based on the comparatively rather small pivotal Study 304 with PFS as primary endpoint. Efficacy results for patients with PD-L1 <1% or PD-L1 1-49% do not show a clinically meaningful improvement in PFS and indicate a clearly detrimental effect on overall survival in a sufficiently mature dataset. It is acknowledged that uncertainties remain regarding inconsistent results in small PD-L1 subgroups of the comparator arm that might have negatively impacted the relative treatment effect of tislelizumab. It is also accepted that the study was not powered for demonstration of an overall survival benefit. However, the given deficiencies in the study design cannot be used as an argument to disregard the data. A lower treatment effect in PD-L1 low expression subgroups is considered biologically plausible and supported by external evidence. Thus, the detrimental OS effect for patients with PD-L1 expression cannot be ignored considering the additional toxicity in the combination treatment setting.

Wording of the indication

The benefit of tislelizumab in non-squamous NSCLC can therefore not be considered established neither in PD-L1 negative patients, nor in PD-L1 low patients. As a result, the indication was restricted to patients whose tumours express PD-L1 in ≥50%.

Patients with locally advanced NSCLC were included in the indication but further characterised to reflect that these patients were not candidates for platinum-based chemoradiation, or metastatic NSCLC.

Patients with known *EGFR/ALK* mutations were excluded. This resulted in exclusion of patients with *EGFR* and *ALK* mutations from the wording of the indication.

The final indication wording was agreed as follows:

Tizveni in combination with pemetrexed and platinum-containing chemotherapy is indicated for the first-line treatment of adult patients with non-squamous NSCLC whose tumours have PD-L1 expression on ≥50% of tumour cells with no EGFR or ALK positive mutations and who have:

- *locally advanced NSCLC and are not candidates for surgical resection or platinum-based chemoradiation, or*
- *metastatic NSCLC.*

2.5.7. Conclusions on the clinical efficacy

A clinically meaningful benefit in overall survival was demonstrated for tislelizumab as monotherapy in patients with locally advanced or metastatic NSCLC after prior chemotherapy.

A clinically meaningful benefit in PFS assessed by IRC was demonstrated for tislelizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel in the intended target population of patients with locally advanced or metastatic squamous NSCLC.

A benefit in PFS assessed by IRC could be shown for tislelizumab in combination with pemetrexed and platinum containing chemotherapy in the intended target population of patients with locally advanced or metastatic non-squamous NSCLC in the ITT. However, the benefit in the PD-L1 negative/low patients is not considered established and the indication was restricted to patients whose tumour express PD-L1 in ≥ 50% of tumour cells.

2.5.8. Clinical safety

Tislelizumab safety data are provided for the treatment of NSCLC as monotherapy or in combination with chemotherapy.

The safety of tislelizumab **monotherapy** in second-/third-line treatment of patients with previously treated locally advanced or metastatic NSCLC ("2L+" used as abbreviation in the following) is supported by safety data from the

- the pivotal Study 303
- the previously treated NSCLC-specific pool and
- the 200 mg Q3W All Indications pool:

Table 91: Studies providing safety data for tislelizumab monotherapy

	303 Study		2L+ NSCLC	
	Tislelizumab (N=534) n (%)	Docetaxel (N=258) n (%)	All[a] (N=636) n (%)	200 mg Q3W All Indications[b] (N=1534) n (%)
Tislelizumab Regimen, n (%)				
200 mg Q3W	534 (100.0)	NA	589 (92.6)	1534 (100.0)
5.0 mg/kg Q3W	0 (0.0)	NA	47 (7.4)	0 (0.0)

The safety of **tislelizumab with chemotherapy combinations** in first-line treatment of patients with locally advanced or metastatic squamous and nonsquamous NSCLC is supported by safety data from

- the pivotal Study 307 in squamous NSCLC,
- the pivotal Study 304 in nonsquamous NSCLC, and from
- pooling of squamous+non-squamous data (pivotal study 307, pivotal study 304 and supportive study 206): Full NSCLC Combination Therapy Safety Analysis Set

Table 92: Studies providing safety data for tislelizumab with chemotherapy combinations

Studies	Squamous NSCLC			Nonsquamous NSCLC		NSCLC	
	Study 307			Study 304		Studies 307+304+206	Studies 307+304
	Arm T+PC	Arm T+nPC	Arm PC	Arm T+PP	Arm PP	T+chemo*	Chemo**
	n	n	n	n	n	n	n
Safety analysis set	120	118	117	222	110	497	227

*chemo includes paclitaxel + carboplatin and nab-paclitaxel + carboplatin from Study 307, pemetrexed + carboplatin/cisplatin from Study 304 and paclitaxel + carboplatin/cisplatin, gemcitabine + carboplatin/cisplatin, pemetrexed + carboplatin/cisplatin from Study 206
**chemo includes paclitaxel + carboplatin and nab-paclitaxel + carboplatin from Study 307 and pemetrexed + carboplatin/cisplatin from Study 304.

At the time of submission, the pivotal studies were ongoing; applied cutoff dates were 10 Aug 2020 for Study 303 (2L+ NSCLC), 30-Sep 2020 for Study 307 (1L sq NSCLC), and 26-Oct-2020 for Study 304 (1L non-sq NSCLC).

For the monotherapy Study 303, the median follow-up was 11.9 months (13.4 vs 10.3 months for tislelizumab vs docetaxel); 20.2% and 4.7% of patients were still on study treatment at the cutoff date. For the 1L combination studies 307 and 304, the median follow-up time was 16.9 months for tislelizumab + chemotherapy groups and 15.6 months for the chemotherapy groups (16.2 months in squamous and 15.3 months in non-squamous patients); 24%-29% of patients in the tislelizumab + chemotherapy groups were still on study treatment compared to 0% with squamous and 5.5% with non-squamous patients in the chemotherapy groups.

Study 303 recruited patients from 109 centres in China, Eastern Europe, Turkey and other regions (Brazil, Mexico, and New Zealand). Studies 307 and 304 were conducted in 46 and 47 centres in China.

Table 93: Studies providing supportive safety data for tislelizumab

	2L monotherapy studies						1L combination therapy study
	302	208	204	102	001	203	206
Phase	III	II	II	I/II	I†	II	II
Disease type	Advanced unresectable/ metastatic ESCC	Previously treated, unresectable HCC	UC	ST [advanced solid tumors] (NSCLC, MM, GC, ESCC, OC, UC, HNSCC, RCC, TNBC, CRC, SCNEC or other tumors with known MSI-H or dMMR, NPC, Child-pugh Class A HCC)	ST (CRC, NSCLC, MM, cuSCC, UM, GC, PC, OC, UC, HNSCC, RCC, TNBC, HCC, ESCC, MCC, CC, GIST, sarcoma, or other tumors with known MSI-H or dMMR))	R/R cHL	Locally advanced or metastatic squamous and nonsquamous NSCLC#
Study design	Phase III randomized, controlled, open-label, global study comparing the efficacy of tislelizumab vs. chemotherapy as second-line treatment in patients with recurrent, advanced, unresectable or metastatic ESCC.	Phase II, open-label, global study investigating the efficacy, safety, and PK of tislelizumab in patients with previously-treated HCC.	Phase II single-arm, multicenter study to evaluate the efficacy and safety of tislelizumab in patients with PD-L1 high, locally advanced or metastatic urothelial carcinoma who had progressed during or following a platinum-containing regimen	Phase I/II multicenter, open-label, study in Chinese patients with advanced solid tumors. The Phase I portion assessed safety, tolerability, PK characteristics, preliminary antitumor activity, and confirmed the MTD, if any, and/or RP2D of tislelizumab. The Phase II portion was conducted as an indication-expansion study to further assess the safety, PK, and preliminary efficacy in patients with malignant solid tumors, including cohorts in patients with NSCLC.	Phase I, open-label, multiple-dose, dose-escalation and expansion study investigating the safety, tolerability, PK, and antitumor activity of tislelizumab in patients with advanced tumors.	Phase II open-label, multicenter, single-arm study to evaluate the efficacy of tislelizumab therapy in adult patients with relapsed or refractory cHL.	Phase II, multi-cohort study of tislelizumab in combination with standard chemotherapy as first-line treatment in Chinese patients with locally advanced or metastatic lung cancer to evaluate the antitumor activity of tislelizumab in combination with platinum-containing doublet chemotherapy.
Participating countries	China (including Taiwan), Belgium, Spain, France, UK, Italy, Japan, Korea, USA, Germany	China (including Taiwan); Germany, Spain, France, UK, Italy, and Poland	China, Korea	China	Australia; New Zealand; USA; South Korea; China (including Taiwan)	China	China
Tislelizumab dose regimen	200 mg Q3W	200 mg Q3W	200 mg Q3W	200mg Q3W, 200mg W1D1, W5+D1 Q3W*	0.5/2/5/10 mg/kg Q2W, 2/5 mg/kg Q3W and 200 mg Q3W	200 mg Q3W	200 mg Q3W
Patients in SAF (N)	255 in Tislelizumab arm	249	113	300 (56 NSCLC)	451 (49 NSCLC)	70	54 (SQ-NSCLC 21, NSQ-NSCLC 16)
Cutoff date	1-Dec-2020	27-Feb-2020	16-Sep-2019	31-May-2020	26-Aug-2020	26-Nov-2018	31-Dec-2019

Study 206 also included a cohort of 17 SCLC patients that were not included in this analysis.
† Study 001 is a two-stage study consisting of a Phase IA component for dose escalation and dose-finding, and a Phase IB component for indication expansion.
*In Study 102, the dose of 200mg W1D1, W5+D1 Q3W means dosing with 200 mg on Day 1 with interval of 4 weeks for Cycle 1 and 3 weeks for cycles thereafter.
CC: cholangiocarcinoma; cHL: classical Hodgkin Lymphoma; CRC: Colorectal cancer; cuSCC: Squamous cell carcinoma; dMMR: deficient Mismatch Repair; ESCC: Esophageal carcinoma; GC: Gastric cancer; GIST: gastrointestinal stromal tumor; HCC: Hepatocellular carcinoma; HNSCC: Head and neck squamous cell carcinoma; MCC: Merkel-cell carcinoma; MM: Melanoma; MSI-H: Microsatellite Instability – High; NPC: Nasopharyngeal carcinoma; NSQ- NSCLC: nonsquamous- non-small cell lung cancer; NSCLC: Non-small cell lung cancer; OC: Ovarian Cancer; PC: Pancreatic cancer; RCC: Renal cell carcinoma; R/R: Relapsed or Refractory; SCNEC: Small cell neuroendocrine carcinoma; SQ-NSCLC: squamous-non-small cell lung cancer; ST: Advanced solid tumor; TNBC: Triple negative breast cancer; UC: Urothelial carcinoma; UM: Uveal melanoma.

Patient exposure

Exposure monotherapy 2L+

Table 94: Extent of treatment exposure

	303 Study		2L+ NSCLC	
	Tislelizumab (N=534) n (%)	**Docetaxel (N=258) n (%)**	**All[a] (N=636) n (%)**	**200 mg Q3W All Indications[b] (N=1534) n (%)**
Duration of Exposure (Months)				
N	534	258	636	1534
Mean (SD)	7.49 (6.831)	3.34 (3.182)	7.77 (7.726)	7.24 (7.285)
Median	5.36	2.10	4.83	4.16
Q1, Q3	2.10, 10.48	1.41, 4.17	2.10, 10.48	2.07, 10.38
Min, Max	0.3, 32.2	0.2, 24.3	0.2, 45.5	0.2, 41.0
Duration of Exposure (Months), n (%)				

	303 Study		2L+ NSCLC	
	Tislelizumab (N=534) n (%)	Docetaxel (N=258) n (%)	All[a] (N=636) n (%)	200 mg Q3W All Indications[b] (N=1534) n (%)
>= 6 Months	244 (45.7)	36 (14.0)	279 (43.9)	615 (40.1)
>= 12 Months	114 (21.3)	6 (2.3)	139 (21.9)	340 (22.2)
>= 18 Months	52 (9.7)	2 (0.8)	70 (11.0)	155 (10.1)
>= 24 Months	19 (3.6)	1 (0.4)	35 (5.5)	65 (4.2)
>= 30 Months	6 (1.1)	0 (0.0)	17 (2.7)	26 (1.7)
Number of Cycle Received, n (%)				
1 -< 4 Cycles	164 (30.7)	150 (58.1)	199 (31.3)	514 (33.5)
4 -< 8 Cycles	103 (19.3)	69 (26.7)	133 (20.9)	360 (23.5)
8 -< 12 Cycles	85 (15.9)	18 (7.0)	91 (14.3)	180 (11.7)
12 -< 18 Cycles	72 (13.5)	14 (5.4)	78 (12.3)	153 (10.0)
18 -< 36 Cycles	96 (18.0)	7 (2.7)	107 (16.8)	278 (18.1)
>= 36 Cycles	14 (2.6)	0 (0.0)	28 (4.4)	49 (3.2)
Relative Dose Intensity (RDI)(%)[d]				
Mean (SD)	97.28 (5.350)	93.89 (8.978)	97.17 (5.855)	97.16 (6.374)
Median	99.51	98.44	99.60	100.00
Q1, Q3	96.43, 100.00	89.08, 100.00	96.43, 100.00	96.92, 100.00
Min, Max	60.4, 106.8	61.8, 106.8	53.8, 106.8	46.2, 107.7

Exposure combination therapy 1L

Exposure to tislelizumab

Table 95: Extent of treatment exposure to tislelizumab (1L NSCLC Safety Analysis Set)

	SQ-NSCLC		NSQ-NSCLC	NSCLC
	307 T+PC (N = 120) n (%)	307 T+nPC (N = 118) n (%)	304 T+PP (N = 222) n (%)	307&304&206 T+chemo* (N = 497) n (%)
Number of Treatment Cycles				
Mean (SD)	14.0 (8.71)	14.1 (9.02)	13.0 (8.78)	13.7 (9.19)
Median	13.0	13.0	10.5	12.0
Q1, Q3	8.0, 20.5	7.0, 22.0	6.0, 21.0	6.0, 21.0
Min, Max	1, 32	1, 32	1, 37	1, 40
Duration of Exposure (Months)				
Mean (SD)	10.47 (6.631)	11.03 (6.850)	9.94 (6.631)	10.47 (6.881)
Median	9.25	10.17	7.85	9.00
Q1, Q3	5.49, 16.64	5.29, 16.79	4.44, 16.36	4.99, 16.56
Min, Max	0.7, 23.2	0.7, 24.1	0.7, 27.1	0.7, 28.3
Duration of Exposure, n (%)				
< 1 months	6 (5.0)	6 (5.1)	14 (6.3)	28 (5.6)
1 - <3 months	16 (13.3)	11 (9.3)	24 (10.8)	55 (11.1)
3 - <6 months	15 (12.5)	25 (21.2)	39 (17.6)	87 (17.5)
6 - <12 months	37 (30.8)	29 (24.6)	65 (29.3)	139 (28.0)
12 - <18 months	24 (20.0)	23 (19.5)	49 (22.1)	101 (20.3)
18 - <24 months	22 (18.3)	22 (18.6)	29 (13.1)	76 (15.3)
≥ 24 months	0 (0.0)	2 (1.7)	2 (0.9)	11 (2.2)
Duration of Exposure, n (%)				
≥ 6 months	83 (69.2)	76 (64.4)	145 (65.3)	327 (65.8)
≥ 12 months	46 (38.3)	47 (39.8)	80 (36.0)	188 (37.8)
≥ 18 months	22 (18.3)	24 (20.3)	31 (14.0)	87 (17.5)

	SQ-NSCLC		NSQ-NSCLC	NSCLC
	307 T+PC (N = 120) n (%)	307 T+nPC (N = 118) n (%)	304 T+PP (N = 222) n (%)	307&304&206 T+chemo* (N = 497) n (%)
≥ 24 months	0 (0.0)	2 (1.7)	2 (0.9)	11 (2.2)
≥ 30 months	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Number of Cycle Received, n (%)				
1 - <4 cycles	20 (16.7)	16 (13.6)	27 (12.2)	66 (13.3)
4 - <8 cycles	9 (7.5)	21 (17.8)	44 (19.8)	82 (16.5)
8 - <12 cycles	24 (20.0)	16 (13.6)	48 (21.6)	95 (19.1)
12 - <18 cycles	27 (22.5)	23 (19.5)	35 (15.8)	90 (18.1)
18 - <36 cycles	40 (33.3)	42 (35.6)	67 (30.2)	160 (32.2)
≥ 36 cycles	0 (0.0)	0 (0.0)	1 (0.5)	4 (0.8)
Relative Dose Intensity (%) [a]				
n	120	118	222	497
Mean (SD)	93.17 (8.125)	88.20 (9.619)	91.36 (8.626)	91.18 (8.843)
Median	96.18	90.98	93.75	93.75
Q1, Q3	89.18, 99.24	82.89, 94.65	86.30, 98.91	86.84, 97.95
Min, Max	62.7, 107.7	54.5, 100.0	57.1, 103.3	54.5, 107.7

[a] Relative dose intensity (%) was defined as the ratio of the actual dose intensity (mg/cycle) versus the planned dose intensity (mg/cycle).

Exposure to chemotherapy

Table 96: Extent of treatment exposure to paclitaxel/nab-paclitaxel (1L NSCLC Safety Analysis Set)

	SQ-NSCLC		
	307 T+PC (N = 120) n (%)	307 T+nPC (N = 118) n (%)	307 PC (N = 117) n (%)
Number of Treatment Cycles			
n	120	118	117
Mean (SD)	4.6 (1.56)	4.0 (1.38)	4.5 (1.47)
Median	4.5	4.0	4.0
Q1, Q3	4.0, 6.0	3.0, 5.0	4.0, 6.0
Min, Max	1, 6	1, 6	1, 6
Duration of Exposure (Months)			
n	120	118	117
Mean (SD)	3.36 (1.196)	3.24 (1.191)	3.22 (1.131)
Median	3.47	3.22	3.09
Q1, Q3	2.76, 4.22	2.76, 3.94	2.76, 4.17
Min, Max	0.7, 5.6	0.7, 5.7	0.1, 5.2
Number of Cycle Received, n (%)			
1 - <4 cycles	21 (17.5)	32 (27.1)	22 (18.8)
4 - <8 cycles	99 (82.5)	86 (72.9)	95 (81.2)
≥ 8 cycles	0 (0.0)	0 (0.0)	0 (0.0)
Relative Dose Intensity (%) [a]			
Mean (SD)	91.39 (9.700)	59.93 (16.360)	93.22 (8.572)
Median	94.83	60.79	97.67
Q1, Q3	85.69, 99.37	47.73, 70.00	88.11, 100.00
Min, Max	62.2, 104.2	23.3, 100.0	62.1, 105.5

Table 97: Extent of treatment exposure to cisplatin/carboplatin (1L NSCLC Safety Analysis Set)

	SQ-NSCLC			NSQ-NSCLC		NSCLC	
	307 T+PC (N = 120) n (%)	307 T+nPC (N = 118) n (%)	307 PC (N = 117) n (%)	304 T+PP (N = 222) n (%)	304 PP (N = 110) n (%)	307&304&206 T+chemo* (N = 497) n (%)	307&304 chemo** (N = 227) n (%)
Number of Treatment Cycles							
n	120	118	117	222	110	497	227
Mean (SD)	4.6 (1.54)	4.0 (1.33)	4.5 (1.48)	4.3 (1.37)	3.9 (1.38)	4.3 (1.42)	4.2 (1.46)
Median	4.5	4.0	4.0	4.0	4.0	4.0	4.0
Q1, Q3	4.0, 6.0	3.0, 5.0	4.0, 6.0	4.0, 6.0	4.0, 4.0	4.0, 6.0	4.0, 6.0
Min, Max	1, 6	1, 6	1, 6	1, 6	1, 6	1, 6	1, 6
Relative Dose Intensity (%)							
n	120	118	117	222	110	497	227
Mean (SD)	92.52 (9.122)	83.25 (12.763)	94.59 (9.877)	92.83 (11.492)	93.00 (10.188)	90.94 (11.772)	93.82 (10.038)
Median	94.81	82.56	96.68	95.51	94.72	94.14	96.09
Q1, Q3	86.64, 99.77	73.78, 95.19	89.11, 100.00	86.48, 100.10	86.58, 99.99	84.12, 99.93	88.29, 100.00
Min, Max	63.5, 110.1	47.0, 105.9	51.7, 123.0	46.8, 124.4	60.7, 113.2	46.8, 124.4	51.7, 123.0

*chemo includes paclitaxel + carboplatin and nab-paclitaxel + carboplatin from study 307, pemetrexed + carboplatin/cisplatin from study 304 and paclitaxel + carboplatin/cisplatin, gemcitabine + carboplatin/cisplatin, pemetrexed + carboplatin/cisplatin from study 206.

**chemo includes paclitaxel + carboplatin and nab-paclitaxel + carboplatin from study 307 and pemetrexed + carboplatin/cisplatin from study 304.

Adverse events

Analysis of adverse events

Treatment emergent adverse events (TEAE) were summarised by MedDRA system organ class (SOC) and preferred term (PT) using MedDRA version 23.0. AEs were graded by the investigators using NCI CTCAE v4.03 for Studies 303 and 206 and NCI CTCAE v5.0 for Studies 304 and 307.

In the pivotal Studies 303, 304 and 307, all AEs were reported until either 30 days after the last dose of study drug or initiation of new anticancer therapy; all imAEs were reported until 90 days after the last dose of tislelizumab, regardless of whether or not the patient started a new anticancer therapy.

A patient reporting the same AE more than once is counted only once when calculating the incidence.

- ***Monotherapy 2L+***

The following tables are provided for the 2/3L NSCLC Safety Analysis Set as described above.

Summary of AEs

Table 98: Overall summary of treatment-emergent adverse events

	303 Study		2L+ NSCLC	200 mg Q3W All Indications
	Tislelizumab (N=534) n (%)	Docetaxel (N=258) n (%)	All (N=636) n (%)	(N=1534) n (%)
Patients with at least one TEAE	509 (95.3)	254 (98.4)	610 (95.9)	1468 (95.7)
Treatment-related TEAE	390 (73.0)	242 (93.8)	457 (71.9)	1125 (73.3)
TEAE with Grade 3 or Higher	206 (38.6)	193 (74.8)	256 (40.3)	669 (43.6)
Treatment-related TEAE with ≥ Grade 3	77 (14.4)	171 (66.3)	93 (14.6)	250 (16.3)
Serious TEAE	174 (32.6)	83 (32.2)	213 (33.5)	516 (33.6)
Treatment-related Serious TEAE	67 (12.5)	59 (22.9)	78 (12.3)	175 (11.4)
TEAE Leading to Death	32 (6.0)	11 (4.3)	37 (5.8)	127 (8.3)

	303 Study		2L+ NSCLC	200 mg Q3W All Indications (N=1534) n (%)
	Tislelizumab (N=534) n (%)	Docetaxel (N=258) n (%)	All (N=636) n (%)	
Treatment-related TEAE Leading to Death	8 (1.5)	4 (1.6)	9 (1.4)	20 (1.3)
TEAE Leading to Treatment Discontinuation	56 (10.5)	32 (12.4)	69 (10.8)	190 (12.4)
Treatment-related TEAE Leading to Treatment Discont.	32 (6.0)	25 (9.7)	40 (6.3)	85 (5.5)
TEAE Leading to Dose Modification	119 (22.3)	89 (34.5)	152 (23.9)	398 (25.9)
Treatment-related TEAE Leading to Dose Modification	68 (12.7)	77 (29.8)	83 (13.1)	235 (15.3)
Immune-mediated TEAE	104 (19.5)	NA	126 (19.8)	276 (18.0)
Immune-mediated TEAE with ≥ Grade 3	35 (6.6)	NA	43 (6.8)	81 (5.3)
Serious Immune-mediated TEAE	40 (7.5)	NA	44 (6.9)	90 (5.9)
Immune-mediated TEAE Leading to Death	2 (0.4)	NA	3 (0.5)	6 (0.4)
Infusion-related Reaction	5 (0.9)	9 (3.5)	7 (1.1)	54 (3.5)
Infusion-related Reaction with ≥ Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.3)

For Tisle, TEAE leading to the dose modification is defined as a TEAE with action taken "Dose delay", "Dose delayed", "Drug interrupted", "Dose interrupted", "Dose held/interrupted" or "Infusion rate decrease" by investigator; for Docetaxel, as a TEAE with action taken "Dose delay", "Dose interrupted", "Infusion rate decrease" or "Dose Reduction" by investigator.

For each row category, a pt with multiple AEs in that category is counted only once.

Most common AEs

Table 99: Most common TEAEs by SOC and PT (≥ 10% patients in any group)

System Organ Class Preferred Term	303 Study		2L+ NSCLC	200 mg Q3W All Indications (N=1534) n (%)
	Tislelizumab (N=534) n (%)	Docetaxel (N=258) n (%)	All (N=636) n (%)	
Patients with at least one TEAE	509 (95.3)	254 (98.4)	610 (95.9)	1468 (95.7)
Investigations	311 (58.2)	174 (67.4)	365 (57.4)	901 (58.7)
Alanine aminotransferase increased	106 (19.9)	38 (14.7)	121 (19.0)	295 (19.2)
Aspartate aminotransferase increased	101 (18.9)	31 (12.0)	121 (19.0)	320 (20.9)
Weight decreased	81 (15.2)	26 (10.1)	104 (16.4)	216 (14.1)
White blood cell count decreased	20 (3.7)	74 (28.7)	25 (3.9)	101 (6.6)
Neutrophil count decreased	15 (2.8)	95 (36.8)	17 (2.7)	65 (4.2)
Respiratory, thoracic and mediastinal disorders	253 (47.4)	111 (43.0)	304 (47.8)	558 (36.4)
Cough	104 (19.5)	40 (15.5)	122 (19.2)	237 (15.4)
Dyspnoea	61 (11.4)	32 (12.4)	73 (11.5)	113 (7.4)
Haemoptysis	57 (10.7)	22 (8.5)	66 (10.4)	88 (5.7)
Metabolism and nutrition disorders	252 (47.2)	118 (45.7)	298 (46.9)	659 (43.0)
Decreased appetite	82 (15.4)	59 (22.9)	99 (15.6)	221 (14.4)
Hypoalbuminaemia	70 (13.1)	41 (15.9)	87 (13.7)	174 (11.3)
Hyperglycaemia	56 (10.5)	29 (11.2)	60 (9.4)	111 (7.2)
Hyponatraemia	49 (9.2)	29 (11.2)	55 (8.6)	130 (8.5)
General disorders and administration site conditions	215 (40.3)	132 (51.2)	254 (39.9)	646 (42.1)
Asthenia	67 (12.5)	56 (21.7)	68 (10.7)	152 (9.9)
Pyrexia	56 (10.5)	26 (10.1)	70 (11.0)	236 (15.4)
Gastrointestinal disorders	194 (36.3)	127 (49.2)	245 (38.5)	683 (44.5)
Constipation	65 (12.2)	42 (16.3)	84 (13.2)	181 (11.8)
Nausea	59 (11.0)	41 (15.9)	76 (11.9)	151 (9.8)
Diarrhoea	35 (6.6)	35 (13.6)	45 (7.1)	136 (8.9)
Blood and lymphatic system disorders	179 (33.5)	174 (67.4)	208 (32.7)	509 (33.2)
Anaemia	152 (28.5)	112 (43.4)	178 (28.0)	422 (27.5)

System Organ Class Preferred Term	303 Study Tislelizumab (N=534) n (%)	303 Study Docetaxel (N=258) n (%)	2L+ NSCLC All (N=636) n (%)	200 mg Q3W All Indications (N=1534) n (%)
Leukopenia	15 (2.8)	69 (26.7)	17 (2.7)	44 (2.9)
Neutropenia	9 (1.7)	81 (31.4)	11 (1.7)	25 (1.6)
Febrile neutropenia	0 (0.0)	33 (12.8)	0 (0.0)	0 (0.0)
Infections and infestations	151 (28.3)	77 (29.8)	191 (30.0)	472 (30.8)
Pneumonia	61 (11.4)	36 (14.0)	72 (11.3)	142 (9.3)
Upper respiratory tract infection	47 (8.8)	25 (9.7)	64 (10.1)	131 (8.5)
Skin and subcutaneous tissue disorders	102 (19.1)	135 (52.3)	135 (21.2)	370 (24.1)
Pruritus	37 (6.9)	5 (1.9)	49 (7.7)	154 (10.0)
Alopecia	5 (0.9)	122 (47.3)	8 (1.3)	6 (0.4)
Endocrine disorders	79 (14.8)	2 (0.8)	95 (14.9)	243 (15.8)
Hypothyroidism	57 (10.7)	2 (0.8)	68 (10.7)	184 (12.0)

Most common related AEs

Table 100: Most common treatment-related TEAEs by SOC and PT (>= 10% patients in any group)

System Organ Class Preferred Term	303 Study Tislelizumab (N=534) n (%)	303 Study Docetaxel (N=258) n (%)	2L+ NSCLC All (N=636) n (%)	200 mg Q3W All Indications (N=1534) n (%)
Patients with at least one Treatment-related TEAE	390 (73.0)	242 (93.8)	457 (71.9)	1125 (73.3)
Investigations	224 (41.9)	151 (58.5)	257 (40.4)	598 (39.0)
Alanine aminotransferase increased	86 (16.1)	33 (12.8)	101 (15.9)	220 (14.3)
Aspartate aminotransferase increased	77 (14.4)	29 (11.2)	94 (14.8)	228 (14.9)
White blood cell count decreased	12 (2.2)	73 (28.3)	13 (2.0)	72 (4.7)
Neutrophil count decreased	8 (1.5)	93 (36.0)	9 (1.4)	44 (2.9)
General disorders and administration site conditions	105 (19.7)	97 (37.6)	118 (18.6)	325 (21.2)
Asthenia	39 (7.3)	44 (17.1)	40 (6.3)	84 (5.5)
Metabolism and nutrition disorders	92 (17.2)	80 (31.0)	99 (15.6)	238 (15.5)
Decreased appetite	33 (6.2)	48 (18.6)	36 (5.7)	91 (5.9)
Skin and subcutaneous tissue disorders	80 (15.0)	129 (50.0)	103 (16.2)	281 (18.3)
Alopecia	4 (0.7)	119 (46.1)	7 (1.1)	5 (0.3)
Endocrine disorders	78 (14.6)	0 (0.0)	93 (14.6)	223 (14.5)
Hypothyroidism	57 (10.7)	0 (0.0)	68 (10.7)	171 (11.1)
Blood and lymphatic system disorders	76 (14.2)	161 (62.4)	82 (12.9)	212 (13.8)
Anaemia	59 (11.0)	98 (38.0)	64 (10.1)	156 (10.2)
Leukopenia	11 (2.1)	67 (26.0)	13 (2.0)	34 (2.2)
Neutropenia	5 (0.9)	78 (30.2)	7 (1.1)	20 (1.3)
Febrile neutropenia	0 (0.0)	33 (12.8)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	69 (12.9)	96 (37.2)	84 (13.2)	226 (14.7)
Nausea	28 (5.2)	33 (12.8)	34 (5.3)	62 (4.0)
Diarrhoea	18 (3.4)	29 (11.2)	22 (3.5)	70 (4.6)
Constipation	12 (2.2)	27 (10.5)	14 (2.2)	28 (1.8)

Table 101: Examples of all-cause and related PTs, Study 303

Preferred Term	All-cause		Related	
	Tislelizumab (N = 534) n (%)	Docetaxel (N = 258) n (%)	Tislelizumab (N = 534) n (%)	Docetaxel (N = 534) n (%)
Anaemia	152 (28.5)	112 (43.4)	59 (11.0)	98 (38.0)
Decreased appetite	82 (15.4)	59 (22.9)	33 (6.2)	48 (18.6)
Weight decreased	81 (15.2)	26 (10.1)	13 (2.4)	18 (7.0)
Fatigue	28 (5.2)	25 (9.7)	16 (3.0)	22 (8.5)
Nausea	59 (11.0)	41 (15.9)	28 (5.2)	33 (12.8)
Diarrhoea	35 (6.6)	35 (13.6)	18 (3.4)	29 (11.2)
Pneumonia	61 (11.4)	36 (14.0)	7 (1.3)	16 (6.2)

Grade ≥ 3 AEs (all-cause)

Table 102: CTCAE Grade 3 or higher TEAEs by SOC and PT (≥1% patients in any group)

System Organ Class Preferred Term	303 Study		2L+ NSCLC	200 mg Q3W All Indications
	Tislelizumab (N=534) n (%)	Docetaxel (N=258) n (%)	All (N=636) n (%)	(N=1534) n (%)
Patients with **at least one Grade 3 or Higher TEAE**	206 (38.6)	193 (74.8)	256 (40.3)	669 (43.6)
Respiratory, thoracic and mediastinal disorders	58 (10.9)	19 (7.4)	65 (10.2)	105 (6.8)
Dyspnoea	9 (1.7)	6 (2.3)	10 (1.6)	19 (1.2)
Pneumonitis	9 (1.7)	0 (0.0)	11 (1.7)	16 (1.0)
Haemoptysis	6 (1.1)	3 (1.2)	6 (0.9)	7 (0.5)
Interstitial lung disease	6 (1.1)	0 (0.0)	6 (0.9)	9 (0.6)
Respiratory failure	5 (0.9)	3 (1.2)	7 (1.1)	10 (0.7)
Infections and infestations	47 (8.8)	38 (14.7)	58 (9.1)	125 (8.1)
Pneumonia	38 (7.1)	24 (9.3)	45 (7.1)	72 (4.7)
Upper respiratory tract infection	5 (0.9)	10 (3.9)	5 (0.8)	11 (0.7)
Investigations	40 (7.5)	82 (31.8)	51 (8.0)	174 (11.3)
Lymphocyte count decreased	8 (1.5)	8 (3.1)	9 (1.4)	16 (1.0)
Gamma-glutamyltransferase increased	6 (1.1)	1 (0.4)	8 (1.3)	32 (2.1)
Aspartate aminotransferase increased	5 (0.9)	1 (0.4)	9 (1.4)	40 (2.6)
Blood alkaline phosphatase increased	5 (0.9)	0 (0.0)	5 (0.8)	17 (1.1)
Alanine aminotransferase increased	4 (0.7)	0 (0.0)	7 (1.1)	22 (1.4)
Blood bilirubin increased	4 (0.7)	1 (0.4)	4 (0.6)	21 (1.4)
Weight decreased	4 (0.7)	0 (0.0)	7 (1.1)	10 (0.7)
Neutrophil count decreased	3 (0.6)	71 (27.5)	4 (0.6)	11 (0.7)
White blood cell count decreased	1 (0.2)	47 (18.2)	1 (0.2)	8 (0.5)
Metabolism and nutrition disorders	37 (6.9)	27 (10.5)	47 (7.4)	129 (8.4)
Hyperglycaemia	8 (1.5)	3 (1.2)	9 (1.4)	16 (1.0)
Hyponatraemia	8 (1.5)	11 (4.3)	8 (1.3)	39 (2.5)
Hypokalaemia	7 (1.3)	6 (2.3)	9 (1.4)	23 (1.5)
Decreased appetite	5 (0.9)	3 (1.2)	5 (0.8)	15 (1.0)
Hypercalcaemia	5 (0.9)	1 (0.4)	9 (1.4)	14 (0.9)
Hypochloraemia	1 (0.2)	3 (1.2)	1 (0.2)	3 (0.2)
Hypophosphataemia	0 (0.0)	3 (1.2)	0 (0.0)	5 (0.3)
Blood and lymphatic system disorders	26 (4.9)	111 (43.0)	30 (4.7)	96 (6.3)
Anaemia	18 (3.4)	16 (6.2)	21 (3.3)	75 (4.9)
Neutropenia	3 (0.6)	72 (27.9)	4 (0.6)	8 (0.5)
Thrombocytopenia	2 (0.4)	3 (1.2)	2 (0.3)	5 (0.3)
Leukopenia	1 (0.2)	41 (15.9)	2 (0.3)	3 (0.2)

System Organ Class Preferred Term	303 Study Tislelizumab (N=534) n (%)	303 Study Docetaxel (N=258) n (%)	2L+ NSCLC All (N=636) n (%)	200 mg Q3W All Indications (N=1534) n (%)
Febrile neutropenia	0 (0.0)	33 (12.8)	0 (0.0)	0 (0.0)
General disorders and administration site conditions	24 (4.5)	28 (10.9)	26 (4.1)	77 (5.0)
Asthenia	6 (1.1)	14 (5.4)	6 (0.9)	13 (0.8)
Fatigue	3 (0.6)	8 (3.1)	3 (0.5)	10 (0.7)
Cardiac disorders	17 (3.2)	6 (2.3)	20 (3.1)	30 (2.0)
Pericardial effusion	6 (1.1)	1 (0.4)	6 (0.9)	8 (0.5)
Vascular disorders	14 (2.6)	3 (1.2)	17 (2.7)	40 (2.6)
Hypertension	13 (2.4)	1 (0.4)	15 (2.4)	28 (1.8)
Gastrointestinal disorders	12 (2.2)	11 (4.3)	18 (2.8)	115 (7.5)
Diarrhoea	4 (0.7)	5 (1.9)	4 (0.6)	12 (0.8)
Dysphagia	1 (0.2)	0 (0.0)	2 (0.3)	21 (1.4)
Ascites	0 (0.0)	0 (0.0)	0 (0.0)	18 (1.2)
Musculoskeletal and connective tissue disorders	10 (1.9)	4 (1.6)	13 (2.0)	32 (2.1)
Pain in extremity	1 (0.2)	3 (1.2)	2 (0.3)	3 (0.2)

Grade ≥3 AEs (related)

Table 103: Treatment-related CTCAE Grade ≥ 3 TEAEs by SOC and PT (≥1% patients in any group)

System Organ Class Preferred Term	303 Study Tislelizumab (N=534) n (%)	303 Study Docetaxel (N=258) n (%)	2L+ NSCLC All (N=636) n (%)	200 mg Q3W All Indications (N=1534) n (%)
Patients with at least one Grade 3 or Higher Treatment-related TEAE	77 (14.4)	171 (66.3)	93 (14.6)	250 (16.3)
Respiratory, thoracic and mediastinal disorders	28 (5.2)	6 (2.3)	30 (4.7)	44 (2.9)
Pneumonitis	9 (1.7)	0 (0.0)	11 (1.7)	16 (1.0)
Interstitial lung disease	6 (1.1)	0 (0.0)	6 (0.9)	9 (0.6)
Investigations	19 (3.6)	79 (30.6)	24 (3.8)	79 (5.1)
Alanine aminotransferase increased	4 (0.7)	0 (0.0)	7 (1.1)	15 (1.0)
Aspartate aminotransferase increased	4 (0.7)	1 (0.4)	8 (1.3)	22 (1.4)
Lymphocyte count decreased	3 (0.6)	8 (3.1)	3 (0.5)	8 (0.5)
Neutrophil count decreased	1 (0.2)	70 (27.1)	1 (0.2)	6 (0.4)
White blood cell count decreased	1 (0.2)	46 (17.8)	1 (0.2)	4 (0.3)
Blood and lymphatic system disorders	6 (1.1)	106 (41.1)	7 (1.1)	30 (2.0)
Anaemia	5 (0.9)	12 (4.7)	5 (0.8)	21 (1.4)
Thrombocytopenia	1 (0.2)	3 (1.2)	1 (0.2)	2 (0.1)
Febrile neutropenia	0 (0.0)	33 (12.8)	0 (0.0)	0 (0.0)
Leukopenia	0 (0.0)	40 (15.5)	1 (0.2)	2 (0.1)
Neutropenia	0 (0.0)	70 (27.1)	1 (0.2)	5 (0.3)
General disorders and administration site conditions	6 (1.1)	21 (8.1)	6 (0.9)	15 (1.0)
Asthenia	1 (0.2)	10 (3.9)	1 (0.2)	1 (0.1)
Fatigue	0 (0.0)	7 (2.7)	0 (0.0)	3 (0.2)
Metabolism and nutrition disorders	6 (1.1)	13 (5.0)	7 (1.1)	27 (1.8)
Hyponatraemia	1 (0.2)	6 (2.3)	1 (0.2)	8 (0.5)
Infections and infestations	5 (0.9)	19 (7.4)	7 (1.1)	18 (1.2)
Pneumonia	5 (0.9)	14 (5.4)	6 (0.9)	13 (0.8)
Gastrointestinal disorders	4 (0.7)	9 (3.5)	7 (1.1)	23 (1.5)

System Organ Class Preferred Term	303 Study Tislelizumab (N=534) n (%)	303 Study Docetaxel (N=258) n (%)	2L+ NSCLC All (N=636) n (%)	200 mg Q3W All Indications (N=1534) n (%)
Diarrhoea	2 (0.4)	5 (1.9)	2 (0.3)	6 (0.4)

- ***Combination therapy 1L***

The following tables are provided for the 1L NSCLC Safety Analysis Set as described above.

Summary of AEs

Table 104: Overall summary of treatment-emergent adverse events (1L NSCLC Safety Analysis Set)

	SQ-NSCLC			NSQ-NSCLC		NSCLC	
	307 T+PC (N = 120) n (%)	307 T+nPC (N = 118) n (%)	307 PC (N = 117) n (%)	304 T+PP (N = 222) n (%)	304 PP (N = 110) n (%)	307&304&206 T+chemo* (N = 497) n (%)	307&304 chemo** (N = 227) n (%)
Patients With at Least One TEAE	120 (100.0)	117 (99.2)	117 (100.0)	222 (100.0)	109 (99.1)	496 (99.8)	226 (99.6)
Treatment-Related	119 (99.2)	117 (99.2)	117 (100.0)	222 (100.0)	107 (97.3)	495 (99.6)	224 (98.7)
Tislelizumab-Related	105 (87.5)	105 (89.0)	NA	190 (85.6)	NA	431 (86.7)	NA
Chemotherapy-Related	119 (99.2)	117 (99.2)	117 (100.0)	221 (99.5)	107 (97.3)	492 (99.0)	224 (98.7)
≥ Grade 3 TEAEs	107 (89.2)	103 (87.3)	99 (84.6)	154 (69.4)	62 (56.4)	394 (79.3)	161 (70.9)
Treatment-Related	104 (86.7)	99 (83.9)	94 (80.3)	143 (64.4)	51 (46.4)	372 (74.8)	145 (63.9)
Tislelizumab-Related	46 (38.3)	51 (43.2)	NA	74 (33.3)	NA	177 (35.6)	NA
Chemotherapy-Related	102 (85.0)	97 (82.2)	94 (80.3)	137 (61.7)	51 (46.4)	359 (72.2)	145 (63.9)
Serious TEAEs	52 (43.3)	50 (42.4)	29 (24.8)	87 (39.2)	25 (22.7)	199 (40.0)	54 (23.8)
Treatment-Related	31 (25.8)	31 (26.3)	17 (14.5)	52 (23.4)	15 (13.6)	123 (24.7)	32 (14.1)
Tislelizumab-Related	25 (20.8)	22 (18.6)	NA	41 (18.5)	NA	95 (19.1)	NA
Chemotherapy-Related	18 (15.0)	25 (21.2)	17 (14.5)	36 (16.2)	15 (13.6)	82 (16.5)	32 (14.1)
TEAEs Led to Death	4 (3.3)	7 (5.9)	5 (4.3)	9 (4.1)	2 (1.8)	21 (4.2)	7 (3.1)
Treatment-Related	1 (0.8)	2 (1.7)	3 (2.6)	4 (1.8)	1 (0.9)	8 (1.6)	4 (1.8)
Tislelizumab-Related	1 (0.8)	2 (1.7)	NA	4 (1.8)	NA	8 (1.6)	NA
Chemotherapy-Related	1 (0.8)	2 (1.7)	3 (2.6)	1 (0.5)	1 (0.9)	4 (0.8)	4 (1.8)
TEAEs Led to Any Treatment Discontinuation	21 (17.5)	38 (32.2)	18 (15.4)	68 (30.6)	11 (10.0)	141 (28.4)	29 (12.8)
Led to Tislelizumab Discontinuation	17 (14.2)	15 (12.7)	NA	32 (14.4)	NA	71 (14.3)	NA
Led to Chemotherapy Discontinuation	11 (9.2)	31 (26.3)	18 (15.4)	58 (26.1)	11 (10.0)	111 (22.3)	29 (12.8)
TEAEs Led to Any Treatment Modification [a]	77 (64.2)	109 (92.4)	51 (43.6)	158 (71.2)	57 (51.8)	366 (73.6)	108 (47.6)
Led to Tislelizumab Modification	57 (47.5)	94 (79.7)	NA	142 (64.0)	NA	312 (62.8)	NA
Led to Chemotherapy Modification	65 (54.2)	108 (91.5)	49 (41.9)	148 (66.7)	57 (51.8)	339 (68.2)	106 (46.7)
Infusion-Related Reaction	5 (4.2)	5 (4.2)	4 (3.4)	2 (0.9)	1 (0.9)	14 (2.8)	5 (2.2)
Immune-mediated TEAEs	36 (30.0)	30 (25.4)	NA	55 (24.8)	NA	127 (25.6)	NA
≥ Grade 3	13 (10.8)	12 (10.2)	NA	24 (10.8)	NA	52 (10.5)	NA
Led to Death	0 (0.0)	1 (0.8)	NA	4 (1.8)	NA	6 (1.2)	NA
Serious	13 (10.8)	14 (11.9)	NA	23 (10.4)	NA	54 (10.9)	NA

	SQ-NSCLC			NSQ-NSCLC		NSCLC	
	307 T+PC (N = 120) n (%)	307 T+nPC (N = 118) n (%)	307 PC (N = 117) n (%)	304 T+PP (N = 222) n (%)	304 PP (N = 110) n (%)	307&304&206 T+chemo* (N = 497) n (%)	307&304 chemo** (N = 227) n (%)
Led to Tislelizumab Discontinuation	8 (6.7)	8 (6.8)	NA	18 (8.1)	NA	38 (7.6)	NA
Led to Tislelizumab Modification	14 (11.7)	18 (15.3)	NA	27 (12.2)	NA	62 (12.5)	NA
Treated With Systemic Corticosteroids/Immunosuppr. Drugs	22 (18.3)	22 (18.6)	NA	39 (17.6)	NA	88 (17.7)	NA
Treated with hormone treatment for selected endocrinopathies categories	18 (15.0)	11 (9.3)	NA	22 (9.9)	NA	53 (10.7)	NA

[a] Treatment modification included dose interruption, dose delay, infusion rate decreased and dose modification (only for chemotherapy).

Table 105: Overall summary of TEAEs, squamous vs non-squamous

	307&206 T+chemo* (N = 259) n (%)	304&206 T+PP (N = 238) n (%)
Patients With at Least One TEAE	258 (99.6)	238 (100.0)
Treatment-Related	257 (99.2)	238 (100.0)
Tislelizumab-Related	228 (88.0)	203 (85.3)
Chemotherapy-Related	256 (98.8)	236 (99.2)
≥ Grade 3 TEAEs	228 (88.0)	166 (69.7)
Treatment-Related	218 (84.2)	154 (64.7)
Tislelizumab-Related	101 (39.0)	76 (31.9)
Chemotherapy-Related	213 (82.2)	146 (61.3)
Serious TEAEs	108 (41.7)	91 (38.2)
Treatment-Related	68 (26.3)	55 (23.1)
Tislelizumab-Related	52 (20.1)	43 (18.1)
Chemotherapy-Related	45 (17.4)	37 (15.5)
TEAEs Led to Death	12 (4.6)	9 (3.8)
Treatment-Related	4 (1.5)	4 (1.7)
Tislelizumab-Related	4 (1.5)	4 (1.7)
Chemotherapy-Related	3 (1.2)	1 (0.4)
TEAEs Led to Any Treatment Discontinuation	70 (27.0)	71 (29.8)
Led to Tislelizumab Discontinuation	38 (14.7)	33 (13.9)
Led to Chemotherapy Discontinuation	51 (19.7)	60 (25.2)
TEAEs Led to Any Treatment Modification	197 (76.1)	169 (71.0)
Led to Tislelizumab Modification	159 (61.4)	153 (64.3)
Led to Chemotherapy Modification	183 (70.7)	156 (65.5)
Infusion-Related Reaction	12 (4.6)	2 (0.8)
Immune-mediated TEAEs	71 (27.4)	56 (23.5)
≥ Grade 3	27 (10.4)	25 (10.5)
Led to Death	2 (0.8)	4 (1.7)
Serious	30 (11.6)	24 (10.1)
Led to Tislelizumab Discontinuation	20 (7.7)	18 (7.6)
Led to Treatment Modification of Tislelizumab	34 (13.1)	28 (11.8)
Treated With Systemic Corticosteroids/Immunosuppressive Drugs	48 (18.5)	40 (16.8)
Treated with hormone treatment for selected endocrinopathies categories	31 (12.0)	22 (9.2)

Most common AEs

Table 106: Most common AEs by PT (≥10.0% pat. In NSCLC T+Chemo group)

	SQ-NSCLC			NSQ-NSCLC		NSCLC	
Preferred Term	**307 T+PC (N = 120) n (%)**	**307 T+nPC (N = 118) n (%)**	**307 PC (N = 117) n (%)**	**304 T+PP (N = 222) n (%)**	**304 PP (N = 110) n (%)**	**307&304&206 T+chemo* (N = 497) n (%)**	**307&304 chemo** (N = 227) n (%)**
Patients With at Least One TEAE	120 (100.0)	117 (99.2)	117 (100.0)	222 (100.0)	109 (99.1)	496 (99.8)	226 (99.6)
Anaemia	107 (89.2)	111 (94.1)	94 (80.3)	186 (83.8)	85 (77.3)	433 (87.1)	179 (78.9)
Neutrophil count decreased	78 (65.0)	72 (61.0)	68 (58.1)	146 (65.8)	55 (50.0)	323 (65.0)	123 (54.2)
White blood cell count decreased	67 (55.8)	68 (57.6)	62 (53.0)	158 (71.2)	62 (56.4)	320 (64.4)	124 (54.6)
Platelet count decreased	44 (36.7)	52 (44.1)	29 (24.8)	121 (54.5)	46 (41.8)	233 (46.9)	75 (33.0)
Alanine aminotransferase increased	56 (46.7)	43 (36.4)	27 (23.1)	115 (51.8)	50 (45.5)	229 (46.1)	77 (33.9)
Aspartate aminotransferase increased	49 (40.8)	42 (35.6)	14 (12.0)	102 (45.9)	51 (46.4)	210 (42.3)	65 (28.6)
Nausea	37 (30.8)	54 (45.8)	35 (29.9)	101 (45.5)	46 (41.8)	206 (41.4)	81 (35.7)
Decreased appetite	54 (45.0)	55 (46.6)	37 (31.6)	79 (35.6)	36 (32.7)	202 (40.6)	73 (32.2)
Leukopenia	58 (48.3)	66 (55.9)	57 (48.7)	65 (29.3)	32 (29.1)	191 (38.4)	89 (39.2)
Neutropenia	53 (44.2)	50 (42.4)	56 (47.9)	84 (37.8)	39 (35.5)	190 (38.2)	95 (41.9)
Alopecia	78 (65.0)	82 (69.5)	72 (61.5)	20 (9.0)	7 (6.4)	188 (37.8)	79 (34.8)
Thrombocytopenia	35 (29.2)	49 (41.5)	33 (28.2)	66 (29.7)	33 (30.0)	157 (31.6)	66 (29.1)
Constipation	40 (33.3)	36 (30.5)	27 (23.1)	54 (24.3)	26 (23.6)	136 (27.4)	53 (23.3)
Vomiting	28 (23.3)	27 (22.9)	20 (17.1)	61 (27.5)	26 (23.6)	121 (24.3)	46 (20.3)
Asthenia	30 (25.0)	24 (20.3)	24 (20.5)	43 (19.4)	17 (15.5)	117 (23.5)	41 (18.1)
Hypoalbuminaemia	30 (25.0)	25 (21.2)	19 (16.2)	39 (17.6)	11 (10.0)	98 (19.7)	30 (13.2)
Pyrexia	25 (20.8)	24 (20.3)	18 (15.4)	42 (18.9)	13 (11.8)	97 (19.5)	31 (13.7)
Rash	26 (21.7)	28 (23.7)	4 (3.4)	36 (16.2)	13 (11.8)	96 (19.3)	17 (7.5)
Hyponatraemia	26 (21.7)	25 (21.2)	20 (17.1)	33 (14.9)	14 (12.7)	89 (17.9)	34 (15.0)
Malaise	24 (20.0)	19 (16.1)	19 (16.2)	42 (18.9)	23 (20.9)	88 (17.7)	42 (18.5)
Blood lactate dehydrogenase increased	22 (18.3)	16 (13.6)	13 (11.1)	41 (18.5)	16 (14.5)	83 (16.7)	29 (12.8)
Blood bilirubin increased	30 (25.0)	18 (15.3)	15 (12.8)	29 (13.1)	10 (9.1)	80 (16.1)	25 (11.0)
Pain in extremity	40 (33.3)	18 (15.3)	27 (23.1)	17 (7.7)	8 (7.3)	80 (16.1)	35 (15.4)
Cough	19 (15.8)	19 (16.1)	8 (6.8)	32 (14.4)	11 (10.0)	76 (15.3)	19 (8.4)
Pneumonia	26 (21.7)	19 (16.1)	13 (11.1)	27 (12.2)	14 (12.7)	75 (15.1)	27 (11.9)
Hypokalaemia	26 (21.7)	20 (16.9)	16 (13.7)	26 (11.7)	5 (4.5)	74 (14.9)	21 (9.3)
Diarrhoea	21 (17.5)	23 (19.5)	8 (6.8)	29 (13.1)	15 (13.6)	73 (14.7)	23 (10.1)

	SQ-NSCLC			NSQ-NSCLC		NSCLC	
Preferred Term	**307 T+PC (N = 120) n (%)**	**307 T+nPC (N = 118) n (%)**	**307 PC (N = 117) n (%)**	**304 T+PP (N = 222) n (%)**	**304 PP (N = 110) n (%)**	**307&304&206 T+chemo* (N = 497) n (%)**	**307&304 chemo** (N = 227) n (%)**
Gamma-glutamyltransferase increased	21 (17.5)	17 (14.4)	15 (12.8)	33 (14.9)	18 (16.4)	71 (14.3)	33 (14.5)
Lymphocyte count decreased	15 (12.5)	22 (18.6)	16 (13.7)	29 (13.1)	6 (5.5)	67 (13.5)	22 (9.7)
Hyperglycaemia	21 (17.5)	13 (11.0)	10 (8.5)	26 (11.7)	15 (13.6)	65 (13.1)	25 (11.0)
Haemoptysis	24 (20.0)	20 (16.9)	13 (11.1)	20 (9.0)	9 (8.2)	64 (12.9)	22 (9.7)
Hypothyroidism	18 (15.0)	16 (13.6)	0 (0.0)	26 (11.7)	1 (0.9)	64 (12.9)	1 (0.4)
Blood creatinine increased	7 (5.8)	9 (7.6)	7 (6.0)	41 (18.5)	5 (4.5)	61 (12.3)	12 (5.3)
Back pain	13 (10.8)	19 (16.1)	5 (4.3)	25 (11.3)	10 (9.1)	60 (12.1)	15 (6.6)
Dyspnoea	17 (14.2)	13 (11.0)	11 (9.4)	29 (13.1)	7 (6.4)	60 (12.1)	18 (7.9)
Weight decreased	14 (11.7)	17 (14.4)	7 (6.0)	26 (11.7)	12 (10.9)	59 (11.9)	19 (8.4)
Arthralgia	26 (21.7)	23 (19.5)	20 (17.1)	6 (2.7)	0 (0.0)	57 (11.5)	20 (8.8)
Blood alkaline phosphatase increased	19 (15.8)	12 (10.2)	11 (9.4)	24 (10.8)	13 (11.8)	55 (11.1)	24 (10.6)
Upper respiratory tract infection	19 (15.8)	14 (11.9)	11 (9.4)	17 (7.7)	6 (5.5)	53 (10.7)	17 (7.5)
Blood creatine phosphokinase increased	20 (16.7)	16 (13.6)	10 (8.5)	14 (6.3)	5 (4.5)	52 (10.5)	15 (6.6)
Hypoaesthesia	27 (22.5)	13 (11.0)	20 (17.1)	6 (2.7)	2 (1.8)	52 (10.5)	22 (9.7)

Most common related AEs

Table 107: Most common treatment-related TEAEs to tislelizumab by SOC and PT (≥ 5.0% patients in any group)

	SQ-NSCLC		NSQ-NSCLC	NSCLC
System Organ Class Preferred Term	**307 T+PC (N = 120) n (%)**	**307 T+nPC (N = 118) n (%)**	**304 T+PP (N = 222) n (%)**	**307&304&206 T+chemo* (N = 497) n (%)**
Patients With at Least One Treatment-related TEAE Related to Tislelizumab	105 (87.5)	105 (89.0)	190 (85.6)	431 (86.7)
Investigations	78 (65.0)	78 (66.1)	127 (57.2)	295 (59.4)
Alanine aminotransferase increased	32 (26.7)	27 (22.9)	64 (28.8)	126 (25.4)
Aspartate aminotransferase increased	28 (23.3)	22 (18.6)	59 (26.6)	112 (22.5)
White blood cell count decreased	20 (16.7)	29 (24.6)	45 (20.3)	95 (19.1)
Neutrophil count decreased	24 (20.0)	32 (27.1)	35 (15.8)	92 (18.5)
Platelet count decreased	20 (16.7)	25 (21.2)	46 (20.7)	92 (18.5)
Blood bilirubin increased	25 (20.8)	15 (12.7)	17 (7.7)	58 (11.7)
Blood lactate dehydrogenase increased	15 (12.5)	13 (11.0)	26 (11.7)	56 (11.3)
Blood creatine phosphokinase increased	17 (14.2)	16 (13.6)	14 (6.3)	49 (9.9)
Gamma-glutamyltransferase increased	9 (7.5)	9 (7.6)	22 (9.9)	40 (8.0)
Blood thyroid stimulating hormone increased	9 (7.5)	9 (7.6)	11 (5.0)	32 (6.4)
Blood creatinine increased	4 (3.3)	4 (3.4)	22 (9.9)	31 (6.2)
Blood alkaline phosphatase increased	12 (10.0)	6 (5.1)	12 (5.4)	30 (6.0)
Lymphocyte count decreased	6 (5.0)	11 (9.3)	10 (4.5)	27 (5.4)
Alpha hydroxybutyrate dehydrogenase increased	5 (4.2)	2 (1.7)	11 (5.0)	20 (4.0)
Blood thyroid stimulating hormone decreased	4 (3.3)	6 (5.1)	4 (1.8)	17 (3.4)
Blood and lymphatic system disorders	48 (40.0)	60 (50.8)	74 (33.3)	184 (37.0)
Anaemia	43 (35.8)	47 (39.8)	61 (27.5)	153 (30.8)
Leukopenia	22 (18.3)	27 (22.9)	20 (9.0)	69 (13.9)
Neutropenia	19 (15.8)	19 (16.1)	28 (12.6)	66 (13.3)

System Organ Class Preferred Term	SQ-NSCLC 307 T+PC (N = 120) n (%)	SQ-NSCLC 307 T+nPC (N = 118) n (%)	NSQ-NSCLC 304 T+PP (N = 222) n (%)	NSCLC 307&304&206 T+chemo* (N = 497) n (%)
Thrombocytopenia	19 (15.8)	24 (20.3)	21 (9.5)	64 (12.9)
Metabolism and nutrition disorders	42 (35.0)	42 (35.6)	66 (29.7)	154 (31.0)
Decreased appetite	22 (18.3)	19 (16.1)	29 (13.1)	73 (14.7)
Hyperglycaemia	7 (5.8)	8 (6.8)	17 (7.7)	32 (6.4)
Hypoalbuminaemia	9 (7.5)	8 (6.8)	11 (5.0)	28 (5.6)
Hyponatraemia	7 (5.8)	6 (5.1)	13 (5.9)	26 (5.2)
Hyperuricaemia	7 (5.8)	7 (5.9)	10 (4.5)	24 (4.8)
Hypokalaemia	7 (5.8)	9 (7.6)	7 (3.2)	23 (4.6)
Hypoproteinaemia	8 (6.7)	3 (2.5)	4 (1.8)	15 (3.0)
Hypocalcaemia	6 (5.0)	4 (3.4)	3 (1.4)	13 (2.6)
Skin and subcutaneous tissue disorders	37 (30.8)	45 (38.1)	46 (20.7)	132 (26.6)
Rash	22 (18.3)	26 (22.0)	27 (12.2)	77 (15.5)
Alopecia	11 (9.2)	12 (10.2)	2 (0.9)	25 (5.0)
General disorders and administration site conditions	28 (23.3)	28 (23.7)	58 (26.1)	123 (24.7)
Asthenia	10 (8.3)	8 (6.8)	19 (8.6)	45 (9.1)
Malaise	8 (6.7)	4 (3.4)	24 (10.8)	36 (7.2)
Pyrexia	8 (6.7)	8 (6.8)	11 (5.0)	28 (5.6)
Gastrointestinal disorders	23 (19.2)	30 (25.4)	56 (25.2)	112 (22.5)
Nausea	3 (2.5)	12 (10.2)	27 (12.2)	42 (8.5)
Vomiting	4 (3.3)	7 (5.9)	15 (6.8)	26 (5.2)
Constipation	5 (4.2)	4 (3.4)	11 (5.0)	20 (4.0)
Diarrhoea	7 (5.8)	4 (3.4)	5 (2.3)	16 (3.2)
Respiratory, thoracic and mediastinal disorders	19 (15.8)	19 (16.1)	43 (19.4)	87 (17.5)
Pneumonitis	7 (5.8)	6 (5.1)	28 (12.6)	44 (8.9)
Endocrine disorders	23 (19.2)	17 (14.4)	32 (14.4)	76 (15.3)
Hypothyroidism	18 (15.0)	15 (12.7)	26 (11.7)	63 (12.7)
Hyperthyroidism	7 (5.8)	2 (1.7)	10 (4.5)	20 (4.0)
Infections and infestations	10 (8.3)	17 (14.4)	17 (7.7)	46 (9.3)
Musculoskeletal and connective tissue disorders	17 (14.2)	17 (14.4)	11 (5.0)	46 (9.3)
Arthralgia	7 (5.8)	8 (6.8)	2 (0.9)	17 (3.4)
Pain in extremity	9 (7.5)	3 (2.5)	3 (1.4)	15 (3.0)
Cardiac disorders	8 (6.7)	12 (10.2)	19 (8.6)	43 (8.7)
Nervous system disorders	15 (12.5)	9 (7.6)	16 (7.2)	42 (8.5)
Hypoaesthesia	7 (5.8)	4 (3.4)	1 (0.5)	13 (2.6)
Hepatobiliary disorders	6 (5.0)	6 (5.1)	4 (1.8)	19 (3.8)

Table 108: Most common treatment-related TEAEs to chemotherapy by SOC and PT (≥ 5.0% patients in any group)

System Organ Class Preferred Term	SQ-NSCLC 307 T+PC (N = 120) n (%)	SQ-NSCLC 307 T+nPC (N = 118) n (%)	SQ-NSCLC 307 PC (N = 117) n (%)	NSQ-NSCLC 304 T+PP (N = 222) n (%)	NSQ-NSCLC 304 PP (N = 110) n (%)	NSCLC 307&304&206 T+chemo* (N = 497) n (%)	NSCLC 307&304 chemo** (N = 227) n (%)
Patients With at Least One Treatment-related TEAE Related to Chemotherapy	119 (99.2)	117 (99.2)	117 (100.0)	221 (99.5)	107 (97.3)	492 (99.0)	224 (98.7)
Blood and lymphatic system disorders	107 (89.2)	111 (94.1)	101 (86.3)	197 (88.7)	88 (80.0)	443 (89.1)	189 (83.3)
Anaemia	98 (81.7)	104 (88.1)	87 (74.4)	177 (79.7)	75 (68.2)	407 (81.9)	162 (71.4)
Leukopenia	57 (47.5)	66 (55.9)	57 (48.7)	65 (29.3)	32 (29.1)	190 (38.2)	89 (39.2)
Neutropenia	52 (43.3)	50 (42.4)	56 (47.9)	84 (37.8)	39 (35.5)	189 (38.0)	95 (41.9)
Thrombocytopenia	34 (28.3)	47 (39.8)	33 (28.2)	66 (29.7)	33 (30.0)	153 (30.8)	66 (29.1)
Investigations	105 (87.5)	103 (87.3)	97 (82.9)	202 (91.0)	95 (86.4)	441 (88.7)	192 (84.6)
Neutrophil count decreased	77 (64.2)	72 (61.0)	68 (58.1)	145 (65.3)	55 (50.0)	320 (64.4)	123 (54.2)
White blood cell count decreased	65 (54.2)	68 (57.6)	62 (53.0)	158 (71.2)	62 (56.4)	318 (64.0)	124 (54.6)
Platelet count decreased	39 (32.5)	52 (44.1)	29 (24.8)	121 (54.5)	46 (41.8)	227 (45.7)	75 (33.0)
Alanine aminotransferase increased	47 (39.2)	38 (32.2)	27 (23.1)	106 (47.7)	48 (43.6)	204 (41.0)	75 (33.0)
Aspartate aminotransferase increased	38 (31.7)	39 (33.1)	13 (11.1)	96 (43.2)	49 (44.5)	187 (37.6)	62 (27.3)
Blood bilirubin increased	23 (19.2)	12 (10.2)	15 (12.8)	26 (11.7)	8 (7.3)	63 (12.7)	23 (10.1)
Gamma-glutamyltransferase increased	15 (12.5)	14 (11.9)	14 (12.0)	31 (14.0)	16 (14.5)	60 (12.1)	30 (13.2)
Lymphocyte count decreased	13 (10.8)	21 (17.8)	15 (12.8)	26 (11.7)	6 (5.5)	60 (12.1)	21 (9.3)
Blood lactate dehydrogenase increased	18 (15.0)	11 (9.3)	9 (7.7)	27 (12.2)	11 (10.0)	58 (11.7)	20 (8.8)
Blood creatinine increased	4 (3.3)	6 (5.1)	7 (6.0)	34 (15.3)	5 (4.5)	47 (9.5)	12 (5.3)
Blood creatine phosphokinase increased	12 (10.0)	7 (5.9)	8 (6.8)	7 (3.2)	4 (3.6)	28 (5.6)	12 (5.3)
Gastrointestinal disorders	62 (51.7)	69 (58.5)	54 (46.2)	135 (60.8)	60 (54.5)	279 (56.1)	114 (50.2)
Nausea	34 (28.3)	48 (40.7)	29 (24.8)	96 (43.2)	44 (40.0)	189 (38.0)	73 (32.2)
Vomiting	24 (20.0)	22 (18.6)	15 (12.8)	55 (24.8)	24 (21.8)	106 (21.3)	39 (17.2)
Constipation	22 (18.3)	12 (10.2)	18 (15.4)	31 (14.0)	15 (13.6)	66 (13.3)	33 (14.5)
Diarrhoea	12 (10.0)	7 (5.9)	7 (6.0)	10 (4.5)	10 (9.1)	29 (5.8)	17 (7.5)
Abdominal distension	6 (5.0)	4 (3.4)	2 (1.7)	5 (2.3)	2 (1.8)	16 (3.2)	4 (1.8)
Metabolism and nutrition disorders	78 (65.0)	72 (61.0)	54 (46.2)	109 (49.1)	53 (48.2)	274 (55.1)	107 (47.1)
Decreased appetite	48 (40.0)	48 (40.7)	36 (30.8)	69 (31.1)	32 (29.1)	177 (35.6)	68 (30.0)
Hypoalbuminaemia	17 (14.2)	11 (9.3)	13 (11.1)	21 (9.5)	8 (7.3)	50 (10.1)	21 (9.3)
Hyponatraemia	9 (7.5)	12 (10.2)	12 (10.3)	20 (9.0)	8 (7.3)	41 (8.2)	20 (8.8)
Hypokalaemia	11 (9.2)	8 (6.8)	5 (4.3)	10 (4.5)	1 (0.9)	29 (5.8)	6 (2.6)
Hyperglycaemia	6 (5.0)	6 (5.1)	3 (2.6)	14 (6.3)	4 (3.6)	26 (5.2)	7 (3.1)
Hyperuricaemia	6 (5.0)	6 (5.1)	4 (3.4)	12 (5.4)	7 (6.4)	24 (4.8)	11 (4.8)
Hypoproteinaemia	10 (8.3)	8 (6.8)	8 (6.8)	6 (2.7)	2 (1.8)	24 (4.8)	10 (4.4)
Hypochloraemia	5 (4.2)	5 (4.2)	6 (5.1)	9 (4.1)	1 (0.9)	20 (4.0)	7 (3.1)
Hypocalcaemia	8 (6.7)	3 (2.5)	3 (2.6)	5 (2.3)	4 (3.6)	16 (3.2)	7 (3.1)
Skin and subcutaneous tissue disorders	86 (71.7)	89 (75.4)	74 (63.2)	55 (24.8)	17 (15.5)	242 (48.7)	91 (40.1)
Alopecia	78 (65.0)	81 (68.6)	72 (61.5)	19 (8.6)	4 (3.6)	186 (37.4)	76 (33.5)
Rash	9 (7.5)	14 (11.9)	4 (3.4)	26 (11.7)	7 (6.4)	53 (10.7)	11 (4.8)
Pruritus	3 (2.5)	6 (5.1)	3 (2.6)	9 (4.1)	1 (0.9)	22 (4.4)	4 (1.8)
General disorders and administration site conditions	56 (46.7)	51 (43.2)	49 (41.9)	84 (37.8)	41 (37.3)	212 (42.7)	90 (39.6)
Asthenia	24 (20.0)	20 (16.9)	23 (19.7)	35 (15.8)	16 (14.5)	98 (19.7)	39 (17.2)
Malaise	17 (14.2)	17 (14.4)	17 (14.5)	37 (16.7)	19 (17.3)	73 (14.7)	36 (15.9)
Pyrexia	11 (9.2)	11 (9.3)	6 (5.1)	9 (4.1)	4 (3.6)	32 (6.4)	10 (4.4)
Nervous system disorders	58 (48.3)	21 (17.8)	41 (35.0)	20 (9.0)	6 (5.5)	109 (21.9)	47 (20.7)
Hypoaesthesia	25 (20.8)	10 (8.5)	19 (16.2)	2 (0.9)	1 (0.9)	41 (8.2)	20 (8.8)
Dizziness	2 (1.7)	4 (3.4)	3 (2.6)	13 (5.9)	3 (2.7)	22 (4.4)	6 (2.6)
Neurotoxicity	15 (12.5)	5 (4.2)	12 (10.3)	0 (0.0)	0 (0.0)	21 (4.2)	12 (5.3)
Peripheral sensory neuropathy	8 (6.7)	0 (0.0)	5 (4.3)	1 (0.5)	0 (0.0)	10 (2.0)	5 (2.2)
Musculoskeletal and connective tissue disorders	52 (43.3)	35 (29.7)	42 (35.9)	12 (5.4)	6 (5.5)	105 (21.1)	48 (21.1)
Pain in extremity	31 (25.8)	8 (6.8)	24 (20.5)	6 (2.7)	4 (3.6)	49 (9.9)	28 (12.3)
Arthralgia	21 (17.5)	15 (12.7)	17 (14.5)	0 (0.0)	0 (0.0)	38 (7.6)	17 (7.5)
Myalgia	6 (5.0)	8 (6.8)	5 (4.3)	1 (0.5)	0 (0.0)	15 (3.0)	5 (2.2)
Respiratory, thoracic and mediastinal disorders	10 (8.3)	10 (8.5)	9 (7.7)	28 (12.6)	13 (11.8)	51 (10.3)	22 (9.7)
Infections and infestations	6 (5.0)	15 (12.7)	8 (6.8)	20 (9.0)	7 (6.4)	42 (8.5)	15 (6.6)

System Organ Class Preferred Term	SQ-NSCLC 307 T+PC (N = 120) n (%)	SQ-NSCLC 307 T+nPC (N = 118) n (%)	SQ-NSCLC 307 PC (N = 117) n (%)	NSQ-NSCLC 304 T+PP (N = 222) n (%)	NSQ-NSCLC 304 PP (N = 110) n (%)	NSCLC 307&304&206 T+chemo* (N = 497) n (%)	NSCLC 307&304 chemo** (N = 227) n (%)
Cardiac disorders	7 (5.8)	14 (11.9)	4 (3.4)	13 (5.9)	3 (2.7)	36 (7.2)	7 (3.1)
Hepatobiliary disorders	9 (7.5)	5 (4.2)	11 (9.4)	2 (0.9)	0 (0.0)	18 (3.6)	11 (4.8)
Hepatic function abnormal	7 (5.8)	4 (3.4)	10 (8.5)	0 (0.0)	0 (0.0)	13 (2.6)	10 (4.4)
Psychiatric disorders	3 (2.5)	1 (0.8)	5 (4.3)	8 (3.6)	9 (8.2)	12 (2.4)	14 (6.2)
Insomnia	3 (2.5)	1 (0.8)	4 (3.4)	5 (2.3)	9 (8.2)	9 (1.8)	13 (5.7)

Table 109: Most common treatment-related TEAEs to chemotherapy and to tislelizumab by SOC and PT (≥10.0% patients in NSCLC T+Chemo group)

System Organ Class Preferred Term	TEAEs related to chemotherapy NSCLC 307&304&206 T+chemo (N = 497) n (%)	TEAEs related to tislelizumab NSCLC 307&304&206 T+chemo (N = 497) n (%)
Patients with at least one treatment-related TEAE	492 (99.0)	431 (86.7)
Investigations	441 (88.7)	295 (59.4)
Alanine aminotransferase increased	204 (41.0)	126 (25.4)
Aspartate aminotransferase increased	187 (37.6)	112 (22.5)
White blood cell count decreased	318 (64.0)	95 (19.1)
Neutrophil count decreased	320 (64.4)	92 (18.5)
Platelet count decreased	227 (45.7)	92 (18.5)
Blood bilirubin increased	63 (12.7)	58 (11.7)
Blood lactate dehydrogenase increased	58 (11.7)	56 (11.3)
Gamma-glutamyltransferase increased	60 (12.1)	0
Lymphocyte count decreased	60 (12.1)	0
Blood and lymphatic system disorders	443 (89.1)	184 (37.0)
Anaemia	407 (81.9)	153 (30.8)
Leukopenia	190 (38.2)	69 (13.9)
Neutropenia	189 (38.0)	66 (13.3)
Thrombocytopenia	153 (30.8)	64 (12.9)
Metabolism and nutrition disorders	274 (55.1)	154 (31.0)
Decreased appetite	177 (35.6)	73 (14.7)
Hypoalbuminaemia	50 (10.1)	0
Skin and subcutaneous tissue disorders	242 (48.7)	132 (26.6)
Rash	53 (10.7)	77 (15.5)
Alopecia	186 (37.4)	0
Endocrine disorders	0	76 (15.3)
Hypothyroidism	0	63 (12.7)
Gastrointestinal disorders	279 (56.1)	0
Nausea	189 (38.0)	0
Vomiting	106 (21.3)	0
Constipation	66 (13.3)	0
General disorders and administration site conditions	212 (42.7)	0
Asthenia	98 (19.7)	0
Malaise	73 (14.7)	0

Grade ≥ 3 AEs (all-cause)

Table 110: CTCAE Grade 3 or higher TEAEs by SOC and PT (≥1.0% patients in NSCLC T+Chemo group)

System Organ Class Preferred Term	SQ-NSCLC			NSQ-NSCLC		NSCLC	
	307 T+PC (N = 120) n (%)	307 T+nPC (N = 118) n (%)	307 PC (N = 117) n (%)	304 T+PP (N = 222) n (%)	304 PP (N = 110) n (%)	307&304&206 T+chemo* (N = 497) n (%)	307&304 chemo** (N = 227) n (%)
Patients With at Least One TEAE with Grade ≥ 3	107 (89.2)	103 (87.3)	99 (84.6)	154 (69.4)	62 (56.4)	394 (79.3)	161 (70.9)
Investigations	77 (64.2)	69 (58.5)	58 (49.6)	85 (38.3)	22 (20.0)	254 (51.1)	80 (35.2)
Neutrophil count decreased	64 (53.3)	54 (45.8)	53 (45.3)	57 (25.7)	14 (12.7)	193 (38.8)	67 (29.5)
White blood cell count decreased	28 (23.3)	32 (27.1)	28 (23.9)	30 (13.5)	5 (4.5)	96 (19.3)	33 (14.5)
Platelet count decreased	6 (5.0)	16 (13.6)	2 (1.7)	19 (8.6)	6 (5.5)	45 (9.1)	8 (3.5)
Alanine aminotransferase increased	3 (2.5)	2 (1.7)	0 (0.0)	8 (3.6)	3 (2.7)	16 (3.2)	3 (1.3)
Lymphocyte count decreased	3 (2.5)	4 (3.4)	4 (3.4)	6 (2.7)	1 (0.9)	14 (2.8)	5 (2.2)
Gamma-glutamyltransferase increased	2 (1.7)	3 (2.5)	1 (0.9)	4 (1.8)	3 (2.7)	9 (1.8)	4 (1.8)
Aspartate aminotransferase increased	2 (1.7)	1 (0.8)	0 (0.0)	4 (1.8)	0 (0.0)	8 (1.6)	0 (0.0)
Weight decreased	2 (1.7)	1 (0.8)	0 (0.0)	2 (0.9)	0 (0.0)	5 (1.0)	0 (0.0)
Blood and lymphatic system disorders	56 (46.7)	68 (57.6)	63 (53.8)	87 (39.2)	38 (34.5)	218 (43.9)	101 (44.5)
Neutropenia	40 (33.3)	32 (27.1)	47 (40.2)	53 (23.9)	25 (22.7)	126 (25.4)	72 (31.7)
Anaemia	12 (10.0)	27 (22.9)	15 (12.8)	33 (14.9)	13 (11.8)	77 (15.5)	28 (12.3)
Leukopenia	19 (15.8)	30 (25.4)	22 (18.8)	24 (10.8)	12 (10.9)	73 (14.7)	34 (15.0)
Thrombocytopenia	8 (6.7)	15 (12.7)	7 (6.0)	25 (11.3)	10 (9.1)	49 (9.9)	17 (7.5)
Febrile neutropenia	5 (4.2)	5 (4.2)	3 (2.6)	2 (0.9)	0 (0.0)	12 (2.4)	3 (1.3)
Bone marrow failure	2 (1.7)	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.9)	5 (1.0)	1 (0.4)
Infections and infestations	13 (10.8)	13 (11.0)	6 (5.1)	20 (9.0)	9 (8.2)	46 (9.3)	15 (6.6)
Pneumonia	6 (5.0)	6 (5.1)	3 (2.6)	13 (5.9)	8 (7.3)	25 (5.0)	11 (4.8)
Upper respiratory tract infection	5 (4.2)	0 (0.0)	1 (0.9)	2 (0.9)	1 (0.9)	7 (1.4)	2 (0.9)
Respiratory, thoracic and mediastinal disorders	9 (7.5)	13 (11.0)	3 (2.6)	20 (9.0)	2 (1.8)	44 (8.9)	5 (2.2)
Pneumonitis	3 (2.5)	3 (2.5)	0 (0.0)	9 (4.1)	1 (0.9)	15 (3.0)	1 (0.4)
Haemoptysis	2 (1.7)	4 (3.4)	0 (0.0)	4 (1.8)	0 (0.0)	10 (2.0)	0 (0.0)
Dyspnoea	0 (0.0)	1 (0.8)	1 (0.9)	5 (2.3)	0 (0.0)	7 (1.4)	1 (0.4)
Metabolism and nutrition disorders	11 (9.2)	7 (5.9)	8 (6.8)	17 (7.7)	4 (3.6)	42 (8.5)	12 (5.3)
Hypokalaemia	3 (2.5)	2 (1.7)	2 (1.7)	2 (0.9)	0 (0.0)	8 (1.6)	2 (0.9)
Hyponatraemia	2 (1.7)	2 (1.7)	3 (2.6)	3 (1.4)	1 (0.9)	8 (1.6)	4 (1.8)
Decreased appetite	2 (1.7)	2 (1.7)	1 (0.9)	3 (1.4)	2 (1.8)	7 (1.4)	3 (1.3)
Hypertriglyceridaemia	4 (3.3)	1 (0.8)	1 (0.9)	1 (0.5)	0 (0.0)	7 (1.4)	1 (0.4)
Hyperglycaemia	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.9)	1 (0.9)	5 (1.0)	1 (0.4)
Gastrointestinal disorders	5 (4.2)	2 (1.7)	3 (2.6)	10 (4.5)	1 (0.9)	18 (3.6)	4 (1.8)
General disorders and administration site conditions	5 (4.2)	3 (2.5)	5 (4.3)	6 (2.7)	6 (5.5)	17 (3.4)	11 (4.8)
Malaise	3 (2.5)	1 (0.8)	0 (0.0)	1 (0.5)	3 (2.7)	6 (1.2)	3 (1.3)
Nervous system disorders	7 (5.8)	1 (0.8)	2 (1.7)	6 (2.7)	3 (2.7)	16 (3.2)	5 (2.2)
Skin and subcutaneous tissue disorders	6 (5.0)	4 (3.4)	0 (0.0)	3 (1.4)	1 (0.9)	13 (2.6)	1 (0.4)
Rash	4 (3.3)	2 (1.7)	0 (0.0)	2 (0.9)	0 (0.0)	8 (1.6)	0 (0.0)
Hepatobiliary disorders	1 (0.8)	3 (2.5)	0 (0.0)	4 (1.8)	0 (0.0)	10 (2.0)	0 (0.0)
Cardiac disorders	0 (0.0)	1 (0.8)	1 (0.9)	7 (3.2)	0 (0.0)	9 (1.8)	1 (0.4)
Musculoskeletal and connective tissue disorders	5 (4.2)	1 (0.8)	1 (0.9)	1 (0.5)	2 (1.8)	8 (1.6)	3 (1.3)
Renal and urinary disorders	0 (0.0)	2 (1.7)	0 (0.0)	4 (1.8)	0 (0.0)	6 (1.2)	0 (0.0)
Injury, poisoning and procedural complications	2 (1.7)	2 (1.7)	1 (0.9)	1 (0.5)	0 (0.0)	5 (1.0)	1 (0.4)

Grade ≥ 3 AEs (related)

In general, the most common drug-related CTCAE Grade ≥ 3 TEAEs were similar to reported CTCAE Grade ≥ 3 TEAEs regardless of drug relatedness (data not shown). Drug-related Grade ≥3 AEs were higher for the combined tislelizumab vs the combined chemotherapy groups (74.8% vs 63.9%).

Serious adverse event/deaths/other significant events

- ***Monotherapy 2L+***

SAEs

Table 111: Serious TEAEs by SOC and PT (≥ 1% patients in any group)

	303 Study		2L+ NSCLC	
System Organ Class Preferred Term	**Tislelizumab (N=534) n (%)**	**Docetaxel (N=258) n (%)**	**All (N=636) n (%)**	**200 mg Q3W All Indications (N=1534) n (%)**
Patients with at least one Serious TEAE	174 (32.6)	83 (32.2)	213 (33.5)	516 (33.6)
Respiratory, thoracic and mediastinal disorders	71 (13.3)	17 (6.6)	77 (12.1)	128 (8.3)
Pneumonitis	15 (2.8)	0 (0.0)	17 (2.7)	24 (1.6)
Haemoptysis	10 (1.9)	4 (1.6)	11 (1.7)	12 (0.8)
Dyspnoea	8 (1.5)	4 (1.6)	8 (1.3)	16 (1.0)
Pleural effusion	8 (1.5)	5 (1.9)	9 (1.4)	13 (0.8)
Immune-mediated pneumonitis	7 (1.3)	0 (0.0)	7 (1.1)	12 (0.8)
Interstitial lung disease	7 (1.3)	0 (0.0)	7 (1.1)	10 (0.7)
Respiratory failure	5 (0.9)	3 (1.2)	6 (0.9)	9 (0.6)
Infections and infestations	38 (7.1)	25 (9.7)	48 (7.5)	112 (7.3)
Pneumonia	35 (6.6)	19 (7.4)	41 (6.4)	75 (4.9)
Gastrointestinal disorders	12 (2.2)	4 (1.6)	18 (2.8)	95 (6.2)
Dysphagia	2 (0.4)	0 (0.0)	3 (0.5)	16 (1.0)
Blood and lymphatic system disorders	5 (0.9)	36 (14.0)	5 (0.8)	11 (0.7)
Anaemia	2 (0.4)	5 (1.9)	2 (0.3)	4 (0.3)
Febrile neutropenia	0 (0.0)	21 (8.1)	0 (0.0)	0 (0.0)
Leukopenia	0 (0.0)	6 (2.3)	0 (0.0)	0 (0.0)
Neutropenia	0 (0.0)	11 (4.3)	0 (0.0)	0 (0.0)
Investigations	5 (0.9)	11 (4.3)	6 (0.9)	20 (1.3)
Neutrophil count decreased	0 (0.0)	8 (3.1)	0 (0.0)	0 (0.0)
White blood cell count decreased	0 (0.0)	4 (1.6)	0 (0.0)	0 (0.0)

Table 112: Treatment-related SAEs by SOC and PT (≥1% patents in any group)

	303 Study		2L+ NSCLC	
System Organ Class Preferred Term	**Tislelizumab (N=534) n (%)**	**Docetaxel (N=258) n (%)**	**All (N=636) n (%)**	**200 mg Q3W All Indications (N=1534) n (%)**
Patients with at least one Treatment-related Serious TEAE	67 (12.5)	59 (22.9)	78 (12.3)	175 (11.4)
Respiratory, thoracic and mediastinal disorders	36 (6.7)	3 (1.2)	38 (6.0)	61 (4.0)
Pneumonitis	14 (2.6)	0 (0.0)	16 (2.5)	23 (1.5)
Immune-mediated pneumonitis	7 (1.3)	0 (0.0)	7 (1.1)	12 (0.8)

System Organ Class Preferred Term	303 Study Tislelizumab (N=534) n (%)	303 Study Docetaxel (N=258) n (%)	2L+ NSCLC All (N=636) n (%)	200 mg Q3W All Indications (N=1534) n (%)
Interstitial lung disease	7 (1.3)	0 (0.0)	7 (1.1)	10 (0.7)
Infections and infestations	4 (0.7)	13 (5.0)	6 (0.9)	18 (1.2)
Pneumonia	4 (0.7)	11 (4.3)	5 (0.8)	16 (1.0)
Investigations	4 (0.7)	11 (4.3)	5 (0.8)	13 (0.8)
Neutrophil count decreased	0 (0.0)	8 (3.1)	0 (0.0)	0 (0.0)
White blood cell count decreased	0 (0.0)	4 (1.6)	0 (0.0)	0 (0.0)
Blood and lymphatic system disorders	3 (0.6)	36 (14.0)	3 (0.5)	6 (0.4)
Anaemia	1 (0.2)	5 (1.9)	1 (0.2)	2 (0.1)
Febrile neutropenia	0 (0.0)	21 (8.1)	0 (0.0)	0 (0.0)
Leukopenia	0 (0.0)	6 (2.3)	0 (0.0)	0 (0.0)
Neutropenia	0 (0.0)	11 (4.3)	0 (0.0)	0 (0.0)

Deaths

Table 113: TEAEs leading to death by SOC and PT; all-cause and related (Study 303)

System Organ Class Preferred Term	Study 303 Tislelizumab (N = 534) n (%)	Study 303 Docetaxel (N = 258) n (%)	Study 303 Tislelizumab (N=534) n (%)	Study 303 Docetaxel (N=258) n (%)
	Patients with at least one TEAE leading to death		Patients with at least one treatment-**related** TEAE leading to death	
	32 (6.0)	11 (4.3)	8 (1.5)	4 (1.6)
Respiratory, thoracic and mediastinal disorders	12 (2.2)	3 (1.2)	3 (0.6)	
Respiratory failure	5 (0.9)	0 (0.0)	2 (0.4)	
Acute respiratory failure	2 (0.4)	0 (0.0)		
Pleural effusion	1 (0.2)	0 (0.0)		
Pneumonitis	1 (0.2)	0 (0.0)	1 (0.2)	
Pulmonary haemorrhage	1 (0.2)	0 (0.0)		
Pulmonary thrombosis	1 (0.2)	0 (0.0)		
Tracheal stenosis	1 (0.2)	0 (0.0)		
Dyspnoea	0 (0.0)	1 (0.4)		
Haemoptysis	0 (0.0)	1 (0.4)		
Hypoxia	0 (0.0)	1 (0.4)		
General disorders and administration site conditions	6 (1.1)	3 (1.2)	3 (0.6)	1 (0.4)
Death	5 (0.9)	2 (0.8)	2 (0.4)	1 (0.4)
Multiple organ dysfunction syndrome	1 (0.2)	0 (0.0)	1 (0.2)	
General physical health deterioration	0 (0.0)	1 (0.4)		
Infections and infestations	6 (1.1)	3 (1.2)	2 (0.4)	2 (0.8)
Pneumonia	6 (1.1)	2 (0.8)	2 (0.4)	1 (0.4)
Septic shock	0 (0.0)	1 (0.4)		1 (0.4)
Cardiac disorders	4 (0.7)	2 (0.8)		1 (0.4)
Acute myocardial infarction	2 (0.4)	0 (0.0)		
Cardiac tamponade	1 (0.2)	0 (0.0)		
Pericardial effusion	1 (0.2)	0 (0.0)		
Acute left ventricular failure	0 (0.0)	1 (0.4)		
Cardiogenic shock	0 (0.0)	1 (0.4)		1 (0.4)
Nervous system disorders	3 (0.6)	0 (0.0)		
Cerebral infarction	2 (0.4)	0 (0.0)		

System Organ Class Preferred Term	Study 303 Tislelizumab (N = 534) n (%)	Study 303 Docetaxel (N = 258) n (%)	Study 303 Tislelizumab (N=534) n (%)	Study 303 Docetaxel (N=258) n (%)
Cerebral artery occlusion	1 (0.2)	0 (0.0)		
Hepatobiliary disorders	2 (0.4)	0 (0.0)	1 (0.2)	
Acute hepatic failure	1 (0.2)	0 (0.0)		
Hepatic function abnormal	1 (0.2)	0 (0.0)	1 (0.2)	
Psychiatric disorders	1 (0.2)	0 (0.0)		
Depression	1 (0.2)	0 (0.0)		

Immune-related AEs

Process for the identification of immune-mediated TEAEs

All reported immune-mediated treatment-emergent adverse events (imAEs) in Study 303 were confirmed. The process of identification of confirmed imAE followed a 2-step process:

- Step 1: Generation of Potential imAE List

Potential imAEs were identified using a predefined list of MedDRA preferred terms ("Look-Up List") based on imAE terms from other approved checkpoint inhibitors and published literature.

TEAEs in the tislelizumab arm with a coded MedDRA PT of the Look-Up List are forwarded for medical review provided the following criteria were met:

  - The TEAE started on or after the date in which the first dose of tislelizumab was administered.
  - The TEAE was linked with treatment with systemic corticosteroids, endocrine therapy, or other immunosuppressants recorded on the concomitant medications eCRF page.
  - The systemic corticosteroids, endocrine therapy, or other immunosuppressants linked to the TEAE, must have started on or after the start date, and no later than the end date for the TEAE. With the exception of TEAEs of hyperthyroidism and hypothyroidism, systemic corticosteroids must have started within 30 days of the TEAE start date.

- Step 2: Medical Evaluation of Potential imAE

All potential imAEs are reviewed by two medical reviewers, or individuals with appropriate training and experience in performing medical review. The medical review is performed to rule out clear alternative aetiologies of potential imAE cases identified in Step 1. The two reviewers evaluate potential imAE cases independently. They considered use of systematic steroid or immunosuppressive therapy, outcome of rechallenge, existence of alternative explanation and the investigator´s assessment of the immune-related check box. If there were discrepancies between the 2 reviewers, adjudication was to be made by a third qualified medical reviewer.

Frequency of immune-mediated TEAEs – Study 303

Note: In the following confirmed immune-mediated events (imAEs) are presented.

Table 114: Overall summary of immune-mediated TEAEs

	303 Study	2L+ NSCLC	
Category CTCAE Grade	**Tislelizumab (N=534) n (%)**	**All (N=636) n (%)**	**200 mg Q3W All Indications (N=1534) n (%)**
Patients with at least one Immune-mediated TEAE	104 (19.5)	126 (19.8)	276 (18.0)
Immune-mediated TEAE with Grade 3 or Higher	35 (6.6)	43 (6.8)	81 (5.3)
Serious Immune-mediated TEAE	40 (7.5)	44 (6.9)	90 (5.9)
Immune-mediated TEAE Leading to Treatment Modification	28 (5.2)	34 (5.3)	89 (5.8)
Immune-mediated TEAE Leading to Treatment Discontinuation	23 (4.3)	29 (4.6)	53 (3.5)
Immune-mediated TEAE Leading to Death	2 (0.4)	3 (0.5)	6 (0.4)
Immune-mediated TEAE Treated with Systemic Steroids	63 (11.8)	78 (12.3)	161 (10.5)
Immune-mediated TEAE Treated with Immunosuppressants	4 (0.7)	4 (0.6)	5 (0.3)
Immune-mediated TEAE Treated with Hormone Therapy	48 (9.0)	56 (8.8)	132 (8.6)

Table 115: ImAEs by category

	303 Study	2L+ NSCLC	
Category Preferred Term	**Tislelizumab (N=534) n (%)**	**All (N=636) n (%)**	**200 mg Q3W All Indications (N=1534) n (%)**
Patients with at least one Immune-mediated TEAE	104 (19.5)	126 (19.8)	276 (18.0)
Immune-mediated hypothyroidism	42 (7.9)	49 (7.7)	116 (7.6)
Immune-mediated pneumonitis	33 (6.2)	38 (6.0)	66 (4.3)
Immune-mediated skin adverse reaction	8 (1.5)	12 (1.9)	27 (1.8)
Immune-mediated hepatitis	7 (1.3)	11 (1.7)	26 (1.7)
Immune-mediated myositis/rhabdomyolysis	7 (1.3)	7 (1.1)	14 (0.9)
Immune-mediated thyroiditis	6 (1.1)	6 (0.9)	12 (0.8)
Immune-mediated nephritis and renal dysfunction	5 (0.9)	5 (0.8)	10 (0.7)
Immune-mediated colitis	4 (0.7)	5 (0.8)	11 (0.7)
Other immune-mediated reactions (Arthritis, imArthritis, Pericarditis, PMR)	3 (0.6)	4 (0.6)	4 (0.3)
Immune-mediated adrenal insufficiency	2 (0.4)	2 (0.3)	4 (0.3)
Immune-mediated myocarditis	2 (0.4)	3 (0.5)	7 (0.5)
Immune-mediated type 1 diabetes mellitus	2 (0.4)	2 (0.3)	6 (0.4)
Immune-mediated hyperthyroidism	1 (0.2)	4 (0.6)	5 (0.3)
Immune-mediated pancreatitis	0 (0.0)	0 (0.0)	1 (0.1)
Immune-mediated pituitary dysfunction	0 (0.0)	0 (0.0)	1 (0.1)

Table 116: Grade ≥ 3 imAEs by category and maximum severity

	303 Study	2L+ NSCLC	
Category CTCAE Grade	**Tislelizumab (N=534) n (%)**	**All (N=636) n (%)**	**200 mg Q3W All Indications (N=1534) n (%)**
Patients with at least one Immune-mediated TEAE	104 (19.5)	126 (19.8)	276 (18.0)
Immune-mediated hypothyroidism	42 (7.9)	49 (7.7)	116 (7.6)
Grade 3	0 (0.0)	0 (0.0)	0 (0.0)
Grade 4	0 (0.0)	0 (0.0)	1 (0.1)
Immune-mediated pneumonitis	33 (6.2)	38 (6.0)	66 (4.3)
Grade 3	13 (2.4)	14 (2.2)	23 (1.5)
Grade 4	5 (0.9)	5 (0.8)	5 (0.3)
Grade 5	2 (0.4)	3 (0.5)	3 (0.2)
Immune-mediated skin adverse reaction	8 (1.5)	12 (1.9)	27 (1.8)
Grade 3	2 (0.4)	4 (0.6)	5 (0.3)
Grade 4	1 (0.2)	1 (0.2)	4 (0.3)
Immune-mediated hepatitis	7 (1.3)	11 (1.7)	26 (1.7)
Grade 3	3 (0.6)	5 (0.8)	14 (0.9)
Grade 4	1 (0.2)	1 (0.2)	1 (0.1)
Grade 5	0 (0.0)	0 (0.0)	2 (0.1)
Immune-mediated myositis/rhabdomyolysis	7 (1.3)	7 (1.1)	14 (0.9)
Grade 3	2 (0.4)	2 (0.3)	5 (0.3)
Grade 4	0 (0.0)	0 (0.0)	1 (0.1)
Immune-mediated nephritis and renal dysfunction	5 (0.9)	5 (0.8)	10 (0.7)
Grade 3	1 (0.2)	1 (0.2)	3 (0.2)
Grade 4	2 (0.4)	2 (0.3)	2 (0.1)
Grade 5	0 (0.0)	0 (0.0)	1 (0.1)
Immune-mediated colitis	4 (0.7)	5 (0.8)	11 (0.7)
Grade 3	1 (0.2)	2 (0.3)	2 (0.1)
Immune-mediated adrenal insufficiency	2 (0.4)	2 (0.3)	4 (0.3)
Grade 3	1 (0.2)	1 (0.2)	1 (0.1)
Grade 4	1 (0.2)	1 (0.2)	1 (0.1)
Immune-mediated myocarditis	2 (0.4)	3 (0.5)	7 (0.5)
Grade 3	0 (0.0)	1 (0.2)	3 (0.2)
Grade 4	1 (0.2)	1 (0.2)	1 (0.1)
Immune-mediated type 1 diabetes mellitus	2 (0.4)	2 (0.3)	6 (0.4)
Grade 3	2 (0.4)	2 (0.3)	5 (0.3)
Immune-mediated pancreatitis	0 (0.0)	0 (0.0)	1 (0.1)
Grade 3	0 (0.0)	0 (0.0)	1 (0.1)

Patients with multiple events for a given category are counted only once at the worst toxicity grade for the category.

Table 117: Time-to-onset of imTEAEs in tislelizumab arm (Study 303)

imAE category	Number of events in category	< 3 months Events (%)	3 to < 6 months Events (%)	6 to < 9 months Events (%)	9 to < 12 months Events (%)	≥ 12 months Events (%)
Immune-mediated hypothyroidism	54	15 (27.8)	22 (40.7)	4 (7.4)	0	13 (24.1)
Immune-mediated pneumonitis	34	12 (35.3)	9 (26.5)	7 (20.6)	3 (8.8)	3 (8.8)
Immune-mediated hepatitis	7	6 (85.7)	1 (14.3)	0	0	0
Immune-mediated myositis/rhabdomyolysis	7	3 (42.9)	1 (14.3)	2 (28.6)	0	1 (14.3)
Immune-mediated thyroiditis	10	4 (40.0)	0	1 (10.0)	2 (20.0)	3 (30.0)
Immune-mediated nephritis and renal dysfunction	5	4 (80.0)	1 (20.0)	0	0	0
Immune-mediated skin adverse reactions	8	5 (62.5)	1 (12.5)	2 (25.0)	0	0
Other immune-mediated reactions	3	2 (66.7)	1 (33.3)	0	0	0
Immune-mediated colitis	4	2 (50.0)	0	1 (25.0)	0	1 (25.0)
Immune-mediated adrenal insufficiency	2	1 (50.0)	1 (50.0)	0	0	0
Immune-mediated myocarditis	2	1 (50.0)	0	1 (50.0)	0	0
Immune-mediated hyperthyroidism	1	0	0	0	0	1 (100)
Immune-mediated type 1 diabetes mellitus	2	0	1 (50.0)	1 (50.0)	0	0

Table 118: Percentage of imAE events resolved and resolving by imAE category (Tislelizumab 200 mg Q3W, All indications, Safety Analysis Set)

	Tislelizumab 200 mg Q3W – All Indications N = 1534				
	Patient-based analysis		Event-based analysis		
imAE category	n	Resolved [a]	n	Resolved [b] (%)	Resolving [b] (%)
Immune-mediated pancreatitis	1	1 (100.0)	1	1 (100.0)	0
Immune-mediated colitis	11	9 (81.8)	11	9 (81.8)	1 (9.1)
Immune-mediated hyperthyroidism	5	4 (80.0)	5	4 (80.0)	0
Immune-mediated myositis/rhabdomyolysis	14	8 (57.1)	16	10 (62.5)	0
Immune-mediated myocarditis	7	4 (57.1)	7	4 (57.1)	1 (14.3)
Immune-mediated skin adverse reaction	27	14 (51.9)	31	16 (51.6)	6 (19.4)
Immune-mediated nephritis and renal dysfunction	10	5 (50.0)	10	5 (50.0)	3 (30.0)
Immune-mediated hepatitis	26	13 (50.0)	40	25 (62.5)	5 (12.5)
Immune-mediated pneumonitis	66	30 (45.5)	68	32 (47.1)	15 (22.1)
Immune-mediated hypothyroidism	116	37 (31.9)	138	59 (42.8)	25 (18.1)
Immune-mediated adrenal insufficiency	4	1 (25.0)	4	1 (25.0)	1 (25.0)
Immune-mediated thyroiditis	12	2 (16.7)	17	6 (35.3)	3 (17.6)
Immune-mediated type 1 diabetes mellitus	6	1 (16.7)	7	2 (28.6)	2 (28.6)
Immune-mediated pituitary dysfunction	1	0	1	0	0
Other immune-mediated reactions	4	2 (50.0)	4	2 (50.0)	0

Resolved includes both 'Recovered/resolved' and 'Recovered/resolved with sequelae' in the CRF.

[a] A patient was considered as resolved in a category if, and only if, all events in the category from this patient were resolved. Percentage was based on the number of patients with at least one immune-mediated adverse event in the category.

[b] Percentages were based on the number of immune-mediated adverse events in the category.

Potential immune-mediated TEAEs

Step 2 of the imAE adjudication process, the medical review of each imAE candidate, was applied only to the tislelizumab arm due to the open-label of the study design. Thus, a direct comparison of imAEs between the tislelizumab and docetaxel arms is not possible.

However, to allow an indirect comparison between the two treatment arms, data were provided for potential imAEs (selected in Step 1) in both arms of Study 303 following targeted re-adjudication.

Table 119: Overall summary of potential immune-mediated TEAEs (Study 303)

Category	Tislelizumab (N = 534) n (%)	Docetaxel (N = 258) n (%)
Patients with at least one Immune-mediated TEAE	**126 (23.6)**	**11 (4.3)**
Immune-mediated TEAE with Grade 3 or higher	48 (9.0)	9 (3.5)
Serious Immune-mediated TEAE	55 (10.3)	6 (2.3)
Immune-mediated TEAE leading to treatment modification	33 (6.2)	4 (1.6)
Immune-mediated TEAE leading to treatment discontinuation	30 (5.6)	1 (0.4)
Immune-mediated TEAE leading to death	9 (1.7)	2 (0.8)
Immune-mediated TEAE treated with systemic steroids	77 (14.4)	8 (3.1)
Immune-mediated TEAE treated with immunosuppressant	4 (0.7)	0 (0.0)
Immune-mediated TEAE treated with hormone therapy	55 (10.3)	3 (1.2)

The most commonly reported potential imAEs by PT in the tislelizumab arm were hypothyroidism (42 patients, 7.9% vs. 1 patient, 0.4% in the docetaxel arm) and pneumonitis (18 patients, 3.4% vs. 0 patients in the docetaxel arm). The most common potential imAE in the docetaxel arm was pneumonia (16 patients, 3% in the tislelizumab arm vs. 9 patients, 3.5% in the docetaxel arm). The only other potential imAEs reported in the docetaxel arm were hyperglycaemia and hypothyroidism in 1 patient each.

Infusion-related reactions

Table 120: Overall summary of infusion-related reactions (IRR)

	Study 303		2L+NSCLC	
Category	Tislelizumab (N = 534) n (%)	Docetaxel (N = 258) n (%)	All (N = 636) n (%)	200 mg Q3W All Indications (N = 1534) n (%)
Patients with at least one IRR	5 (0.9)	9 (3.5)	7 (1.1)	54 (3.5)
IRR on with Grade ≥3	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.3)
- Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.3)
Serious IRR	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.2)
IRR leading to treatment modification	4 (0.7)	5 (1.9)	5 (0.8)	7 (0.5)
IRR leading to treatment discontinuation	0 (0.0)	1 (0.4)	0 (0.0)	2 (0.1)
IRR leading to death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Resolved IRR [a]	5 (0.9)	8 (3.1)	7 (1.1)	51 (3.3)

a A patient was considered as resolved if all the events were resolved.

- ***Combination therapy 1L***

SAEs

Table 121: SAES by SOC and PT (≥1% patients in NSCLC T+Chemo group (combination therapy group))

	SQ-NSCLC			NSQ-NSCLC		NSCLC	
System Organ Class Preferred Term	**307 T+PC (N = 120) n (%)**	**307 T+nPC (N = 118) n (%)**	**307 PC (N = 117) n (%)**	**304 T+PP (N = 222) n (%)**	**304 PP (N = 110) n (%)**	**307&304&206 T+chemo (N = 497) n (%)**	**307&304 chemo (N = 227) n (%)**
Patients With at Least One Serious TEAE	52 (43.3)	50 (42.4)	29 (24.8)	87 (39.2)	25 (22.7)	199 (40.0)	54 (23.8)
Respiratory, thoracic and mediastinal disorders	14 (11.7)	16 (13.6)	4 (3.4)	30 (13.5)	3 (2.7)	64 (12.9)	7 (3.1)
Pneumonitis	6 (5.0)	5 (4.2)	0 (0.0)	15 (6.8)	1 (0.9)	28 (5.6)	1 (0.4)
Haemoptysis	4 (3.3)	4 (3.4)	1 (0.9)	4 (1.8)	0 (0.0)	12 (2.4)	1 (0.4)
Dyspnoea	1 (0.8)	0 (0.0)	0 (0.0)	5 (2.3)	0 (0.0)	7 (1.4)	0 (0.0)
Infections and infestations	14 (11.7)	12 (10.2)	7 (6.0)	16 (7.2)	6 (5.5)	42 (8.5)	13 (5.7)
Pneumonia	12 (10.0)	6 (5.1)	5 (4.3)	12 (5.4)	6 (5.5)	30 (6.0)	11 (4.8)
Blood and lymphatic system disorders	8 (6.7)	10 (8.5)	6 (5.1)	12 (5.4)	6 (5.5)	32 (6.4)	12 (5.3)
Thrombocytopenia	2 (1.7)	1 (0.8)	3 (2.6)	7 (3.2)	3 (2.7)	10 (2.0)	6 (2.6)
Febrile neutropenia	2 (1.7)	4 (3.4)	1 (0.9)	1 (0.5)	0 (0.0)	7 (1.4)	1 (0.4)
Anaemia	1 (0.8)	1 (0.8)	2 (1.7)	3 (1.4)	2 (1.8)	5 (1.0)	4 (1.8)
Investigations	7 (5.8)	8 (6.8)	3 (2.6)	11 (5.0)	4 (3.6)	28 (5.6)	7 (3.1)
Neutrophil count decreased	4 (3.3)	4 (3.4)	2 (1.7)	2 (0.9)	0 (0.0)	10 (2.0)	2 (0.9)
Platelet count decreased	1 (0.8)	2 (1.7)	0 (0.0)	5 (2.3)	2 (1.8)	10 (2.0)	2 (0.9)
Aspartate aminotransferase increased	2 (1.7)	0 (0.0)	0 (0.0)	3 (1.4)	1 (0.9)	5 (1.0)	1 (0.4)
Gastrointestinal disorders	3 (2.5)	4 (3.4)	2 (1.7)	12 (5.4)	1 (0.9)	20 (4.0)	3 (1.3)
General disorders and administration site conditions	7 (5.8)	3 (2.5)	7 (6.0)	9 (4.1)	4 (3.6)	19 (3.8)	11 (4.8)
Pyrexia	2 (1.7)	1 (0.8)	2 (1.7)	5 (2.3)	3 (2.7)	8 (1.6)	5 (2.2)
Nervous system disorders	5 (4.2)	1 (0.8)	0 (0.0)	8 (3.6)	2 (1.8)	15 (3.0)	2 (0.9)
Cerebral infarction	1 (0.8)	1 (0.8)	0 (0.0)	2 (0.9)	0 (0.0)	5 (1.0)	0 (0.0)
Metabolism and nutrition disorders	1 (0.8)	4 (3.4)	0 (0.0)	7 (3.2)	0 (0.0)	12 (2.4)	0 (0.0)
Cardiac disorders	1 (0.8)	2 (1.7)	2 (1.7)	7 (3.2)	0 (0.0)	11 (2.2)	2 (0.9)
Hepatobiliary disorders	1 (0.8)	3 (2.5)	1 (0.9)	3 (1.4)	0 (0.0)	9 (1.8)	1 (0.4)
Injury, poisoning and procedural complications	2 (1.7)	3 (2.5)	0 (0.0)	1 (0.5)	0 (0.0)	6 (1.2)	0 (0.0)
Renal and urinary disorders	0 (0.0)	2 (1.7)	0 (0.0)	4 (1.8)	0 (0.0)	6 (1.2)	0 (0.0)
Skin and subcutaneous tissue disorders	4 (3.3)	1 (0.8)	1 (0.9)	0 (0.0)	0 (0.0)	5 (1.0)	1 (0.4)

Treatment-related SAEs

Table 122: SAES related to tislelizumab by SOC and PT

	SQ-NSCLC		NSQ-NSCLC	NSCLC
System Organ Class Preferred Term	**307 T+PC (N = 120) n (%)**	**307 T+nPC (N = 118) n (%)**	**304 T+PP (N = 222) n (%)**	**307&304&206 T+chemo* (N = 497) n (%)**
Patients With at Least One Serious TEAE Related to Tislelizumab	25 (20.8)	22 (18.6)	41 (18.5)	95 (19.1)
Respiratory, thoracic and mediastinal disorders	8 (6.7)	8 (6.8)	15 (6.8)	35 (7.0)
Pneumonitis	5 (4.2)	4 (3.4)	15 (6.8)	26 (5.2)
Immune-mediated pneumonitis	1 (0.8)	2 (1.7)	0 (0.0)	4 (0.8)
Interstitial lung disease	1 (0.8)	2 (1.7)	0 (0.0)	3 (0.6)
Dyspnoea	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Pleural effusion	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)
Pneumothorax	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.2)
Blood and lymphatic system disorders	4 (3.3)	3 (2.5)	6 (2.7)	14 (2.8)
Thrombocytopenia	2 (1.7)	1 (0.8)	2 (0.9)	5 (1.0)
Anaemia	1 (0.8)	0 (0.0)	2 (0.9)	3 (0.6)
Bone marrow failure	1 (0.8)	1 (0.8)	0 (0.0)	2 (0.4)
Febrile neutropenia	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.2)
Hypofibrinogenaemia	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.2)
Immune-mediated pancytopenia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Leukopenia	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.2)
Lymphadenitis	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)
Pancytopenia	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)
Investigations	4 (3.3)	3 (2.5)	7 (3.2)	14 (2.8)
Aspartate aminotransferase increased	2 (1.7)	0 (0.0)	3 (1.4)	5 (1.0)
Alanine aminotransferase increased	1 (0.8)	0 (0.0)	3 (1.4)	4 (0.8)
Neutrophil count decreased	2 (1.7)	1 (0.8)	0 (0.0)	3 (0.6)
Platelet count decreased	0 (0.0)	0 (0.0)	3 (1.4)	3 (0.6)
Blood creatine phosphokinase increased	0 (0.0)	2 (1.7)	0 (0.0)	2 (0.4)
Electrocardiogram ST-T segment abnormal	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.2)
Gamma-glutamyltransferase increased	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)
Infections and infestations	3 (2.5)	2 (1.7)	5 (2.3)	10 (2.0)
Pneumonia	2 (1.7)	1 (0.8)	3 (1.4)	6 (1.2)
Infection	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.2)
Lymph gland infection	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)
Pyelonephritis acute	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.2)
Rash pustular	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)
Gastrointestinal disorders	1 (0.8)	2 (1.7)	5 (2.3)	9 (1.8)
Immune-mediated enterocolitis	0 (0.0)	0 (0.0)	3 (1.4)	3 (0.6)
Ascites	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.2)
Chronic gastritis	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)
Colitis	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.2)
Diarrhoea	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.2)

	SQ-NSCLC		NSQ-NSCLC	NSCLC
System Organ Class Preferred Term	**307 T+PC (N = 120) n (%)**	**307 T+nPC (N = 118) n (%)**	**304 T+PP (N = 222) n (%)**	**307&304&206 T+chemo* (N = 497) n (%)**
Stomatitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Vomiting	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)
Cardiac disorders	1 (0.8)	1 (0.8)	4 (1.8)	7 (1.4)
Myocarditis	0 (0.0)	1 (0.8)	2 (0.9)	4 (0.8)
Immune-mediated myocarditis	1 (0.8)	0 (0.0)	1 (0.5)	2 (0.4)
Right ventricular failure	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)
General disorders and administration site conditions	4 (3.3)	1 (0.8)	2 (0.9)	7 (1.4)
Pyrexia	2 (1.7)	0 (0.0)	1 (0.5)	3 (0.6)
Chest discomfort	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.2)
Death	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.2)
Malaise	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.2)
Non-cardiac chest pain	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)
Metabolism and nutrition disorders	1 (0.8)	3 (2.5)	2 (0.9)	6 (1.2)
Decreased appetite	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.2)
Diabetes mellitus	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)
Hyperkalaemia	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)
Hypoalbuminaemia	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.2)
Hypoproteinaemia	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.2)
Type 1 diabetes mellitus	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.2)
Hepatobiliary disorders	0 (0.0)	2 (1.7)	1 (0.5)	5 (1.0)
Immune-mediated hepatitis	0 (0.0)	1 (0.8)	1 (0.5)	3 (0.6)
Hepatic failure	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.2)
Hepatic function abnormal	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Nervous system disorders	2 (1.7)	0 (0.0)	2 (0.9)	4 (0.8)
Guillain-Barre syndrome	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)
Hydrocephalus	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.2)
Immune-mediated encephalitis	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.2)
Neuralgia	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)
Skin and subcutaneous tissue disorders	4 (3.3)	0 (0.0)	0 (0.0)	4 (0.8)
Rash	2 (1.7)	0 (0.0)	0 (0.0)	2 (0.4)
Drug eruption	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.2)
Rash erythematous	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.2)
Renal and urinary disorders	0 (0.0)	1 (0.8)	2 (0.9)	3 (0.6)
Acute kidney injury	0 (0.0)	1 (0.8)	1 (0.5)	2 (0.4)
Tubulointerstitial nephritis	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)
Musculoskeletal and connective tissue disorders	0 (0.0)	0 (0.0)	1 (0.5)	2 (0.4)
Myositis	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)
Rhabdomyolysis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Endocrine disorders	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.2)
Autoimmune thyroiditis	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.2)

Deaths

Table 123: TEAEs leading to death by SOC and PT

	SQ-NSCLC			NSQ-NSCLC		NSCLC	
System Organ Class Preferred Term	**307 T+PC (N = 120) n (%)**	**307 T+nPC (N = 118) n (%)**	**307 PC (N = 117) n (%)**	**304 T+PP (N = 222) n (%)**	**304 PP (N = 110) n (%)**	**307&304&206 T+chemo* (N = 497) n (%)**	**307&304 chemo** (N = 227) n (%)**
Patients With at Least One TEAE Leading to Death	4 (3.3)	7 (5.9)	5 (4.3)	9 (4.1)	2 (1.8)	21 (4.2)	7 (3.1)
Respiratory, thoracic and mediastinal disorders	2 (1.7)	2 (1.7)	0 (0.0)	5 (2.3)	1 (0.9)	10 (2.0)	1 (0.4)
Pneumonitis	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.4)	1 (0.9)	3 (0.6)	1 (0.4)
Dyspnoea	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	2 (0.4)	0 (0.0)
Haemoptysis	1 (0.8)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)
Respiratory failure	1 (0.8)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)
Asphyxia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.2)	0 (0.0)
Cardiac disorders	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.9)	0 (0.0)	3 (0.6)	0 (0.0)
Myocarditis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	2 (0.4)	0 (0.0)
Atrial fibrillation	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.2)	0 (0.0)
General disorders and administration site conditions	0 (0.0)	2 (1.7)	3 (2.6)	1 (0.5)	0 (0.0)	3 (0.6)	3 (1.3)
Death	0 (0.0)	2 (1.7)	2 (1.7)	1 (0.5)	0 (0.0)	3 (0.6)	2 (0.9)
Multiple organ dysfunction syndrome	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Nervous system disorders	2 (1.7)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	3 (0.6)	0 (0.0)
Cerebellar haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.2)	0 (0.0)
Cerebrovascular accident	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Hydrocephalus	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Hepatobiliary disorders	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Hepatic failure	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Infections and infestations	0 (0.0)	1 (0.8)	2 (1.7)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.9)
Pneumonia	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Septic shock	0 (0.0)	0 (0.0)	2 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.9)
Metabolism and nutrition disorders	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Hypokalaemia	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Musculoskeletal and connective tissue disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Rhabdomyolysis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Vascular disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.4)
Embolism	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.4)

Related AEs leading to death

TEAEs leading to death that were considered to be **related to tislelizumab** were reported for a total of 8 patients (1.6%), including 4 patients in the Study 304 T+PP group (3 with pneumonitis and 1 patient with myocarditis), 2 patients in the Study 307 T+nPC group (1 each with death with no cause given and hepatic failure), 1 patient in the Study 307 T+PC group (hydrocephalus) and 1 patient in the Study 206 T+chemo group (dyspnoea and myocarditis).

TEAEs leading to death that were considered to be **related to chemotherapy** were reported for a total of 4 patients (0.8%) in the NSCLC T+chemo group (1 patient each with death with no cause given, hepatic failure, hydrocephalus and pneumonitis) and 4 patients (1.8%) in the NSCLC chemo group (2 patients with septic shock and 1 patient each with death with no cause given and pneumonitis).

Immune-related AEs

Frequency of immune-mediated TEAEs

Note: In the following confirmed immune-mediated events (imAEs) for the 1L combination treatment are presented. The methodology of identifying imAEs is presented and discussed subsequently.

Table 124: Overall summary of immune-mediated TEAEs

	SQ-NSCLC		NSQ-NSCLC	NSCLC
	307 T+PC (N = 120) n (%)	307 T+nPC (N = 118) n (%)	304 T+PP (N = 222) n (%)	307&304&206 T+chemo* (N = 497) n (%)
Patients With at Least One imAE	36 (30.0)	30 (25.4)	55 (24.8)	127 (25.6)
imAE with Grade ≥ 3	13 (10.8)	12 (10.2)	24 (10.8)	52 (10.5)
Serious imAE	13 (10.8)	14 (11.9)	23 (10.4)	54 (10.9)
imAE Leading to Permanent Discontinuation of tislelizumab	8 (6.7)	8 (6.8)	18 (8.1)	38 (7.6)
imAE Leading to tislelizumab Modification	14 (11.7)	18 (15.3)	27 (12.2)	62 (12.5)
imAE Leading to Death	0 (0.0)	1 (0.8)	4 (1.8)	6 (1.2)
imAE Treated with Systemic Steroids	22 (18.3)	22 (18.6)	38 (17.1)	87 (17.5)
imAE Treated with Immunosuppressants	1 (0.8)	1 (0.8)	4 (1.8)	6 (1.2)
imAE Treated with Hormone Therapy	18 (15.0)	11 (9.3)	22 (9.9)	53 (10.7)

Table 125: ImAEs by category

	SQ-NSCLC		NSQ-NSCLC	NSCLC
imAE Category Preferred Term	**307 T+PC (N = 120) n (%)**	**307 T+nPC (N = 118) n (%)**	**304 T+PP (N = 222) n (%)**	**307&304&206 T+chemo* (N = 497) n (%)**
Patients With at Least One imAE	36 (30.0)	30 (25.4)	55 (24.8)	127 (25.6)
Immune-Mediated Hypothyroidism	15 (12.5)	9 (7.6)	19 (8.6)	45 (9.1)
Immune-Mediated Pneumonitis	9 (7.5)	12 (10.2)	21 (9.5)	45 (9.1)
Immune-Mediated Skin Adverse Reaction	7 (5.8)	5 (4.2)	7 (3.2)	19 (3.8)
Immune-Mediated Hepatitis	1 (0.8)	3 (2.5)	3 (1.4)	8 (1.6)
Immune-Mediated Colitis	2 (1.7)	1 (0.8)	4 (1.8)	7 (1.4)
Immune-Mediated Myocarditis	1 (0.8)	2 (1.7)	3 (1.4)	7 (1.4)
Immune-Mediated Myositis/Rhabdomyolysis	1 (0.8)	3 (2.5)	1 (0.5)	6 (1.2)
Immune-Mediated Nephritis And Renal Dysfunction	0 (0.0)	3 (2.5)	2 (0.9)	5 (1.0)
Immune-Mediated Type 1 Diabetes Mellitus	0 (0.0)	1 (0.8)	4 (1.8)	5 (1.0)
Immune-Mediated Hyperthyroidism	0 (0.0)	1 (0.8)	2 (0.9)	3 (0.6)
Immune-Mediated Nervous System Disorder	1 (0.8)	0 (0.0)	1 (0.5)	2 (0.4)

imAE Category Preferred Term	SQ-NSCLC 307 T+PC (N = 120) n (%)	SQ-NSCLC 307 T+nPC (N = 118) n (%)	NSQ-NSCLC 304 T+PP (N = 222) n (%)	NSCLC 307&304&206 T+chemo* (N = 497) n (%)
Immune-Mediated Thyroiditis	2 (1.7)	0 (0.0)	0 (0.0)	2 (0.4)

Table 126: Grade ≥ 3 imAEs by category and maximum grade

	SQ-NSCLC		NSQ-NSCLC	NSCLC
imAE Category Maximum Grade	**307 T+PC (N=120) n (%)**	**307 T+nPC (N=118) n (%)**	**304 T+PP (N=222) n (%)**	**307&304&206 T+chemo* (N=497) n (%)**
Patients With at Least One imAE	36 (30.0)	30 (25.4)	55 (24.8)	127 (25.6)
Immune-Mediated Pneumonitis	9 (7.5)	12 (10.2)	21 (9.5)	45 (9.1)
Grade 3	4 (3.3)	5 (4.2)	5 (2.3)	15 (3.0)
Grade 4	0 (0.0)	1 (0.8)	1 (0.5)	2 (0.4)
Grade 5	0 (0.0)	0 (0.0)	3 (1.4)	3 (0.6)
Immune-Mediated Skin Adverse Reaction	7 (5.8)	5 (4.2)	7 (3.2)	19 (3.8)
Grade 3	5 (4.2)	2 (1.7)	4 (1.8)	11 (2.2)
Immune-Mediated Hepatitis	1 (0.8)	3 (2.5)	3 (1.4)	8 (1.6)
Grade 3	1 (0.8)	1 (0.8)	3 (1.4)	6 (1.2)
Grade 5	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.2)
Immune-Mediated Colitis	2 (1.7)	1 (0.8)	4 (1.8)	7 (1.4)
Grade 3	0 (0.0)	1 (0.8)	2 (0.9)	3 (0.6)
Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Immune-Mediated Myocarditis	1 (0.8)	2 (1.7)	3 (1.4)	7 (1.4)
Grade 3	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)
Grade 4	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)
Grade 5	0 (0.0)	0 (0.0)	1 (0.5)	2 (0.4)
Immune-Mediated Myositis/Rhabdomyolysis	1 (0.8)	3 (2.5)	1 (0.5)	6 (1.2)
Grade 3	1 (0.8)	1 (0.8)	1 (0.5)	3 (0.6)
Grade 4	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.2)
Grade 5	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Immune-Mediated Nephritis And Renal Dysfunction	0 (0.0)	3 (2.5)	2 (0.9)	5 (1.0)
Grade 3	0 (0.0)	1 (0.8)	1 (0.5)	2 (0.4)
Immune-Mediated Type 1 Diabetes Mellitus	0 (0.0)	1 (0.8)	4 (1.8)	5 (1.0)
Grade 3	0 (0.0)	0 (0.0)	3 (1.4)	3 (0.6)
Grade 4	0 (0.0)	1 (0.8)	1 (0.5)	2 (0.4)
Immune-Mediated Nervous System Disorder	1 (0.8)	0 (0.0)	1 (0.5)	2 (0.4)
Grade 3	1 (0.8)	0 (0.0)	1 (0.5)	2 (0.4)
Immune-Mediated Thyroiditis	2 (1.7)	0 (0.0)	0 (0.0)	2 (0.4)
Grade 3	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.2)

Table 127: ImAEs leading to permanent discontinuation of tislelizumab

	SQ-NSCLC		NSQ-NSCLC	NSCLC
imAE Category Preferred Term	307 T+PC (N = 120) n (%)	307 T+nPC (N = 118) n (%)	304 T+PP (N = 222) n (%)	307&304&206 T+chemo* (N = 497) n (%)
Patients with at least one Immune-mediated TEAE Leading to Permanent Discontinuation of Tislelizumab	8 (6.7)	8 (6.8)	18 (8.1)	38 (7.6)
Immune-Mediated Pneumonitis	5 (4.2)	4 (3.4)	9 (4.1)	20 (4.0)
Immune-Mediated Myocarditis	1 (0.8)	2 (1.7)	2 (0.9)	6 (1.2)
Immune-Mediated Myositis/Rhabdomyolysis	0 (0.0)	3 (2.5)	1 (0.5)	5 (1.0)
Immune-Mediated Hypothyroidism	1 (0.8)	1 (0.8)	2 (0.9)	4 (0.8)
Immune-Mediated Colitis	0 (0.0)	0 (0.0)	3 (1.4)	3 (0.6)
Immune-Mediated Hepatitis	0 (0.0)	2 (1.7)	0 (0.0)	3 (0.6)
Immune-Mediated Skin Adverse Reaction	0 (0.0)	0 (0.0)	2 (0.9)	2 (0.4)
Immune-Mediated Nervous System Disorder	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.2)

Table 128: ImAEs by outcome and category in combined T+chemo group and monotherapy

imAE category	Number of events in category	Recovered/ resolved	Recovering/ resolving	Not recovered/ not resolved	Fatal	Unknown
		n (%)	n (%)	n (%)	n (%)	n (%)
Immune-mediated hypothyroidism (mono)	155	59 (38.1)	27 (17.4)	69 (44.5)	0	0
Immune-mediated hypothyroidism (combo)	76	47 (61.8)	17 (22.4)	11 (14.5)	0	0
Immune-mediated pneumonitis (mono)	80	40 (50.0)	15 (18.8)	21 (26.3)	4 (5.0)	0
Immune-mediated pneumonitis (combo)	49	21 (42.9)	15 (30.6)	9 (18.4)	3 (6.1)	0
Immune-mediated hepatitis (mono)	58	40 (69.0)	5 (8.6)	11 (19.0)	2 (3.4)	0
Immune-mediated hepatitis (combo)	12	8 (66.7)	3 (25.0)	0	1 (8.3)	0
Immune-mediated skin adverse reactions (mono)	38	21 (55.3)	7 (18.4)	10 (26.3)	0	0
Immune-mediated skin adverse reactions (combo)	20	16 (80.0)	4 (20.0)	0	0	0
Immune-mediated colitis (mono)	23	19 (82.6)	3 (13.0)	1 (4.3)	0	0
Immune-mediated colitis (combo)	7	5 (71.4)	1 (14.3)	1 (14.3)	0	0
Immune-mediated myositis/rhabdomyolysis (mono)	16	10 (62.5)	0	6 (37.5)	0	0
Immune-mediated myositis/rhabdomyolysis (combo)	10	9 (90.0)	0	0	1 (10.0)	0
Immune-mediated hyperthyroidism (mono)	12	11 (91.7)	0	1 (8.3)	0	0
Immune-mediated hyperthyroidism (combo)	4	4 (100)	0	0	0	0
Immune-mediated thyroiditis (mono)	18	7 (38.9)	3 (16.7)	8 (44.4)	0	0
Immune-mediated thyroiditis (combo)	2	1 (50.0)	0	1 (50.0)	0	0
Immune-mediated myocarditis (mono)	7	4 (57.1)	1(14.3)	2 (28.6)	0	0
Immune-mediated myocarditis (combo)	7	4 (57.1)	1 (14.3)	0	2 (28.6)	0
Immune-mediated nephritis and renal dysfunction (mono)	10	5 (50.0)	3 (30.0)	1 (10.0)	1 (10.0)	0
Immune-mediated nephritis and renal dysfunction (combo)	7	4 (57.1)	2 (28.6)	1 (14.3)	0	0
Other immune-mediated reactions (mono)	10	4 (40.0)	6 (60.0)	0	0	0
Other immune-mediated reactions (combo)	0	0	0	0	0	0
Immune-mediated adrenal insufficiency (mono)	6	1 (16.7)	2 (33.3)	3 (50.0)	0	0
Immune-mediated adrenal insufficiency (combo)	0	0	0	0	0	0
Immune-mediated nervous system disorder (mono)	0	0	0	0	0	0
Immune-mediated nervous system disorder (combo)	2	1 (50.0)	0	1 (50.0)	0	0
Immune-mediated pituitary dysfunction (mono)	1	0	0	1 (100.0)	0	0
Immune-mediated pituitary dysfunction (combo)	0	0	0	0	0	0
Immune-mediated type 1 diabetes mellitus (mono)	11	4 (36.4)	2 (18.2)	5 (45.5)	0	0
Immune-mediated type 1 diabetes mellitus (combo)	5	1 (20.0)	2 (40.0)	2 (40.0)	0	0
Immune-mediated pancreatitis (mono)	1	1 (100.0)	0	0	0	0
Immune-mediated pancreatitis (combo)	0	0	0	0	0	0

Potential immune-mediated TEAEs

Please refer to the "Process for the identification of immune-mediated TEAEs" above.

Table 129: <u>Potential</u> immune-mediated TEAEs in combination therapy studies

Category	307 T+PC N=120 n (%)	307 T+nPC N=118 n (%)	307 PC N=117 n (%)	304 T+PP N=222 n (%)	304 PP N=110 n (%)	307,304 & 206 T+chemo *N=497 n (%)	307&304 T+chemo** N=460 n (%)
Patients with at least one im TEAE	43 (35.8)	37 (31.4)	3 (2.6)	62 (27.9)	3 (2.7)	148 (29.8)	142 (30.9)
Im TEAE ≥ Grade 3	14 (11.7)	13 (11.0)	1 (0.9)	29 (13.1)	3 (2.7)	59 (11.9)	56 (12.2)
Serious im TEAE	16 (13.3)	14 (11.9)	3 (2.6)	28 (12.6)	2 (1.8)	62 (12.5)	58 (12.6)
Im TEAE leading to modification	14 (11.7)	19 (16.1)	0 (0.0)	30 (13.3)	0 (0.0)	66 (13.3)	63 (13.7)
Im TEAE leading to discontinuation	9 (7.5)	9 (7.6)	0 (0.0)	19 (8.6)	0 (0.0)	41 (8.2)	37 (8.0)
Im TEAE leading to death	0 (0.0)	2 (1.7)	0 (0.0)	4 (1.8)	1 (0.9)	7 (1.4)	6 (1.3)
Im TEAE treated with systemic steroids	26 (21.7)	27 (22.9)	3 (2.6)	44 (19.8)	2 (1.8)	102 (20.5)	97 (21.1)
Im TEAE treated with immunosuppressants	1 (0.8)	1 (0.8)	0 (0.0)	4 (1.8)	1 (0.9)	6 (1.2)	6 (1.3)
ImTEAE treated with hormone therapy	21 (17.5)	14 (11.9)	0 (0.0)	24 (10.8)	1 (0.9)	61 (12.3)	59 (12.8)

The most commonly reported PTs in the chemotherapy control arm for Studies 304 and 307 were immune-mediated pneumonitis (1.8% and 1.7%, respectively). Other potential imAE reported in the chemotherapy control arms of Study 304 were Type 1 diabetes Mellitus (0.9%), and rash maculopapular (0.9%) in the chemotherapy control arm of Study 307.

<u>Infusion-related reactions</u>

Table 130: Overall summary of infusion-related reactions

	SQ-NSCLC			NSQ-NSCLC		NSCLC	
	307 T+PC (N = 120) n (%)	307 T+nPC (N = 118) n (%)	307 PC (N = 117) n (%)	304 T+PP (N = 222) n (%)	304 PP (N = 110) n (%)	307&304&206 T+chemo* (N = 497) n (%)	307&304 chemo** (N = 227) n (%)
Patient with at least one IRR	5 (4.2)	5 (4.2)	4 (3.4)	2 (0.9)	1 (0.9)	14 (2.8)	5 (2.2)
IRR with Grade ≥ 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
IRR leading to discontinuation	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.4)
IRR leading to dose modification	3 (2.5)	0 (0.0)	3 (2.6)	2 (0.9)	1 (0.9)	6 (1.2)	4 (1.8)

Adverse drugs reactions

Selection of ADRs

The clinical database of the studies where tislelizumab was administered either as monotherapy or combination therapy were screened for ADR candidates using an ADR screening tool. ADR candidates included two types of events namely pre-qualified ADR candidates and ADR candidates identified through numerical screening rules.

Pre-qualified ADR candidates

Pre-qualified ADR candidates were events that are associated with the drug based on current knowledge. Pre-qualified ADR candidates were identified using the eCRS and Excel files produced by the Statistical programming and quantitative Safety groups.

Numerical screening rule to identify other non-pre-qualified ADR candidates

Other ADR candidates were events for which an excess (based on medical review) versus comparator is observed or for which reasonable frequency is observed under tislelizumab. These were identified using a numerical screening rule (i.e. algorithmically), based on all TEAEs. Within the randomised period subset of each pivotal study at MedDRA HLT and PT level the following selection criteria were applied:

- AEs with >2% higher incidence for tislelizumab vs. respective comparator arm
- AEs with lower bound of relative risk (between tislelizumab arm and comparator arm) 95% confidence interval >1.0.
- SAEs with >0.5% difference in incidence for tislelizumab vs. respective comparator arm.
- Drug-related AEs (any drug component) with >0.5% difference in incidence for tislelizumab vs. respective comparator arm.

In addition, based on the respective monotherapy and the combination therapy safety pools, the following rules were applied to flag potential ADR candidates:

- AEs with >2% incidence
- AEs leading to tislelizumab discontinuation with >0.5% incidence.

A medical assessment was also made on the laboratory toxicities from the laboratory data.

All identified ADR candidates underwent medical review using the Bradford Hill criteria to assess the plausibility of a causal association between tislelizumab and these candidate ADRs. Event severity, relationship, pharmacological action, and the safety profile of other drugs with similar mechanism of action where all considered in relation to the Bradford Hill Criteria.

Once a causal association has been medically established, the eCRS (case retrieval strategy) was updated with the proposed ADRs and an ADR table generated.

ADRs identified with tislelizumab in the monotherapy and combination therapy pools are shown in the following table.

Table 131: Frequency and frequency category of ADRs with tislelizumab by SOC and ADR

	Tislelizumab monotherapy 200 mg Q3W N = 1534			Tislelizumab combination therapy N = 497		
Adverse drug reactions	**All grades n (%)**	**Grades 3-4 n (%)**	**Frequency category (All Grades)**	**All grades n (%)**	**Grades 3-4 n (%)**	**Frequency category (All Grades)**
Infections and infestations						
Pneumonia	148 (9.6)	64 (4.2)	Common	77 (15.5)	25 (5.0)	Very common
Blood and lymphatic system disorders						
Anaemia	448 (29.2)	77 (5.0)	Very common	439 (88.3)	78 (15.7)	Very common
Thrombocytopenia	136 (8.9)	16 (1.0)	Common	333 (67.0)	91 (18.3)	Very common
Neutropenia	85 (5.5)	19 (1.2)	Common	430 (86.5)	291 (58.6)	Very common
Lymphopenia	69 (4.5)	17 (1.1)	Common	68 (13.7)	14 (2.8)	Very common
Endocrine disorders						
Hypothyroidism	204 (13.3)	1 (0.07)	Very common	77 (15.5)	0	Very common
Hyperthyroidism	85 (5.5)	0	Common	54 (10.9)	0	Very common
Thyroiditis	17 (1.1)	0	Common	3 (0.6)	1 (0.2)	Uncommon
Adrenal insufficiency	7 (0.5)	3 (0.2)	Uncommon	0	0	-
Hypophysitis	1 (0.07)	0	Rare	0	0	-
Metabolism and nutrition disorders						
Hyperglycaemia	143 (9.3)	23 (1.5)	Common	81 (16.3)	7 (1.4)	Very common
Hyponatraemia	140 (9.1)	42 (2.7)	Common	94 (18.9)	8 (1.6)	Very common
Hypokalaemia	113 (7.4)	23 (1.5)	Common	79 (15.9)	8 (1.6)	Very common
Diabetes mellitus	11 (0.7)	5 (0.3)	Uncommon	6 (1.2)	4 (0.8)	Common
Nervous system disorders						
Guillain-Barre syndrome	0	0	-	1 (0.2)	1 (0.2)	Uncommon
Eye disorders						
Uveitis	4 (0.3)	0	Uncommon	0	0	-
Cardiac disorders						
Myocarditis	12 (0.8)	4 (0.3)	Uncommon	9 (1.8)	2 (0.4)	Common
Pericarditis	1 (0.07)	0	Rare	0	0	-
Vascular disorders						
Hypertension	73 (4.8)	29 (1.9)	Common	25 (5.0)	4 (0.8)	Common
Respiratory, thoracic and mediastinal disorders						
Cough	237 (15.4)	5 (0.3)	Very common	76 (15.3)	2 (0.4)	Very common
Dyspnoea	113 (7.4)	18 (1.2)	Common	60 (12.1)	5 (1.0)	Very common
Pneumonitis	80 (5.2)	31 (2.0)	Common	60 (12.1)	17 (3.4)	Very common
Gastrointestinal disorders						
Nausea	151 (9.8)	3 (0.2)	Common	206 (41.4)	2 (0.4)	Very common
Diarrhoea	137 (8.9)	12 (0.8)	Common	73 (14.7)	3 (0.6)	Very common
Stomatitis	46 (3.0)	5 (0.3)	Common	29 (5.8)	2 (0.4)	Common
Pancreatitis	15 (1.0)	8 (0.5)	Uncommon	1 (0.2)	0	Uncommon
Colitis	5 (0.3)	0	Uncommon	6 (1.2)	3 (0.6)	Common
Hepatobiliary disorders						
Hepatitis	40 (2.6)	18 (1.2)	Common	21 (4.2)	7 (1.4)	Common

Adverse drug reactions	Tislelizumab monotherapy 200 mg Q3W N = 1534			Tislelizumab combination therapy N = 497		
	All grades n (%)	Grades 3-4 n (%)	Frequency category (All Grades)	All grades n (%)	Grades 3-4 n (%)	Frequency category (All Grades)
Skin and subcutaneous tissue disorders						
Rash	221 (14.4)	15 (1.0)	Very common	131 (26.4)	13 (2.6)	Very common
Pruritus	154 (10.0)	0	Very common	34 (6.8)	1 (0.2)	Common
Severe skin reaction	1 (0.07)	0	Rare	0	0	-
Musculoskeletal and connective tissue disorders						
Arthralgia	132 (8.6)	4 (0.3)	Common	78 (15.7)	0	Very common
Myalgia	24 (1.6)	0	Common	19 (3.8)	0	Common
Myositis	14 (0.9)	4 (0.3)	Uncommon	1 (0.2)	1 (0.2)	Uncommon
Arthritis	6 (0.4)	0	Uncommon	5 (1.0)	0	Common
Renal and urinary disorders						
Nephritis	3 (0.2)	1 (0.07)	Uncommon	2 (0.4)	0	Uncommon
General disorders and administration site conditions						
Fatigue	352 (22.9)	30 (2.0)	Very common	214 (43.1)	11 (2.2)	Very common
Decreased appetite	221 (14.4)	14 (0.9)	Very common	202 (40.6)	7 (1.4)	Very common
Investigations						
Aspartate aminotransferase increased	320 (20.9)	40 (2.6)	Very common	210 (42.3)	8 (1.6)	Very common
Alanine aminotransferase increased	295 (19.2)	22 (1.4)	Very common	229 (46.1)	16 (3.2)	Very common
Blood bilirubin increased	183 (11.9)	30 (2.0)	Very common	90 (18.1)	2 (0.4)	Very common
Blood alkaline phosphatase increased	111 (7.2)	17 (1.1)	Common	55 (11.1)	2 (0.4)	Very common
Blood creatinine increased	79 (5.1)	2 (0.1)	Common	61 (12.3)	0	Very common
Injury, poisoning and procedural complications						
Infusion related reaction	3 (0.2)	1 (0.07)	Uncommon	12 (2.4)	0	Common

A subject with multiple occurrences of an ADR under one treatment is counted only once in the ADR category for that treatment.

MedDRA version 25.1. CTCAE version v4.03 for all studies except for studies 304 and 307: version v5.0, Case Retrieval Strategy version released 20230405.

Frequency category is 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)

Patients who crossed over from the chemotherapy control arms in studies 304 and 307 to Tislelizumab monotherapy were not included. SCLC patients from study 206 are not included.

Laboratory findings

Laboratory abnormalities worsening from baseline with tislelizumab as monotherapy (N=1534) and in combination with chemotherapy (N=497) are summarised in the following table. This table also serves as the basis to support the presentation of "laboratory abnormalities" in section 4.8. of the SmPC, where the proportions of patients who experienced a shift from baseline to a grade 3 or 4 laboratory abnormality are reported.

Table 132: Laboratory abnormalities worsening from baseline with tislelizumab as monotherapy and in combination with chemotherapy

	Tislelizumab monotherapy N = 1534			Tislelizumab combination therapy N = 497‡		
Laboratory abnormality parameter	**All grades n/m (%)**	**Grades 3-4 n/m (%)**	**Frequency category (All Grades)**	**All grades n/m (%)**	**Grades 3-4 n/m (%)**	**Frequency category (All Grades)**
Haematology						
Haemoglobin increased	56/14941911 (3.7)	2/1494 (0.1)	Common	8/495 (1.6)	0/495 (0.0)	Common
Haemoglobin decreased	563/1494 (37.7)	66/1494 (4.4)	Very common	460/495 (92.9)	80/495 (16.2)	Very common
Leukocytes decreased	216/494 (14.3)	14/1494 (0.9)	Very common	439/495 (88.7)	163/495 (32.9)	Very common
Lymphocytes increased	23/1475(1.6)	-	Common	-	-	-
Lymphocytes decreased	577/1475(39.1)	126/1475 (8.5)	Very common	-	-	-
Neutrophils decreased	163/1476 (11.0)	25/1476 (1.7)	Very common	445/494 (90.1)	302/494 (61.1)	Very common
Platelets decreased	248/1910 (13.0)	17/1495 (1.1)	Very common	365/495 (73.7)	94/495 (19.0)	Very common
Biochemistry						
ALT increased	434/1491 (29.1)	30/1491 (2.0)	Very common	278/495 (56.2.4)	23/495 (4.6)	Very common
Albumin decreased	625/1908 (32.8)	6/1491 (0.4)	Very common	-	-	-
Alkaline phosphatase increased	465/1491 (31.2)	56/1907 (2.9)	Very common	164/494 (33.2)	4/494 (0.8)	Very common
AST increased	471/1491 (31.6)	48/1491 (3.2)	Very common	265/495 (53.5)	13/495 (2.6)	Very common
Bilirubin increased	280/1486 (18.8)	32/1486 (2.2)	Very common	141/495 (28.5)	8/495 (1.6)	Very common
Creatine kinase increased	165/894 (18.5)	18/894 (2.0)	Very common	102/457 (22.3)	7/457 (1.5)	Very common
Creatinine increased	180/1491 (12.1)	13/1491 (0.9)	Very common	94/495 (19.0)	12/495 (2.4)	Very common
Potassium increased	143/1486 (9.6)	13/1486 (0.9)	Common	55/495 (11.1)	10/495 (2.0)	Very common
Potassium decreased	210/1486 (14.1)	33/1486 (2.2)	Very common	146/495 (29.5)	31/495 (6.3)	Very common
Sodium increased	99/1486 (6.7)	1/1486 (0.1)	Common	39/495 (7.9)	1/495 (0.2)	Common
Sodium decreased	494/1486 (33.2)	84/486 (5.7)	Very common	289/495 (58.4)	55/495 (11.1)	Very common

† Tislelizumab monotherapy "All doses, all indications" pool
‡ Tislelizumab + chemotherapy NSCLC T+chemo arm (Studies 307, 304 and 206)
Frequency category is 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).
Patients who crossed over from the chemotherapy control arms in studies 304 and 307 to Tislelizumab monotherapy were not included. SCLC patients from Study 206 are not included.
n is the number of patient with worsen toxicity grade compared with baseline. m is the number of patients with both baseline and post-baseline laboratory test assessments.

In vitro biomarker test for patient selection for safety

Not applicable.

Safety in special populations

Safety by age

Table 133: Overview of controlled and non-controlled studies by age group in tislelizumab treated patients (200 mg Q3W)

	Age 65 - 74 years n (%)	Age 75 - 84 years n (%)	Age ≥ 85 years n (%)
Controlled studies			
Study 302 (N= 255)	85 (33.3)	13 (5.1)	0 (0.0)
Study 303 (N= 534)	155 (29.0)	14 (2.6)	1 (0.1)
Study 304 (N=222)	56 (25.2)	3 (1.4)	0 (0.0)
Study 307 (N= 238)	91 (38.2)	0 (0.0)	0 (0.0)
Non-controlled studies			
Study 102 (N=300)	72 (24.0)	5 (1.7)	0 (0.0)
Study 001 (N=13)	6 (46.2)	1 (7.7)	0 (0.0)
Study 208 (N=249)	75 (30.1)	24 (9.6)	1 (0.4)
Study 204 (N=113)	38 (33.6)	6 (5.3)	0 (0.0)
Study 203 (N=70)	4 (5.7)	0 (0.0)	0 (0.0)
Study 206 (N=37)	11 (29.7)	1 (2.7)	0 (0.0)

N= number of patients in tislelizumab-containing arms

- *Monotherapy*

Table 134: Summary of TEAEs by age group (< 65, ≥65-<75, ≥75 years)

	< 65			>=65-<75			>=75		
	303 Study			303 Study			303 Study		
System Organ Class Preferred Term	**Tislelizumab (N=364) n (%)**	**Docetaxel (N=171) n (%)**	**200 mg Q3W All Indications (N=1034) n (%)**	**Tislelizumab (N=155) n (%)**	**Docetaxel (N=76) n (%)**	**200 mg Q3W All Indications (N=435) n (%)**	**Tislelizumab (N=15) n (%)**	**Docetaxel (N=11) n (%)**	**200 mg Q3W All Indications (N=65) n (%)**
Patients with **at least one** TEAE	348 (95.6)	167 (97.7)	991 (95.8)	146 (94.2)	76 (100.0)	413 (94.9)	15 (100.0)	11 (100.0)	64 (98.5)
Treatment-related TEAE	266 (73.1)	158 (92.4)	762 (73.7)	114 (73.5)	75 (98.7)	322 (74.0)	10 (66.7)	9 (81.8)	41 (63.1)
TEAE with **≥ Grade 3**	136 (37.4)	124 (72.5)	428 (41.4)	63 (40.6)	60 (78.9)	211 (48.5)	7 (46.7)	9 (81.8)	30 (46.2)
Treatment-related ≥ G 3	47 (12.9)	108 (63.2)	160 (15.5)	29 (18.7)	57 (75.0)	83 (19.1)	1 (6.7)	6 (54.5)	7 (10.8)
Serious TEAE	113 (31.0)	52 (30.4)	331 (32.0)	55 (35.5)	27 (35.5)	160 (36.8)	6 (40.0)	4 (36.4)	25 (38.5)
Treatment-related SAE	38 (10.4)	37 (21.6)	110 (10.6)	27 (17.4)	20 (26.3)	58 (13.3)	2 (13.3)	2 (18.2)	7 (10.8)
TEAE Leading to **Death**	19 (5.2)	5 (2.9)	80 (7.7)	12 (7.7)	4 (5.3)	42 (9.7)	1 (6.7)	2 (18.2)	5 (7.7)
Treatment-related Death	3 (0.8)	1 (0.6)	12 (1.2)	5 (3.2)	2 (2.6)	7 (1.6)	0 (0.0)	1 (9.1)	1 (1.5)
TEAE Leading to Treatment **Discontinuation**	30 (8.2)	17 (9.9)	113 (10.9)	24 (15.5)	11 (14.5)	68 (15.6)	2 (13.3)	4 (36.4)	9 (13.8)
Related Discontinuation	13 (3.6)	12 (7.0)	44 (4.3)	18 (11.6)	9 (11.8)	36 (8.3)	1 (6.7)	4 (36.4)	5 (7.7)
TEAE Leading to Dose **Modification**	76 (20.9)	54 (31.6)	246 (23.8)	41 (26.5)	30 (39.5)	126 (29.0)	2 (13.3)	5 (45.5)	26 (40.0)
Related Modification	43 (11.8)	47 (27.5)	148 (14.3)	24 (15.5)	27 (35.5)	74 (17.0)	1 (6.7)	3 (27.3)	13 (20.0)
Immune-mediated TEAE	70 (19.2)	NA	179 (17.3)	33 (21.3)	NA	89 (20.5)	1 (6.7)	NA	8 (12.3)
imTEAE with ≥ Grade 3	18 (4.9)	NA	44 (4.3)	16 (10.3)	NA	34 (7.8)	1 (6.7)	NA	3 (4.6)
Infusion-related Reaction	2 (0.5)	5 (2.9)	39 (3.8)	2 (1.3)	3 (3.9)	12 (2.8)	1 (6.7)	1 (9.1)	3 (4.6)
IRR with ≥ Grade 3	0 (0.0)	0 (0.0)	4 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Table 135: Safety by age in Study 303 and 200 mg Q3W; all indications

	303 Tislelizumab N=534			200 mg Q3W all indications N=1534		
MedDRA terms	**Age < 65 years N=364 n (%)**	**Age 65-<75 years N=155 n (%)**	**Age ≥75 years N=15 n (%)**	**Age < 65 years N=1034 n (%)**	**Age 65-<75 years N=435 n (%)**	**Age ≥75 years N=65 n (%)**
Total AEs	348 (95.6)	146 (94.2)	15 (100.0)	991 (95.8)	413 (94.9)	64 (98.5)
Grade >= 3 AEs	136 (37.4)	63 (40.6)	7 (46.7)	428 (41.4)	211 (48.5)	30 (46.2)
Serious AEs - total	113 (31.0)	55 (35.5)	6 (40.0)	331 (32.0)	160 (36.8)	25 (38.5)
Fatal	19 (5.2)	12 (7.7)	1 (6.7)	80 (7.7)	42 (9.7)	5 (7.7)
Hospitalisation/prolong existing hospitalisation	109 (29.9)	53 (34.2)	5 (33.3)	308 (29.8)	150 (34.5)	21 (32.3)
Life-threatening	9 (2.5)	6 (3.9)	0 (0.0)	31 (3.0)	16 (3.7)	0 (0.0)
Disability/incapacity	1 (0.3)	1 (0.6)	0 (0.0)	2 (0.2)	2 (0.5)	0 (0.0)
Other (medically significant)	0 (0.0)	2 (1.3)	1 (6.7)	11 (1.1)	9 (2.1)	3 (4.6)
AE leading to treatment discontinuation	30 (8.2)	24 (15.5)	2 (13.3)	113 (10.9)	68 (15.6)	9 (13.8)
Blood and lymphatic system disorders	119 (32.7)	52 (33.5)	8 (53.3)	345 (33.4)	148 (34.0)	16 (24.6)
Cardiac disorders	39 (10.7)	23 (14.8)	0 (0.0)	92 (8.9)	49 (11.3)	2 (3.1)
Ear and labyrinth disorders	5 (1.4)	0 (0.0)	1 (6.7)	19 (1.8)	4 (0.9)	1 (1.5)
Endocrine disorders	60 (16.5)	18 (11.6)	1 (6.7)	177 (17.1)	58 (13.3)	8 (12.3)
Eye disorders	28 (7.7)	16 (10.3)	2 (13.3)	72 (7.0)	38 (8.7)	6 (9.2)
Gastrointestinal disorders	133 (36.5)	56 (36.1)	5 (33.3)	448 (43.3)	206 (47.4)	29 (44.6)
General disorders and administration site conditions	156 (42.9)	51 (32.9)	8 (53.3)	428 (41.4)	184 (42.3)	34 (52.3)
Hepatobiliary disorders	14 (3.8)	4 (2.6)	2 (13.3)	60 (5.8)	34 (7.8)	9 (13.8)
Immune system disorders	2 (0.5)	1 (0.6)	0 (0.0)	9 (0.9)	5 (1.1)	0 (0.0)
Infections and infestations	105 (28.8)	44 (28.4)	2 (13.3)	332 (32.1)	122 (28.0)	18 (27.7)
Injury, poisoning and procedural complications	12 (3.3)	10 (6.5)	0 (0.0)	42 (4.1)	27 (6.2)	2 (3.1)
Investigations	213 (58.5)	92 (59.4)	6 (40.0)	633 (61.2)	240 (55.2)	28 (43.1)
Metabolism and nutrition disorders	169 (46.4)	78 (50.3)	5 (33.3)	426 (41.2)	211 (48.5)	22 (33.8)
Musculoskeletal and connective tissue disorders	109 (29.9)	46 (29.7)	2 (13.3)	276 (26.7)	114 (26.2)	18 (27.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	26 (7.1)	9 (5.8)	0 (0.0)	66 (6.4)	22 (5.1)	5 (7.7)
Nervous system disorders	40 (11.0)	26 (16.8)	1 (6.7)	125 (12.1)	65 (14.9)	14 (21.5)
Product issues	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)
Psychiatric disorders	25 (6.9)	13 (8.4)	0 (0.0)	74 (7.2)	40 (9.2)	4 (6.2)

MedDRA terms	303 Tislelizumab N=534			200 mg Q3W all indications N=1534		
	Age < 65 years N=364 n (%)	Age 65-<75 years N=155 n (%)	Age ≥75 years N=15 n (%)	Age < 65 years N=1034 n (%)	Age 65-<75 years N=435 n (%)	Age ≥75 years N=65 n (%)
Renal and urinary disorders	19 (5.2)	16 (10.3)	1 (6.7)	100 (9.7)	55 (12.6)	4 (6.2)
Reproductive system and breast disorders	5 (1.4)	3 (1.9)	0 (0.0)	20 (1.9)	7 (1.6)	1 (1.5)
Respiratory, thoracic and mediastinal disorders	179 (49.2)	70 (45.2)	4 (26.7)	379 (36.7)	161 (37.0)	18 (27.7)
Skin and subcutaneous tissue disorders	69 (19.0)	32 (20.6)	1 (6.7)	231 (22.3)	114 (26.2)	25 (38.5)
Vascular disorders	23 (6.3)	10 (6.5)	0 (0.0)	65 (6.3)	45 (10.3)	3 (4.6)
CMQ sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	44 (12.1)	22 (14.2)	0 (0.0)	103 (10.0)	67 (15.4)	10 (15.4)

- *Combination therapy 1L*

Table 136: Summary of TEAEs by age (pooled 1L NSCLC data)

	NSCLC			
	<65 years		>=65 years	
	307&304&206 T+chemo (N=335) n (%)	307&304 chemo (N=156) n (%)	307&304&206 T+chemo (N=162) n (%)	307&304 chemo (N=71) n (%)
Patients With **at Least One** TEAE	334 (99.7)	155 (99.4)	162 (100)	71 (100)
Treatment-Related	334 (99.7)	154 (98.7)	161 (99.4)	70 (98.6)
≥ Grade 3 TEAEs	259 (77.3)	110 (70.5)	135 (83.3)	51 (71.8)
Treatment-Related	243 (72.5)	100 (64.1)	129 (79.6)	45 (63.4)
Serious TEAEs	120 (35.8)	34 (21.8)	79 (48.8)	20 (28.2)
Treatment-Related	66 (19.7)	20 (12.8)	57 (35.2)	12 (16.9)
TEAEs Led to **Death**	14 (4.2)	4 (2.6)	7 (4.3)	3 (4.2)
Treatment-Related	6 (1.8)	2 (1.3)	2 (1.2)	2 (2.8)
TEAEs Led to Any Treatment **Discontinuation**	85 (25.4)	15 (9.6)	56 (34.6)	14 (19.7)
Led to Tislelizumab Discontinuation	39 (11.6)	NA	32 (19.8)	NA
Led to Chemotherapy Discontinuation	67 (20.0)	15 (9.6)	44 (27.2)	14 (19.7)
TEAEs Led to Any Treatment **Modification** (a)	244 (72.8)	65 (41.7)	122 (75.3)	43 (60.6)
Led to Tislelizumab Modification	210 (62.7)	NA	102 (63.0)	NA
Led to Chemotherapy Modification	222 (66.3)	63 (40.4)	117 (72.2)	43 (60.6)
Infusion-Related Reaction	9 (2.7)	4 (2.6)	5 (3.1)	1 (1.4)
Immune-mediated TEAEs	73 (21.8)	NA	54 (33.3)	NA
≥ Grade 3	27 (8.1)	NA	25 (15.4)	NA

	NSCLC			
	<65 years		>=65 years	
	307&304&206 T+chemo (N=335) n (%)	307&304 chemo (N=156) n (%)	307&304&206 T+chemo (N=162) n (%)	307&304 chemo (N=71) n (%)
Led to Death	5 (1.5)	NA	1 (0.6)	NA
Serious	27 (8.1)	NA	27 (16.7)	NA
Led to Tislelizumab Discontinuation	18 (5.4)	NA	20 (12.3)	NA

(a) Treatment modification included dose interruption, dose delay, infusion rate decreased and dose modification (only for chemotherapy).

Table 137: Safety by age category in the combination therapy pool

	NSCLC			
	307&304&206 T+chemo N=497		307&304 Chemo N=227	
MedDRA terms	Age < 65 years N=335 n (%)	Age 65-<75 years N=158 n (%)	Age < 65 years N=156 n (%)	Age 65-<75 years N=71 n (%)
Total AEs	**334 (99.7)**	**158 (100.0)**	**155 (99.4)**	**71 (100.0)**
Grade >= 3 AEs	259 (77.3)	133 (84.2)	110 (70.5)	51 (71.8)
Serious AEs – total	120 (35.8)	77 (48.7)	34 (21.8)	20 (28.2)
Fatal	14 (4.2)	7 (4.4)	4 (2.6)	3 (4.2)
Hospitalisation/prolong existing hospitalisation	116 (34.6)	73 (46.2)	31 (19.9)	18 (25.4)
Life-threatening	5 (1.5)	7 (4.4)	1 (0.6)	0 (0.0)
Disability/incapacity	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Other (medically significant)	1 (0.3)	2 (1.3)	1 (0.6)	0 (0.0)
AE leading to Tislelizumab discontinuation	39 (11.6)	31 (19.6)	0 (0.0)	0 (0.0)
AEs by SOC				
Blood and lymphatic system disorders	303 (90.4)	150 (94.9)	138 (88.5)	65 (91.5)
Cardiac disorders	48 (14.3)	25 (15.8)	14 (9.0)	2 (2.8)
Ear and labyrinth disorders	6 (1.8)	2 (1.3)	3 (1.9)	2 (2.8)
Endocrine disorders	56 (16.7)	24 (15.2)	2 (1.3)	1 (1.4)
Eye disorders	15 (4.5)	8 (5.1)	2 (1.3)	3 (4.2)
Gastrointestinal disorders	231 (69.0)	109 (69.0)	87 (55.8)	47 (66.2)
General disorders and administration site conditions	197 (58.8)	107 (67.7)	78 (50.0)	43 (60.6)
Hepatobiliary disorders	25 (7.5)	7 (4.4)	12 (7.7)	2 (2.8)
Immune system disorders	2 (0.6)	3 (1.9)	4 (2.6)	0 (0.0)
Infections and infestations	112 (33.4)	62 (39.2)	36 (23.1)	17 (23.9)
Injury, poisoning and procedural complications	29 (8.7)	10 (6.3)	6 (3.8)	1 (1.4)
Investigations	311 (92.8)	150 (94.9)	139 (89.1)	63 (88.7)
Metabolism and nutrition disorders	225 (67.2)	125 (79.1)	89 (57.1)	48 (67.6)
Musculoskeletal and connective tissue disorders	150 (44.8)	67 (42.4)	52 (33.3)	23 (32.4)

	NSCLC			
	307&304&206 T+chemo N=497		307&304 Chemo N=227	
MedDRA terms	Age < 65 years N=335 n (%)	Age 65-<75 years N=158 n (%)	Age < 65 years N=156 n (%)	Age 65-<75 years N=71 n (%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	22 (6.6)	12 (7.6)	13 (8.3)	7 (9.9)
Nervous system disorders	111 (33.1)	59 (37.3)	46 (29.5)	18 (25.4)
Product issues	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Psychiatric disorders	45 (13.4)	16 (10.1)	21 (13.5)	14 (19.7)
Renal and urinary disorders	28 (8.4)	13 (8.2)	4 (2.6)	1 (1.4)
Reproductive system and breast disorders	5 (1.5)	3 (1.9)	2 (1.3)	2 (2.8)
Respiratory, thoracic and mediastinal disorders	167 (49.9)	85 (53.8)	50 (32.1)	27 (38.0)
Skin and subcutaneous tissue disorders	178 (53.1)	92 (58.2)	69 (44.2)	34 (47.9)
Vascular disorders	26 (7.8)	15 (9.5)	14 (9.0)	2 (2.8)
CMQ sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	88 (26.3)	48 (30.4)	34 (21.8)	20 (28.2)

Hepatic impairment:

Table 138: Overall summary of TEAEs by baseline hepatic impairment

	Normal			Impairment		
	303 Study			303 Study		
System Organ Class Preferred Term	Tislelizumab (N=494) n (%)	Docetaxel (N=236) n (%)	200 mg Q3W All Indications (N=1243) n (%)	Tislelizumab (N=40) n (%)	Docetaxel (N=22) n (%)	200 mg Q3W All Indications (N=285) n (%)
Patients with at least one TEAE	470 (95.1)	233 (98.7)	1188 (95.6)	39 (97.5)	21 (95.5)	274 (96.1)
Treatment-related TEAE	362 (73.3)	222 (94.1)	932 (75.0)	28 (70.0)	20 (90.9)	189 (66.3)
TEAE ≥ Grade 3	189 (38.3)	174 (73.7)	521 (41.9)	17 (42.5)	19 (86.4)	145 (50.9)
Related TEAE ≥ Grade 3	69 (14.0)	152 (64.4)	199 (16.0)	8 (20.0)	19 (86.4)	50 (17.5)
Serious TEAE	157 (31.8)	79 (33.5)	404 (32.5)	17 (42.5)	4 (18.2)	110 (38.6)
Treatment-related SAEs	61 (12.3)	55 (23.3)	143 (11.5)	6 (15.0)	4 (18.2)	31 (10.9)
TEAE Leading to Death	26 (5.3)	11 (4.7)	85 (6.8)	6 (15.0)	0 (0.0)	41 (14.4)
Related TEAE Leading to Death	7 (1.4)	4 (1.7)	13 (1.0)	1 (2.5)	0 (0.0)	6 (2.1)
TEAE Leading to Discontinuation	51 (10.3)	29 (12.3)	152 (12.2)	5 (12.5)	3 (13.6)	35 (12.3)
Related TEAE Leading to Treatment Discontinuation	31 (6.3)	22 (9.3)	75 (6.0)	1 (2.5)	3 (13.6)	9 (3.2)
TEAE Leading to Dose Modification	113 (22.9)	82 (34.7)	306 (24.6)	6 (15.0)	7 (31.8)	90 (31.6)
Treatment-related TEAE Leading to Dose Modification	66 (13.4)	71 (30.1)	186 (15.0)	2 (5.0)	6 (27.3)	48 (16.8)
Immune-mediated TEAE	100 (20.2)	NA	234 (18.8)	4 (10.0)	NA	41 (14.4)

System Organ Class Preferred Term	Normal 303 Study Tislelizumab (N=494) n (%)	Normal 303 Study Docetaxel (N=236) n (%)	Normal 303 Study 200 mg Q3W All Indications (N=1243) n (%)	Impairment 303 Study Tislelizumab (N=40) n (%)	Impairment 303 Study Docetaxel (N=22) n (%)	Impairment 303 Study 200 mg Q3W All Indications (N=285) n (%)
Immune-mediated TEAE with Grade 3 or Higher	34 (6.9)	NA	70 (5.6)	1 (2.5)	NA	11 (3.9)

Safety by gender

Overall, no clinically meaningful differences in the AE profile between male and female subgroups were observed in the tislelizumab monotherapy treatment groups (apart from a higher incidence of weight decreased in the male population in the tislelizumab treatment arm of Study 303 [15.4% vs 9.5%]). In the pooled tislelizumab + chemotherapy group, SAEs (41.5% vs. 32.9%) and immune-mediated TEAEs (25.5% vs 18.8%) were reported at higher incidences (≥ 5% difference) for male patients compared to females.

Safety by race

As the 1L combination therapy Studies 304 and 307 were conducted exclusively in China, analyses by race and region were only performed in the monotherapy setting.

In Study 303, 80% of the study population was Asian and 17% White; in the 200 mg Q3W All Indications group, 80% of patients were Asian, 17% White and 3% other race types. The following tables focus on results for Asian and White to improve readability and due to the only small proportion of other race types [other: n=17 and 7 in treatment arms of Study 303 and n=47 in the 200 mg Q3W All Indications group].

Table 139: Overall summary of TEAEs by race (Asian and White [without other], Study 303 and All Doses and All Indications)

	Asian			White		
	Study 303			Study 303		
	Tisleli-zumab (N = 423) n (%)	Doce-taxel (N = 210) n (%)	200 mg Q3W All Indica-tions (N = 1234) n (%)	Tisleli-zumab (N = 94) n (%)	Doce-taxel (N = 41) n (%)	All Doses and All Indica-tions (N = 253) n (%)
Patients with at least one TEAE	409 (96.7)	207 (98.6)	1184 (95.9)	84 (89.4)	40 (97.6)	238 (94.1))
Treatment-related TEAE	321 (75.9)	196 (93.3)	934 (75.7)	60 (63.8)	39 (95.1)	163 (64.4)
Grade 3 or higher TEAE	165 (39.0)	158 (75.2)	527 (42.7)	34 (36.2)	28 (68.3)	119 (47.0)
Grade ≥ 3 related TEAE	64 (15.1)	141 (67.1)	216 (17.5)	11 (11.7)	23 (56.1)	29 (11.5)
Serious TEAE	144 (34.0)	66 (31.4)	416 (33.7)	24 (25.5)	13 (31.7)	82 (32.4)
Treatment-related SAE	59 (13.9)	47 (22.4)	157 (12.7)	7 (7.4)	10 (24.4)	16 (6.3)
TEAE leading to death	22 (5.2)	9 (4.3)	90 (7.3)	7 (7.4)	2 (4.9)	29 (11.5)
TEAE leading to treatment discontinuation	41 (9.7)	26 (12.4)	152 (12.3)	13 (13.8)	5 (12.2)	31 (12.3)
TEAE leading to dose modification	89 (21.0)	66 (31.4)	310 (25.1)	25 (26.6)	18 (43.9)	75 (29.6)
Immune-mediated TEAE	78 (18.4)	NA	227 (18.4)	15 (16.0)	NA	42 (16.6)
Grade 3 or higher	25 (5.9)	NA	66 (5.3)	5 (5.3)	NA	12 (4.7)

Table 140: TEAEs with incidence ≥ 10% by race, SOC and PT (Asian and White, Study 303 and 200 mg Q3W All Indications)

	Asian			White		
	Study 303			Study 303		
System Organ Class Preferred Term	Tisleli-zumab (N = 423) n (%)	Doce-taxel (N = 210) n (%)	200 mg Q3W All Indica-tions (N = 1234) n (%)	Tisleli-zumab (N = 94) n (%)	Doce-taxel (N = 41) n (%)	200 mg Q3W All Indica-tions (N = 253) n (%)
Patients with at least one TEAE	409 (96.7)	207 (98.6)	1184 (95.9)	84 (89.4)	40 (97.6)	238 (94.1)
Investigations	276 (65.2)	157 (74.8)	813 (65.9)	31 (33.0)	15 (36.6)	73 (28.9)
ALT increased	98 (23.2)	38 (18.1)	271 (22.0)	8 (8.5)	0 (0.0)	22 (8.7)
AST increased	92 (21.7)	30 (14.3)	286 (23.2)	8 (8.5)	1 (2.4)	26 (10.3)
Weight decreased	77 (18.2)	21 (10.0)	205 (16.6)	4 (4.3)	5 (12.2)	9 (3.6)
Blood bilirubin increased	27 (6.4)	14 (6.7)	143 (11.6)	0 (0.0)	1 (2.4)	7 (2.8)
White blood cell count decr.	20 (4.7)	72 (34.3)	101 (8.2)	0 (0.0)	2 (4.9)	0 (0.0)
Neutrophil count decreased	15 (3.5)	91 (43.3)	64 (5.2)	0 (0.0)	4 (9.8)	1 (0.4)

	Asian			White		
	Study 303			Study 303		
System Organ Class Preferred Term	Tisleli-zumab (N = 423) n (%)	Doce-taxel (N = 210) n (%)	200 mg Q3W All Indica-tions (N = 1234) n (%)	Tisleli-zumab (N = 94) n (%)	Doce-taxel (N = 41) n (%)	200 mg Q3W All Indica-tions (N = 253) n (%)
Metabolism and nutrition disorders	215 (50.8)	100 (47.6)	557 (45.1)	31 (33.0)	84 (33.2)15 (36.6)	
Decreased appetite	69 (16.3)	46 (21.9)	168 (13.6)	11 (11.7)	11 (26.8)	42 (16.6)
Hypoalbuminaemia	66 (15.6)	37 (17.6)	163 (13.2)	4 (4.3)	4 (9.8)	11 (4.3)
Hyperglycaemia	50 (11.8)	26 (12.4)	99 (8.0)	4 (4.3)	2 (4.9)	10 (4.0)
Hyponatraemia	44 (10.4)	28 (13.3)	121 (9.8)	3 (3.2)	0 (0.0)	5 (2.0)
Hypokalaemia	42 (9.9)	12 (5.7)	99 (8.0)	1 (1.1)	1 (2.4)	6 (2.4)
Respiratory, thoracic and mediastinal disorders	214 (50.6)	91 (43.3)	452 (36.6)	34 (36.2)	15 (36.6)	90 (35.6)
Cough	93 (22.0)	36 (17.1)	202 (16.4)	10 (10.6)	3 (7.3)	31 (12.3)
Haemoptysis	51 (12.1)	21 (10.0)	78 (6.3)	3 (3.2)	1 (2.4)	7 (2.8)
Dyspnoea	45 (10.6)	22 (10.5)	82 (6.6)	15 (16.0)	8 (19.5)	26 (10.3)
General disorders and administration site conditions	169 (40.0)	106 (50.5)	489 (39.6)	40 (42.6)	22 (53.7)	136 (53.8)
Asthenia	54 (12.8)	46 (21.9)	92 (7.5)	12 (12.8)	9 (22.0)	52 (20.6)
Pyrexia	49 (11.6)	25 (11.9)	202 (16.4)	7 (7.4)	1 (2.4)	28 (11.1)
Fatigue	10 (2.4)	12 (5.7)	67 (5.4)	14 (14.9)	11 (26.8)	48 (19.0)
Blood and lymphatic system disorders	155 (36.6)	144 (68.6)	448 (36.3)	20 (21.3)	26 (63.4)	51 (20.2)
Anaemia	132 (31.2)	98 (46.7)	373 (30.2)	16 (17.0)	12 (29.3)	43 (17.0)
Leukopenia	14 (3.3)	60 (28.6)	43 (3.5)	1 (1.1)	9 (22.0)	1 (0.4)
Neutropenia	7 (1.7)	57 (27.1)	23 (1.9)	2 (2.1)	20 (48.8)	2 (0.8)
Febrile neutropenia	0 (0.0)	25 (11.9)	0 (0.0)	0 (0.0)	7 (17.1)	0 (0.0)
Gastrointestinal disorders	155 (36.6)	99 (47.1)	521 (42.2)	30 (31.9)	21 (51.2)	135 (53.4)
Constipation	55 (13.0)	38 (18.1)	147 (11.9)	6 (6.4)	3 (7.3)	26 (10.3)
Nausea	41 (9.7)	30 (14.3)	108 (8.8)	16 (17.0)	8 (19.5)	39 (15.4)
Vomiting	30 (7.1)	15 (7.1)	95 (7.7)	3 (3.2)	3 (7.3)	17 (6.7)
Diarrhoea	27 (6.4)	24 (11.4)	94 (7.6)	5 (5.3)	6 (14.6)	35 (13.8)

	Asian			White		
	Study 303			Study 303		
System Organ Class Preferred Term	Tislelizumab (N = 423) n (%)	Docetaxel (N = 210) n (%)	200 mg Q3W All Indications (N = 1234) n (%)	Tislelizumab (N = 94) n (%)	Docetaxel (N = 41) n (%)	200 mg Q3W All Indications (N = 253) n (%)
Abdominal pain	8 (1.9)	6 (2.9)	52 (4.2)	2 (2.1)	1 (2.4)	20 (7.9)
Infections and infestations	122 (28.8)	60 (28.6)	379 (30.7)	25 (26.6)	14 (34.1)	75 (29.6)
Pneumonia	47 (11.1)	29 (13.8)	118 (9.6)	13 (13.8)	6 (14.6)	20 (7.9)
Upper respiratory tract infection	44 (10.4)	23 (11.0)	125 (10.1)	3 (3.2)	2 (4.9)	6 (2.4)
Skin and subcutaneous tissue disorders	86 (20.3)	115 (54.8)	282 (22.9)	12 (12.8)	18 (43.9)	74 (29.2)
Pruritus	31 (7.3)	4 (1.9)	116 (9.4)	4 (4.3)	0 (0.0)	31 (12.3)
Alopecia	4 (0.9)	107 (51.0)	4 (0.3)	0 (0.0)	13 (31.7)	0 (0.0)
Endocrine disorders	64 (15.1)	0 (0.0)	205 (16.6)	14 (14.9)	1 (2.4)	35 (13.8)
Hypothyroidism	46 (10.9)	0 (0.0)	157 (12.7)	10 (10.6)	1 (2.4)	25 (9.9)
Nervous system disorders	51 (12.1)	31 (14.8)	144 (11.7)	10 (10.6)	15 (36.6)	46 (18.2)
Headache	13 (3.1)	6 (2.9)	28 (2.3)	4 (4.3)	5 (12.2)	14 (5.5)
Psychiatric disorders	35 (8.3)	28 (13.3)	91 (7.4)	2 (2.1)	3 (7.3)	23 (9.1)
Insomnia	27 (6.4)	23 (11.0)	75 (6.1)	1 (1.1)	1 (2.4)	14 (5.5)

Immunological events

For tislelizumab monotherapy, 18.3% of patients were tested positive for treatment emergent antidrug antibodies (ADA), and neutralising antibodies (NAb) were detected in 0.9% of patients of 1,916 ADA evaluable patients treated at the recommended dose of 200 mg Q3W. For tislelizumab combination therapy, ADA was detected in 24.0% of 492 evaluable patients and NAb in 1.4% of patients.

Please see section 2.6.2.2 pharmacodynamics for a detailed assessment of immunogenicity.

Safety related to drug-drug interactions and other interactions

Formal pharmacokinetic interaction studies have not been conducted. As tislelizumab is a monoclonal antibody that is cleared from the circulation through catabolism and not metabolised by cytochrome P450 (CYP) enzymes or other drug metabolizing enzymes, inhibition or induction of these enzymes by co-administered medicinal products is not anticipated to affect the pharmacokinetics of tislelizumab.

Discontinuation due to adverse events

- *Monotherapy 2L+*

Table 141: TEAEs leading to treatment discontinuation by SOC and PT (≥ 1% patients in any group)

	303 Study		2L+ NSCLC	
System Organ Class Preferred Term	**Tislelizumab (N=534) n (%)**	**Docetaxel (N=258) n (%)**	**All (N=636) n (%)**	**200 mg Q3W All Indications (N=1534) n (%)**
Patients with at least one TEAE Leading to Treatment Discontinuation	56 (10.5)	32 (12.4)	69 (10.8)	190 (12.4)
Respiratory, thoracic and mediastinal disorders	28 (5.2)	3 (1.2)	32 (5.0)	53 (3.5)
Pneumonitis	9 (1.7)	0 (0.0)	12 (1.9)	15 (1.0)
Interstitial lung disease	6 (1.1)	0 (0.0)	6 (0.9)	7 (0.5)
Infections and infestations	7 (1.3)	5 (1.9)	8 (1.3)	20 (1.3)
Pneumonia	7 (1.3)	4 (1.6)	8 (1.3)	18 (1.2)
Investigations	0 (0.0)	3 (1.2)	1 (0.2)	5 (0.3)
Neutrophil count decreased	0 (0.0)	3 (1.2)	0 (0.0)	0 (0.0)

- *Combination therapy 1L*

Table 142: TEAEs leading to treatment discontinuation by SOC and PT (≥ 1% patients in combined+chemo or chemo group)

	SQ-NSCLC			NSQ-NSCLC		NSCLC	
System Organ Class Preferred Term	**307 T+PC (N=120) n (%)**	**307 T+nPC (N=118) n (%)**	**307 PC (N=117) n (%)**	**304 T+PP (N=222) n (%)**	**304 PP (N=110) n (%)**	**307&304&206 T+chemo (N=497) n (%)**	**307&304 chemo (N=227) n (%)**
Patients With at Least One TEAE Event Leading to Treatment Discontinuation	21 (17.5)	38 (32.2)	18 (15.4)	68 (30.6)	11 (10.0)	141 (28.4)	29 (12.8)
Blood and lymphatic system disorders	3 (2.5)	15 (12.7)	5 (4.3)	17 (7.7)	3 (2.7)	39 (7.8)	8 (3.5)
Anaemia	1 (0.8)	9 (7.6)	3 (2.6)	11 (5.0)	1 (0.9)	25 (5.0)	4 (1.8)
Thrombocytopenia	3 (2.5)	2 (1.7)	3 (2.6)	6 (2.7)	0 (0.0)	13 (2.6)	3 (1.3)
Neutropenia	1 (0.8)	2 (1.7)	0 (0.0)	2 (0.9)	2 (1.8)	5 (1.0)	2 (0.9)
Investigations	4 (3.3)	15 (12.7)	6 (5.1)	15 (6.8)	3 (2.7)	36 (7.2)	9 (4.0)
Blood creatinine increased	0 (0.0)	2 (1.7)	0 (0.0)	10 (4.5)	0 (0.0)	12 (2.4)	0 (0.0)
Neutrophil count decreased	1 (0.8)	6 (5.1)	4 (3.4)	1 (0.5)	0 (0.0)	8 (1.6)	4 (1.8)

System Organ Class Preferred Term	SQ-NSCLC 307 T+PC (N=120) n (%)	SQ-NSCLC 307 T+nPC (N=118) n (%)	SQ-NSCLC 307 PC (N=117) n (%)	NSQ-NSCLC 304 T+PP (N=222) n (%)	NSQ-NSCLC 304 PP (N=110) n (%)	NSCLC 307&304&206 T+chemo (N=497) n (%)	NSCLC 307&304 chemo (N=227) n (%)
Platelet count decreased	0 (0.0)	5 (4.2)	1 (0.9)	1 (0.5)	1 (0.9)	7 (1.4)	2 (0.9)
White blood cell count decreased	1 (0.8)	4 (3.4)	2 (1.7)	2 (0.9)	0 (0.0)	7 (1.4)	2 (0.9)
Respiratory, thoracic and mediastinal disorders	8 (6.7)	6 (5.1)	0 (0.0)	11 (5.0)	0 (0.0)	28 (5.6)	0 (0.0)
Pneumonitis	3 (2.5)	1 (0.8)	0 (0.0)	11 (5.0)	0 (0.0)	17 (3.4)	0 (0.0)
Immune-mediated pneumonitis	1 (0.8)	2 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.6)	0 (0.0)
Gastrointestinal disorders	2 (1.7)	1 (0.8)	1 (0.9)	9 (4.1)	1 (0.9)	14 (2.8)	2 (0.9)
General disorders and administration site conditions	0 (0.0)	2 (1.7)	3 (2.6)	7 (3.2)	3 (2.7)	10 (2.0)	6 (2.6)
Cardiac disorders	1 (0.8)	3 (2.5)	0 (0.0)	4 (1.8)	0 (0.0)	9 (1.8)	0 (0.0)
Myocarditis	0 (0.0)	3 (2.5)	0 (0.0)	1 (0.5)	0 (0.0)	5 (1.0)	0 (0.0)
Immune-mediated myocarditis	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	2 (0.4)	0 (0.0)
Infections and infestations	2 (1.7)	3 (2.5)	1 (0.9)	3 (1.4)	2 (1.8)	8 (1.6)	3 (1.3)
Pneumonia	2 (1.7)	2 (1.7)	0 (0.0)	1 (0.5)	2 (1.8)	5 (1.0)	2 (0.9)
Metabolism and nutrition disorders	0 (0.0)	2 (1.7)	0 (0.0)	6 (2.7)	0 (0.0)	8 (1.6)	0 (0.0)
Nervous system disorders	3 (2.5)	1 (0.8)	0 (0.0)	2 (0.9)	0 (0.0)	8 (1.6)	0 (0.0)

Table 143: Percentage of imAE events resolved and resolving by imAE category (Tislelizumab 200 mg Q3W, All indications, Safety Analysis Set)

imAE category	Tislelizumab 200 mg Q3W – All Indications N = 1534 Patient-based analysis n	Resolved [a]	Event-based analysis n	Resolved [b] (%)	Resolving [b] (%)
Immune-mediated pancreatitis	1	1 (100.0)	1	1 (100.0)	0
Immune-mediated colitis	11	9 (81.8)	11	9 (81.8)	1 (9.1)
Immune-mediated hyperthyroidism	5	4 (80.0)	5	4 (80.0)	0
Immune-mediated myositis/rhabdomyolysis	14	8 (57.1)	16	10 (62.5)	0
Immune-mediated myocarditis	7	4 (57.1)	7	4 (57.1)	1 (14.3)

	Tislelizumab 200 mg Q3W – All Indications N = 1534				
	Patient-based analysis		Event-based analysis		
imAE category	n	Resolved [a]	n	Resolved [b] (%)	Resolving [b] (%)
Immune-mediated skin adverse reaction	27	14 (51.9)	31	16 (51.6)	6 (19.4)
Immune-mediated nephritis and renal dysfunction	10	5 (50.0)	10	5 (50.0)	3 (30.0)
Immune-mediated hepatitis	26	13 (50.0)	40	25 (62.5)	5 (12.5)
Immune-mediated pneumonitis	66	30 (45.5)	68	32 (47.1)	15 (22.1)
Immune-mediated hypothyroidism	116	37 (31.9)	138	59 (42.8)	25 (18.1)
Immune-mediated adrenal insufficiency	4	1 (25.0)	4	1 (25.0)	1 (25.0)
Immune-mediated thyroiditis	12	2 (16.7)	17	6 (35.3)	3 (17.6)
Immune-mediated type 1 diabetes mellitus	6	1 (16.7)	7	2 (28.6)	2 (28.6)
Immune-mediated pituitary dysfunction	1	0	1	0	0
Other immune-mediated reactions	4	2 (50.0)	4	2 (50.0)	0

Source: 1L/2L NSCLC Response to CHMP Day 180 LoOIs Appendix 2-EU_D180_Table_ 2.7.4.2.2.7

Data cutoff: 001-26AUG2020, 102-31MAY2020, 203-26NOV2018, 204-16SEP2019, 208-27FEB2020, 303-10AUG2020, 302-01DEC2020. Data extraction: 001-26AUG2020, 102-30JUN2020, 203-15JAN2019, 204-16OCT2019, 208-15APR2020, 303-27OCT2020, 302-15JAN2021.

Resolved includes both 'Recovered/resolved' and 'Recovered/resolved with sequelae' in the CRF.

[a] A patient was considered as resolved in a category if, and only if, all events in the category from this patient were resolved. Percentage was based on the number of patients with at least one immune-mediated adverse event in the category.

[b] Percentages were based on the number of immune-mediated adverse events in the category.

Adverse events were coded using MedDRA version 23.0.

Post marketing experience

Tislelizumab is registered in China for the treatment of several cancers. The first marketing authorisation for tislelizumab was granted in China on 26-Dec-2019 for rrHL, followed by indications in 2L+ urothelial carcinoma, 1L squamous and non-squamous NSCLC, 2L/3L HCC and 2L/3L NSCLC.

Tislelizumab is also registered in the European union as monotherapy for the treatment of adult patients with unresectable, locally advanced or metastatic oesophageal squamous cell carcinoma after prior platinum-based chemotherapy. The marketing authorisation for Tevimbra (EMEA/H/C/005919) was granted on 15/09/2023.

2.5.9. Discussion on clinical safety

The safety of tislelizumab monotherapy in the 2L NSCLC setting is supported by Study 303, by data from 102 previously treated NSCLC patients from two phase 1/2 studies (n=636 2L+ NSCLC in total), and a pooled safety dataset from patients treated with 200 mg Q3W tislelizumab monotherapy across different indications (n=1534; including NSCLC, ESCC, HCC, UC und r/r cHL).

The safety of tislelizumab in combination with chemotherapy in the 1L NSCLC setting is supported by Study 304 in non-squamous NSCLC and Study 307 in squamous NSCLC. In addition, 1L NSCLC safety data were pooled across histologies and adding 54 patients from the phase II Study 206 (in total n=497 in the combined NSCLC T+chemo group).

Median follow-up for tislelizumab monotherapy in Study 303 was 13.4 months and about 16.9 months for the 1L combination Studies 304 and 307.

This amount of safety data can be considered adequate to describe the toxicity profile of tislelizumab. It is however noted that the pivotal 1L Studies 304 and 307 were conducted exclusively in China Study 303 recruited only about 20% of patients from other regions than China (mainly Eastern Europe) and did not enrol patients with more than 2 prior lines of systemic chemotherapy (whereas the proposed 2L+ NSCLC indication refers to patients after prior chemotherapy without restricting the use of tislelizumab to 2L or 3L).

Median **exposure** to tislelizumab as monotherapy in Study 303 was longer than exposure to docetaxel (5.4 months vs. 2.1 months). Median exposure to tislelizumab in the tislelizumab + chemotherapy combinations was slightly higher for patients with squamous NSCLC in Study 307 compared to patients with non-squamous NSCLC in Study 304 (about 9.7 vs 7.9 months). Platinum-based combination chemotherapy was planned to be given for 4-6 treatment cycles and patients received a median number of 4.0 cycles across treatment arms of both 1L studies. For non-squamous NSCLC, pemetrexed was allowed as maintenance treatment; median duration of exposure to pemetrexed was 7.5 months for the T+PP combination and 4.9 month for the PP group.

In the squamous NSCLC Study 307, the median relative dose intensity (RDI) of chemotherapy was lower in the nab-paclitaxel arm (T+nPC arm) compared to the T+PC arm and the PC arm [RDI for nab-paclitaxel was 61% vs 95-98% for paclitaxel; RDI for platinum compound was 83% in T+nPC arm vs 95% in paclitaxel arms]. Higher rates of treatment discontinuations (32% vs 18%) and dose modifications (92% vs 64%) were observed in the T+nPC group compared to the T+PC arm. Weekly administration of nab-paclitaxel was new to most of the Chinese investigators in this open-label study; as a result, it may have led to a more cautious toxicity assessment and an increased chance of dose modifications in the nab-paclitaxel treatment arm.

Most common AEs in the tislelizumab monotherapy group of Study 303 (≥ 15%) were anaemia (28.5%), ALT increased (19.9%) and AST increased (18.9%), cough (19.5%), decreased appetite (15.4%), and weight loss (15.2%). As expected, lower rates of haematological toxicities and alopecia were observed for tislelizumab compared to docetaxel.

The safety profile was overall **comparable between** the **tislelizumab monotherapy groups** (in Study 303, the 2L+ NSCLC pool and the 200 mg Q3W All Indications pool). However, some differences were notable in the All Indications dataset, reflecting the mix of tumour types in this pool (e.g., lower rates of respiratory and metabolism disorders, but higher rates of gastrointestinal, skin and hepatobiliary disorders in the pooled dataset compared to the tislelizumab group of Study 303).

The most commonly reported events (≥ 40%) in the combined NSCLC T+chemo group (Studies 304, 307 and 206) were anaemia, neutrophil count, white blood cell count and platelet count decreased, ALT and AST increased, nausea, and decreased appetite. These are known toxicities associated with chemotherapy; however, for all of these events higher incidences were observed in the combined tislelizumab + chemotherapy group than in the combined chemotherapy group (≥ 10% difference for neutrophil count decreased [+10.8%], platelet count decreased [+13.9%], ALT increased [+12.2%], and AST increased [+13.7%]).

In Study 303, **Grade ≥ 3 AEs** were reported at lower incidences for tislelizumab monotherapy than for docetaxel (49% vs 75%), mainly driven by lower rates of haematological toxicities. Most common

severe events (≥ 2% of patients in the tislelizumab arm) were: pneumonia (7.1% vs 9.3%), anaemia (3.4% vs 6.2%), and hypertension (2.4% vs 0.4% for tislelizumab vs docetaxel, respectively).

In the 1L studies, Grade ≥ 3 AEs were more common in the tislelizumab + chemotherapy groups than for the chemotherapy groups for both squamous and non-squamous NSCLC patients (79% vs 71% for combined T+chemo vs chemo). This difference was mainly driven by higher incidences of haematological toxicities; but higher incidences of Grade ≥ 3 AEs in the tislelizumab arms (though with smaller differences) were also observed for the SOC infections (9.3% vs 6.6%) and for the PTs pneumonitis, haemoptysis and rash.

Regarding the comparison for **squamous vs non-squamous** patients, similar incidences were reported for most categories of AEs apart from Grade ≥ 3 AEs that were more frequent in patients with squamous histology. The higher rate of Grade ≥ 3 AEs in squamous NSCLC is more likely due to the different backbone chemotherapy regimens than to histology, since this difference was similarly observed for the control arms of Studies 304 and 307. All grade AEs with higher rates (≥ 10.0%) in squamous vs non-squamous NSCLC patients were e.g. alopecia, arthralgia, hypoaesthesia and pain in extremity, reflecting the safety profiles of the individual chemotherapies.

In Study 303, about one third of patients experienced a **serious adverse event** in both treatment arms. In the docetaxel group, higher incidences were mainly reported for serious haematological events (in the SOCs of blood disorders [14.0% vs. 0.9%], and investigation [4.3% vs. 0.9% for docetaxel vs tislelizumab, respectively]). For tislelizumab, incidences were higher for respiratory disorders (13.3% vs 6.6 for docetaxel), with pneumonitis/ILD driving this difference (together 5.4% for tislelizumab vs 0% for docetaxel). For some other SOCs, smaller, but numerically higher incidences were reported in the tislelizumab compared to the docetaxel arm, as e.g. for cardiac disorders (3.0% vs. 1.6%), nervous system (2.4% vs. 0.4%), musculoskeletal (2.1% vs. 0.4%), metabolism (1.9% vs. 0.4%), hepatobiliary (1.5% vs. 0.8%), renal (1.1% vs 0.4%) and endocrine disorders (0.6% vs. 0.0%).

In the 1L studies, the overall incidence of serious TEAEs was higher for the combined NSCLC T+chemo group (40.0%) than for the combined chemo group (23.8%). The largest difference was observed in the SOC of respiratory disorders, where higher incidences were reported for serious pneumonitis, haemoptysis und dyspnoea in the tislelizumab treatment arms. Moreover, higher rates of serious pneumonia, febrile neutropenia and decreased neutrophil counts were observed in the tislelizumab than the chemotherapy only groups.

In Study 303, similar percentages of patients **discontinued** study treatment for TEAEs in the tislelizumab and docetaxel groups (10.5% and 12.4%). In the tislelizumab group, the most common (≥ 1%) reasons for treatment discontinuation were pneumonitis (1.7%), interstitial lung disease (1.1%), and pneumonia (1.3%). Dose modifications occurred in 22% in the tislelizumab and 35% in the docetaxel arm.

In the 1L studies, AEs that led to discontinuation were more common in the combined NSCLC T+chemo group than for the combined chemotherapy group (28.4% vs 12.8%). Most common AEs leading to treatment discontinuations and contributing to differences between the tislelizumab and the control arms were seen for haematological abnormalities, pneumonitis (4%), and myocarditis (1.4%).

TEAE leading to **death** were reported for 6% of patients (n=32) in the tislelizumab group in Study 303 and for 4.3% of patients in the docetaxel arm. Grade 5 AEs reported in ≥ 2 patients included pneumonia (1.1%), respiratory failure (0.9%), death (0.9%), acute respiratory failure (0.4%), acute myocardial infarction (0.4%), and cerebral infarction (0.4%). The slightly higher proportion of AEs leading to death in the tislelizumab arm were mainly driven by events in the SOC of respiratory disorders.

In the 1L studies, a total of 21 patients (4.2%) in the combined NSCLC T+chemo group and 7 patients (3.1%) in the combined chemo group had TEAEs which led to death. The most common TEAEs which led to death in the NSCLC T+chemo group were AEs in the SOC respiratory, thoracic and mediastinal disorders. They were reported more frequently for T+chemo patients vs chemo patients in both the squamous and non-squamous NSCLC groups (2.0% vs 0.4% in the combined chemotherapy group). Pneumonitis, dyspnoea, haemoptysis and respiratory failure were observed in ≥ 2 patients in the combined T+chemo group. Of note, 3 patients died to pneumonitis (0.6%), 2 patients died due to myocarditis (0.4%) and 1 patient died due to hepatitis (0.2%) resulting in a rate of 1.2% of (at least possibly) immune-associated fatal events in the combined T+chemo group.

The incidences of **related AEs** are lower in the tislelizumab group of Study 303 compared to docetaxel across all categories (with the exception of AEs leading to death that were reported with similar rates). Overall, tislelizumab related AEs in Study 303 reflected the AEs that were observed regardless of treatment relationship.

In the 1L studies, treatment related AEs were reported for nearly all patients (≥99%) with higher incidences for related Grade ≥ 3 and serious AEs in the combined T+chemo group than the combined chemo group (75% vs 64% and 25% vs 14%, respectively). The overall profile of most common related TEAEs was similar to the most frequently reported TEAEs regardless of treatment relationship. All grade chemotherapy-related haematological toxicities, elevation of liver parameters and nausea were reported with higher incidences in the tislelizumab +chemotherapy groups vs. the chemotherapy control groups.

There appeared to be a trend for investigators to consider AEs to be more frequently related to chemotherapy as opposed to tislelizumab in Study 303. A similar imbalance regarding causality assessment was noted in the 1L combination studies. Knowledge about incidences of ADRs that were more frequently reported for chemotherapy than for checkpoint inhibitors likely impacted the causality assessment of specific AEs. Examples from other studies with checkpoint inhibitors confirmed a similar pattern.

The above description of safety data focuses on the presentation of adverse events that were reported in the pivotal studies (Study 303 for tislelizumab monotherapy and Studies 304 and 307 for the combination of tislelizumab with chemotherapy), since for these datasets comparative safety with a control group were available within the pivotal studies. However, the comparison of the tislelizumab treatment arms of the pivotal studies with the respective pooled datasets for monotherapy and combination arms did not show any meaningful differences .

Adverse drug reactions (ADRs) for tislelizumab monotherapy that are included in section 4.8 of the SmPC are based on the "200 mg Q3W All Indications dataset" (N=1534). This dataset also includes indications for which no approval is currently foreseen in the EU. Nonetheless, given the similar posology of tislelizumab, a pooled analysis across suitable studies is considered to provide the best estimate of frequency and thus, this approach is considered acceptable.

The combined 1L NSCLC tislelizumab + chemotherapy pool (n=497) is considered adequate to determine the ADRs for the combination treatment.

The methodology to determine ADRs is considered acceptable.

For tislelizumab monotherapy, the most common adverse reaction was anaemia (29.2%). The most common grade 3/4 adverse reactions were anaemia (5.0%) and pneumonia (4.2%). 1.2% of patients experienced adverse reactions leading to death. The adverse reactions leading to death were pneumonia (0.78%), hepatitis (0.13%), pneumonitis (0.07%), dyspnoea (0.07%), decreased appetite (0.07%) and thrombocytopenia (0.07%). Among the 1 534 patients, 40.1% were exposed to tislelizumab for longer than 6 months, and 22.2% were exposed for longer than 12 months.

For tislelizumab given in combination with chemotherapy, the most common adverse reactions were anaemia (88.3%), neutropenia (86.5%), thrombocytopenia (67.0%), alanine aminotransferase increased (46.1%), fatigue (43.1%), aspartate aminotransferase increased (42.3%), nausea (41.4%), decreased appetite (40.6%) and rash (26.4%). The most common grade 3/4 adverse reactions were neutropenia (58.6%), thrombocytopenia (18.3%), anaemia (15.7%), pneumonia (5.0%), pneumonitis (3.4%), alanine aminotransferase increased (3.2%), lymphopenia (2.8%), rash (2.6%) and fatigue (2.2%). 1.6% of patients experienced adverse reactions leading to death. The adverse reactions leading to death were pneumonitis (0.60%), dyspnoea (0.40%), myocarditis (0.40%), pneumonia (0.20%) and hypokalaemia (0.20%). Among the 497 patients, 65.8% were exposed to tislelizumab for longer than 6 months, and 37.8% were exposed for longer than 12 months.

As severe infusion-related reactions (grade 3 or higher) have been reported for tislelizumab monotherapy and in combination, a warning to monitor for signs and symptoms of infusion-related reactions, as well as dose recommendation have been included in section 4.4 and 4.2 of the SmPC.

In general, **laboratory** findings in Study 303 reflected the known safety profiles of each drug; haematological toxicities were reported more frequently for docetaxel treated patients, while increases in liver enzymes (AST, ALT, ALP) and CK were more common for tislelizumab treated patients. In addition, an increase in creatinine was slightly more pronounced in the tislelizumab treatment group compared to the docetaxel group. In the combined NSCLC T+chemo group, laboratory data indicate a worsening of haematologic toxicities and a more pronounced increase of liver parameters and creatinine by the addition of tislelizumab to chemotherapy. This is reflected accordingly in section 4.8 of the SmPC.

Immune-related AEs

Incidences of imAE

19.5% of patients in the tislelizumab group in Study 303 had an immune-mediated TEAE (18.0% in the pooled dataset across indications). Most common imAEs (≥ 2%) in the tislelizumab arm were hypothyroidism (7.9%) and pneumonitis (6.2%). 6.6% of patients experienced Grade ≥ 3 imAEs, the most common was pneumonitis (3.7% including 0.4% of fatal events); other Grade ≥ 3 imAEs were hepatitis (0.7%), nephritis and skin ADRs (0.6% each), adrenal insufficiency, type 1 diabetes mellitus and myositis/rhabdomyolysis (0.4% each) as well as myocarditis and colitis (0.2% each). For 7.5% of patients imAEs were serious. ImAEs led to discontinuation of tislelizumab in 23 patients (4.3%), most commonly due to pneumonitis (n=18); further reasons were hepatitis (n=2), myocarditis, nephritis/renal failure, skin adverse reactions and type 1 diabetes mellitus (n=1 each). For 38.4% of patients in the pooled monotherapy dataset imAEs were resolved; endocrine events resolved at lower rates, e.g. hypothyroidism in 31.9%, adrenal insufficiency in 25% and thyroiditis and type 1 diabetes mellitus in 16.7% of patients.

In the 11 studies, 25.6% of patients had immune-mediated TEAEs in the combined NSCLC T+chemo group. Overall, incidences were similar for both squamous and non-squamous NSCLC. Most common imAEs were observed for pneumonitis (9.1%), hypothyroidism (9.1%) and skin adverse reactions (3.8%). Grade ≥ 3 events were reported in 10.5% of patients, the most common were pneumonitis (4.0%), skin adverse reaction (2.2%), hepatitis (1.4%) myositis/rhabdomyolysis (1.0%), type 1 diabetes (1.0%) and myocarditis (0.8%). Most of these were Grade 3 events; however, Grade 4 imAEs occurred for pneumonitis, type 1 diabetes, myocarditis, and myositis/rhabdomyolysis. Immune-mediated TEAEs were fatal for 3 patients with pneumonitis (0.6%), 2 patients with myocarditis (0.4%) and 1 patient each with hepatitis (hepatic failure) and myositis/rhabdomyolysis (0.2%). 10.9% of patients experienced serious imAE ImAEs led to discontinuation of tislelizumab in 7.6% of patients, the most common were pneumonitis (4.0%), myocarditis (1.2%) and myositis/rhabdomyolysis (1.0%).

Overall, imAEs resolved during the study in approximately half of NSCLC patients (53.5% across both pivotal studies).

In order to mitigate the safety concern around immune mediated adverse reactions, a patient card will be distributed to the patients in order to increase the awareness of patients on the signs and symptoms relevant to the early recognition/identification of the potential immune-related ARs and prompt them about when to seek medical attention (see RMP and Annex II).

In section 4.4 of the SmPC it has been clarified that the majority of these events improved with interruption of tislelizumab, administration of corticosteroids and/or supportive care. Immune-related adverse reactions have also been reported after the last dose of tislelizumab. Immune-related adverse reactions affecting more than one body system can occur simultaneously.

Warnings and recommendations about immune-related pneumonitis (including fatal cases), immune-related hepatitis (including fatal cases), immune-related skin rash or dermatitis (including cases of severe cutaneous adverse reactions (SCARs)), immune-related colitis, immune-related endocrinopathies (including thyroid disorders, adrenal insufficiency, hypophysitis and type 1 diabetes mellitus), immune-related nephritis with renal dysfunction and other clinically important immune-related adverse reactions (myositis, myocarditis, arthritis, polymyalgia rheumatica, pericarditis and Guillain-Barre syndrome) were included in section 4.4 of the SmPC. Treatment modifications recommendation have also been included in section 4.2 of the SmPC for all these immune-related adverse reactions.

As solid organ transplant rejection has been reported in the post-marketing setting in patients treated with PD-(L)1 inhibitors a warning that treatment with tislelizumab may increase the risk of rejection in solid organ transplant recipients has been included in section 4.4 of the SmPC.

Safety in special populations

Overall, no consistent, clinically meaningful differences could be observed by analyses of subgroups across histology, disease stage, body weight, ECOG status and mild/moderate renal impairment. Approximately 20% of patients had mild or moderate hepatic impairment at study baseline in the pooled monotherapy population across indications with a numerical trend towards more severe and serious AEs and higher incidences of dose modifications in the hepatic impairment subgroup. In the combination treatment setting, data are too limited to draw conclusions (17 and 12 patients with mild or moderate hepatic dysfunction in the tislelizumab arms of Studies 304 and 307). Regarding gender, the toxicity profile did not show meaningful differences for tislelizumab monotherapy and is difficult to interpret in the 1L NSCLC combination treatment setting due to the low proportion of female patients (17%). Regarding smoking history, for some categories a slightly worse safety profile was reported for current/previous smokers versus never smokers; however, similar differences were also observed in the control groups.

Age: Generally, an increase of AE rates is expected with increasing age and a trend towards a more unfavourable safety profile was observed in the ≥ 65 years old subgroup compared to younger patients also in the tislelizumab studies; in Study 303, for tislelizumab monotherapy, this was similarly reported in both treatment arms, whereas increases of Grade ≥ 3 AEs and SAEs in elderly were more pronounced in the tislelizumab and chemotherapy combination arms compared to patients treated with chemotherapy only. The safety data for tislelizumab in patients ≥ 75 years are limited (n=4 in the chemotherapy combinations arms). This limited data for patients beyond 75 years of age is reflected in sections 4.2 and 4.8 of the SmPC.

Race and region: As the 1L combination therapy Studies 304 and 307 were conducted exclusively in China, an analysis by race and region was only performed in the monotherapy setting, where the majority of patients was also Asian (80% in Study 303 and 69% in the All Doses and All Indications

Group). Higher incidences of laboratory-related adverse events were reported in the Asian subgroup than in the White subgroup in the tislelizumab arm of Study 303. A similar trend was observed in patients treated with chemotherapy and in the pooled dataset across indications. However, no significant differences in the "more objective" laboratory safety evaluations were detected despite the lower frequency of laboratory abnormalities reported as AEs in White patients vs. Asian patients. Therefore, the apparent discrepancies observed are more likely explained by regional differences in interpretation of the clinical relevance of laboratory abnormalities and data do not sustain a different pattern of tolerability in different races. It is considered reassuring that, for example, incidences of leukopenia and neutropenia, which were reported with a notably lower frequency in the White subgroup compared to the Asian subgroup, were consistent between the pooled monotherapy population and a meta-analysis of studies with PD-1 inhibitors as monotherapy. Frequency of AEs, other than laboratory abnormalities, was generally similar across regions which is not suggestive of a general pattern of underreporting in study sites enrolling White patients. Overall, the totality of the reported safety data does not further support concerns that the results mainly derived from Asian patients would not be applicable to European patients.

2.5.10. Conclusions on the clinical safety

Safety data for tislelizumab for the treatment of NSCLC generally reflect the known toxicity profile of checkpoint inhibitors as monotherapy and the additional toxicities in combination with chemotherapy. No new safety issues have been identified compared to already authorised checkpoint inhibitors.

2.6. Risk Management Plan

Safety concerns

Important identified risks	• Immune-mediated adverse reactions
Important potential risks	• Reproductive and developmental toxicity
Missing information	• None

Pharmacovigilance plan

No additional pharmacovigilance activities.

Risk minimisation measures

Table 144: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risk		
Immune-mediated Adverse Reactions	Routine Risk Minimisation Measures: SmPC Section 4.2 where guidelines for withholding or permanent discontinuation of treatment are provided. SmPC Section 4.4 where advice is provided regarding monitoring and management of immune-mediated adverse reactions. SmPC Section 4.8 where the adverse drug reactions of immune-mediated adverse reactions are listed. PL Section 2 and PL Section 4 where guidance on how to early identify signs and symptoms and seek medical attention is included. Additional Risk Minimisation Measures: Patient Card Legal Status: Restricted medical prescription	Routine Pharmacovigilance Activities Beyond Adverse Reactions Reporting and Signal Detection: Targeted follow-up checklist Additional Pharmacovigilance Activities: None
Important Potential Risk		
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 and 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: Targeted follow-up checklist Additional Pharmacovigilance Activities: None
Missing Information		
None		

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

Conclusion

The CHMP considers that the risk management plan version 1.0 is acceptable.

2.7. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the

requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

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.

2.8. Product information

User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Tizveni (tislelizumab) is included in the additional monitoring list as:

-it is a biological product that is not covered by the previous category and authorised after 1 January 2011.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Approved indication:

Tizveni in combination with pemetrexed and platinum-containing chemotherapy is indicated for the first-line treatment of adult patients with non-squamous non-small cell lung cancer whose tumours have PD-L1 expression on ≥50% of tumour cells with no EGFR or ALK positive mutations and who have:

- locally advanced NSCLC and are not candidates for surgical resection or platinum-based chemoradiation, or
- metastatic NSCLC.

Tizveni in combination with carboplatin and either paclitaxel or nab-paclitaxel is indicated for the first-line treatment of adult patients with squamous non-small cell lung cancer who have:

- locally advanced NSCLC and are not candidates for surgical resection or platinum-based chemoradiation, or
- metastatic NSCLC.

Tizveni as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer after prior platinum-based therapy. Patients with EGFR mutant or ALK positive NSCLC should also have received targeted therapies before receiving tislelizumab.

3.1.2. Available therapies and unmet medical need

Second-/third-line treatment options for advanced or metastatic NSCLC without oncogenic driver mutations

Before ICI therapy was available, there were 2 established chemotherapeutic agents available globally for the treatment of locally advanced or metastatic NSCLC with no actionable oncogenic driver after prior chemotherapy: docetaxel for patients with either non-squamous or squamous NSCLC and pemetrexed for patients with non-squamous NSCLC who did not receive pemetrexed as first-line treatment (Planchard et al 2018, Ettinger et al 2019). Erlotinib can also be considered for patients who cannot receive cytotoxic chemotherapy due to poor performance status (Tarceva USPI 2010, Planchard et al 2018). Overall, the therapeutic benefit of these further lines of treatment has been restricted by limited improvements in survival, low response rates, and significant toxicities (Stinchcombe and Socinski 2008, Al-Farsi and Ellis 2014, Nadler et al 2018). Presently, pembrolizumab (Keytruda), nivolumab (Opdivo), and atezolizumab (Tecentriq) are approved in the US and EU for the second-line treatment of metastatic NSCLC (Keytruda USPI 2021, Keytruda SmPC 2021, Opdivo SmPC 2021, Opdivo USPI 2021, Tecentriq SmPC 2021, Tecentriq USPI 2021).

First-line treatment options for advanced or metastatic NSCLC without oncogenic driver aberrations

Multiple regimens for the 1L treatment of patients with metastatic oncogenic-driver-negative NSCLC regardless of PD-L1 expression are approved and recommendable across Europe, most of them containing one or more immune checkpoint inhibitors and histology-selected platinum-based chemotherapy:

-Pembrolizumab + carboplatin + paclitaxel/nab-paclitaxel for squamous histology[1]

- Pembrolizumab + carboplatin + pemetrexed for non-squamous histology[1]

- Atezolizumab + bevacizumab + carboplatin + paclitaxel for non-squamous histology[2]

- Atezolizumab + carboplatin + nab-paclitaxel for non-squamous histology[2]

- Nivolumab + ipilimumab + 2 cycles of platinum-doublet, regardless of histology[3]

Additionally, pembrolizumab[1], atezolizumab[2] and cemiplimab[4] as monotherapy are approved for the subgroup of patients with high PD-L1 expression (≥50%). (*[1] Keytruda SmPC,[2] Tecentriq SmPC,[3] Opdivo SmPC,[4] Libtayo SmPC)* Concerning patients with locally advanced (stage IIIB) disease that are not candidates for platinum-based chemoradiation, the usual approach is the same as for patients with metastatic disease.

3.1.3. Main clinical studies

The open-label study BGB-A317-303 randomly assigned 805 patients with locally advanced or metastatic NSCLC in a 2:1 ratio to receive either tislelizumab or docetaxel. All patients had received 1 platinum-based chemotherapy regimen (**2nd line NSCLC**).

The open-label study BGB-A317-307 randomly assigned 360 patients with locally advanced or metastatic **squamous NSCLC** in a 1:1:1 ratio to receive either tislelizumab combined with paclitaxel plus carboplatin or tislelizumab combined with nab-paclitaxel plus carboplatin or paclitaxel plus carboplatin **as first-line treatment**.

The open-label study BGB-A317-304 randomly assigned 334 patients with locally advanced or metastatic **non-squamous NSCLC** in a 2:1 ratio to receive either tislelizumab combined with carboplatin or cisplatin plus pemetrexed or carboplatin/cisplatin plus pemetrexed **as first-line treatment.**

3.2. Favourable effects

Results from primary analyses:

Monotherapy 2L+ NSCLC

Efficacy in ITT analysis set

- **OS** (primary endpoint): **HR 0.66** (95% CI: 0.56, 0.79)
- **PFS** (per investigator; secondary endpoint): **HR 0.63** (95% CI: 0.53, 0.75)

Efficacy in PD-L1 positive analysis set (TC ≥ 25%)

- **OS** (primary endpoint): **HR 0.54** (95% CI: 0.41, 0.71)
- **PFS** (per investigator; secondary endpoint): **HR 0.38** (95% CI: 0.29, 0.50)

Combination therapy 1st line squamous NSCLC

Efficacy in ITT analysis set

Arm T+PC vs PC

- **PFS** (per IRC; primary endpoint): **HR 0.45** (95% CI: 0.33, 0.62)
- **OS** (secondary endpoint): **HR 0.68** (95% CI: 0.45, **1.01**)

Arm T+nPC vs PC

- **PFS** (per IRC; primary endpoint): **HR 0.43** (95% CI: 0.31, 0.60)
- **OS** (secondary endpoint): **HR 0.75** (95% CI: 0.50, **1.12**)

Combination therapy 1st line non-squamous NSCLC

Efficacy in ITT analysis set

- **PFS** (per IRC; primary endpoint): **HR 0.63** (95% CI: 0.47, 0.86)
- **OS** (secondary endpoint): **HR 0.90** (95% CI: 0.63, **1.28**)

Efficacy in the PD-L1 TC>=50% population

- **PFS** (per IRC; primary endpoint): **HR 0.31** (95% CI: 0.18, 0.55)
- **OS** (secondary endpoint): **HR 0.39** (95% CI: 0.22, 0.71)

3.3. Uncertainties and limitations about favourable effects

Monotherapy 2L+ NSCLC

- 30% of patients were never smokers, 55% non-squamous and only 20% were female, which is not considered fully representative of an EU NSCLC patient population. 80% of the patients were enrolled in China. Nonetheless, the totality of efficacy results do not raise concerns that these differences in baseline characteristics have a relevant impact on the study outcome.

Combination therapy 1st line (squamous NSCLC and non-squamous)

- Only Asian patients were included, the median age of 62 years (for squamous) and 61 years for non-squamous) is considered low (expected 69 years), 8 % female patients only (for squamous) and 36% never smoker (for non-squamous) are not considered fully representative of an European patient population. However, the overall study results support that the observed differences in baseline characteristics do not have a meaningful impact on the efficacy outcome. Therefore, the conclusions based on these pivotal studies can be considered also relevant for a European patient population.
- No data are available for patients older than 75. This is reflected in section 4.8 of the SmPC.

3.4. Unfavourable effect

Monotherapy 2L+ NSCLC

- The incidences of treatment-related AEs (73% vs 93.8%), all cause and treatment-related Grade ≥ 3 AEs (38.6% vs 74.8% and 14.4% vs. 66.3%), treatment-related SAEs (12.5% vs 22.9%) and AEs leading to dose modification (22.3% vs 34.5%) were less frequent in the tislelizumab arm of Study 303 than in the docetaxel arm. Similar frequencies in both treatment arms were reported for all cause SAEs (32.6% vs 32.2%), AEs leading to death (6% vs 4.3%) and AEs leading to treatment discontinuation (10.5% vs 12.4%).
- Most common AEs in the tislelizumab group of Study 303 (≥ 15%) were anaemia (28.5%), ALT increased (19.9%) and AST increased (18.9%), cough (19.5%), decreased appetite (15.4%), and weight loss (15.2%).

- 19.5% of patients in the tislelizumab group in Study 303 had an immune-mediated TEAE. The most common imAEs (≥ 2%) in the tislelizumab arm were hypothyroidism (7.9%) and pneumonitis (6.2%). 6.6% of patients experienced Grade ≥ 3 imAEs, the most common was pneumonitis (3.7% including 0.4% of fatal events); other Grade ≥ 3 imAEs were hepatitis (0.7%), nephritis and skin ADRs (0.6% each), adrenal insufficiency, type 1 diabetes mellitus and myositis/rhabdomyolysis (0.4% each) as well as myocarditis and colitis (0.2% each). For 7.5% of patients imAEs were serious. ImAEs led to discontinuation of tislelizumab in 4.3% of patients. For 38.4% of patients in the pooled monotherapy dataset imAEs were resolved; endocrine events resolved at lower rates, e.g. hypothyroidism in 31.9%, adrenal insufficiency in 25% and thyroiditis and type 1 diabetes mellitus in only 16.7% of patients.

Combination therapy 1L NSCLC

- The incidences of all cause and treatment-related Grade ≥ 3 AEs (79.3% vs 70.9% and 74.8% vs 63.9%), all cause and treatment-related SAEs (40% vs 23.8% and 24.7% vs 14.1%), treatment discontinuations due to AEs (28.4% vs 12.8%) and dose modifications due to AEs (73.6% vs. 47.6%) were all more frequent in the combined tislelizumab + chemotherapy group compared to the combined chemotherapy control.
- The most commonly reported events in the combined NSCLC T+chemo group (≥ 40%) were anaemia, neutrophil count, white blood cell count and platelet count decreased, ALT and AST increased, nausea, and decreased appetite. For all these events, higher incidences were observed in the combined T+chemo group than in the combined chemotherapy group (≥ 10% difference for neutrophil count decreased [+10.8%], platelet count decreased [+13.9%], ALT increased [+12.2%], and AST increased [+13.7%]).
- 25.6% of patients in the combined NSCLC T+chemo group had immune-mediated AEs; most common imAEs were pneumonitis (9.1%), hypothyroidism (9.1%) and skin adverse reactions (3.8%). Grade ≥ 3 events were reported in 10.5% of patients, the most frequent were pneumonitis (4.0%), skin adverse reaction (2.2%), hepatitis (1.4%), myositis/rhabdomyolysis (1.0%), type 1 diabetes mellitus (1.0) and myocarditis (0.8%). Fatal imAEs occurred for pneumonitis (0.6%), myocarditis (0.4%) as well as hepatitis and myositis/rhabdomyolysis (0.2% each). 10.9% of patients experienced serious imAE, and imAEs led to discontinuation of tislelizumab in 7.6% of patients. Overall, imAEs resolved during the study in approximately half of NSCLC patients (53.5% across both pivotal studies).

3.5. Uncertainties and limitations about unfavourable effects

Monotherapy 2L+ NSCLC

- No safety data are available for tislelizumab in patients with ECOG PS >1 and after more than 2 prior lines of therapy; this is reflected in section 4.4 and 5.1 of the SmPC.
- There are only limited safety data in patients with ≥ 75 years; this is reflected in section 4.8 of the SmPC.

Combination therapy 1L NSCLC

- Studies in 1L NSCLC were conducted exclusively in China with the possible impact of regional differences regarding clinical practice or baseline/disease characteristics on safety data; however, subgroup analysis of race in the 2L monotherapy setting and the results of the

inspection reports including on-site inspections in China did not further support concerns that the Asian patients derived safety data would not be applicable to European patients.

- The evaluation of the safety profile in females is hampered by the low proportion of enrolled females (17% of study population). However, no clinically meaningful differences in the AE profile between male and female subgroups were observed in the tislelizumab monotherapy treatment groups.

3.6. Effects Table

Table 145: Effects table for Tizveni as monotherapy for the treatment of advanced / metastatic NSCLC after prior chemotherapy (Study 303; data cut-off: 15 Jul-2021)]

Effect	Short Description	Unit	Tislelizumab 200 mg Q3W	Docetaxel	Uncertainties/ Strength of evidence
Favourable Effects					
OS median	Time from randomisation until death	months	16.9	11.9	Impact of high rate of dropouts in docetaxel population Uncertainties regarding external validity
		HR, 95% CI	0.66 (0.56, 0.79)		
PFS median	Time from the date of randomisation to first tumour progression or death	months	4.2	2.6	
		HR, 95% CI	0.63 (0.53, 0.75)		
Unfavourable Effects					
Tolerability					
	Grade ≥3 AE • *drug related*	%	39 *14*	75 *66*	
	Serious AE • *drug related*	%	33 *13*	32 *23*	
	AE leading to death • *drug related*	%	6.0 *1.5*	4.3 *1.6*	
	AE leading to discont. • *drug related*	%	11 *6*	12 *10*	
Immune-mediated AE					
	All cause imAE • *Grade ≥ 3* • *serious*	%	19.5 *6.6* *7.5*	NR	
Most frequent imAE (≥1%)					
	Hypothyroidism	%	7.9	NR	
	Pneumonitis	%	6.2	NR	
	Skin adverse reaction	%	1.5	NR	
	Hepatitis	%	1.3	NR	

Effect	Short Description	Unit	Tislelizumab 200 mg Q3W	Docetaxel	Uncertainties/ Strength of evidence
	Myositis/rhabdomyolysis	%	1.3	NR	
	Thyroiditis	%	1.1	NR	

Table 146: Effects table for Tizveni in combination with chemotherapy for the 1L treatment of advanced/metastatic NSCLC (data cut-off for non-squamous Study 304: 26-Oct-2020; data cut-off for squamous Study 307: 30-Sep 2020)

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects 1L squamous NSCLC						
Arm T+PC vs PC						
PFS median	Time from randomisation to first tumour progression or death	months	7.7	5.5	Only Asian patients were included No data are available for patients older than 75.	
		HR, 95% CI	0.45 (0.33, 0.62)			
OS median	Time from the date of randomisation until death	months	22.8	20.2		
		HR, 95% CI	0.68 (0.45, 1.01)			
Arm T+nPC vs PC						
PFS median	Time from randomisation to first tumour progression or death	months	9.6	5.5		
		HR, 95% CI	0.43 (0.31, 0.60)			
OS median	Time from the date of randomisation until death	months	NE	20.2		
		HR, 95% CI	0.75 (0.50, 1.12)			
Favourable Effects 1L non-squamous NSCLC (TC PD-L1 >=50%)						
PFS median	Time from randomisation to first tumour progression or death	months	14.6	4.6	Only Asian patients were included. No data are available for patients older than 75.	
		HR, 95% CI	0.31 (0.18, 0.55)			
OS median	Time from the date of randomisation until death	months	NE	13.1		
		HR, 95% CI	0.39 (0.22, 0.71)			

Effect	Short Description	Unit	Pooled T+chemo (Studies 307 + 304+206)	Pooled chemo (Studies 307 + 304+206)	Uncertainties/ Strength of evidence	References
Unfavourable Effects						
Tolerability						
	Grade ≥3 AE • *drug related*	%	79.3 *74.8*	70.9 *63.9*	Studies in 1L NSCLC conducted exclusively in China;	clinical AR, CSR, SCS
	Serious AE • *drug related*	%	40.0 *24.7*	23.8 *14.1*		
	AE leading to death • *drug related*	%	4.2 *1.6*	3.1 *1.8*		

	AE leading to discont.	%	28.4	12.8
Immune-mediated AE				
	All cause imAE • *Grade ≥ 3* • *serious*	%	25.6 *10.5* *10.9*	NR
Most frequent imAE (≥1%)				
	Hypothyroidism	%	9.1	NR
	Pneumonitis	%	9.1	NR
	Skin adverse reaction	%	3.8	NR
	Hepatitis	%	1.6	NR
	Colitis	%	1.4	NR
	Myocarditis	%	1.4	NR
	Myositis/rhabdomyolysis	%	1.2	NR
	Nephritis	%	1.0	NR
	Type 1 diabetes mell.	%	1.0	NR

Abbreviations: drug-related: related to tislelizumab and/or chemotherapy; NR: not reported; CSR: clinical study report, SCS: summary of clinical safety, T+nPC: Tislelizumab + nab-paclitaxel

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Monotherapy 2L+ NSCLC

A clinically meaningful benefit in overall survival was demonstrated in patients with locally advanced or metastatic NSCLC after prior chemotherapy. The described safety profile of tislelizumab monotherapy in the sought indication was as expected for PD-1 inhibitors without new safety concerns.

Combination therapy 1L NSCLC

A clinically meaningful benefit in PFS was demonstrated for the addition of tislelizumab to combination chemotherapy in patients with locally advanced or metastatic squamous NSCLC; a positive trend in OS can be considered supportive.

In patients with non-squamous NSCLC, a benefit in PFS was also shown in the overall study population; however, the treatment effect was driven by the subgroup of patients whose tumour express PD-L1 in ≥ 50% of tumour cells.

The safety profile of tislelizumab in combination with chemotherapy reflects the added toxicities of the single components, as already observed for other PD-(L)1 /chemotherapy combinations treatments in this setting.

3.7.2. Balance of benefits and risks

Monotherapy 2L+ NSCLC

In view of the relevant improvement in overall survival, the benefit of treatment with tislelizumab is considered to outweigh its associated risks.

Combination therapy 1L NSCLC

For squamous NSCLC, the clinically meaningful benefit in PFS is acknowledged and is considered to outweigh the observed added toxicities.

For non-squamous NSCLC, a clinically meaningful benefit in PFS is considered established for the addition of tislelizumab in the patients whose tumour express PD-L1 in ≥ 50% of tumour cells and is considered to outweigh the observed added toxicities.

3.8. Conclusions

The overall benefit/risk balance of Tizveni is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Tizveni is favourable in the following indication(s):

-in combination with pemetrexed and platinum-containing chemotherapy for the first-line treatment of adult patients with non-squamous non-small cell lung cancer whose tumours have PD-L1 expression on ≥50% of tumour cells with no EGFR or ALK positive mutations and who have:

- locally advanced NSCLC and are not candidates for surgical resection or platinum-based chemoradiation, or
- metastatic NSCLC.

-in combination with carboplatin and either paclitaxel or nab-paclitaxel for the first-line treatment of adult patients with squamous non-small cell lung cancer who have:

- locally advanced NSCLC and are not candidates for surgical resection or platinum-based chemoradiation, or
- metastatic NSCLC.

-as monotherapy for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer after prior platinum-based therapy. Patients with EGFR mutant or ALK positive NSCLC should also have received targeted therapies before receiving tislelizumab.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

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.

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

- **Risk Management Plan (RMP)**

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

An updated RMP should be submitted:

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

- **Additional risk minimisation measures**

Prior to the launch of Tizveni in each Member State, the MAH must agree about the content and format of the Patient Card, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The Patient Card is aimed at increasing the awareness of patients on the signs and symptoms relevant to the early recognition/identification of the potential immune-related ARs and prompt them about when to seek medical attention. It also contains prompts to enter the contact details of the physician and to alert other physicians that the patient is being treated with Tizveni. The Patient Card is designed to be carried by the patient at all times and presented to any healthcare professional who may help them.

The MAH shall ensure that in each Member State where Tizveni is marketed, all healthcare professionals and patients/carers who are expected to prescribe and use Tizveni have access to/are provided with the Patient Card disseminated through healthcare professionals.

The Patient Card shall contain the following key elements:

- Description of the main signs or symptoms of the immune-related ARs (pneumonitis, colitis, hepatitis, endocrinopathies, immune-mediated skin adverse reactions, nephritis and other immune-related ARs) and infusion-related reactions, and the importance of notifying their treating physician immediately if symptoms occur.
- The importance of not attempting to self-treat any symptoms without consulting their healthcare professional first.
- The importance of carrying the Patient Card at all times and to show it at all medical visits to healthcare professionals other than the prescriber (e.g. emergency healthcare professionals).
- A warning message to inform healthcare professionals treating the patient at any time, including in emergency conditions, that the patient is being treated with Tizveni.
- A reminder that all known or suspected adverse drug reactions (ADRs) can also be reported to local regulatory authorities.
- The contact details of their Tizveni prescriber.

The Patient Card reminds patients about key symptoms that need to be reported immediately to the physician.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the review of available data, it is considered that tislelizumab is not a new active substance, as it is a constituent of a medicinal product previously authorised within the European Union. Tislelizumab is contained in the marketing authorisation Tevimbra which was authorised in the Union on 15/09/2023.