EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 July 2023
EMA/CHMP/359838/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tevimbra

International non-proprietary name: tislelizumab

Procedure No. EMEA/H/C/005919/0000

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	Antidrug Antibodies
ADCC	Antibody-Dependent Cellular Cytotoxicity
ADCP	Antibody-Dependent Cellular Phagocytosis
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event Of Special Interest
AET	Analytical Evaluation Threshold
ALK	Anaplastic Lymphoma Kinase
ALT	Alanine Aminotransferase
ASCO	American Society Of Clinical Oncology
AST	Aspartate Aminotransferase
Aucss	Area Under The Concentration Time Curve At Steady State
BOR	Best Overall Response
C1q	Subcomponent Of The C1 Complex Of The Classical Pathway Of Complement Activation
CAPA	Corrective Action And Preventive Action
CBR	Clinical Benefit Rate
CCIT	Container Closure Integrity Testing
CCS	Container Closure System
CDC	Complement-Dependent Cytotoxicity
Cdx	Companion Diagnostic
Cgmp	Current Good Manufacturing Practice
CHMP	Committee For Evaluation Of Human Medicinal Products
CHO	Chinese Hamster Ovary
Chp	Chinese Pharmacopoeia
CI	Confidence Interval
CL	Clearance
CMC	Chemistry, Manufacturing, And Controls
CMH	Cochran-Mantel-Haenszel
Cmin, Cmin,Ss	Minimum Concentration, Minimum Concentration At Steady State
CPI	Checkpoint Inhibitor
CPP	Critical Process Parameter
CPS	Combined Positive Score
CR	Complete Response
Creatine Kinase-MB	Creatine Kinase Myocardial Band
CRR	Complete Response Rate
CSR	Clinical Study Report
DCR	Disease Control Rate
DNA	Deoxyribonucleic Acid
DOR	Duration Of Response
DP	Drug Product
DS	Drug Substance
EAC	Esophageal Adenocarcinoma
EC	Esophageal Cancer
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
Egfr	Estimated Glomerular Filtration Rate
ELISA	Enzyme-Linked Immunosorbent Assay
EMA	European Medicines Agency
EOPCB	End-Of-Production Cell Bank
EORTC	European Organisation For Research And Treatment Of Cancer
EP	European Pharmacopoeia
EQ-5D-5L	Euroqol 5-Dimension 5-Level
E-R	Exposure-Response
ESCC	Esophageal Squamous Cell Carcinoma
ESMO	European Society For Medical Oncology
EU	Endotoxin Unit
EU	European Union

Fcγr	Fc-Gamma Receptor
FMP	Final Manufacturing Process
GEJ	Gastroesophageal Junction
HC	Heavy Chain
HCB	Host Cell Bank
HCC	Hepatocellular Carcinoma
HR	Hazard Ratio
Hrqol	Health-Related Quality Of Life
HRT	Hormone Replacement Therapy
IC50	Inhibitory Concentration 50%
ICC	Investigator-Chosen Chemotherapy
ICH	International Council For Harmonization Of Technical Requirements For Pharmaceuticals For Human Use
Igg4	Immunoglobulin G4
Igg4	Immunoglobulin G4
IND	Investigational New Drug
IPC	In-Process Control
ISI	Integrated Summary Of Immunogenicity
ITT	Intention-To-Treat
IV	Intravenous(-Ly)
JP	Japanese Pharmacopoeia
KD	Equilibrium Dissociation Constant
KPP	Key Process Parameter
LC	Light Chain
LDH	Lactate Dehydrogenase
LER	Low Endotoxin Recovery
LIVCA	Limit Of In Vitro Cell Age
MAA	Marketing Authorisation Application
MCB	Master Cell Bank
Meddra	Medical Dictionary For Regulatory Activities
MHCB	Master Host Cell Bank
MO	Major Objection
MTD	Maximum Tolerated Dose
NA	Not Available
Nab	Neutralizing Antibody
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria For Aes
NE	Not Estimable Or Not Evaluable
NOR	Normal Operating Range
NR	Not Reported
NSCLC	Non-Small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall Survival
PACMP	Post-Approval Change Management Protocol
PAR	Proven Acceptable Range
PBRER	Periodic Benefit-Risk Evaluation Report
PD	Progressive Disease
PD-1	Programmed Cell Death Protein-1
PDE	Permitted Daily Exposure
PD-L1, PD-L2	Programmed Cell Death Ligand-1, Programmed Cell Death Ligand-2
PE	Polyethylene
PFS	Progression-Free Survival
Ph. Eur.	European Pharmacopoeia
PIP	Paediatric Investigation Plan
PK	Pharmacokinetic(S)
Poppk	Population Pharmacokinetics
PP	Process Parameter
PPQ	Process Performance Qualification
PR	Partial Response
PRS	Primary Reference Standard
PS	Performance Status
PT	Preferred Term
PVC	Polyvinyl Chloride
Q2W	Once Every 2 Weeks

Q3W	Once Every 3 Weeks
QA	Quality Attribute
Qbd	Quality By Design
QLQ-C30	Quality-Of-Life Questionnaire-Core 30 (30 Questions)
QLQ-OES18	Quality-Of-Life Questionnaire-Oesophageal Cancer Module (18 Questions)
RECIST	Response Evaluation Criteria In Solid Tumours
RH	Relative Humidity
RP2D	Recommended Phase II Dose
RRF	Risk-Ranking And Filtering
RS	Reference Standard
SBP	Summary Of Biopharmaceutic Studies And Associated Analytical Methods
SCAR	Severe Cutaneous Adverse Reaction
SCB	Safety Cell Bank
SCE	Summary Of Clinical Efficacy
SCP	Summary Of Clinical Pharmacology Studies
SCS	Summary Of Clinical Safety
SD	Stable Disease
SEER	Surveillance, Epidemiology, And End Results
SJS	Stevens-Johnson Syndrome
SOC	Standard Of Care
SP263	PD-L1 Antibody
TAP	Tumour Area Positive Score
TEAE	Treatment-Emergent Adverse Event
TEN	Toxic Epidermal Necrolysis
TIC	Tumour Immune Cell
TNF	Tumour Necrosis Factor
TNM	Tumour Node Metastasis
TSE	Transmissible Spongiform Encephalopathy
TTR	Time To Response
ULN	Upper Limit Of Normal
UNK	Unknown
USP	United States Pharmacopoeia
V2, V3	Peripheral Volumes 2 And 3
Vc	Central Volume Of Distribution
Vcps	Visually Estimated Combined Positive Score
W1D1, W5D1	Week 1 Day 1, Week 5 Day 1
WBC	White Blood Cell
WCB	Working Cell Bank
WRS	Working Reference Standard

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 tislelizumab, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

Tislelizumab, was designated as an orphan medicinal product EU/3/20/2357 on 13 November 2020 in the following condition: treatment of adult patients with unresectable, recurrent, locally advanced or metastatic oesophageal squamous cell carcinoma after prior chemotherapy.

The applicant applied for the following indication: Tevimbra as monotherapy is indicated for the treatment of adult patients with unresectable, recurrent, locally advanced or metastatic oesophageal squamous cell carcinoma after prior chemotherapy.

1.2. 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).

1.3. 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.

1.4. Information relating to orphan market exclusivity

1.4.1. 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.

1.4.2. 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 claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.5. Scientific Advice

The applicant received the following protocol assistance on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
14 December 2017	EMEA/H/SA/3646/2/2017/II	Dr Paolo Foggi and Dr Kolbeinn Gudmundsson

The Scientific Advice pertained to the following *clinical* aspects:

- The Design and elements of the proposed pivotal study 302 including eligibility criteria, stratification factors, geographic distribution, comparator, primary endpoint, interim analysis and statistical plan; the appropriateness of said study to support approval in the sought indication was in particular discussed.

  In their advice, the CHMP overall acknowledged the design (open label monotherapy vs ICC) and the main elements of the study, including most eligibility criteria, the comparators, primary endpoint (OS) and the proposed statistical methodology. It was pointed out that the results of a single trial should be compelling to support approval. It was further recommended to the applicant to ensure representativeness of EU patients, to explore other stratification factors, to plan in advance for biomarker subgroup analyses and to consider generating comparative data vs best supportive care for less fit patients. The planned interim analysis of study 302 as proposed was discouraged on the basis of immaturity. A general comment to justify the dose and schedule of the product for further clinical development also ensued.

- The size of the safety database to be generated (approximately 300 oesophageal squamous cell cancer patients and approximately 1000 patients with various tumour types with monotherapy) to support a future approval. The CHMP considered it of reasonable size to allow assessment.
- The safety management plan. This was also endorsed by the CHMP.
- The appropriateness of the proposed instruments to measure quality of life (EORTC QLQC30, EORTC OES-18 and EQ-5D). These were considered adequate for the proposed patient population and line of treatment.

  It may be noted that the main clinical study 302 subject of this MAA (refer to section 2.6.5) is overall compliant with the above advice received, as the Applicant has retained the design, introduced other stratification factors, used OS as primary and removed the interim analysis.

  In the interest of transparency, it is also noted here that the Applicant, either directly or through its co-developer also received Scientific advice in other indications that are not discussed in this report. These include first line hepatocellular carcinoma (EMEA/3646/1/2017/II) first line unresectable or metastatic esophageal squamous cell cancer (EMEA/SA/3646/3/2018/II) esophageal cancer, first line gastric or gastroesophageal junction adenocarcinoma (EMA/SA/3646/4/2018/II) as well as advice in solid tumours in general (EMA/SA/0000121172).

1.6. 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 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 CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	28 June 2023
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, GCP and GLP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
– A GCP inspection at 1 clinical investigator site in Germany and 1 sponsor site in USA between 5 July and 16 November 2022. The outcome of the inspection carried out was issued on	20 January 2023
– A pre-approval GMP inspection at 1 manufacturing site in China between 13 March and 17 March 2023. The outcome of the inspection carried out was issued on 22/05/2023 (GMP certificate).	22 May 2023
– A GLP inspection at 1 Contract Research Organisation in China between 14 November and 18 November 2022. The outcome of the inspection carried out was issued on	20 January 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	7 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 and/or in an oral explanation to be sent to the applicant on	30 March 2023
The applicant submitted the responses to the CHMP List of Outstanding Issues on	16 June 2023
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	5 July 2023

The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Tevimbra on	20 July 2023
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product	20 July 2023

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The initially claimed therapeutic indication was: "Tevimbra as monotherapy is indicated for the treatment of adult patients with unresectable, recurrent, locally advanced or metastatic oesophageal squamous cell carcinoma after prior chemotherapy."

2.1.2. Epidemiology and risk factors

Oesophageal cancer (OC) is the eighth most common cancer and the sixth most common cause of cancer-related death worldwide, with an estimated 604,100 new cases and 544,076 deaths (5.5% of all cancer mortality) observed in 2020 (GLOBOCAN 2020, accessed 04 March 2021). In 2018, the highest mortality rates of EC were found in Eastern Asia (with an age-standardized rate of 10.7), Eastern Africa (8.2), Southern Africa (7.2), and Northern Europe (4.3) (Huang et al 2021). Although EC is a rare disease in Europe (annual incidence approximately 1/13,300, according to Orphanet), it remains a highly fatal disease and a major cause of cancer mortality.

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

2.1.3. Clinical presentation, diagnosis and stage/prognosis

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

regional disease and 6.1% for patients with distant metastases. Patients diagnosed or treated once OSCC has progressed face a very poor prognosis (Abraham et al 2020).

2.1.4. Management

Depending on the clinical situation, patients with advanced (metastatic, unresectable, or recurrent after curative therapy) OSCC have different palliative treatment options. Platinum-based doublet chemotherapy (cisplatin/oxaliplatin/carboplatin plus fluoropyrimidines or taxanes) is usually offered as first-line palliative therapy aiming at an extension of survival of patients with good performance status (Lordick et al. 2016, Muro et al. 2019, NCCN 2020). Unfit patients (ECOG PS >1) are treated with best supportive care. Localized treatments such as radiotherapy (including external radiation or brachytherapy) and endoscopic therapies (stents) are applied for the symptomatic treatment of obstruction and dysphagia.

At the time of the initiation of the pivotal study (Study 302) for this submission, there were no approved therapies for patients with advanced or metastatic OSCC after failure of 1st line therapy. Back then, single-agent palliative chemotherapy (taxanes, irinotecan) was recommended and commonly used in medical practice for patients with good PS scores (0 or 1) following 1st line systemic therapy worldwide (NCCN 2017).

Nivolumab received a positive opinion from EMA in October 2020 as monotherapy for the treatment of patients with unresectable advanced, recurrent or metastatic OSCC after prior fluoropyrimidine- and platinum-based combination chemotherapy based on the results of ATTRACTION-3 (Kato et al 2019).

Unmet medical need

Efficacy of palliative systemic chemotherapy used in the 2nd line setting of advanced and/or metastatic OSCC has been described to be limited with fewer than 20% of patients responding to treatment and poor long-term survival (median OS of approx. 3 to 7 months). On the other hand, single-agent palliative chemotherapy is associated with substantial haematological, gastrointestinal, and neurological toxicities. As such, there was an urgent need for efficacious therapies for OSCC with improved tolerability in the 2nd line setting (Burkart et al 2007, Mizota et al 2011, Shirakawa et al 2014, Song and Zhang 2014).

PD-1 inhibitors have demonstrated survival improvement over chemotherapy in patients with advanced or metastatic OSCC previously treated with systemic therapy (Kato et al 2019, Kojima et al 2020).

2.2. About the product

Tislelizumab is a humanized IgG4 variant monoclonal antibody that binds to the T-cell surface receptor programmed cell death protein 1 (PD-1) with high specificity and affinity (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 claimed indication for tislelizumab is for the treatment of adult patients with unresectable, recurrent, locally advanced or metastatic oesophageal squamous cell carcinoma after prior chemotherapy.

Approved indication:
Tevimbra as monotherapy is indicated for the treatment of adult patients with unresectable, locally advanced or metastatic oesophageal squamous cell carcinoma after prior platinum-based chemotherapy.
Tevimbra treatment must be initiated and supervised by physicians experienced in the treatment of cancer.

The recommended dose of Tevimbra is 200 mg administered by intravenous infusion once every 3 weeks. Patients should be treated with Tevimbra until disease progression or unacceptable toxicity.

No dose reductions of Tevimbra as monotherapy are recommended. Tevimbra should be withheld or discontinued as described in Table 1.

Detailed guidelines for the management of immune-related adverse reactions are described in section 4.4.

Table 1: Recommended treatment modifications for Tevimbra

Immune-related adverse reaction	**Severity[1]**	**Tevimbra 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 Tevimbra 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 Tevimbra 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 Tevimbra 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 Tevimbra 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 applicant Novartis Europharm Limited submitted on 1 March 2022 an application for Marketing Authorisation to the European Medicines Agency (EMA) for tislelizumab, through the centralised procedure falling within the Article 3(1) and point 1 and 4 of Annex of Regulation (EC) No 726/2004.

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).

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

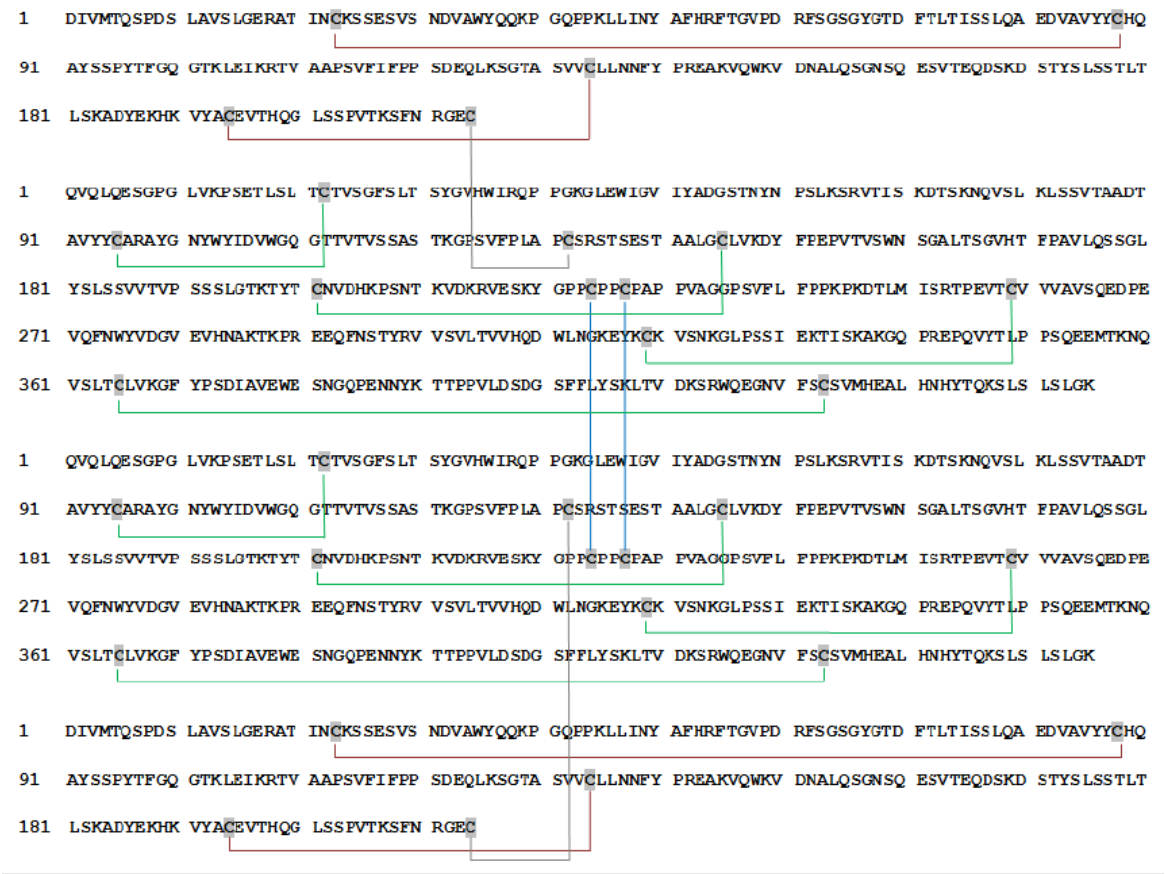


Figure 1. Primary structure of tislelizumab

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 includes 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-sterilized 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 characterization 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 characterization 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 characterization 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.

Characterization

Structure, physicochemical characteristics and biological properties of tislelizumab were elucidated by release tests and additional characterization 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 characterization 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 characterized 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 characterize 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 characterization, 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 (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 optimized 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.

2.5. Non-clinical aspects

2.5.1. Introduction

Tislelizumab is a humanized 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.

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

2.5.2. Pharmacology

2.5.3. 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 (reports 126-128, 135). The experiments include also allogeneic xenograft models of epidermioid carcinoma, colon and lung cancers (Studies 126, 127 and 128). 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 noticed in some animals (Reports: R01-vivo-127 and 125 colon cancers; R01-vivo-126 epidermoid carcinoma; R01-vivo-128 lung cancer). Of note, tumour inoculation had only marginal effect on animal weight and no significant difference could be noted between treated animals and controls.

2.5.3.1. 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 optimize 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). 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 nonclinical proof of concept of tislelizumab.

2.5.3.2. Safety pharmacology programme

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

2.5.3.3. Pharmacodynamic drug interactions

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

2.5.4. 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, Cmax and exposure increased dose-proportionally. 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 Cmax and AUC increased slightly more than dose-proportionally. T ½ ranged from 7-11 days, approximatively. In the first 13-week repeat-dose study in monkeys (P14-057-CD), tislelizumab Cmax 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 the second 13-week repeat-dose study in monkeys (2270246), tislelizumab Cmax and AUC increased approximatively dose proportional at day 1. Light accumulation between d1 and d71 could be seen especially in male animals. 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.

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" 2.5.5.8..

Metabolism and excretion

No metabolism and excretion studies were submitted as part of this application.

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.

2.5.5. Toxicology

2.5.5.1. Single dose toxicity

The Applicant performed a single-dose toxicology study in the non relevant species mice (M14-057-JD), where 0/30/100 mg/kg tislelizumab was administered IV once to 10 female and 10 male animals/group and followed by a 28-day recovery period. The following parameters were analysed: clinical observations, body weight, food consumption, upon necropsy: macroscopic evaluation (gross findings), and no sign of toxicity was observed. No TK analysis was performed so the exposure is not known in this study.

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.

2.5.5.2. Repeat dose toxicity

The Applicant performed a first 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 euthanized after 13-week of dosing on Day 91 and the remaining 2 monkeys/sex/group were euthanized on Day 133) following a 6-week recovery period. No sign of toxicity was observed and the NOAEL was set 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. 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.

2.5.5.3. Genotoxicity

No genotoxicity studies were submitted as part of this application.

2.5.5.4. Carcinogenicity

No carcinogenicity studies were submitted as part of this application.

2.5.5.5. Reproductive and developmental toxicity

No dedicated in vivo 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. Moreover, the effects of PD-1/PD-L1 on prenatal and postnatal development, including maternal function, suggest that inhibition of PD-1/PD-L 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.

2.5.5.6. Toxicokinetic data

See section 2.5.4.

2.5.5.7. Tolerance

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

2.5.5.8. 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, the Applicant's conclusion that "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." is found acceptable.

2.5.6. Ecotoxicity/environmental risk assessment

The applicant has provided a justification for not performing an environmental risk assessment. As tislelizumab is a protein composed of natural amino acids, 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).

2.5.7. Discussion on non-clinical aspects

Tislelizumab is a humanized 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.

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. Although most experiments were performed in very artificial conditions using transfectants and complex cell-based assays, the Applicant appropriately addressed the question raised. Importantly, in the responses, the Applicant provided additional figures showing a weak positive staining for PD-1 on resting T cells and an increase of the positive population in the same donor following stimulation, as expected. This is considered an important proof that tislelizumab is able to bind to naïve PD-1 and together with the new data (from the Retrogenix assay) contributes to clear up the doubts about tislelizumab possible insufficient binding. In several experiments, the Applicant compared tislelizumab binding or activity to other anti-PD-1 mAbs such as nivolumab and pembrolizumab. Most of the results seem to indicate at least equal performance of tislelizumab, but the variability of the methods and missing statistical analysis do not allow a conclusive statement on the comparison.

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. 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 an initial 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 Cmax 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. Although for none of the newly developed validation methods GLP compliance was claimed, the new methods are considered fit for purpose and suitable to be used in support of the pivotal GLP toxicology study.

Of note a REC has been made, since the Applicant committed to communicate the results of the long-term stability study for the bioassay samples (stability of tislelizumab in monkey serum), by amendment to the PK bioanalysis method (BAL-22-031-1470 REP).

As tislelizumab is expected to be degraded to small peptides and individual amino acids, the omission of metabolism and excretion studies is supported.

The toxicity of tislelizumab was assessed in several studies in cynomolgus monkeys, the relevant species.

The GLP TCR studies submitted in the original application were not considered GLP compliant therefore the study results were replaced with Retrogenix assay Given the totality of evidence presented, the validity and the GLP compliance of the two TCR studies was questioned and a GLP inspection triggered. The Applicant was asked to answer the various criticisms presented above and to perform the studies again, selecting a more adequate positive control (e.g. tissue slides with inflamed tonsils). The Applicant preferred to perform a Retrogenix assay instead. 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 (20µg/ml versus 1µg/ml respectively), the signal appears to be strong and specific. These results, together with the data provided for answer 45 contribute to clear up the doubts about tislelizumab possible insufficient binding. The major objection is therefore considered solved. However, 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, the Applicant's conclusion that "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" is found acceptable.

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.

Importantly, despite the Applicant declared the pivotal toxicology study as GLP-compliant, the outcome of the triggered GLP inspection was negative. The Applicant acknowledged this conclusion and proposed several actions to mitigate the negative inspection outcome. In particular, the Applicant communicated the initiation of a new in vivo 13-week repeat dose toxicology study for tislelizumab in an OECD-GLP-compliant facility. Although this new in vivo study was not requested by the CHMP its results needed to be evaluated within the totality of data. 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 and the specificity findings have been resolved.

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.

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.

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, treatment with tislelizumab during pregnancy may lead to abortion or still births. This risk is reflected in the SmPC. No developmental and reproductive toxicity studies or animal fertility studies have been conducted with tislelizumab.

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

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, considering the above data, tislelizumab is not expected to pose a risk to the environment.

2.5.8. Conclusion on non-clinical aspects

Overall, the Applicant performed an adequate package of in vitro and in vivo non-clinical studies with tislelizumab. 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) because of doubts about the plausibility of the results reported in the respective study reports and the negative inspection history of the facility. 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. The Applicant acknowledged this conclusion and proposed several actions to mitigate the negative inspection outcome. In particular, the Applicant communicated the initiation of a new in vivo 13-week repeat-dose toxicology study for tislelizumab in an OECD-GLP-compliant facility. Although this new in vivo study was not requested by the CHMP its results needed to be evaluated within the totality of data. Therefore, the Applicant provided the final report of the additional repeat-dose toxicity study in cynomolgus monkeys as requested. 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)".

2.6. Clinical aspects

2.6.1. 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**

Study number	Study status	Study design	Objective(s) of the study	Patient population (region)	Test product(s); dosage regimen; route of administration	Number of patients [a]
Pivotal study in ESCC indication						
BGB-A317-302	Ongoing	Phase III, randomized, controlled, open-label, multicenter study	Efficacy assessed by OS, PFS, ORR, DOR, and DCR; HRQoL; safety and tolerability; PK, and immunogenicity	Patients with histologically confirmed advanced or metastatic ESCC and tumor progression during or after first-line systemic therapy (Global)	Tislelizumab arm: 200 mg Q3W; IV ICC arm: One of the following: Paclitaxel 135 to 175 mg/m^2 IV Q3W starting on Day 1) [b] Docetaxel (75 mg/m^2 IV Q3W starting on Day 1) [c] Irinotecan (125 mg/m^2 IV on Days 1 and 8, and then Q3W)	512 (256 randomized to each treatment arm; 255 received Tislelizumab and 240 received ICC)
Supportive studies including patients with ESCC						
BGB-A317-Study_001	Completed	Phase IA/IB, open-label, multicenter, 2-part, dose-escalation and indication-expansion study	Safety, tolerability, PK, dose selection, and preliminary antitumor activity	Patients with advanced or metastatic solid tumors [d] (Global)	Tislelizumab: 0.5, 2, 5, 10 mg/kg Q2W; 2, 5 mg/kg Q3W; 200 mg Q3W; IV	451 (26 with ESCC)
BGB-A317-102	Completed	Phase I/II, open-label, single-arm, multicenter, 2-part, dose-verification and indication-expansion [c] study	Safety and tolerability, determination of the MTD and RP2D in Chinese patients, anti-tumor activity	Patients with advanced or metastatic solid tumors [e] (China)	Tislelizumab: 200 mg Q3W; IV or 200 mg W1D1, W5D1 Q3W [f] (PK substudy); IV	300 (26 with ESCC)

[a] Includes enrolled and randomized patients (as applicable).
[b] Paclitaxel could also be given at doses of 80 to 100 mg/m^2 on a weekly schedule according to local and/or country-specific guidelines for standard of care; in Japan, paclitaxel was given at doses of 100 mg/m^2 on Days 1, 8, 15, 22, 29, and 36, followed by 1 week of rest.
[c] The docetaxel dose that was used in Japan was 70 mg/m^2 on Day 1, and then every 3 weeks.
[d] In Study 001, the disease types included: colorectal carcinoma, non-small cell lung cancer, melanoma, cutaneous squamous cell carcinoma, uveal melanoma, gastric cancer, pancreatic cancer, ovarian cancer, urothelial bladder cancer, head and neck squamous cell carcinoma, renal cell carcinoma, triple-negative breast cancer, hepatocellular carcinoma, esophageal carcinoma, Merkel-cell carcinoma, cholangiocarcinoma, sarcoma, gastro-intestinal stromal tumor, or other solid tumors with MSI-H or dMMR (plus other cancers that were deemed to be likely to benefit from PD-1 inhibition)
[e] In Study 102, the disease types included: non-small cell lung cancer, melanoma, gastric cancer, esophageal carcinoma, ovarian cancer, urothelial carcinoma, head and neck squamous cell carcinoma, renal cell carcinoma, triple-negative breast cancer, hepatocellular carcinoma, small cell neuroendocrine carcinoma, nasopharyngeal carcinoma, and MSI-H or dMMR colorectal carcinoma
[f] In Study 102, the dose of 200 mg in W1D1, W5D1 Q3W equates to dosing with 200 mg on Day 1 with an interval of 4 weeks for Cycle 1 and once every 3 weeks for cycles thereafter.

Source: Table 1-3 SCE

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Clinical studies that contributed to the characterization of the clinical pharmacology properties of tislelizumab are presented in Table 1-1. 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 1-1 were also used in the popPK analysis and to characterize ER relationships.

Table 1-1 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 2-8 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

Source: /vob/CVDT482G1/mas/mas_1/model/pgm_001/PopPK/EMA_analysis/summary_by_STUDYID.csv

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) electrochemiluminescent (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

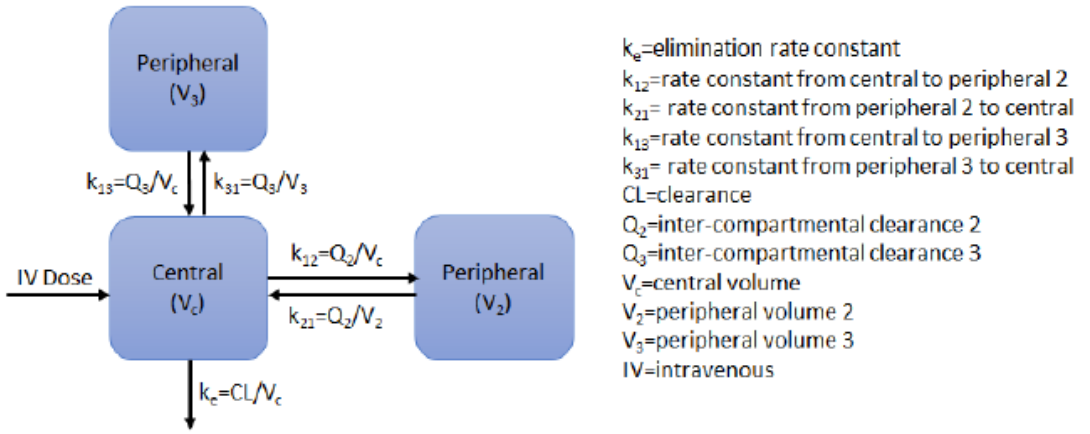
In the early studies (BGB-A317-001 and BGB-A317-102), PK parameters were derived using standard noncompartmental methods with WinNonlin Professional or SAS®.

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 1-1 above) to

quantitatively describe the PK properties of tislelizumab and identify sources of interindividual variability.

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 3).

Figure 3. PopPK model diagram for tislelizumab



Parameter estimates for the final PopPK model for tislelizumab are presented in Table 11.

Table 11. 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%

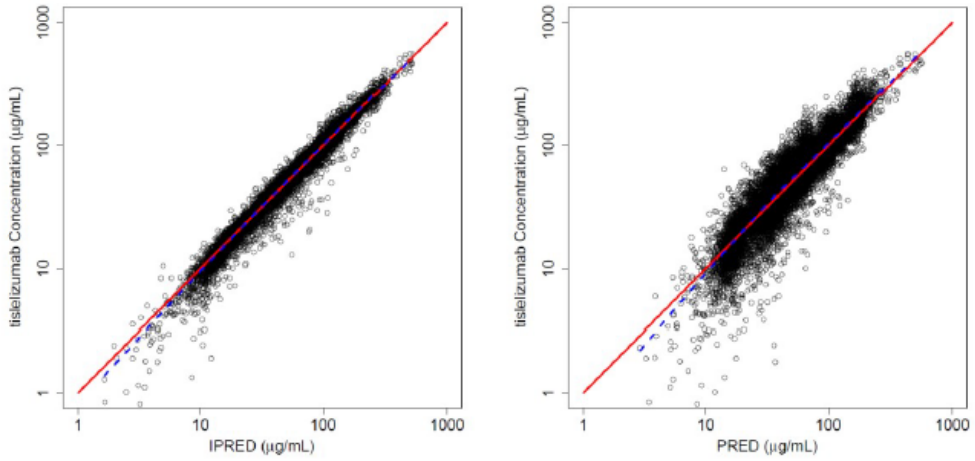
In Amendment 1 to the popPK report, discrepancies regarding the baseline body weight of two subjects from BGB-A317-302 study were corrected and PK parameters were re-estimated using the final PopPK model and the updated PopPK dataset with corrected weights. The estimated PK parameters using updated dataset 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.

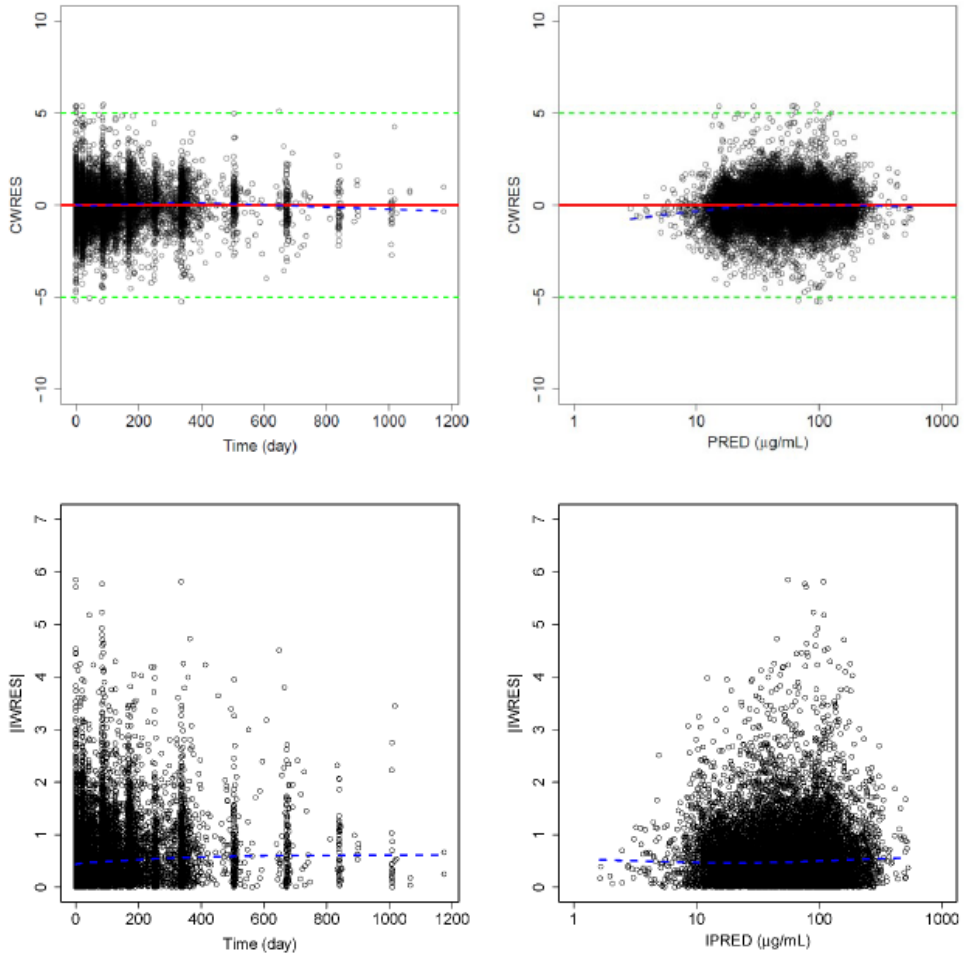
The general goodness-of-fit plots of the final PopPK model are shown in Figure 6 and Figure 7, where a good agreement between the predicted concentrations and the observed concentrations was observed and no apparent bias was observed in the residuals plots over time and across predicted concentrations.

Figure 6. Predicted versus observed concentration for the final PopPK model



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.

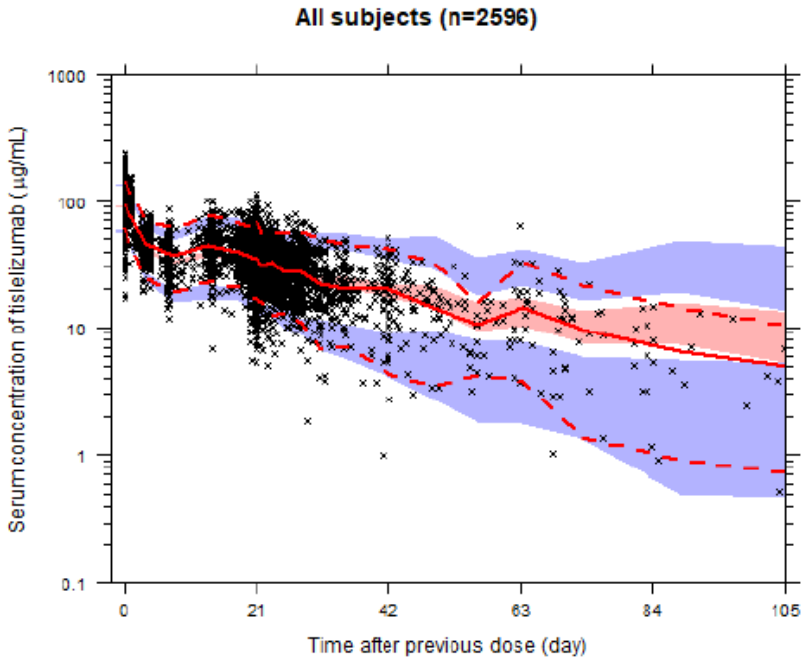
Figure 7. Residual diagnostic plots for the final PopPK model

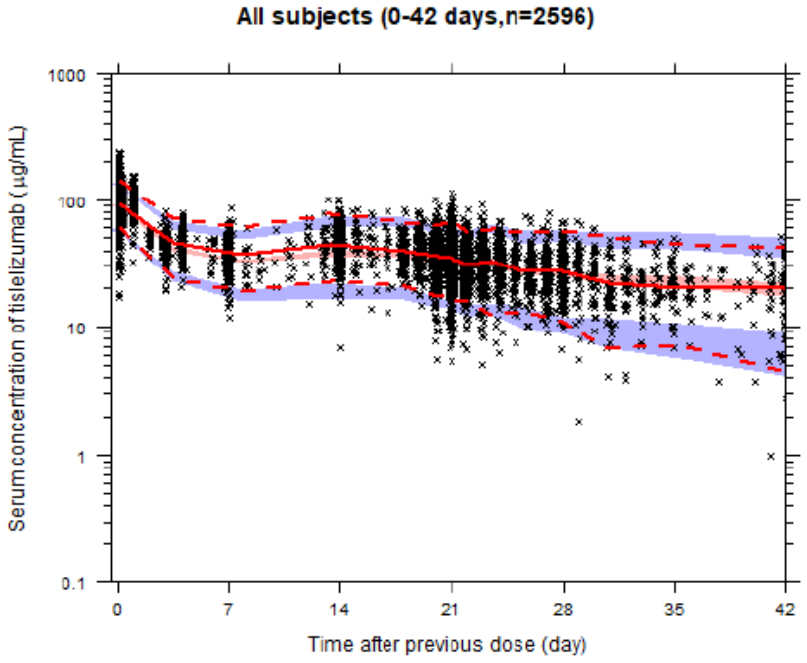


Conditional weighted residuals (CWRES) vs time (top left) and population predicted concentrations (PRED, top right). Absolute individual weighted residuals (|IWRES|) vs time (bottom left) and individual predicted concentrations (IPRED, bottom right). Points are individual data. Red solid lines represent 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.

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 11. Prediction-corrected visual predictive check of tislelizumab serum concentration-time profiles across all studies





Absorption

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

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

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

Distribution

Noncompartmental analysis:

In study 102, gemotric 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 with a coefficient variation (CV) of 31%. Clearance was estimated to be 0.153 L/day with an inter-individual variability of 26.3%.

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

Dose proportionality and time dependencies

In study 001, drug exposure (Cmax 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 Cmax 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, Cmax, and predose Ctrough). Referring to the population PK analysis, the accumulation ratios are 2.14, 1.62, and 2.49 for AUCss, Cmax,ss and Cmin,ss.

PK in target population

Study BGB-A317-302 (Study 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.

A total of 255 patients received tislelizumab at a dose of 200 mg administered intravenously Q3W. Study treatment was administered until disease progression, intolerable toxicity, or another treatment discontinuation criterion was met.

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, stratified by regions up to Cycle 17, are presented in Table 2-9. A total of 254 patients were included in the PK data analysis set, one patient was excluded from the PK summary. The serum concentrations observed in the ESCC patients from this study were generally consistent with those observed in patients from other studies after receiving treatment with tislelizumab at 200 mg Q3W. Results in the Asia and Europe/North America subgroups were similar and consistent with those of the overall population.

Table 2-9 Summary of tislelizumab serum concentrations in Study 302 (PK Analysis Set)

Timepoint	Cycle/	Asia (N = 200) GM (GCV%)	Europe/North America (N = 53) GM (GCV%)	All (N = 253) GM (GCV%)
Predose (C_{min}) µg/mL	Cycle 1	NC (n = 193)	NC (n = 52)	NC (n = 245)
	Cycle 2	17.1 (26.3%) (n = 170)	14.6 (36.2%) (n = 42)	16.6 (29.1%) (n = 212)
	Cycle 5	39.4 (31.3%) (n = 77)	34.3 (43.2%) (n = 17)	38.5 (33.9%) (n = 94)
	Cycle 9	45.5 (41.1%) (n = 47)	45.2 (42.7%) (n = 6)	45.4 (40.9%) (n = 53)
	Cycle 17	44.1 (64.4%) (n = 24)	NA	44.1 (64.4%) (n = 24)
Postdose (C_{max}) µg/mL	Cycle 1	66.2 (21.1%) (n = 196)	58.9 (20.5%) (n = 49)	64.6 (21.5%) (n = 245)
	Cycle 5	109.0 (20.3%) (n = 77)	99.1 (26.0%) (n = 16)	107.0 (21.5%) (n = 93)

Source: [Study 302-Table 14.4.1c, Table 4.4.1, Listing 16.2.5.3 and Listing 16.2.5.3a] (Data cutoff 01-Dec-2020). [Study 302-Table 23]

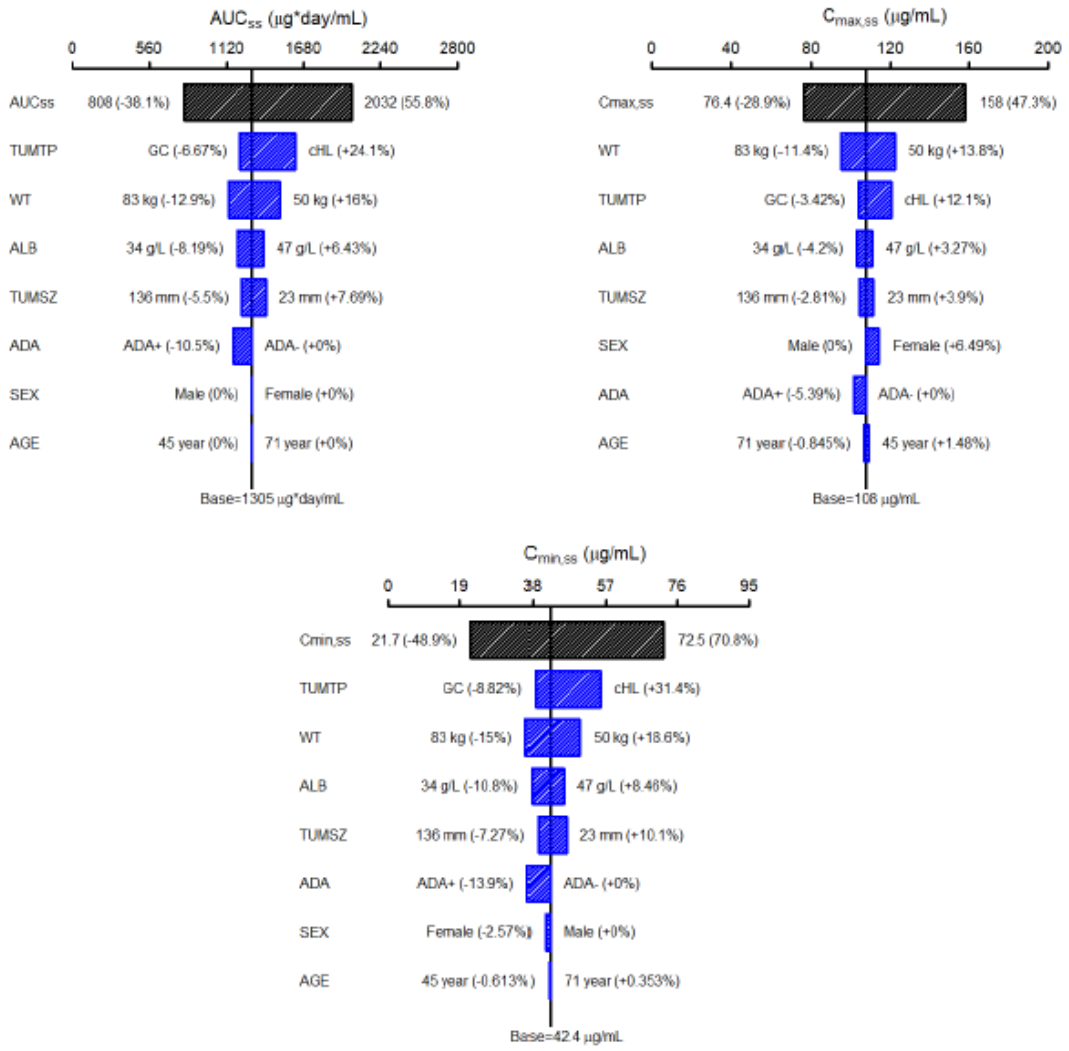
Abbreviations: C_{max}, maximum serum concentration (end of infusion, postdose); C_{min}, minimum serum concentration (predose); GCV, geometric coefficient of variation; GM, geometric mean; M/F, male/female; NA, not available; NC, not calculated.

Population: 254 patients; Sex (M/F): 216/38; Age: 61.4 (40-83); Body weight: 59.3 (37.5-99) kg. 3.5% (39/1100) of samples were excluded from the summary due to aberrant sample collection information.

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.

Figure 15. Sensitivity analysis plot comparing the effect of covariates on tislelizumab steady state exposure (AUC_{ss}, $C_{max,ss}$ and $C_{min,ss}$)

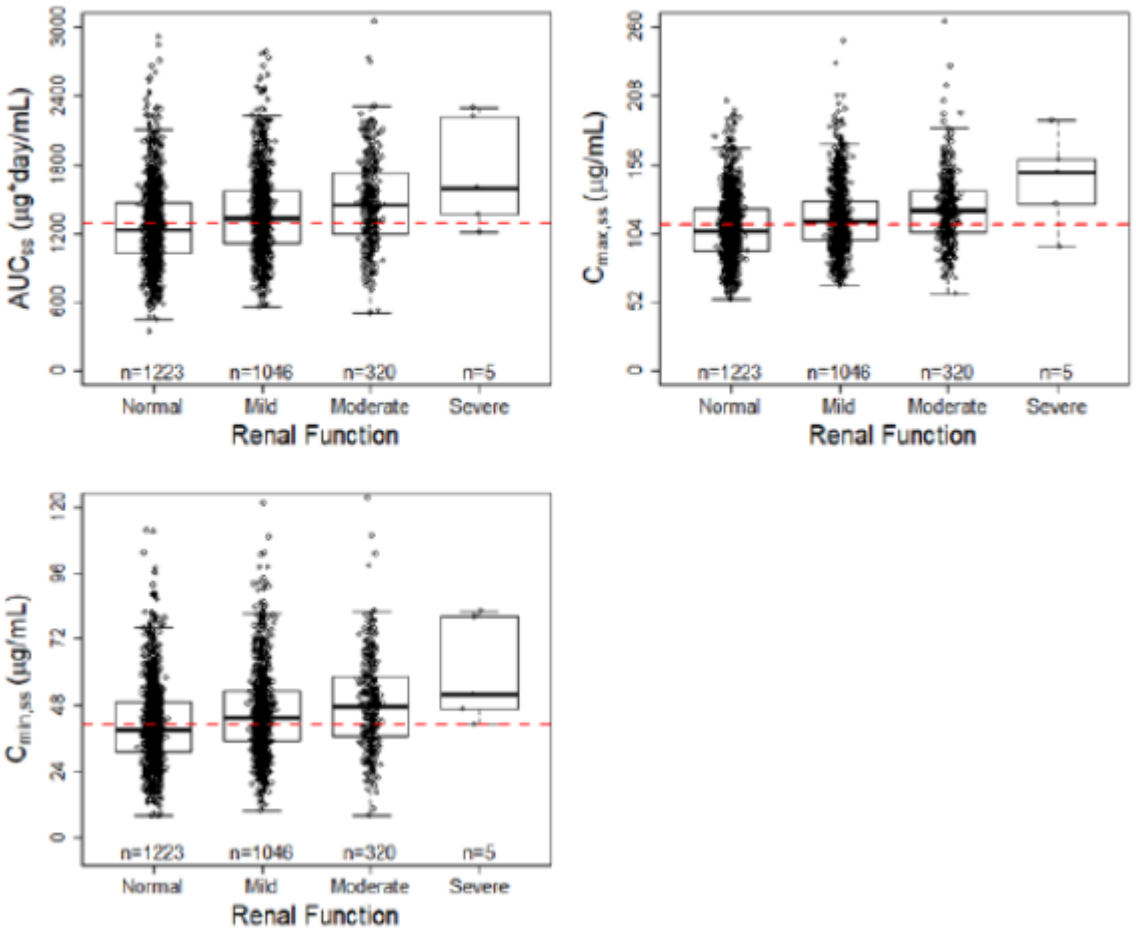


The black vertical line refers to the predicted exposure (AUC_{ss}, $C_{max,ss}$, and $C_{min,ss}$) of tislelizumab in a typical subject after 200 mg Q3W for 30 weeks which serve as the reference values. All percentage values shown in each plot are the relative changes in exposure relative to the reference 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.

Impaired renal function

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 3-5).

Figure 3-5 Steady-state tislelizumab exposure by renal function



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).

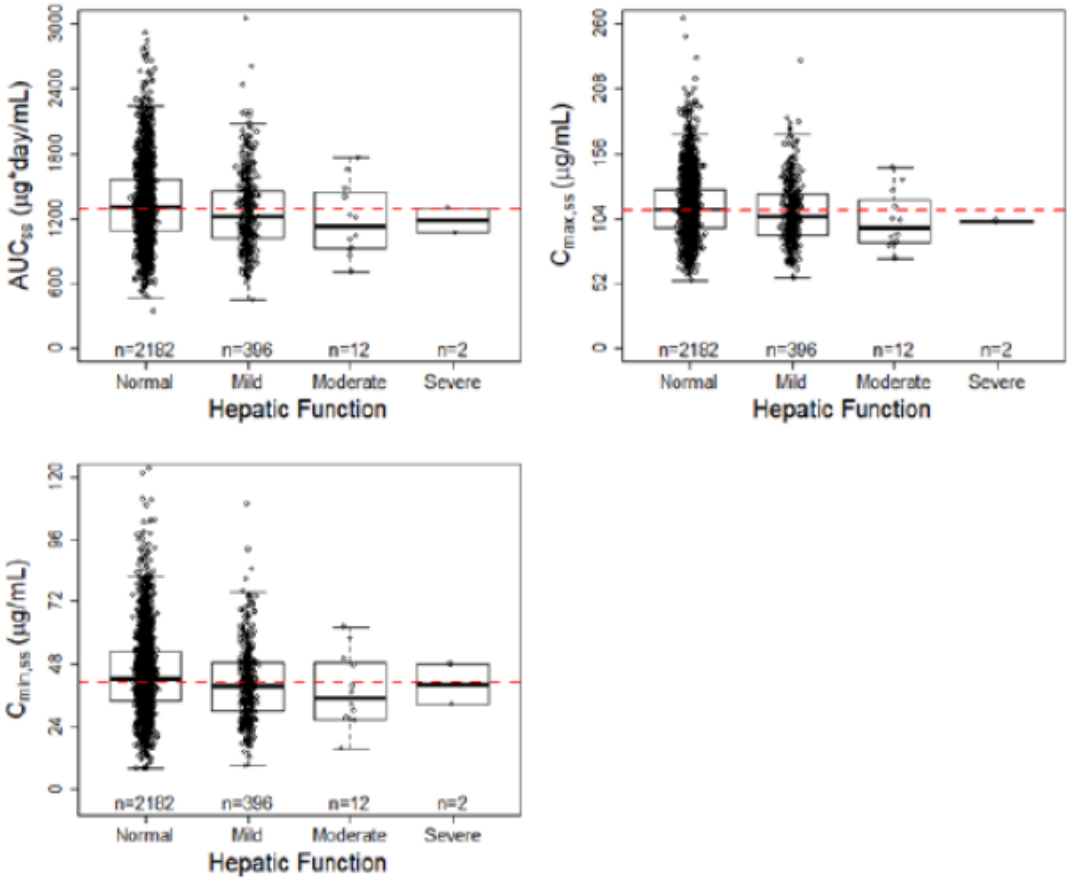
Notes: The steady-state exposures ($C_{min,ss}$ and AUC_{ss}) of tislelizumab were computed for each patient. AUC_{ss} was calculated as dose/CL. $C_{min,ss}$ was calculated as the minimum concentration on the 21st days after the 10th consecutive doses of tislelizumab Q3W [PopPK Report-Section 5.5 and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

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

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, Cmax,ss and Cmin,ss) in mild, moderate, or severe hepatic impairment were up to 8.71% lower, 15.4% lower, and 9.12% lower, respectively, compared with those of 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 (Figure 3-6).

Figure 3-6 Steady-state tislelizumab exposure by hepatic function



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).

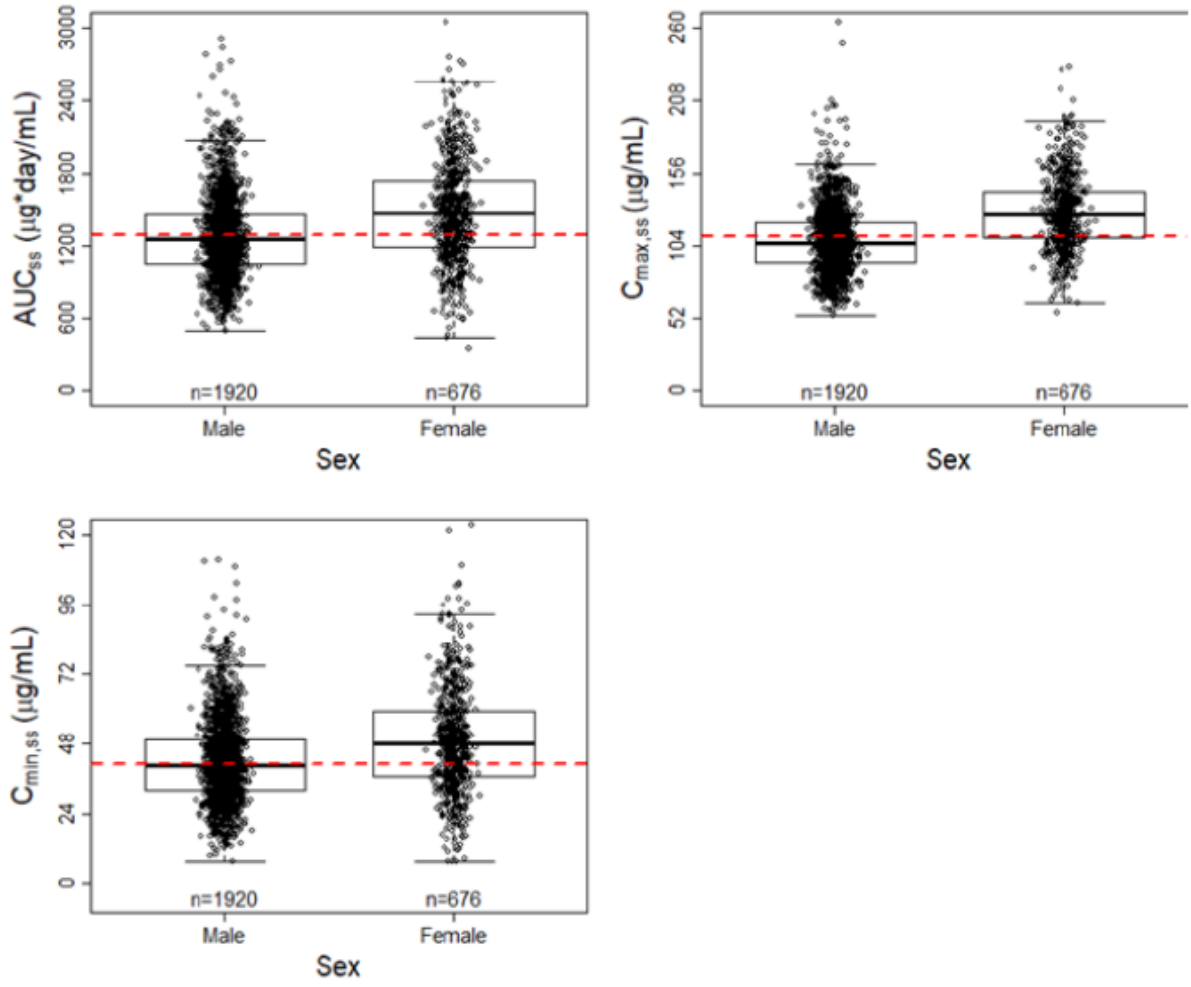
Notes: The steady-state exposures ($C_{min,ss}$ and AUC_{ss}) of tislelizumab were computed for each patient. AUC_{ss} was calculated as dose/CL. $C_{min,ss}$ was calculated as the minimum concentration on the 21st days after the 10th consecutive doses of tislelizumab Q3W [PopPK Report-Section 5.5 and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

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

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, Cmax,ss and Cmin,ss) in female subjects was 14.7% to 19.0% higher compared with those of in male subjects (Figure 3-1).

Figure 3-1 **Simulated steady state exposures of tislelizumab by gender following 200 mg Q3W dosing**



Source: [PopPK Report-Figure 21].

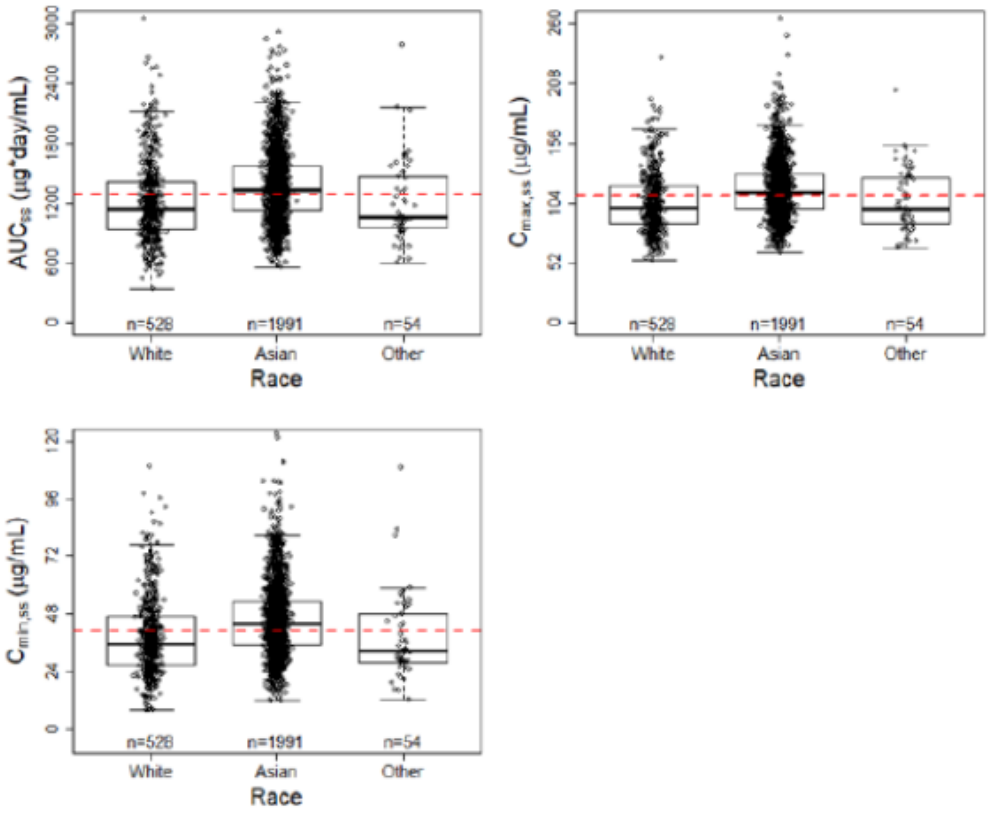
Circles are the simulated steady state tislelizumab exposure in individual subjects. The boxes represent the 25th to 75th percentiles (the interquartile range). The solid black horizontal line in the middle of each box represents the median. The whiskers represent the range of data points within 1.5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

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 in Figure 3-3. The simulated geometric mean exposures (AUCss, Cmax,ss, and Cmin,ss) of the Asian patient population (the majority of Asian patients are Chinese) from 12 studies were approximately 12% to 21% higher than those of white patients.

Figure 3-3 Simulated steady state exposures of tislelizumab by race following 200 mg Q3W dosing



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).

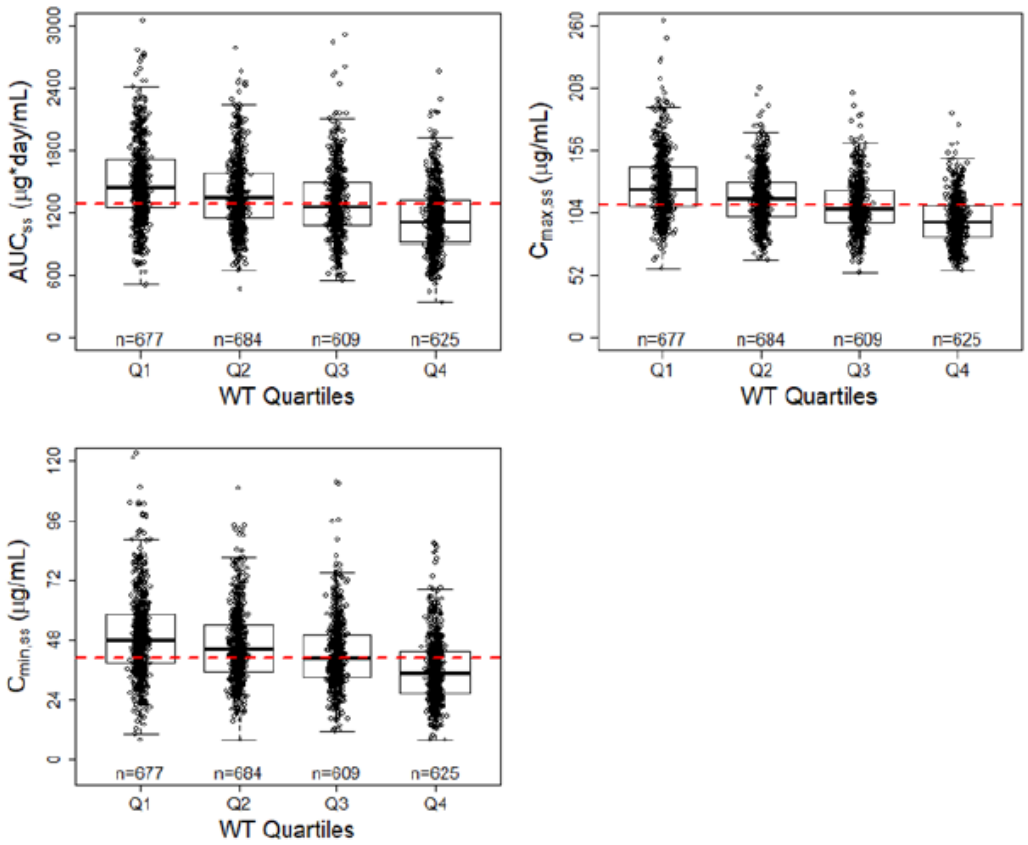
Notes: The steady-state exposures ($C_{min,ss}$ and AUC_{ss}) of tislelizumab were computed for each patient. AUC_{ss} was calculated as dose/CL. $C_{min,ss}$ was calculated as the minimum concentration on the 21st day after 10 consecutive doses of tislelizumab 200 mg Q3W [PopPK Report-Section 5.5 and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

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

Weight

Body weight was identified as a significant covariate on the CL, and Vc of tislelizumab in the final PopPK model. Increased body weight was associated with increased CL and Vc values. Therefore, subjects with higher body weight are predicted to have lower exposure. The geometric mean simulated exposures (AUCss, Cmax,ss and Cmin,ss) in the lowest and highest quartile of body weight were up to 14.5% higher and 17.3% lower, respectively, compared with those of the overall population (Figure 16).

Figure 16. Simulated steady state exposures of tislelizumab by body weight quartiles following 200 mg Q3W dosing



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.

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 16). 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 16. 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 17. The geometric mean simulated exposures (AUCss, Cmax,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 17. Comparison of the predicted steady state exposures in patients stratified by body weight quartiles

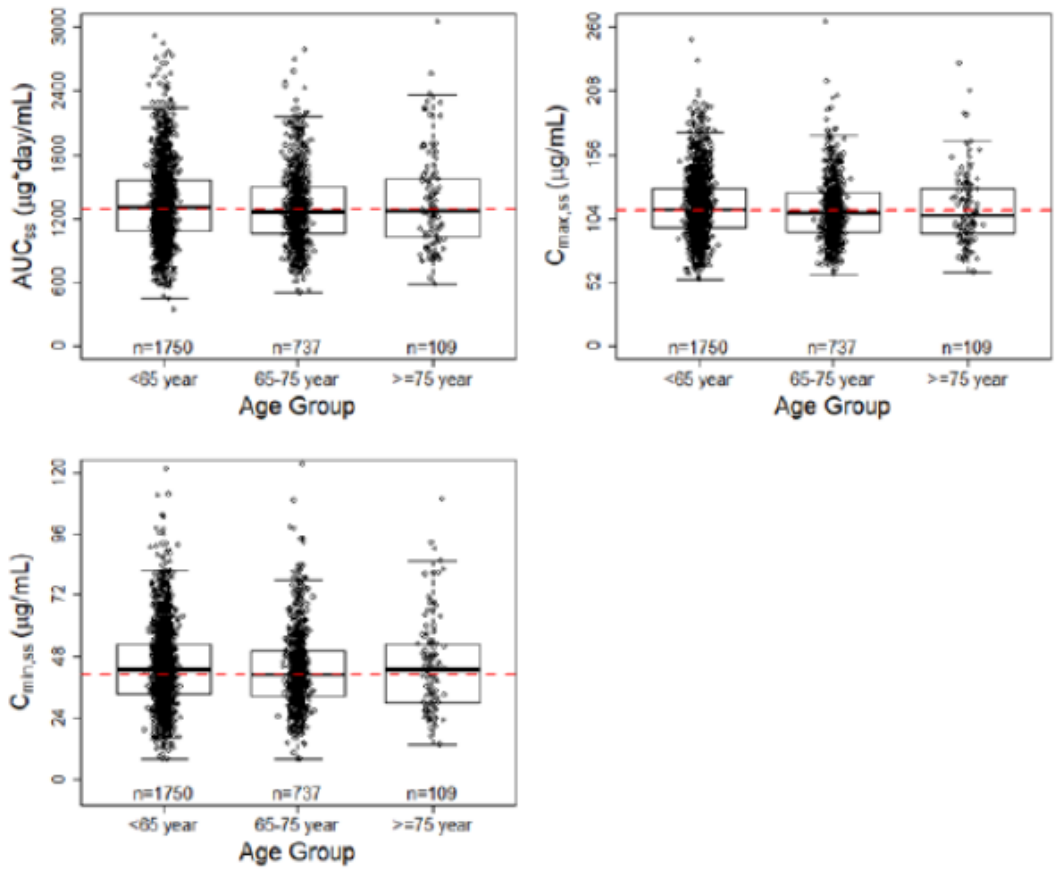
Summary exposure		Body Weight Quartiles							
		Q1		Q2		Q3		Q4	
		200 mg	3 mg/kg	200 mg	3 mg/kg	200 mg	3 mg/kg	200 mg	3 mg/kg
No. of subjects (%)		677 (26.1)		684 (26.4)		609 (23.5)		625 (24.1)	
AUC_{ss} (µg*day/mL)	geometric mean (%CV)	1444 (28.3)	1099 (27.6)	1340 (25.0)	1233 (24.9)	1258 (25.8)	1311 (25.8)	1096 (27.1)	1371 (26.8)
	% difference [a]	12.6	-11.7	4.47	-0.987	-1.91	5.26	-14.6	10.1
$C_{max,ss}$ (µg/mL)	geometric mean (%CV)	124 (21.4)	94.5 (20.8)	114 (18.9)	105 (18.8)	107 (19.7)	112 (19.7)	95.4 (20.3)	119 (20.1)
	% difference [a]	12.7	-11.6	3.63	-1.78	-2.50	4.62	-13.4	11.6
$C_{min,ss}$ (µg/mL)	geometric mean (%CV)	46.9 (35.5)	35.7 (34.7)	43.4 (32.2)	39.9 (32.0)	40.2 (33.2)	41.9 (33.1)	33.9 (35.6)	42.4 (35.0)
	% difference [a]	14.5	-10.2	5.84	0.318	-1.92	5.25	-17.3	6.58
Body weight (kg) [min, median, max]		[31.9, 52, 57]		[57.2, 61, 65]		[65.2, 70, 74]		[74.1, 81, 170]	

[a] %difference from the geometric mean simulated exposures of the overall population for 200 mg Q3W or 3 mg/kg Q3W,respectively

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 3-4.

Figure 3-4 **Simulated steady state exposures of tislelizumab by age group following 200 mg Q3W dosing**



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.

Children

Tislelizumab has no study conducted in pediatric 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, Cmax,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 in Table 21 and Figure 23.

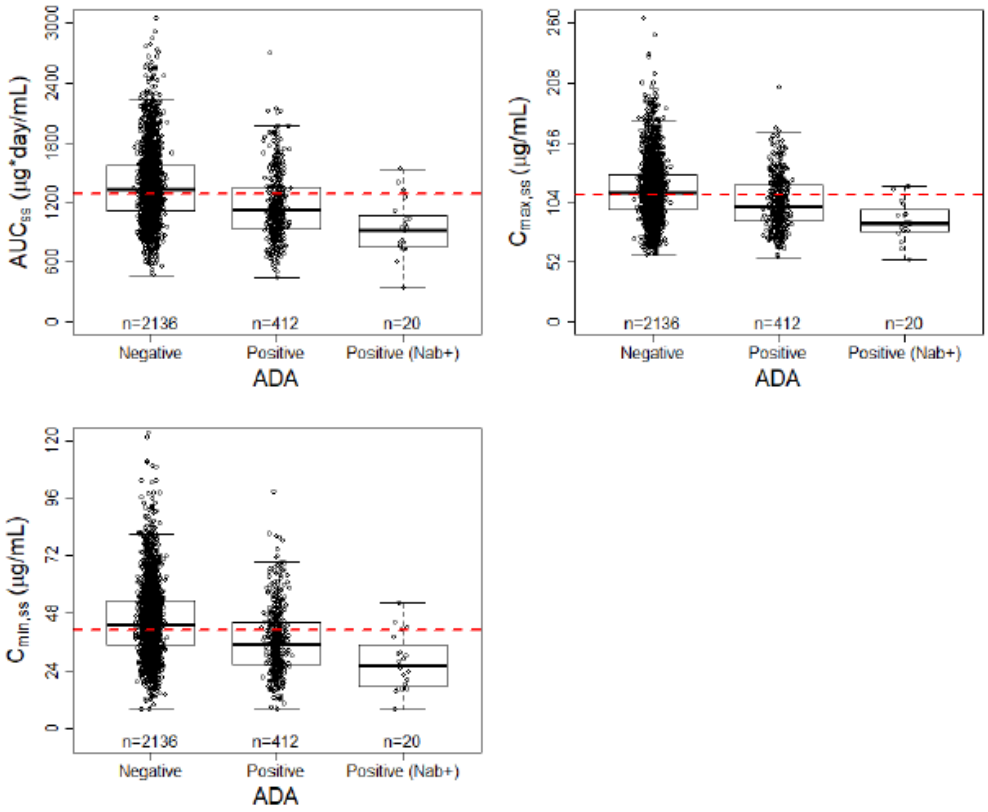
The geometric mean simulated exposures (AUCss, Cmax,ss and Cmin,ss) in ADA positive subjects were up to 20.5% lower compared with those of in ADA negative subjects (Table 21).

Table 21. Geometric mean (%CV) simulated steady state exposure of tislelizumab by ADA status following 200 mg 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.

Figure 23. Simulated steady state exposures of tislelizumab by ADA following 200 mg Q3W dosing



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.

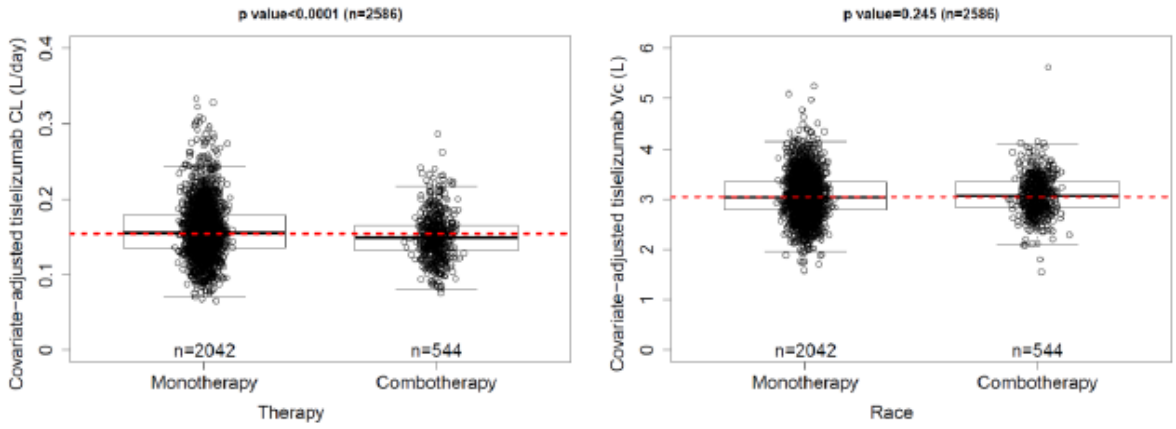
Pharmacokinetic interaction studies

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 30. The result suggested a significant correlation ($p < 0.0001$) between the covariate-adjusted CL and therapy. In order to evaluate the impact of therapy on tislelizumab exposure, the predicted steady state exposures following 200 mg Q3W dosing were summarized and plotted by therapy (Table 27 and Figure 31). The mean simulated exposures (AUCss, Cmax,ss and Cmin,ss) in subjects with combotherapy were up to 8.79% higher compared with those of subjects with monotherapy in the overall population (Table 27). These differences were very small relative to the overall variability of exposures and are not considered clinically significant.

Figure 30. Impact of therapy on the covariate-adjusted tislelizumab CL and V_c based on the final PopPK model



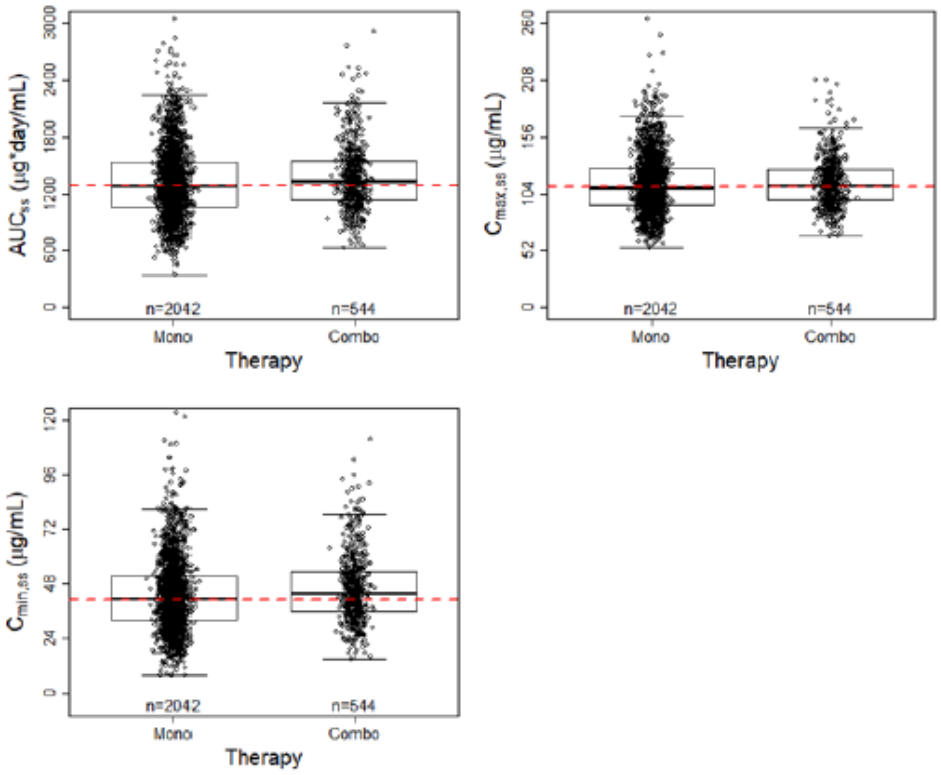
Circles are the covariate-adjusted tislelizumab CL and V_c values in individual subjects. The boxes represent the 25th to 75th percentiles (the interquartile range). The solid black horizontal line in the middle of each box represents the median. The whiskers represent the range of data points within 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.

Table 27. Geometric mean (%CV) simulated steady state exposure of tislelizumab by therapy following 200 mg 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.

Figure 31. Simulated steady state exposures of tislelizumab by therapy following 200 mg Q3W dosing



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.

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 mainly support the proposed dosing regimen of 200 mg Q3W.

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

Mechanism of action

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

Primary and Secondary pharmacology

Immunogenicity

Immunogenicity 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 titer 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 5-3).

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 5-3).

Table 5-3 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-CP-012-Table 2], [Study 208 IAR-Table 2], [Study 302 IAR-Table 2], [Study 303 IAR-Table 2], [Study 206 CSR-Table 14.3.8], [Study 304 IAR-Table 2], [Study 307 IAR-Table 2]
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 (Table 5-9). 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 5-9).

Table 5-9 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 titer levels

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

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

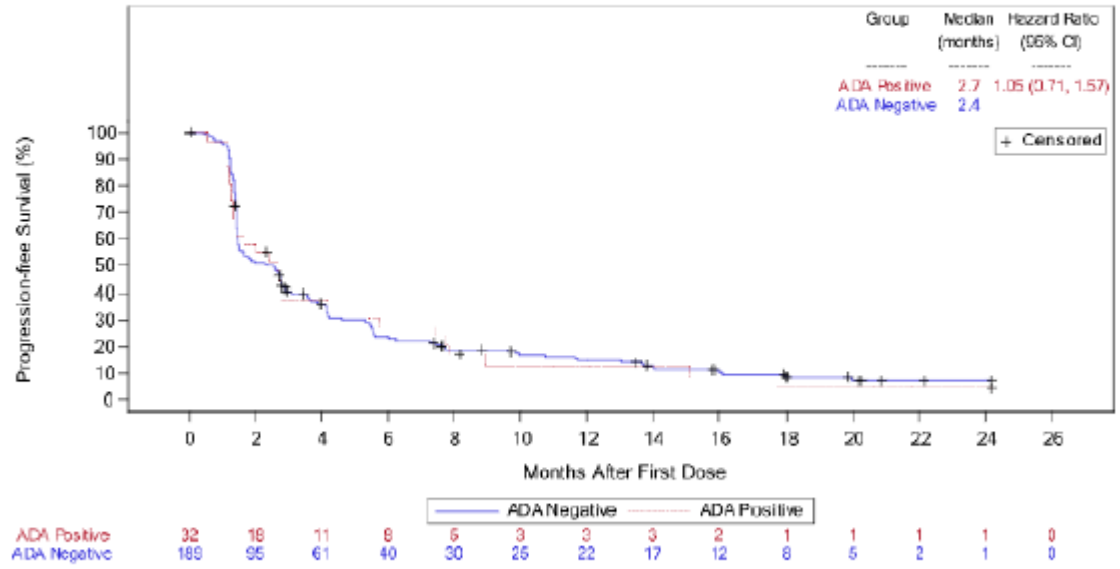
Impact of ADA on clinical efficacy

Table 5-10 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)

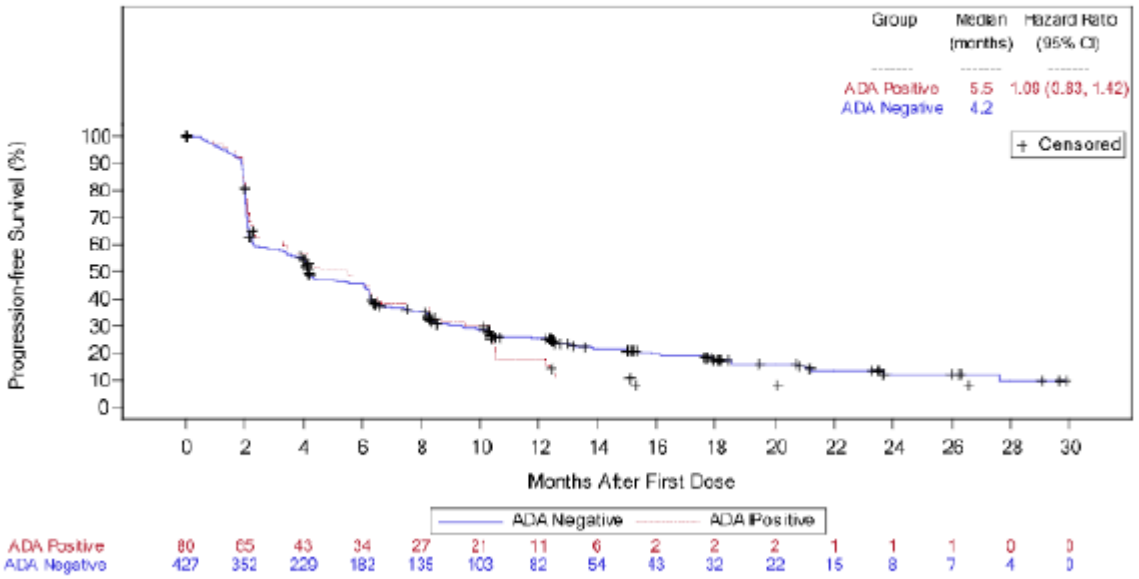
Source: [Report BGB-A317-CP-012-Table 9 and Table 10]. [Study 208 IAR-Table 7], [Study 302 IAR-Table 7], [Study 303 IAR-Table 7], [Study 304 IAR-Table 7], [Study 307 IAR-Table 7]
ESCC=esophageal cancer, HCC=hepatocellular carcinoma; NSCLC=non-small cell lung cancer
T+PC=tislelizumab + paclitaxel + carboplatin;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

Figure 5-16 Progression-free survival by ADA status after tislelizumab monotherapy – Study 302 (ADA evaluable patients)



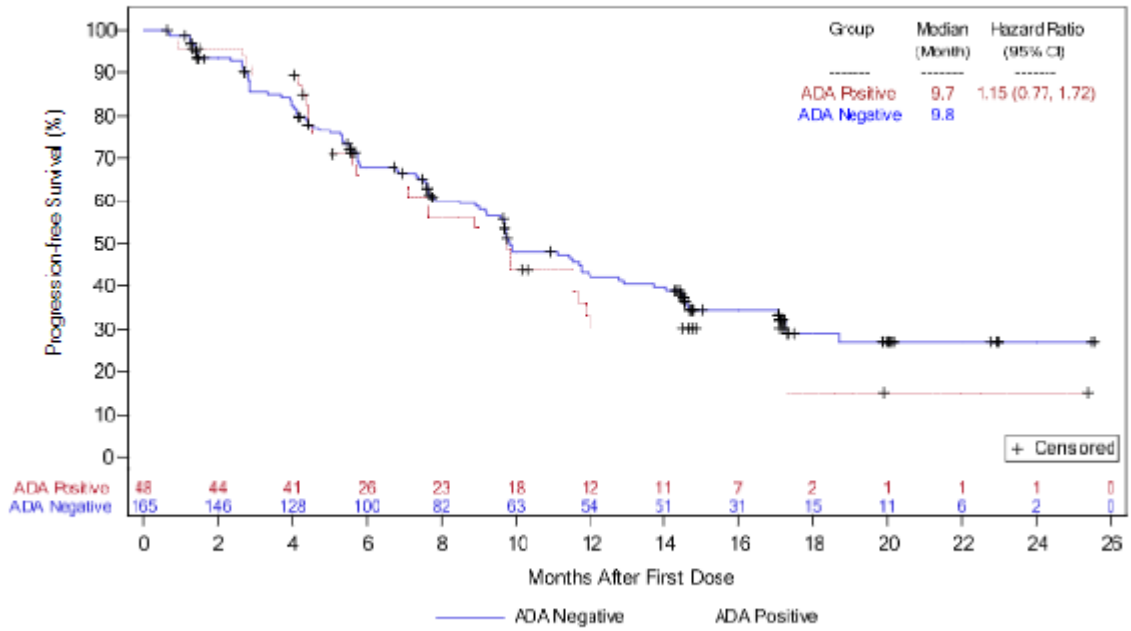
Source: [Study 302 IAR Memo-Appendix Figure 27]
ADA positive=patients with treatment-emergent ADA.

Figure 5-17 Progression-free survival by ADA status after tislelizumab monotherapy – Study 303 (ADA evaluable patients)



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

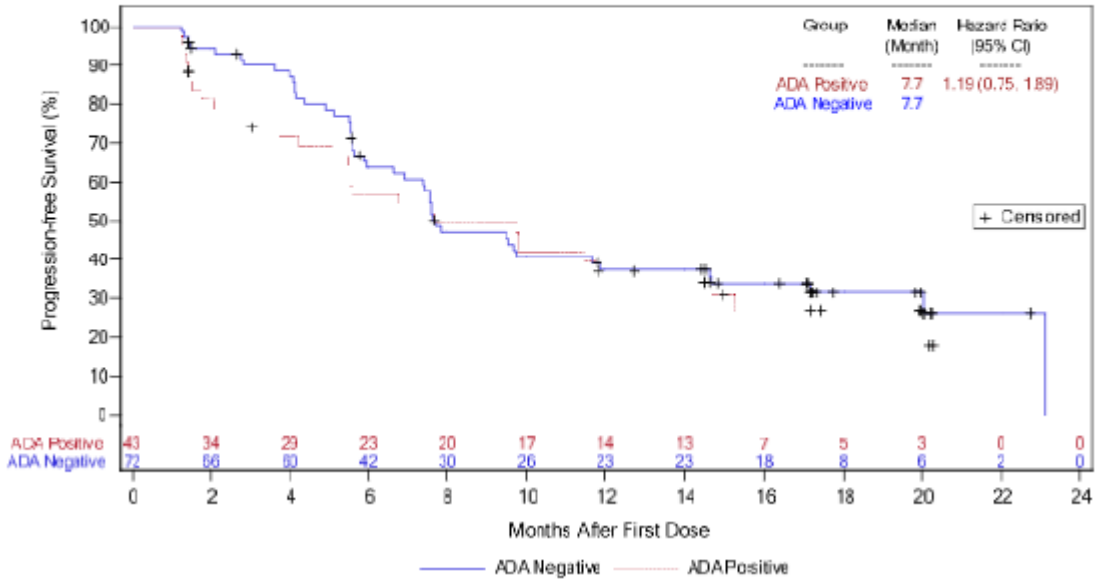
Figure 5-18 **Progression-free survival by ADA status after tislelizumab + pemetrexed + cisplatin or carboplatin – Study 304 (ADA evaluable patients)**



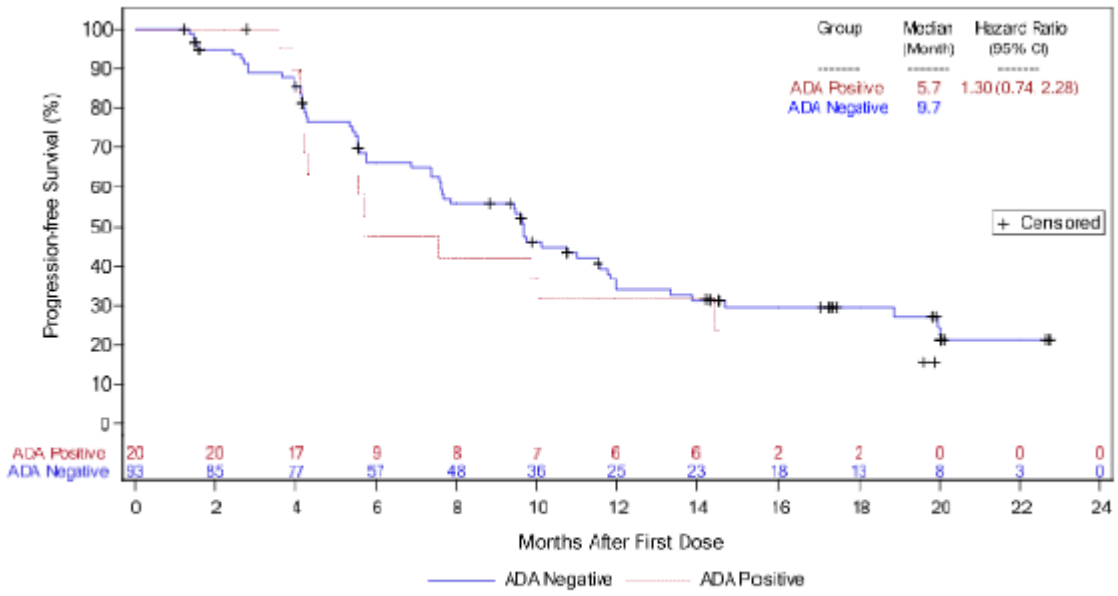
Source: [Study 304 IAR Memo-Appendix Figure 20]
ADA positive=patients with treatment-emergent ADA.

Figure 5-19 **Progression-free survival by ADA status after tislelizumab + paclitaxel or Nab-paclitaxel + carboplatin – Study 307 (ADA evaluable patients)**

T+PC arm

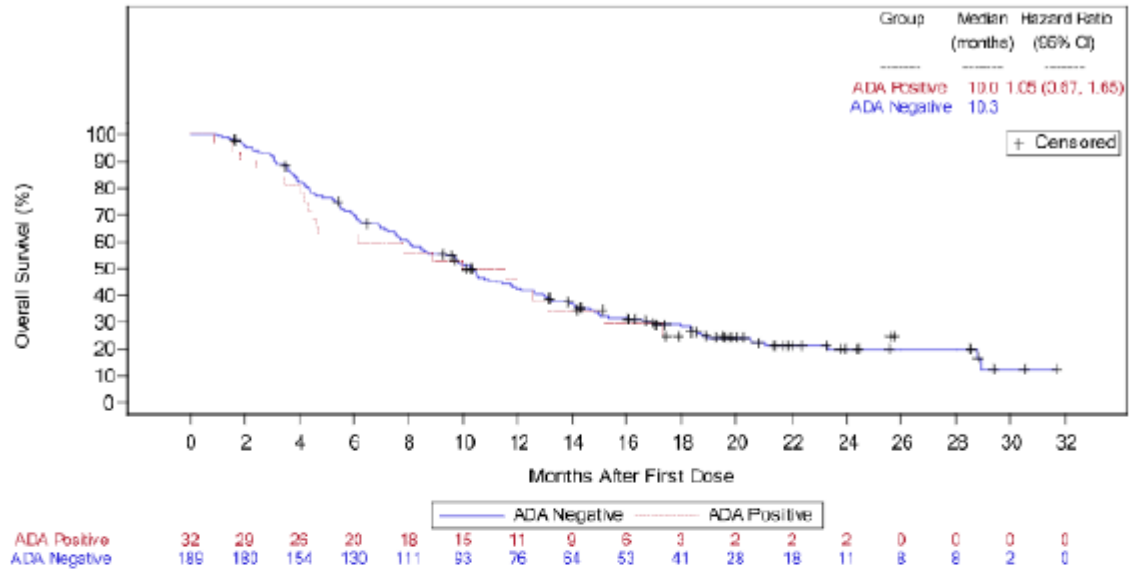


T+nPC arm



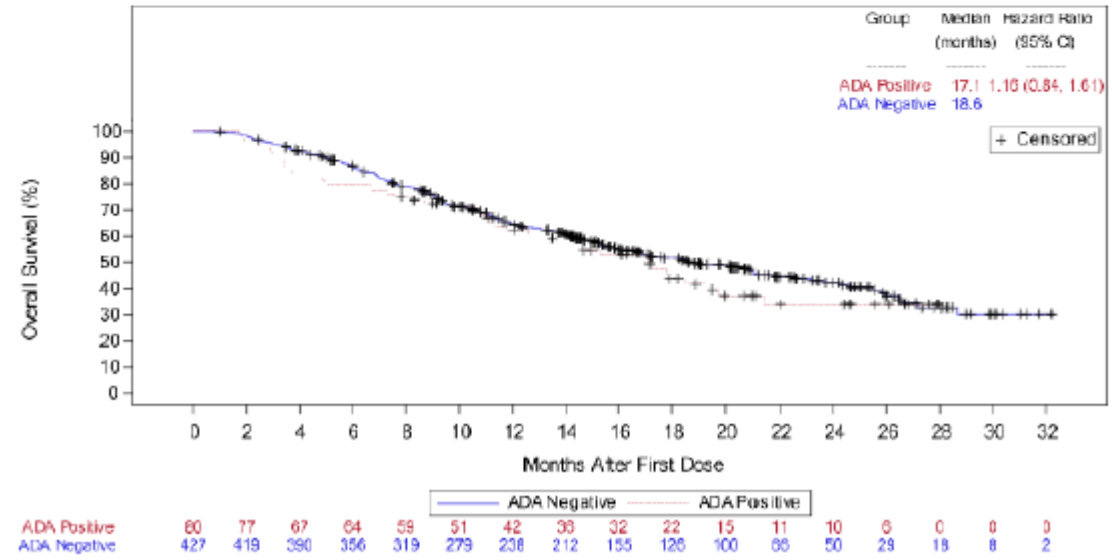
Source: [Study 307 IAR Memo-Appendix Figure 22]
T+PC=tislelizumab + paclitaxel + carboplatin; T+nPC=tislelizumab + *Nab*-paclitaxel + carboplatin
ADA positive=patients with treatment-emergent ADA.

Figure 5-12 **Overall survival by ADA status after tislelizumab monotherapy – Study 302 (ADA evaluable patients)**



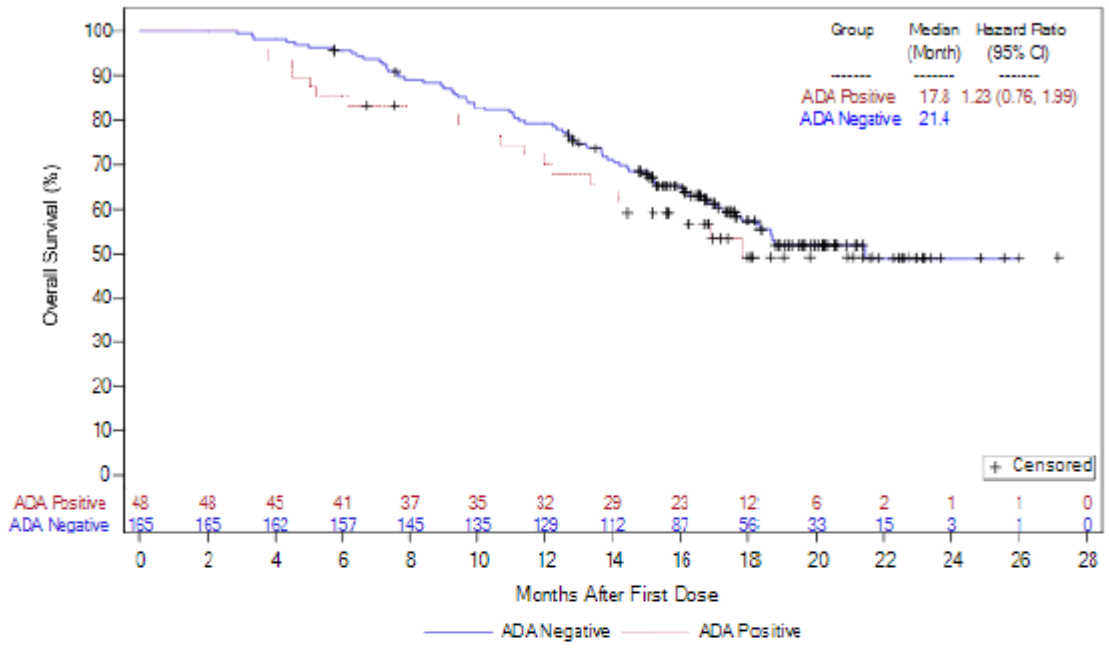
Source: [Study 302 IAR Memo-Appendix Figure 22]
ADA positive=patients with treatment-emergent ADA

Figure 5-13 **Overall survival by ADA status after tislelizumab monotherapy – Study 303 (ADA evaluable patients)**



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

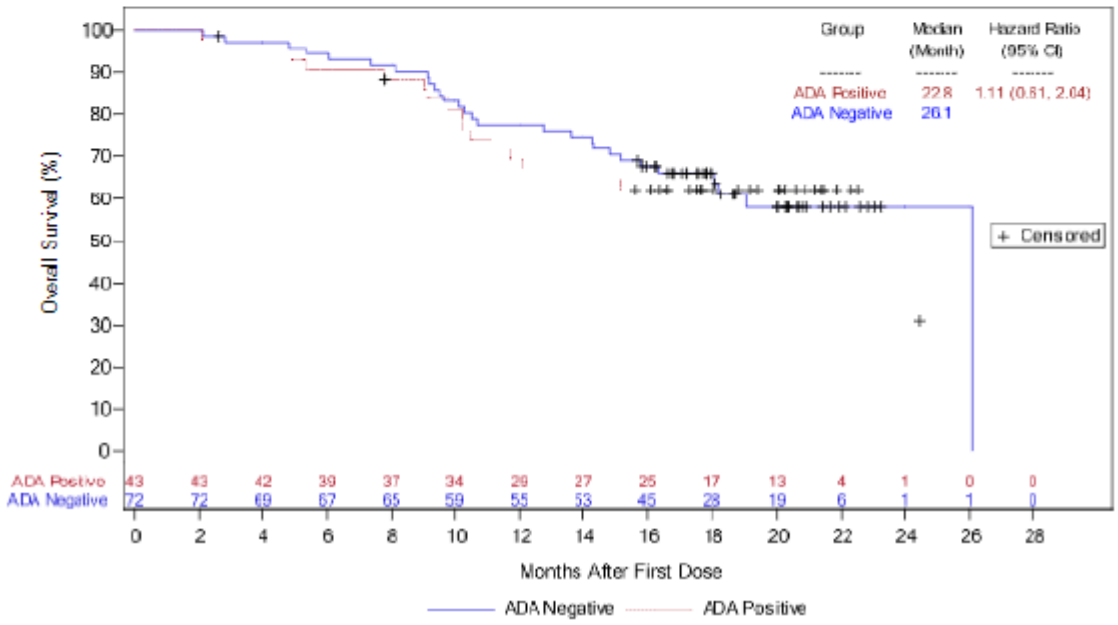
Figure 5-14 Overall survival by ADA status after tislelizumab + pemetrexed + cisplatin or carboplatin – Study 304 (ADA evaluable patients)

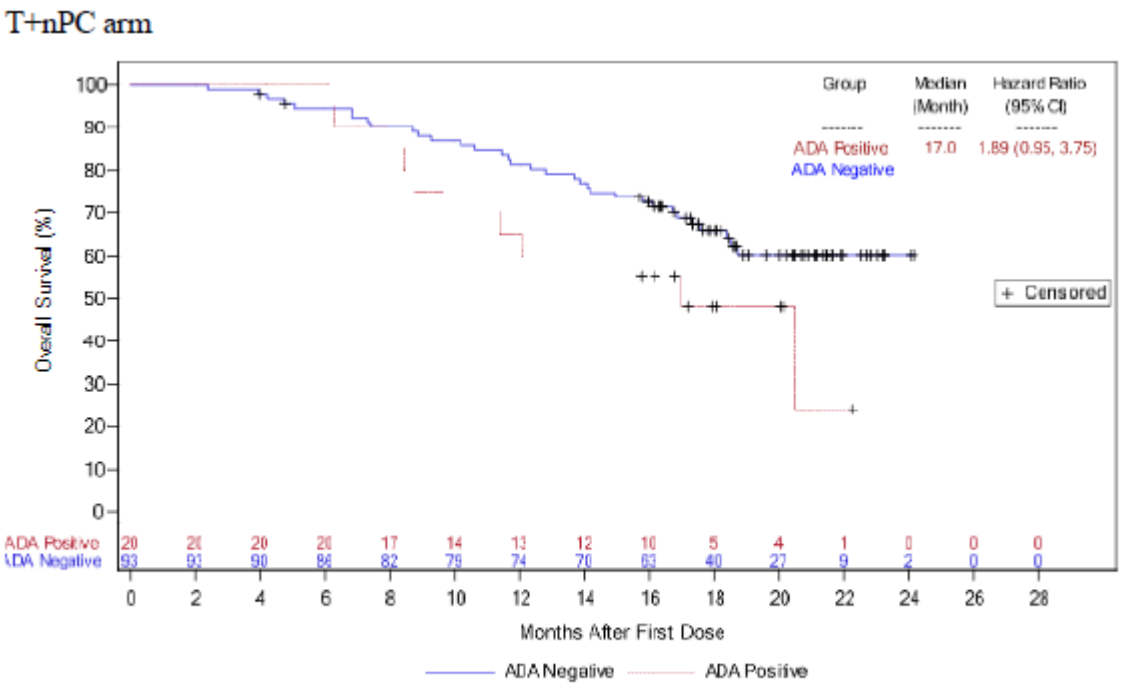


Source: [Study 304 IAR Memo-Appendix Figure 31]
ADA positive=patients with treatment-emergent ADA.

Figure 5-15 Overall survival by ADA status after tislelizumab + paclitaxel or *Nab*-paclitaxel + carboplatin – Study 307 (ADA evaluable patients)

T+PC arm





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.

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 titers in ADA-positive patients, with most AEs occurring in patients with low titers <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 5-14).

Table 5-14 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 titer, 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 hyponatremia (4.3% vs. 2.0%) and hypokalemia (2.6% vs. 1.3%).
- Blood and lymphatic system disorders (9.9% vs. 5.3%), with small differences of 1-3% in anemia (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 anemia (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 hematological 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 hemoptysis (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 hypokalemia (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 diarrhea (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 hemoptysis (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 anemia (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 5-3) across the 10 clinical studies did not experience immune-mediated AEs or AESIs, and none had hypersensitivity AEs.

Exposure-response analyses

Exposure-efficacy analysis:

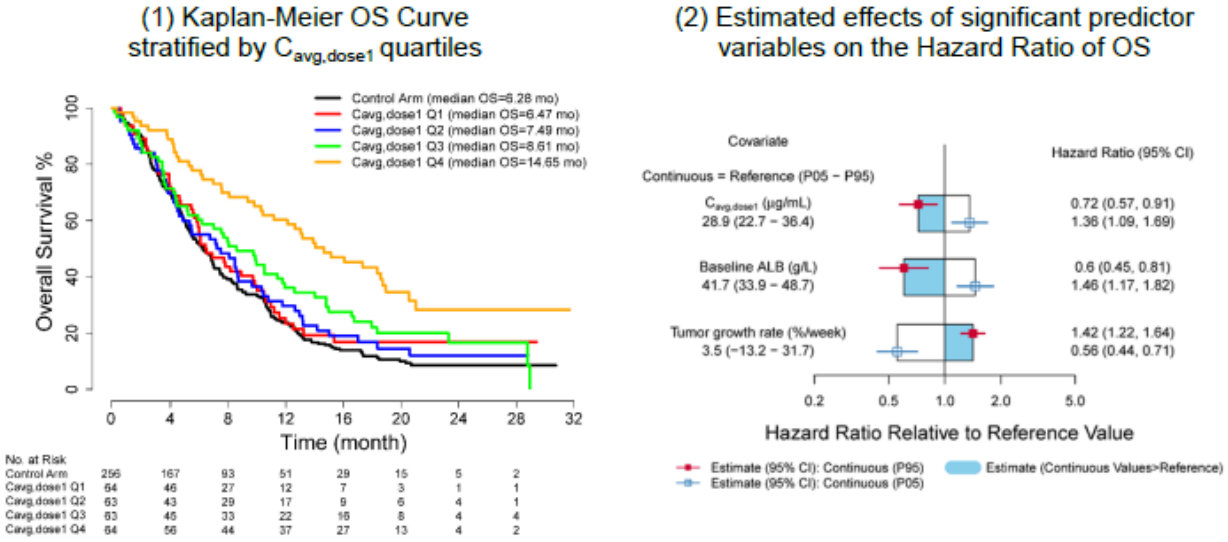
Exposure-OS Analysis: Kaplan-Meier survival curves stratified by quartiles of model-predicted Cavg,dose1 for tislelizumab-treated subjects (N = 254) showed that subjects in the highest exposure quartile had longer OS compared to subjects in the lower exposure quartiles (Figure 3-8 [1]). To further investigate the relationship between exposure and OS, a Cox proportional hazards model analysis was performed using Cavg,dose1, baseline subject characteristics (tumour size, ECOG Performance Status score, albumin level, LDH, AST, ALT, bilirubin, eGFR, ADA status, PDL1, age, weight, race, and sex) and tumour growth rate. This Cox regression analysis results showed that albumin, tumour growth rate, and tislelizumab Cavg,dose1 were significant predictors for OS ($p < 0.01$) (Figure 3-8 [2]).

Since tislelizumab exposure appeared to have a significant effect on OS, 2 sensitivity analyses were performed using the OS data from the (1) Tislelizumab Arm only and (2) both Tislelizumab and Control (ICC) Arms against exposure as a categorical variable (quartiles). Both sensitivity analyses identified albumin level, tumour growth rate, and the highest exposure quartile as significant predictors of OS (Figure 3-9). These analyses also showed that the effect on OS is not consistent across the exposure quartiles as the lowest exposure quartile had a smaller hazard ratio compared to the second and third exposure quartiles.

Further analysis of the OS data from Study 302 identified confounding baseline factors and imbalances in prognostic factors favouring subjects in the highest exposure quartile. For instance, longer OS was observed in subjects with smaller baseline tumour size, higher baseline albumin level and the imbalances in distribution of these factors favouring the highest exposure quartile over the lowest exposure quartile are presented in Figure 3-10. Of note, albumin and baseline tumour size were also significant covariates on tislelizumab clearance, which indicates that exposure is not an independent variable and the observed E-R relationship is likely confounded by these baseline disease-related factors.

There is no meaningful association between the exposure and efficacy across the exposures evaluated in Study 302 population.

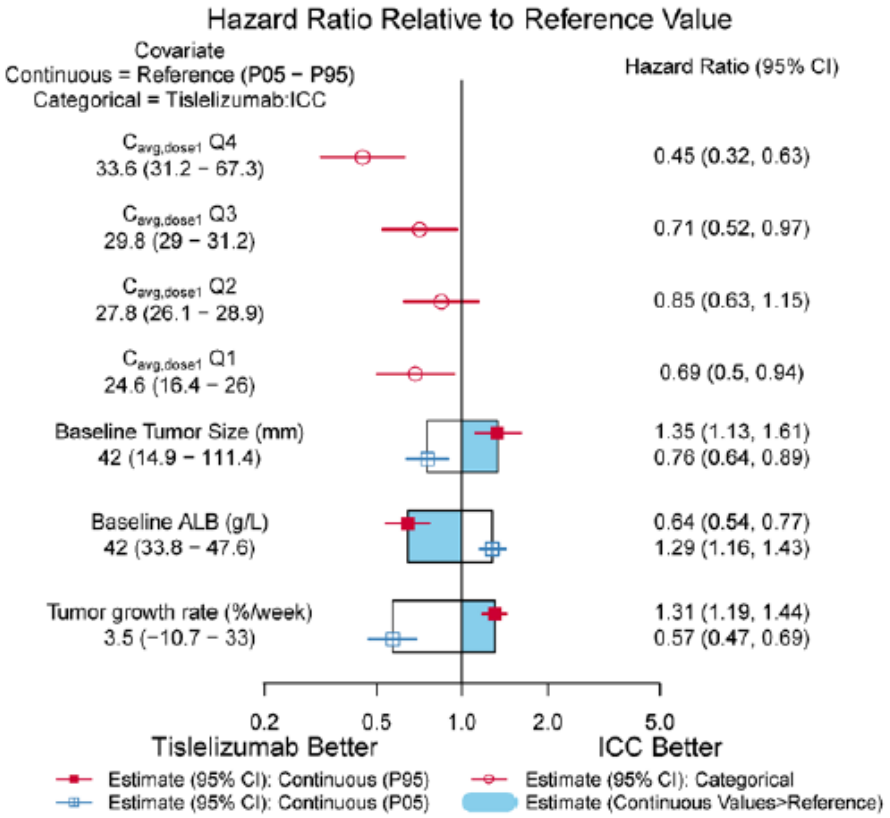
Figure 3-8 Exposure-Response Relationship for Overall Survival in Tislelizumab-Treated ESCC Subjects (Study 302)



Source: [Study 302 ER Report-Figure 3 and Figure 6]
Abbreviations: 302, BGB-A317-302; ALB, albumin; $C_{avg,dose1}$, average concentration of the first dose; CI, confidence interval; ESCC, esophageal squamous cell carcinoma; ICC, investigator-chosen chemotherapy; OS, overall survival; Q1/Q2/Q3/Q4, concentration quartiles from lowest to highest.

Notes: The left panel shows Kaplan-Meier curves stratified by quartiles of model-predicted $C_{avg,dose1}$ for tislelizumab treated group (n = 254) and ICC group (n = 256). The right panel shows the effect of each covariate on the hazard ratio of overall survival relative to a subject with reference values of covariates. The hazard ratio at the 5th and 95th percentiles (P05 and P95) are shown relative to the reference values. The shaded region of the box shows the estimate of the hazard ratio relative to the reference value when values of the continuous covariate are greater than the reference.

Figure 3-9 Estimated Effects of Significant Prognostic Factors and Exposure Quartiles on the Hazard Ratio of OS Based on the Combined Dataset

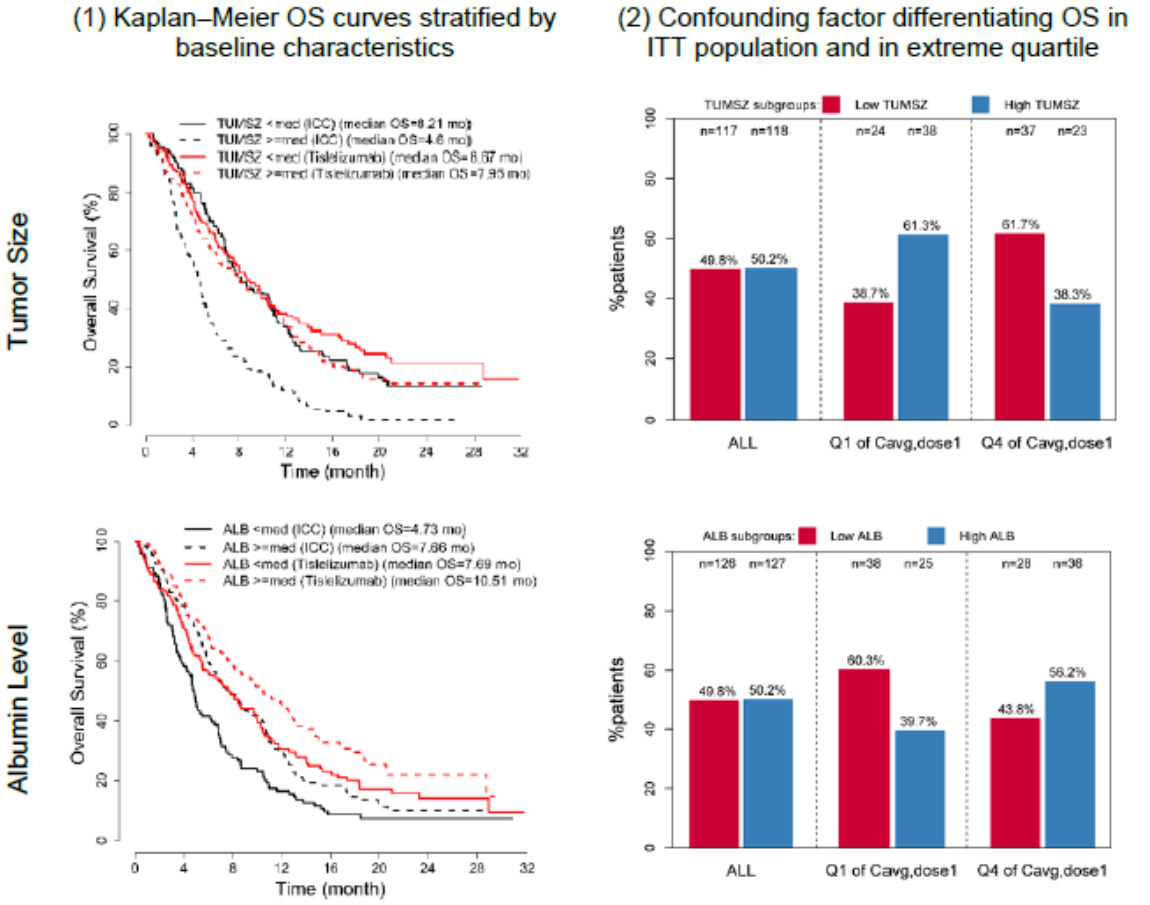


Source: [Study 302 ER Report-Figure 8]

Abbreviations: ALB, albumin; $C_{avg,dose1}$, average concentration of the first dose; ICC, investigator-chosen chemotherapy.

Notes: Final model with all predictor variables for all subjects in study BGB-A317-302. The graph describes the effect of each covariate on the hazard ratio of overall survival relative to a subject with reference values of covariates. The hazard ratio at the 5th and 95th percentiles (P05–P95) are shown relative to the reference values. The shaded region of the box shows the estimate of the hazard ratio relative to the reference value when values of the continuous covariate are greater than the reference.

Figure 3-10 Baseline Confounding Factors That May Affect Overall Survival

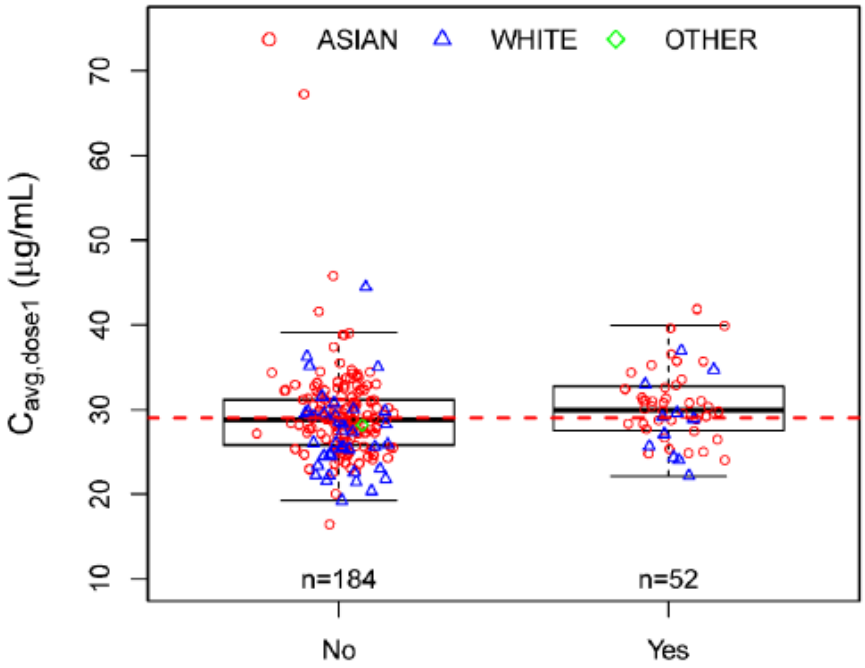


Source: [Study 302 ER Report-Figure 4 and Figure 5]

Abbreviations: ALB, albumin; $C_{avg,dose1}$, average concentration of the first dose; ICC, investigator-chosen chemotherapy; ITT, intention-to-treat; TUMSZ, baseline tumor size; Q1/Q4, lowest and highest quartiles of $C_{avg,dose1}$.

Exposure-ORR Analysis: Analysis of exposure with the secondary endpoint of ORR showed that the range of tislelizumab exposure values was similar between responders (subjects with objective response, N = 52) and non-responders (N = 184) in Study 302. The mean tislelizumab Cavg,dose1 was 30.3 ± 4.30 µg/mL in responders compared with 29.0 ± 5.16 µg/mL in non-responders, respectively (Figure 3-11).

Figure 3-11 Relationship Between Exposure and ORR in ESCC Subjects (Study 302)

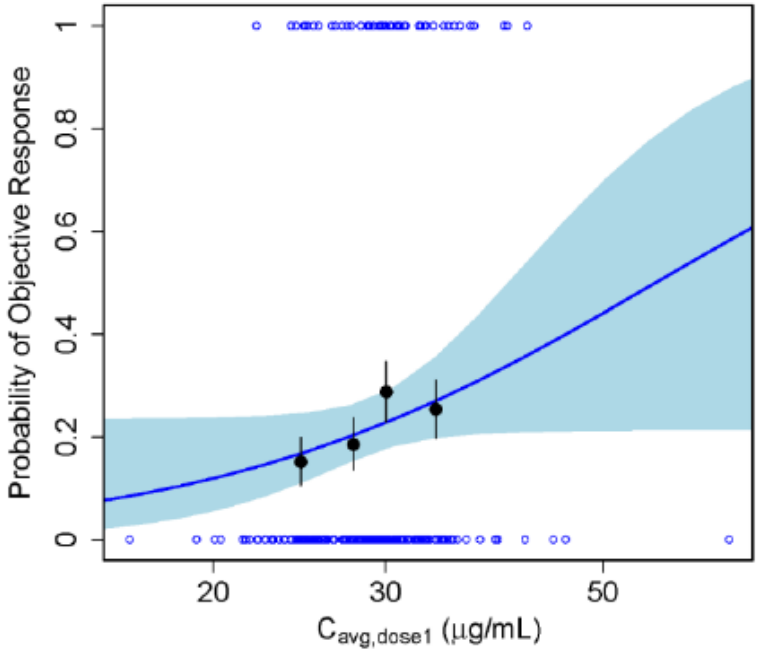


Source: [Study 302 ER Report-Figure 11]

Abbreviations: $C_{avg,dose1}$, average serum concentration of the first dose; IQR, interquartile range.

Notes: The mean $C_{avg,dose1}$ values were 30.3 µg/mL in responders compared with 29.0 µg/mL in non-responders. The relationship between tislelizumab exposure and ORR of overall population in study BGB A317 302. Symbols are the model-predicted exposure metrics. The median is represented by the horizontal black line in the middle of each box. The lower and upper ends of the box plot represent the 25th and 75th percentile (the lower and upper quartiles, respectively). The bars extend to the most extreme data point which is no more than 1.5×IQR from the box. The dashed red horizontal line represents the median value of overall in study BGB A317 302.

Figure 3-12 Probability of Objective Response vs Tislelizumab Exposure in ESCC Subjects (Study 302)



Source: [Study 302 ER Report-Figure 13]

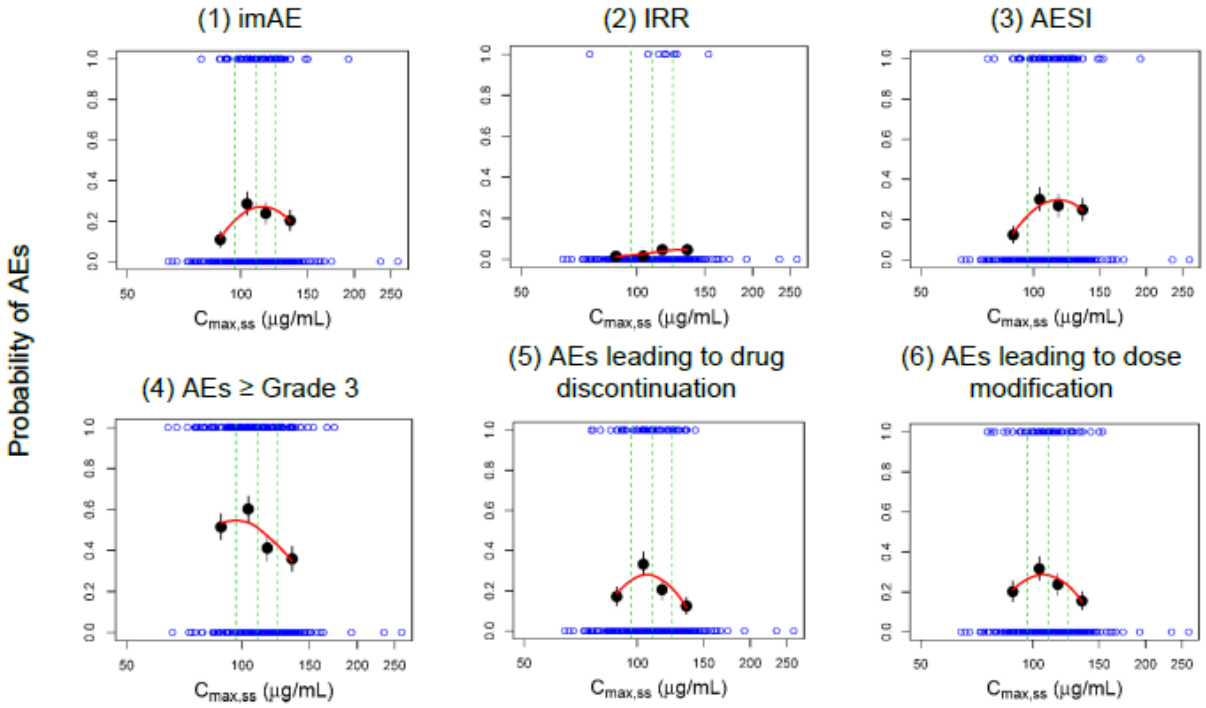
Abbreviations: 302, BGB-A317-302; $C_{avg,dose1}$, average serum concentration of the first dose; ESCC, esophageal squamous cell carcinoma; PK, pharmacokinetics.

Notes: The open blue symbols reflect the observed events. The filled black symbols are the observed probability of events and the error bars are SE [sqrt (P*(1-P)/N)] for quantiles (at 100x(1/4)th percentiles) of exposures (plotted at the median value within each quantile). The blue line is the model predicted probability. The light blue shaded area is the 95% prediction interval. (Probability - 0: Non-responder; 1: Responder).

Exposure-safety analysis:

No consistent and clinically relevant ER relationship was observed between tislelizumab exposure metrics and the safety endpoints of probability of any AEs ≥ Grade 3, imAEs, AEs leading to treatment discontinuation, IRRs, AESIs, AEs leading to dose modification, and SAEs among tislelizumab-treated subjects (N = 254) in Study 302 (Figure 3-15 and Figure 3-16).

Figure 3-15 Probability of Selected AEs vs Tislelizumab Exposure in ESCC Subjects (Study 302)

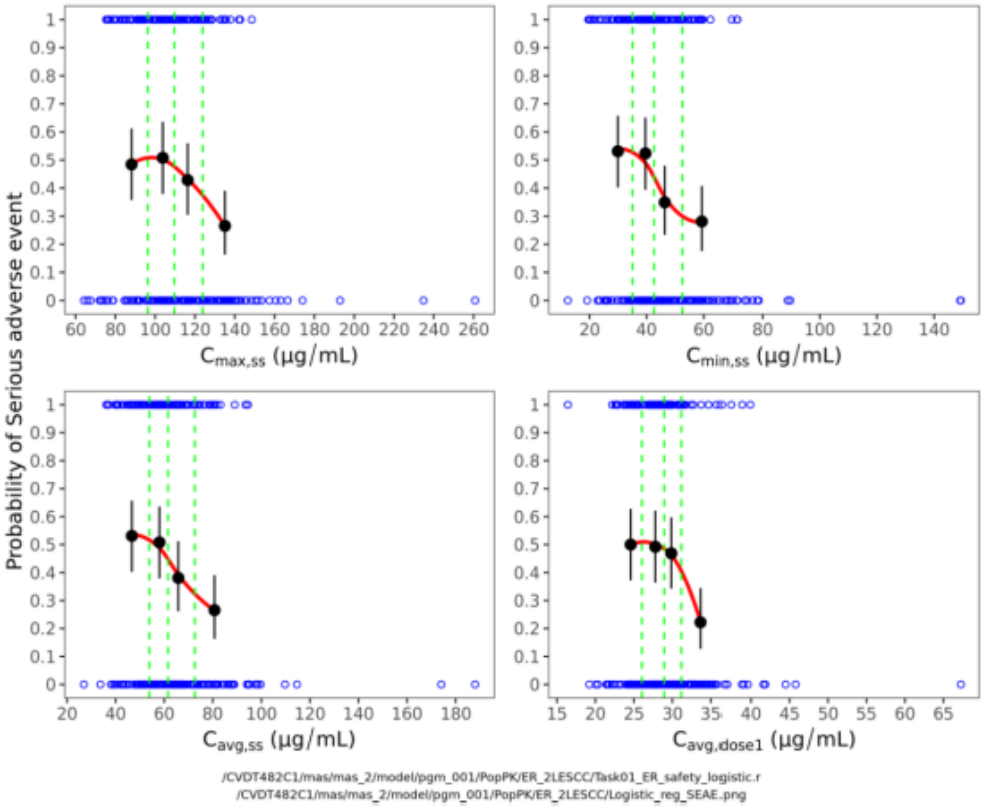


Source: [Study 302 ER Report-Figure 21, Figure 23, Figure 25, Figure 15, Figure 17 and Figure 19]

Abbreviations: 302, BGB-A317-302; AE, adverse event; AESI, adverse event of special interest; imAE, immune-mediated adverse event; IRR: infusion-related reaction; vs, versus.

Notes: The data were collected from Studies 302. 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)], where P is probability of AE and N is the number of subjects in each quartile bin, for quantiles (25%, 50%, and 75%, green vertical dotted lines) of exposures (plotted at the median value within each quantile). The red lines are smooth curves to show the relationship between 2 variables.

Figure 3-16 Probability of serious AE versus exposure



Source: [Study 302 ER Report Amendment 2-Figure 3-2]

2.6.3. Discussion on clinical pharmacology

The clinical pharmacology package of tislelizumab comprised 12 clinical studies contributing to the characterization of tislelizumab pharmacokinetics. 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 electrochemiluminescent (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 titer. 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 characterization 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 Nab 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 analyzed 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.

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 data provided.

Referring to the above 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. EC PK (observed exposure profiles) seem similar to NSCLC which constitutes the majority of data (44.3%), thus the combined diagnostics are adequate to describe the fit of EC subjects as well. For further confirmation, VPCs stratified per cancer type and for Study 302 were presented upon request. The model fit was less good than for the VPCs reported for "All subjects" mainly driven by data from NSCLC patients, and underpredicted concentrations <21 days after dosing whereas overpredicting was observed at later time points. In addition, diagnostic goodness-of-fit plots stratified for Study 302 and for EC were provided upon request. Based on the data provided, the current model appears to have acceptable descriptive and predictive performance.

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 EC 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. Cmax 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, Cmax 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 characterize 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 5^{th} and 95^{th} percentile exposures in the overall population compared to the typical individual, which are ~ 55.8%, 47.3%, and 70.8% for AUC,ss, Cmax,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

The effects of various covariates on tislelizumab PK were assessed in population PK analyses. The following factors had no clinically relevant effect on the exposure of tislelizumab: age (range 18 to 90 years), weight (range 32 to 130 kg), gender, race (White, Asian and other), mild to moderate renal impairment (creatinine clearance [CLCr] $\geq$30 ml/min), mild to moderate hepatic impairment (total bilirubin $\leq$3 times ULN and any AST), and tumour burden.

Mild and moderate renal impairment had no effect on the exposure of tislelizumab and no dose adjustment is needed for these patients. Based on the limited number of patients with severe renal impairment (n = 5), the effect of severe renal impairment on the pharmacokinetics of tislelizumab is not conclusive. As for other mAbs, there is no mechanistic rationale for an increase in exposure with reduced renal function. 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 pediatric 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 or in combination with chemotherapy in patients with different tumour types. Anti-drug antibodies were determined by screening and confirmatory assays, followed by the analysis of ADA titer.

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%. 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-response (E-R) analyses were performed specifically for the ESCC study 302 to understand the relationships between PK and efficacy, as well as safety parameters.

Exposure-efficacy analyses

The exposure-efficacy relationship of OS in the ITT population was explored by Kaplan-Meier curves stratified by exposure (Cavg,dose1) quartiles. A longer OS was observed in the highest tislelizumab exposure quartile compared to those patients in the lower three quartiles. The median survival in the tislelizumab arm for patients with the highest quartile of exposure was 14.65 months.

In order to investigate the potential confounding effects of baseline patient characteristics and tumour growth rate (TGR) on the observed E-R relationship of OS, a Cox proportional hazards model for OS was developed based on tislelizumab treated patients in study BGB-A317-302. Albumin, tumour growth rate, and tislelizumab Cavg,dose1were found to be significant covariates in this analysis. Since patients' baseline prognostic factors are known to confound E-R relationships for monoclonal antibodies and statistically significant E-R relationship was observed in this analysis, a Cox proportional hazards model was developed with tislelizumab exposure quartile instead of continuous exposure as a sensitivity analysis. The results show that besides ALB and TGR, only the highest exposure quartile (Q4) was a significant predictor relative to the lowest exposure quartile (Q1) in the final model. Another set of sensitivity analysis was performed using the OS data from both arms of the study and tislelizumab exposure as a categorical variable (quartiles). Along with tumour size, albumin and TGR, only the highest exposure quartile was significant. However, due to lack of consistency in drug effect at different exposures quartiles the applicant considers the E-R relationship likely confounded by the imbalance in baseline factors. Overall, patients in the highest Cavg,dose1 quartile (Q4) exhibited more favorable prognostic factors (median tumour size 30 mm in Q4 vs 58 mm in Q1; 28.1% female in Q4 vs 10.9% in Q1; 29.7% patients with ECOG = 0 in Q4 vs 25% in Q1; 0% patients with ALB<35 g/L in Q4 vs 17% in Q1) compared with patients in the lowest Cavg,dose1 quartile (Q1). Taken together, these results suggest that tislelizumab exposure is not an independent predictor variable of OS. This assumption is further supported by sensitivity analyses excluding patients with missing tumour growth rate values, extremely low albumin, high eGFR or small baseline tumour size showing tislelizumab exposure is not significant Comparable results were obtained for the overall ESCC population including studies 001, 102 and 302.: There appears to be a positive trend between exposure and efficacy, this trend is not statistically significant after adjusting for CL and other baseline characteristics.

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. In the current analysis, the observed tislelizumab E-R relationship for OS was likely a result of increased tislelizumab clearance in patients with poorer prognosis rather than a true exposure effect on the drug efficacy.

The exposure-response relationship of the ORR was explored by exposure boxplots and the probability of response plots. The mean exposure values were similar between responders and non-responders. The mean Cavg, dose1 values were 30.3 µg/mL in responders compared with 29.0 µg/mL in non-responders. The probability of response plots showed that a slight trend between tislelizumab exposure and the ORR. However, logistic regression models for the ORR indicated that neither tislelizumab Cavg, dose1 nor race has a significant effect on E-R relationship for the ORR.

Exposure-safety analyses

The relationship between tislelizumab exposure and clinical safety endpoints was explored based on data from study BGB-A317-302. This analysis results showed that there was no evidence of higher tislelizumab exposure leading to increased rates of any AE ≥ grade 3, immune-mediated AE, AEs leading to treatment discontinuation, infusion-related reaction, AEs of special interest, and AEs leading to dose modification. In Amendment 2 of the ER Report, the relationship between tislelizumab exposure and serious AEs was also investigated. No increased incidence of SAEs with increasing

exposure was observed. Also, no significant differences or consistent trends were observed between Asians and Whites for the safety events tested. Hence, it is concluded that no clinically relevant exposure-safety relationship was observed based on the selected safety endpoints from the study BGB-A317-302. This is agreed.

2.6.4. Conclusions on clinical pharmacology

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

2.6.5. Clinical efficacy

The clinical studies providing efficacy data in support of the application of tislelizumab for the treatment of patients with unresectable, recurrent, locally advanced or metastatic ESCC after prior systemic therapy are presented in Table 3-3-1. Study 302, a pivotal, open-label, multicenter, randomized Phase III study comparing the efficacy and safety of tislelizumab vs. ICC in patients with unresectable, recurrent, locally advanced or metastatic ESCC is the principal basis for the submission. Supportive data derive from the early, uncontrolled single-arm studies 001 and 102.

2.6.5.1. Dose-response study

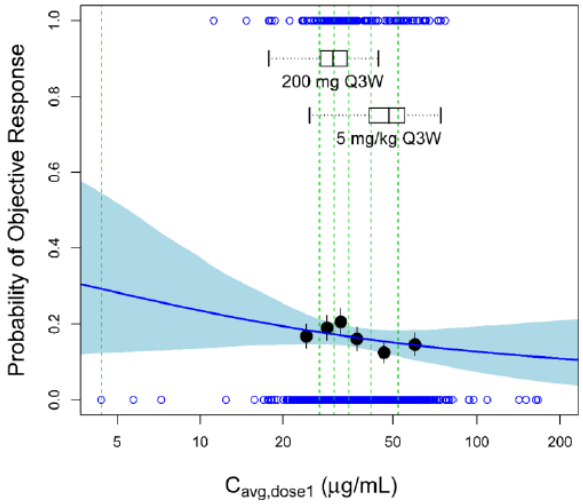
Study 001 was 2-stage open-label study consisting of a Phase 1A dose escalation and dose-finding component to establish the MTD or RP2D(s) followed by a Phase 1B component to investigate efficacy and safety of the RP2D in patients with advanced or metastatic solid tumours.

Dose levels investigated were 0.5, 2.0, 5.0, and 10 mg/kg Q2W and 2 mg/kg, 5 mg/kg, and 200 mg flat Q3W.

The recommended dosing regimen of 200 mg Q3W was selected based on the claimed similarity of preliminary efficacy and safety results at the 2 mg/kg and 5 mg/kg dose levels, dose-proportional PK characteristics of tislelizumab across a range of 0.5 mg/kg to 10 mg/kg with no correlation between clearance and body weight, and the 200 mg Q3W flat dosing regimen Q3W showing tislelizumab concentrations within the range of concentrations observed from the 2 mg/kg and 5 mg/kg doses.

Further support for the selected dosing regimen derives from the exposure-response analysis which comprised data from the early clinical studies 001, 102, 203, and 204. No significant or clinically meaningful ER relationships were observed between exposure and efficacy (ORR) or safety endpoints based on the data including dose ranges up to 10 mg/kg.

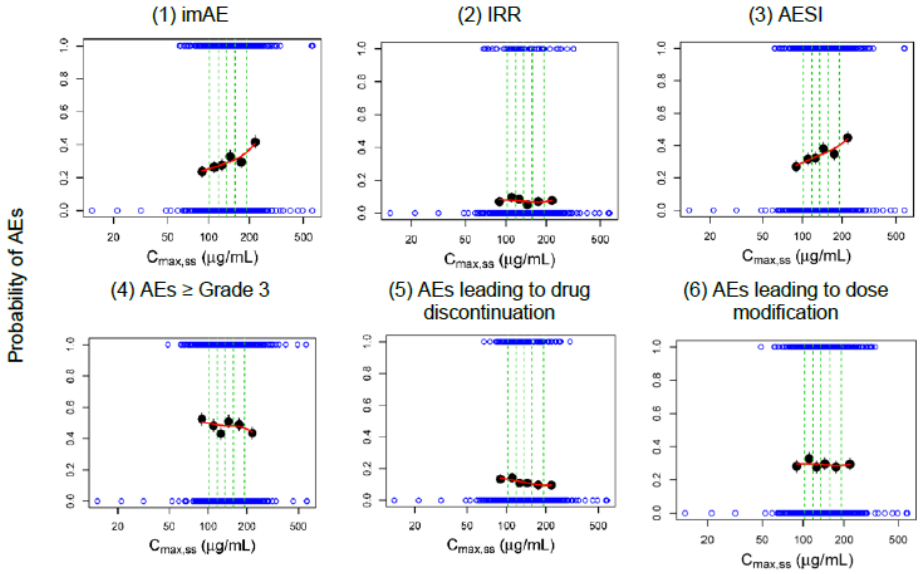
Figure 3 - 3 - 1 Logistic regression of probability of ORR vs. tislelizumab exposure in patients with solid tumours



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.

Source: Figure 3 Exposure-Response Report BGB-A317-CP-009

Figure 3 - 3 - 2 Probability of selected AEs vs. tislelizumab exposure in subjects with advanced tumours



Source: [ER Report 3-Figure 18, Figure 22, Figure 24, Figure 12, Figure 14, Figure 16]

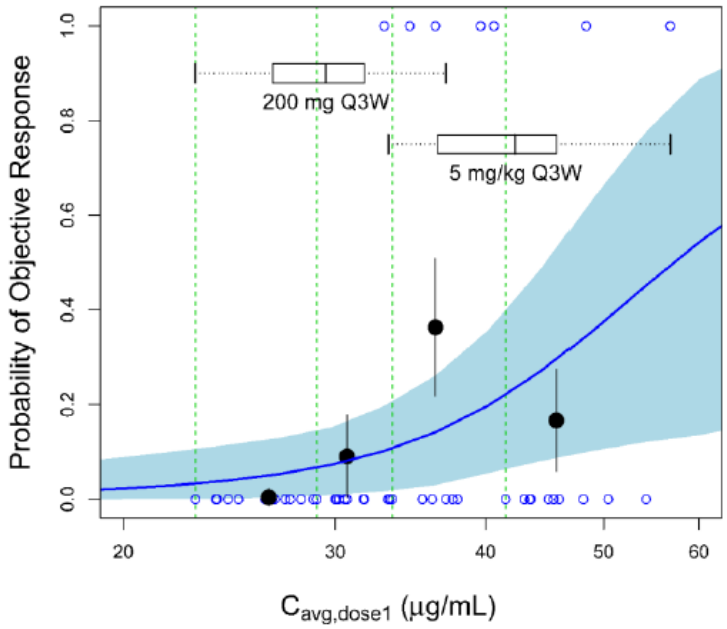
Abbreviations: AE, adverse event; AESI, adverse event of special interest; imAE, immune-mediated adverse event; IRR: infusion-related reaction; PI, prediction interval; PK, pharmacokinetics; vs, versus.

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.

Source: Figure 3-17 SCP

However, a trend towards increased efficacy (ORR) with increasing tislelizumab concentrations was seen in the ESCC population.

Figure 3 - 3 - 3 Logistic regression of probability of ORR vs. tislelizumab exposure in patients with ESCC

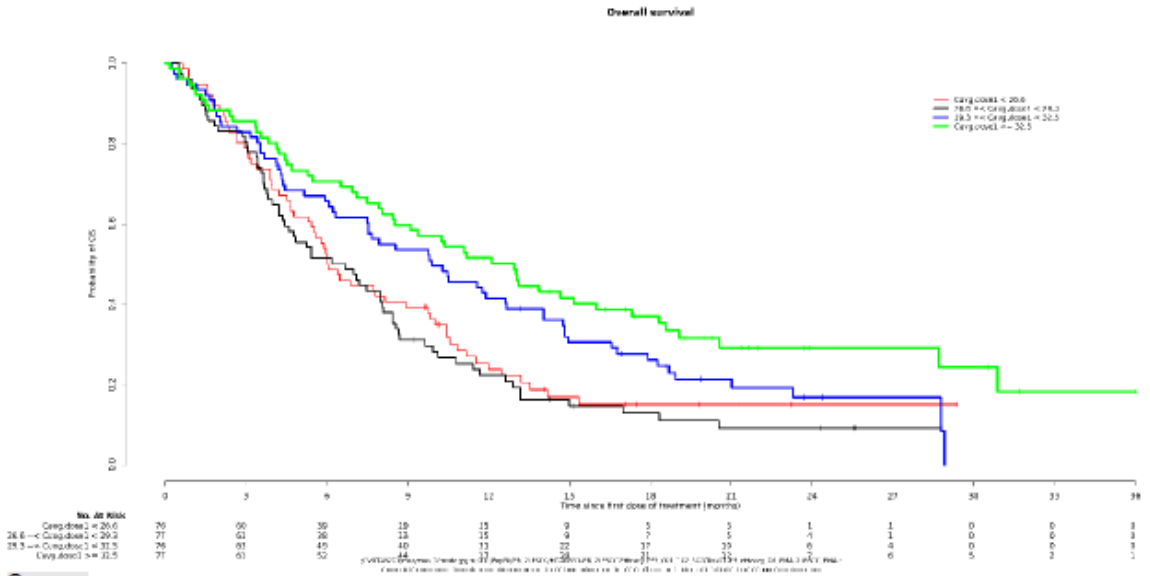


The open blue circles reflect the observed events. The filled black symbols are the observed probability of events and the error bars are SE [sqrt (P*(1-P)/N)] for quantiles (at 100x(1/4)th percentiles) of exposures (plotted at the median value within each quantile) , where P is probability of event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

Source: Figure 5 Exposure-Response Report BGB-A317-CP-009

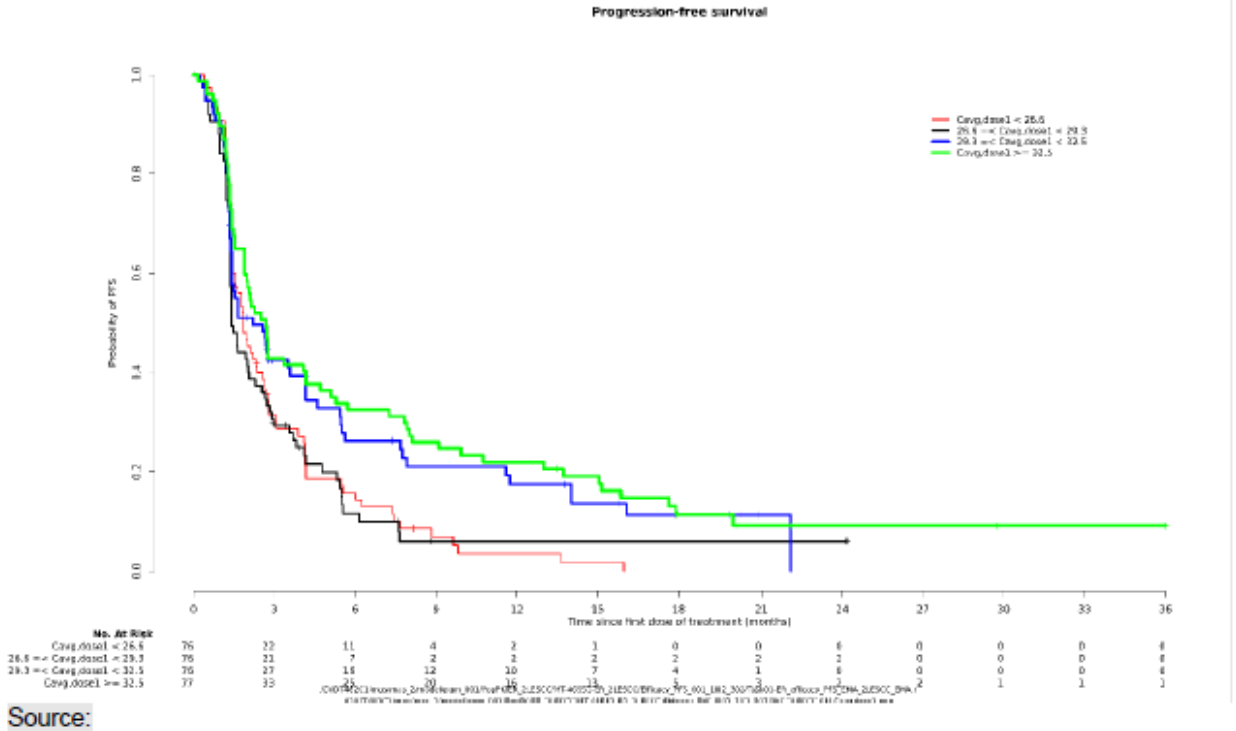
This trend was consistently observed in the exposure-efficacy analysis (both for OS and ORR) conducted for Study 302 separately (see section 3.3.1). In both analyses, p-value was only slightly above 0.05. Upon request, the applicant provided exposure-response analyses for the overall ESCC population by developing a model that includes data from Studies 001, 102 and Study 302.

Figure 2-13 **Kaplan-Meier OS curves stratified by Cavg,dose1 – 2L ESCC patients from studies 001, 102 and 302**



Source:
/CVDT482C1/mas/mas_2/model/pgm_001/PopPK/ER_2LESCC/MT-46551-ER_2LESCC/Efficacy_PFS_001_102_302/Task01-ER_efficacy_OS_EMA_2LESCC_EMA.r;
/CVDT482C1/mas/mas_2/model/pgm_001/PopPK/ER_2LESCC/MT-46551-ER_2LESCC/Efficacy_PFS_001_102_302/OS-2LESCC-KM-Cavgdose1.png

Figure 2-14 **Kaplan-Meier PFS curves stratified by Cavg,dose1 – 2L ESCC patients from studies 001, 102 and 302**



Source:
/CVDT482C1/mas/mas_2/model/pgm_001/PopPK/ER_2LESCC/MT-46551-ER_2LESCC/Efficacy_PFS_001_102_302/Task01-ER_efficacy_PFS_EMA_2LESCC_EMA.r;
/CVDT482C1/mas/mas_2/model/pgm_001/PopPK/ER_2LESCC/MT-46551-ER_2LESCC/Efficacy_PFS_001_102_302/PFS-2LESCC-KM-Cavgdose1.png

Also, 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 is statistically significant in the base model, after adjusting for CL and other baseline covariates, the association between Cavg,dose1 and efficacy outcome is no longer statistically significant in the final model.

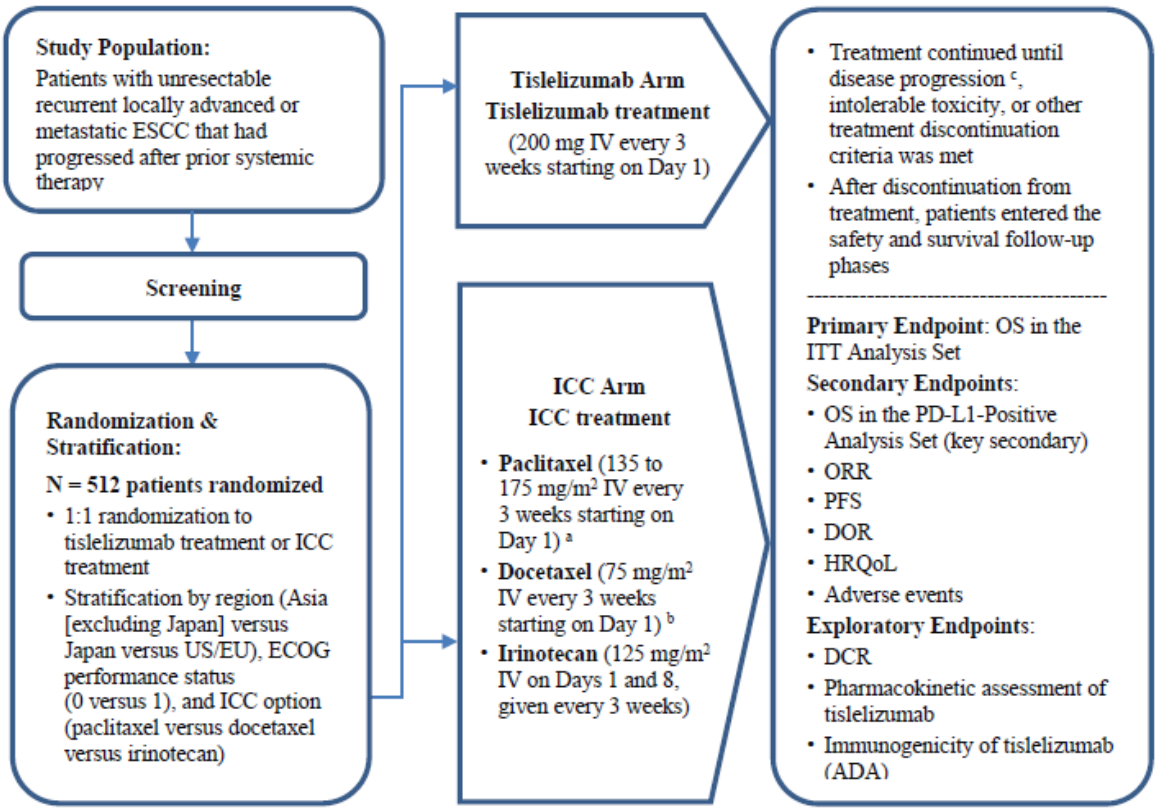
For discussion of exposure-response analyses for efficacy, see section 2.6.3.

2.6.5.2. Main study

Pivotal Study 302

Study 302 is an open-label, multicenter, randomized Phase 3 study comparing the efficacy and safety of tislelizumab versus ICC (paclitaxel, docetaxel, or irinotecan) in patients with unresectable recurrent locally advanced or metastatic ESCC after prior systemic therapy. The study design schematic is presented in Figure 3-3-4.

Figure 3 - 3 - 4 Study Design of Study 302



Source: [Study 302-Figure 1]
Abbreviations: 302, BGB-A317-302; ADA, antidrug antibody; CSR, clinical study report; DCR, disease control rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; ESCC, esophageal squamous cell carcinoma; EU, European Union; HRQoL, health-related quality of life; ICC, investigator-chosen chemotherapy; ITT, intent-to-treat; IV, intravenous(ly); ORR, objective response rate; OS, overall survival; PD-L1, programmed cell death ligand-1; PFS, progression-free survival; US, United States.
[a] Paclitaxel could also be given at doses of 80 to100 mg/m2 on a weekly schedule according to local and/or country-specific guidelines for standard of care; in Japan, paclitaxel was given at doses of 100 mg/m2 on Days 1, 8, 15, 22, 29, and 36, followed by 1 week of rest.
[b] The docetaxel dose that was used in Japan was 70 mg/m2 on Day 1, and then once every 3 weeks.
[c] At the discretion of the investigator, patients who were randomized to receive tislelizumab could be treated beyond progression under protocol-defined conditions [Study 302-Section 9.3.3.1].

Source: Figure 1-1 SCE

The overall study design is endorsed. Given the choice of treatments in the comparator arm, the open-label study design is considered acceptable. The selected stratification factors (region, ECOG PS, ICC option) are considered adequate; however, it is noted that the Applicant has chosen to stratify by three regions in Asia (Asia excluding Japan vs Japan vs US/EU).The Applicant should clarified that the inclusion of Japan as a separate factor was to ensure that baseline characteristics in Japanese patients were balanced between treatment arms to support future regulatory activities in Japan.

Study treatment continued until occurrence of disease progression, intolerable toxicity or other discontinuation criteria were met. In certain circumstances (patient is stable and deriving clinical benefit), the investigator was allowed to decide that patients randomized to receive tislelizumab could be treated beyond initial progression.

Methods

Study Participants

Inclusion criteria (excerpt):

1. Female or male, age ≥ 18 years
2. Histologically confirmed diagnosis of ESCC
3. Tumour progression during or after first-line systemic platinum-based (clarified per Protocol Amendment 3.0) treatment for advanced unresectable or metastatic ESCC
4. *Note*: Patients whose disease progressed during treatment or ≤ 6 months (180 days) after cessation of neoadjuvant/adjuvant treatment (chemotherapy or chemoradiotherapy) were eligible provided all other criteria were met.
5. At least 1 measurable/evaluable lesion by RECIST v1.1
6. ECOG PS score of 0 or 1
7. Laboratory data meeting the criteria below ≤ 14 days before randomization
    a. Absolute neutrophil count ≥ 1500 cells/mm^3
    b. Platelet count ≥ 100,000 cells/mm^3
    c. Hemoglobin ≥ 9 g/dL or ≥ 5.6 mmol/L
    d. Estimated glomerular filtration rate ≥ 30 mL/min/1.73 m^2
    e. Serum total bilirubin ≤ 1.5 x upper limit of normal (ULN)
    f. Prothrombin time/international normalized ratio ≤ 1.5 x ULN
    g. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x ULN (or ≤ 5.0 x ULN in patients with liver metastases)
8. HBV or HCV infection
9. Females of childbearing potential not pregnant and willing to use highly effective methods of birth control

10. Nonsterile males with female sexual partner(s) of childbearing potential must have agreed to use a highly effective form of birth control

Exclusion criteria (excerpt):

1. Receipt of ≥ 2 prior lines of systemic treatments for advanced unresectable or metastatic ESCC.
2. History of gastrointestinal perforation and/or fistula or aorto-esophageal fistula ≤ 6 months before randomization
3. Tumour invasion into organs located adjacent to the esophageal disease site (eg, aorta or respiratory tract) at an increased risk of fistula
4. Uncontrollable pleural effusion, pericardial effusion, or ascites requiring frequent drainage
5. Received prior therapies targeting PD-1 or PD-L1
6. Active brain or leptomeningeal metastasis
7. Had active autoimmune disease or history of autoimmune diseases at high risk for relapse
8. Condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone or equivalents) or other immunosuppressive medications
9. Received any radiopharmaceuticals (except for examination or diagnostic use of radiopharmaceuticals) ≤ 42 days before randomization.
10. Had received any chemotherapy, any immunotherapy (eg, interleukin, interferon, or thymoxin), or any investigational therapies within 28 days or 5 half-lives of the first study treatment administration
11. Any serious or unstable pre-existing medical conditions, psychiatric disorders, or other conditions that could interfere with the patient's safety, obtaining informed consent, or compliance with study procedures
12. Known history of or any evidence of interstitial lung disease, non-infectious pneumonitis, pulmonary fibrosis diagnosed based on imaging or clinical findings, or uncontrolled systemic diseases, including diabetes, hypertension, acute lung diseases, etc
13. Had severe chronic or active infection (including tuberculosis infection, etc) requiring systemic antibacterial, antifungal, or antiviral therapy, ≤ 14 days before Cycle 1 Day 1
14. Known history of HIV
15. Had any cardiovascular risk factors such as ongoing cardiac chest pain, symptomatic pulmonary embolism, history of acute myocardial infarction, history of heart failure (NYHA III or IV), ventricular arrhythmia > Grade 2 in severity, cerebrovascular accident or transient ischemic attack, uncontrolled hypertension, syncope or seizure
16. Pregnant or breastfeeding woman

Overall, the key eligibility criteria for participation in Study 302 are deemed acceptable. The study population was deemed adequate by CHMP (Scientific Advice Procedure No.: EMEA/H/SA/3646/2/2017/II). However, it is noted that the population is somewhat selected accounting for the fact that approx. 50% of ESCC patients have ECOG PS 2-4 at the time of initiation of 2nd line treatment (Jaffe et al. Thorac Cancer, 2022).

The provision of tumour tissue was not mandatory for enrolment in this study; PD-L1 status was missing for approx. 30% of patients (please see section 3.3.4.5).

Treatments

Tislelizumab

Tislelizumab was administered on Day 1 of each 21-day cycle at a dose of 200 mg by intravenous infusion (see Table 3-3-2). The initial infusion (Cycle 1, Day 1) was delivered over 60 minutes. If this was well-tolerated, subsequent infusions were administered over 30 minutes.

Investigator-Chosen Chemotherapy

The choice of chemotherapy (paclitaxel, docetaxel or irinotecan) and treatment regimen was based on local and/or country-specific guidelines and investigators' discretion, taking into account prior therapy and the performance status of the patient. The first dose of paclitaxel, docetaxel, or irinotecan was dependent upon the patient's baseline body surface area. Subsequent doses were recalculated if the change of body surface area (increase or decrease) from baseline was ≥ 10%.

Table 3 - 3 - 1 Dosing regimen of tislelizumab and investigator-chosen chemotherapy

Arm	Drug	Treatment Regimen	Route of Administration	Duration of Treatment
Tislelizumab	Tislelizumab	200 mg every 3 weeks starting on Day 1	Intravenous infusion	Section 9.1 Section 9.3.3
Investigator-Chosen Chemotherapy	Paclitaxel	135 to 175 mg/m² every 3 weeks starting on Day 1 • Note: Paclitaxel could also be given in doses of 80 to 100 mg/m² on a weekly schedule according to local and/or country-specific guidelines for standard of care • Japan: 100 mg/m² on Days 1, 8, 15, 22, 29, and 36, followed by 1 week of rest		
	Docetaxel	75 mg/m² every 3 weeks starting on Day 1 • Japan: 70 mg/m² every 3 weeks starting on Day 1		
	Irinotecan	125 mg/m² on Days 1 and 8, given every 3 weeks		

Source: Section 3.3.2 in Study 302 Protocol Amendment Version 4.0 (Appendix 16.1.1).

The selected ICC options were standard of care at the time of initiation of Study 302 and are considered acceptable as active comparator. Treatment schedules and doses are in line with recommendations in current treatment guidelines (2022 NCCN Guidelines, Lordick et al. 2016).

Dose Delay or Modification

Tislelizumab

No dose reductions of tislelizumab were allowed in this study. Dose delay or interruption of < 12 weeks was permitted. If the delay of tislelizumab was > 12 weeks, treatment was stopped permanently.

Toxicity management guidelines were in place that requested withholding or permanent discontinuation in case of immune-related adverse events or infusion-related reactions. Respective guidance has been implemented in the SmPC.

ICC

Guidance on dose delay, interruption or modification for paclitaxel, docetaxel or irinotecan was provided in the protocol.

Chemotherapy treatment might be delayed up to 21 days if the reason for the delay was toxicity/adverse event. If any chemotherapy agent was held for > 6 weeks from the anticipated treatment date, or the dose level -2 was not tolerated, chemotherapy was permanently discontinued.

Concomitant medication

Most concomitant medications and therapies were allowed if deemed necessary in keeping with the local standards of medical care at the discretion of the investigator for the supportive care (e.g., antiemetics, antidiarrheals, pain medications, and nutritional support) and in a patient's well-being.

The following medications were prohibited or restricted at the time of screening and during the administration of tislelizumab:

- Immunosuppressive agents (except to treat a drug-related adverse event)
- Systemic corticosteroids > 10 mg daily (prednisone or equivalent), except to treat or control a drug-related adverse event or for short-term use as prophylactic treatment
- Live vaccines ≤ 28 days before the first dose of tislelizumab and 60 days after the last dose of tislelizumab
- Herbal remedies with immune-stimulating properties (eg, mistletoe extract) or that were known to potentially interfere with liver or other major organ functions (eg, hypericin).

During all study treatment, concurrent antineoplastic therapy and extensive radiation therapy were prohibited or restricted at the time of screening and during the administration of study treatment.

Permitted and prohibited concomitant medication at screening and during study treatment is considered adequate.

Objectives

Primary Objective

To compare the overall survival (**OS**) in the Intent-to-Treat (**ITT**) Analysis Set after treatment with tislelizumab versus ICC when given as second-line treatment in patients with advanced unresectable or metastatic ESCC.

Key Secondary Objective:

- To compare **OS** in the **PD-L1-Positive Analysis Set** (PD-L1 expression status of visually-estimated Combined Positive Score [vCPS] ≥ 10%, based on Ventana PD-L1 (SP263) assay) after treatment with tislelizumab versus ICC when given as second-line treatment in patients with advanced unresectable or metastatic ESCC

Other Secondary Objectives:

- To compare the following endpoints as assessed by the investigator per Response Evaluation Criteria in Solid Tumours Version 1.1 (RECIST v1.1) between tislelizumab and chemotherapy treatments: objective response rate (**ORR**), progression-free survival (**PFS**), and duration of response (**DOR**)
- To compare Health-related Quality of Life (**HRQoL**) between tislelizumab and chemotherapy treatments, assessed by 3 patient-reported outcome questionnaires, including the European

Organization for Research on Treatment of Cancer Quality of Life Questionnaire-Core 30 (**EORTC QLQ-C30**), the EORTC Quality of Life Questionnaire-Oesophageal Cancer Module (**EORTC QLQ-OES18**), and the European Quality of Life 5-Dimension 5-Level Questionnaire (**EQ-5D-5L**)

- To compare the **safety and tolerability** between tislelizumab and chemotherapy treatments

Outcomes/endpoints

Primary Efficacy Endpoint

The primary efficacy endpoint for this study was overall survival in the ITT Analysis Set, defined as the time from the date of randomization to the date of death from any cause. In the absence of death on or before the data cutoff date, overall survival was censored either at the date that the patient was last known to be alive or the date of data cutoff, whichever occurred earlier.

Secondary Efficacy Endpoints

- Overall survival in patients with PD-L1 vCPS $\geq$ 10%
- Objective response rate, as assessed by the investigator per RECIST v1.1, in the ITT Analysis Set and patients with PD-L1 vCPS $\geq$ 10%
- Duration of response for responders (patients who achieved a CR or PR), as assessed by the investigator per RECIST v1.1, defined as progression/death event-free time counted from the date that the response criteria were first met to the date of first documented radiological progressive disease or death (whichever occurred first)
- PFS, defined as the time from the date of randomization to the date of first documentation of disease progression assessed by the Investigators per RECIST v1.1 or death from any cause, whichever occurred first
- Health-related Quality of Life (HRQoL): Questionnaires EORTC QLQ-C30, EORTC QLQ-OES18, and EQ-5D-5L

Sample size

The study was planned to enrol 500 patients in order to observe 400 deaths. This was expected to provide 82% power to detect an overall survival HR of 0.75 at the 1-sided significance level of α=0.025, corresponding to an improvement in median overall survival from 6 months to 8 months, in the ITT Analysis Set. Assumptions were based on recently published results of anti-PD-1 therapies in second-line treatment of ESCC (Kojima et al 2020; Kato et al 2019; Huang et al 2020).

Randomisation and blinding (masking)

In total, 512 patients were randomized 1:1 to tislelizumab treatment or ICC treatment. Stratification was conducted by region (Asia [excluding Japan] versus Japan versus US/EU), ECOG performance status (0 versus 1), and ICC option (paclitaxel versus docetaxel versus irinotecan). The choice of ICC was determined by the investigator before randomization. ICC option was included as further stratification factor to minimize any potential impact of local clinical practice on study outcome and data interpretation.

Statistical methods

No estimand was defined for this study. It is rather clear that the primary analysis of OS targets a treatment policy estimand (see below), however for secondary analyses the estimand is less clear.

The primary analysis population was planned to be the Intention-to-Treat (ITT) analysis set including all randomized patients.

The PD-L1 positive analysis set was planned to include patients whose tumour and immune cell score (TIC score) met the pre-defined cut-off (specified in the statistical analysis plan) using VENTANA PD-L1 (SP263) CDx Assay. TIC score is the total percentage of the tumour area covered by tumour cells with PD-L1 membrane staining and tumour-associated immune cells with PD-L1 staining at any intensity.

The primary endpoint of OS was planned to be compared between tislelizumab and ICC arms in the ITT analysis set by means of a stratified log-rank test, stratified by selected stratification factors of ECOG performance status (0 vs 1) and ICC option (paclitaxel vs docetaxel vs irinotecan), using a significance level of one-sided 0.025.

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

The primary analysis was stratified only by selected stratification factors of those used in randomized treatment allocation. This is not fully in line with current regulatory guidance (EMA/CHMP/295050/2013, EMA/CHMP/ICH/453276/2016 Rev.1). However, the applicant provided an analysis stratified for all strata of randomization and this analysis provided consistent results.

It was planned that, if the null hypothesis for OS in the ITT analysis set is rejected, the key secondary endpoint, OS in the PD-L1 positive analysis set, would be tested sequentially. The familywise type I error was planned to be strongly controlled at the one-sided level 0.025. Only OS in the ITT and in the PD-L1 positive analysis sets were planned with multiplicity control, all further analyses are descriptive.

Cochran-Mantel-Haenszel (CMH) test adjusting for selected stratification factors (ECOG and ICC option) in the ITT analysis set and the PD-L1 positive analysis set was planned to be provided for ORR per RECIST v1.1. The two-sided 95% CIs for the odds ratio in ORR was planned to be calculated, as well as Clopper-Pearson 95% CIs of ORR for each treatment arm.

A log-rank test stratified by selected stratification factors (ECOG and ICC option) was planned to be used to analyse the PFS differences between two treatment arms. The stratified Cox regression was planned to be used to estimate the hazard ratio of PFS. A 95% confidence interval (CI) of HR in PFS was planned to be constructed. Data for patients without disease progression or death at the time of analysis was planned to be censored at the time of the last tumour assessment. Data for patients who are lost to follow-up prior to documented disease progression was planned to be censored at the last tumour assessment date when the patient is known to be progression-free. Data for patients who start to receive new anti-cancer therapy was planned to be censored at the last tumour assessment date prior to the introduction of new therapy. The applicant provided sensitivity analyses with different censoring rules.

In order to avoid excessive reliance on unadjusted Kaplan-Meier curves, the applicant was asked to provide restricted mean survival time (RMST) over the study period, adjusting for the stratification factors and PD-L1. Given the baseline imbalance noted for Europe and North America this may provide a useful supplement to the KM analyses and inform the benefit-risk assessment.

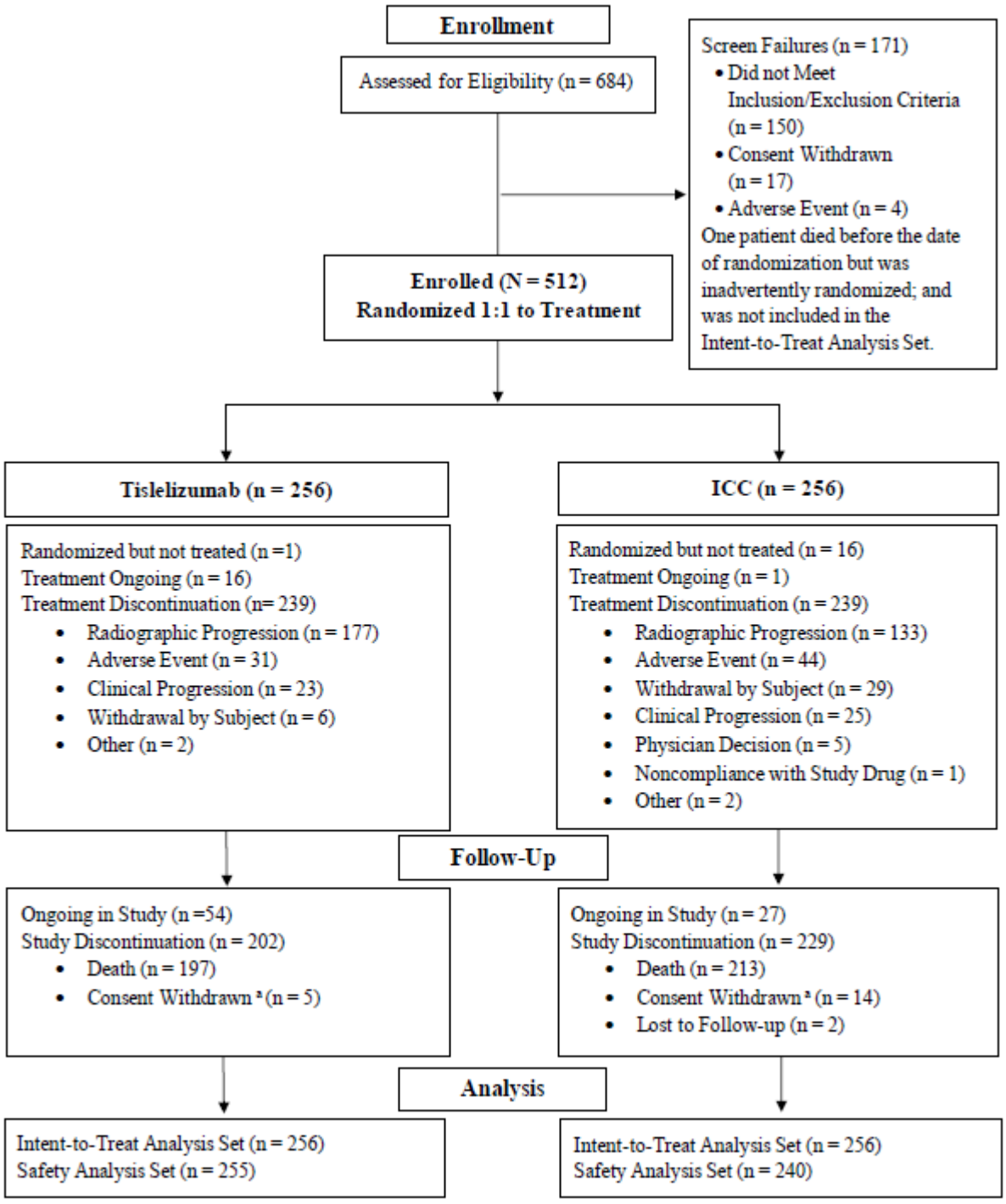
Initially an interim analysis was planned, but it was removed in amendment 4. A simple design without the interim analysis is supported. The applicant clarified the reasons that led to removal of the interim analysis in the responses to the LoQ as requested, please see study conduct below.

Results

Participant flow

A total of 684 patients from 132 sites in 11 countries/regions (Belgium, France, Germany, Italy, Japan, Korea, Mainland China, Spain, Taiwan, UK, and the US) signed informed consent forms. Patient disposition of all enrolled study participants is presented in Figure 3-3-5.

Figure 3 - 3 - 5 BGB-A317-302 Study Profile



Source: Table 14.1.1.1.1, Table 14.1.1.2.1, and Table 14.1.1.3. Data cutoff: 01DEC2020. Data extraction: 15JAN2021.
[a] Consent withdrawal corresponds with voluntary withdrawal by subject in Table 9.

Source: Figure 2 CSR Study 302

More patients in the ICC as compared to the tislelizumab arm were randomized but not treated or withdrew from the study, which is presumably a consequence of the open-label design of the study. The higher proportion of patients in the control group who were not treated at all or discontinued treatment early due to withdrawal of consent could have had an impact on the performance of the control arm. Sensitivity analyses provided reassurance that this did not substantially impact study results (see below).

By the data cutoff date (01 Dec 2020), more than 90% of patients had discontinued study treatment, mostly due to radiographic progression. Approximately 80% of patients discontinued the study due to death (77% vs. 83.2% in the tislelizumab vs. ICC arm). At the data cutoff date, 20% of patients in the tislelizumab arm and 10% of patients in the ICC arm remained on study.

Recruitment

The first patient enrolled in Study BGB-A317-302 was randomized on 26 January 2018. In Asia, the randomization of the last patient occurred on 11 September 2019; in Europe/North America, the randomization of the last patient occurred on 04 March 2020. Data cutoff is 1 December 2020.

The median study follow-up time was 8.49 months (range: 0.2 to 31.7 months) for the tislelizumab arm and 5.80 months (range: 0.0 to 30.8 months) for the ICC arm.

Conduct of the study

Protocol deviations

In the ITT analysis set, 11.7% of patients had important protocol deviations, of whom approximately 2% of patients had critical (=important protocol deviations with significant impact on efficacy and/or safety analyses) protocol deviations.

Table 2: Summary of Critical Protocol Deviations (ITT Analysis Set)

Classification PD Term	Tislelizumab (N = 256) n (%)	ICC (N = 256) n (%)	Total (N = 512) n (%)
Patients With at Least One Critical Protocol Deviation	5 (2.0)	6 (2.3)	11 (2.1)
Disallowed Medications	3 (1.2)	1 (0.4)	4 (0.8)
Prohibited Medication received by subjects	3 (1.2)	1 (0.4)	4 (0.8)
IP Admin/Study Treatment	1 (0.4)	0 (0.0)	1 (0.2)
Wrong study drug administered to subjects	1 (0.4)	0 (0.0)	1 (0.2)
Inc or Excl Criteria	1 (0.4)	2 (0.8)	3 (0.6)
Inclusion Criteria not met: Tumor progression during or after first-line systemic treatment	1 (0.4)	1 (0.4)	2 (0.4)
Exclusion Criteria met: Prior malignancy active within the previous 2 years before randomization	0 (0.0)	1 (0.4)	1 (0.2)
Withdrawal Criteria	0 (0.0)	3 (1.2)	3 (0.6)
Subject continues receiving treatment after withdrawal criteria are met	0 (0.0)	3 (1.2)	3 (0.6)

Abbreviations: ICC = investigator chosen chemotherapy: paclitaxel vs docetaxel vs irinotecan ; PD: Protocol Deviation.
Percentages were based on N.
Deviation categories are not mutually exclusive.
Multiple deviations within the same category are counted once per patient.
Patient was randomized to tislelizumab but received irinotecan for the first cycle.

Protocol amendments

The original global protocol for this study was dated 13 July 2017. Key changes to the protocol are summarized below.

Amendment Version 1.0 (Global, Dated 07 November 2017)

- Evaluation of objective response rate, PFS, and duration of response using immune-related RECIST was removed because the tool had not been validated.
- The stratification factors were modified (gender was replaced with ECOG PS score and ICC option) per the request from the US FDA.
- Alternative paclitaxel and docetaxel treatment regimens were added to provide Japan-specific regimens per the request from the PMDA.
- Clarified that patients who had received ≥ 2 prior systemic treatments for advanced unresectable or metastatic ESCC were excluded.
- Management guidance for infusion-related reactions, severe hypersensitivity reactions, flu-like symptoms, and renal function abnormalities were added.
- The guidance for the immune-mediated adverse event management was modified and updated.

Amendment Version 2.0 (Global, Dated 06 December 2017)

- The requirement of treatment beyond radiographic progression was further clarified per the request from the US FDA.
- Criteria for dose modification of paclitaxel, docetaxel and irinotecan and permanent discontinuation of chemotherapy regimens were clarified, and dose modifications guidelines for specific adverse events and other toxicities were provided, per request from the US FDA.

Amendment Version 3.0 (Global, Dated 08 November 2018)

- CK (creatine kinase) and CK-MB (creatine kinase cardiac muscle isoenzyme) tests and management guidance were added to monitor the risk of myocarditis more closely.
- Incorporated the US FDA request of implementing measures to further decrease the potential for viral reactivation: Continuous treatment for 6 months after treatment discontinuation was required for patients with detectable HBsAg or HBV DNA; continuous effective antiviral therapy was required for patients who had detectable HCV and were receiving treatment at screening.
- The criterion to exclude patients who had a history of anterior organ transplant, including stem-cell allograft, was added per the request from the French National Agency for the Safety of Medicines and Health Products (ANSM).
- Immune-mediated adverse event management guidelines were updated: "Tislelizumab must be permanently discontinued for any onset of Grade 4 or recurrent Grade 3 immune-mediated adverse events."
- A new appendix of "Determining Line of Therapy in ESCC" was added to further clarify the definition of first-line systemic treatment in inclusion criteria, and first-line or front-line systemic treatment was defined as "platinum-based regimen."

Amendment Version 4.0 (Global, Dated 20 March 2020)

- Updated the statistical estimation of the sample size to increase the sample size from 450 to 500 and increase target number of death events from 336 to 400, with the following consideration: (1) overall survival HR was adjusted from 0.73 to 0.75 based on recently published results of anti-PD-1 therapies in second-line treatment of ESCC and (2) addition of a dropout rate of 5%.
- The predefined interim analysis was removed due to the lack of geographically representative population for the analysis, which resulted from the disparity in global enrollment rates.
- The overall survival in patients with PD-L1 vCPS ≥ 10% was added as the key secondary endpoint of this study to reflect the clinical relevance and importance of the PD-L1 biomarker in ESCC observed in competitors' published data. (Note: PD-L1 assessment [by Ventana PD-L1 SP263 CDx Assay] was not started before the key secondary endpoint was added in this protocol amendment, and PD-L1 status of each patient was unknown.)

Baseline data

Demographics

Table 3 - 3 - 2 Summary of demographic and baseline characteristics (ITT analysis set)

Parameter	Tislelizumab (N = 256)	ICC (N = 256)	Total (N = 512)
Age (years)			
n	256	256	512
Mean (SD)	61.4 (8.43)	61.6 (8.01)	61.5 (8.21)
Median	62.0	63.0	62.0
Q1, Q3	55.0, 67.0	55.0, 66.0	55.0, 67.0
Min, Max	40, 86	35, 81	35, 86
Age Group, n (%)			
<65 years	157 (61.3)	161 (62.9)	318 (62.1)
>=65 years	99 (38.7)	95 (37.1)	194 (37.9)
Gender, n (%)			
Female	39 (15.2)	41 (16.0)	80 (15.6)
Male	217 (84.8)	215 (84.0)	432 (84.4)
Race, n (%)			
Asian	201 (78.5)	207 (80.9)	408 (79.7)
Chinese	161 (62.9)	163 (63.7)	324 (63.3)
Japanese	25 (9.8)	25 (9.8)	50 (9.8)
Korean	15 (5.9)	16 (6.3)	31 (6.1)
Asian Indian	0 (0.0)	3 (1.2)	3 (0.6)
White or Caucasian	53 (20.7)	44 (17.2)	97 (18.9)
Not Reported [a]	1 (0.4)	0 (0.0)	1 (0.2)
Unknown	1 (0.4)	2 (0.8)	3 (0.6)
Black or African American	0 (0.0)	2 (0.8)	2 (0.4)
Other	0 (0.0)	1 (0.4)	1 (0.2)
Region, n (%)			
Asia	201 (78.5)	203 (79.3)	404 (78.9)
Europe/North America	55 (21.5)	53 (20.7)	108 (21.1)
Ethnicity, n (%)			
Not Hispanic or Latino	252 (98.4)	252 (98.4)	504 (98.4)
Hispanic or Latino	2 (0.8)	2 (0.8)	4 (0.8)
Not Reported [b]	1 (0.4)	0 (0.0)	1 (0.2)
Unknown	1 (0.4)	2 (0.8)	3 (0.6)

Parameter	Tislelizumab (N = 256)	ICC (N = 256)	Total (N = 512)
ECOG Status, n (%)			
0	66 (25.8)	60 (23.4)	126 (24.6)
1	190 (74.2)	196 (76.6)	386 (75.4)
BMI (kg/m^2)			
n	254	256	510
Mean (SD)	21.27 (3.393)	21.62 (3.569)	21.45 (3.483)
Median	21.06	21.15	21.10
Q1, Q3	18.75, 23.18	18.85, 23.89	18.83, 23.48
Min, Max	14.0, 37.7	14.3, 33.1	14.0, 37.7
PD-L1 Status, n (%)			
vCPS >= 10%	80 (31.3)	62 (24.2)	142 (27.7)
vCPS < 10%	100 (39.1)	122 (47.7)	222 (43.4)
Missing	76 (29.7)	72 (28.1)	148 (28.9)
Smoking Status, n (%)			
Never	68 (26.6)	63 (24.6)	131 (25.6)
Former	162 (63.3)	159 (62.1)	321 (62.7)
Current	26 (10.2)	33 (12.9)	59 (11.5)
Missing	0 (0.0)	1 (0.4)	1 (0.2)

Source: Table 2-2 SCE Study 302 (with updated PD-L1 status after re-classification)

Baseline disease characteristics

Table 3 - 3 - 3 Disease history and characteristics at study entry (ITT analysis set), excerpt

Description	Tislelizumab (N = 256)	ICC (N = 256)	Total (N = 512)
Number of Patient With Metastatic Diagnosis at Study Entry, n (%)			
Yes	251 (98.0)	236 (92.2)	487 (95.1)
No	5 (2.0)	20 (7.8)	25 (4.9)
Time from Metastatic Diagnosis to Study Entry (months)			
n	251	236	487
Mean (SD)	6.66 (6.585)	7.09 (6.791)	6.87 (6.682)
Median	5.26	5.37	5.36
Q1, Q3	1.18, 9.86	1.95, 10.00	1.54, 9.92
Min, Max	0.2, 43.5	0.2, 53.0	0.2, 53.0
Prior Systemic Therapy, n (%)			
Chemotherapy	94 (36.7)	101 (39.5)	195 (38.1)
Chemo-Radiotherapy	161 (62.9)	155 (60.5)	316 (61.7)
Other *	1 (0.4)	0 (0.0)	1 (0.2)

Source: Table 14 CSR Study 302

Prior anticancer therapy

Overall, a higher percentage of patients in the ITT population received neo-/adjuvant treatment in the tislelizumab as compared to the ICC arm (19.9% vs. 12.5%). Other parameters of prior anticancer therapy were balanced between the treatment groups of the ITT.

Table 3 - 3 - 4 Prior anticancer systemic therapy (ITT analysis set), excerpt

	Tislelizumab (N = 256)	ICC (N = 256)	Total (N = 512)
Patients With at Least One Prior Systemic Therapy, n (%)	256 (100.0)	256 (100.0)	512 (100.0)
Patients With Prior Line of Platinum-based Systemic Therapy [a], n (%)	246 (96.1)	252 (98.4)	498 (97.3)
Number of Prior Line of Systemic Therapies [b], n (%)			
0	1 (0.4)	1 (0.4)	2 (0.4)
1	255 (99.6)	255 (99.6)	510 (99.6)
Prior Neo-Adjuvant/Adjuvant Treatment or Definitive Chemoradiotherapy as First Line Systemic Therapies [c], n (%)			
Neo-Adjuvant/Adjuvant Treatment	51 (19.9)	32 (12.5)	83 (16.2)
Definitive Chemoradiotherapy	26 (10.2)	32 (12.5)	58 (11.3)

Source: Table 15 CSR Study 302

Imbalances in baseline characteristics and prior anticancer therapies by region and treatment

Table 3-3-6 below summarizes relevant imbalances observed between the Asia and Europe/North America population and respective treatment groups:

Table 3 - 3 - 5 Overview of relevant imbalances in baseline characteristics and prior anticancer therapy by region and treatment (ITT analysis set)

	Europe/North America			Asia		
	Tislelizumab (N = 55)	**ICC (N = 53)**	**Total (N = 108)**	**Tislelizumab (N = 201)**	**ICC (N = 203)**	**Total (N = 404)**
Age (years)						
Median	65.0	65.0	65.0	61.0	62.0	61.0
Min, Max	41, 86	35, 80	35, 86	40, 83	41, 81	40, 83
Gender, n (%)						
Male	37 (67.3)	36 (67.9)	73 (67.6)	180 (89.6)	179 (88.2)	359 (88.9)
ECOG PS, n (%)						
1	32 (58.2)	35 (66.0)	67 (62.0)	158 (78.6)	161 (79.3)	319 (79.0)
PD-L1 Status, n (%)						
vCPS ≥ 10%	22 (40.0)	9 (17.0)	31 (28.7)	58 (28.9)	53 (26.1)	111 (27.5)
vCPS < 10%	25 (45.5)	35 (66.0)	60 (55.6)	75 (37.3)	87 (42.9)	162 (40.1)
Missing	8 (14.5)	9 (17.0)	17 (15.7)	68 (33.8)	63 (31.0)	131 (32.4)
Prior Neoadjuvant/ Adjuvant Treatment as 1st Line Systemic Therapy, n (%)	1 (1.8)	2 (3.8)	3 (2.8)	50 (24.9)	30 (14.8)	80 (19.8)

Source: Excerpt from Tables 14.1.2.1a and 14.1.5.1a CSR Study 302; updated after PD-L1 status reclassification

Patients in the Asia subgroup were younger as compared to those in the Europe/North America subgroup (median age of 61.0 years versus 65.0 years, respectively), had a higher percentage of males (88.9% versus 67.6%), and had a higher percentage of ECOG PS scores of 1 (79.0% versus 62.0%). While percentages of patients with a PD-L1 vCPS ≥ 10% were similar in the Asia subgroup (27.5%) and Europe/North America subgroup (28.7%), the percentages of patients with PD-L1 vCPS < 10% were higher in the Europe/North America subgroup (55.6%) than in the Asia subgroup (40.1%). This difference may be explained by the equally higher percentage of patients with missing PD-L1 status in the Asian population (32.4% vs. 15.7% in Europe/North America). Nevertheless, it cannot be excluded that a higher rate of patients with PD-L1 vCPS < 10% was enrolled in Europe/North America as compared to Asia in Study 302. Fewer patients in the Europe/North America subgroup had neo-

/adjuvant therapy as first-line anticancer systemic therapy (Europe/North America: 2.8% vs. Asia: 19.8%). This different proportion of neo-/adjuvant treatment obviously reflects regional differences in standard clinical practise. Generally, the imbalances observed between the Asia and Europe/North America subgroups yield uncertainties as regards to the external validity of the study.

In addition, imbalances observed in PD-L1 expression and ECOG performance status specifically between treatment arms of the Europe/North America subgroup (PD-L1 vCPS ≥ 10%: tislelizumab = 40.0% vs. ICC = 17.0% and ECOG PS 1: tislelizumab = 58.2% vs. ICC = 66.0%) yield uncertainties with regard to the validity and credibility of study results in the EU population.

Numbers analysed

Table 3 - 3 - 6 Analysis sets

Analysis Set	Tislelizumab (N = 256) n (%)	ICC (N = 256) n (%)	Total (N = 512) n (%)
Intent-to-Treat (ITT) Analysis Set	256 (100.0)	256 (100.0)	512 (100.0)
PD-L1 Positive Analysis Set	89 (34.8)	68 (26.6)	157 (30.7)
Per Protocol (PP) Analysis Set	250 (97.7)	234 (91.4)	484 (94.5)
Safety Analysis Set	255 (99.6)	240 (93.8)	495 (96.7)
PK Analysis Set	254 (99.2)	Not Collected	254 (49.6)
ADA Analysis Set	221 (86.3)	Not Collected	221 (43.2)

Source: Post-Text Table 14.1.1.3. Data cutoff: 01DEC2020. Data extraction: 15JAN2021.
Abbreviations: ICC = investigator chosen chemotherapy: paclitaxel vs docetaxel vs irinotecan.
Percentages were based on N.
unblind/bgb_a317/bgb_a317_302/csr/dev/pgm/intext/t-as.sas 22MAR2021 06:18 t-02-as-i.rtf

Source: Table 12 CSR Study 302

Outcomes and estimation

ITT analysis set

Overall survival (Primary Efficacy Analysis)

Table 3 - 3 - 7 Overall Survival (ITT analysis set)

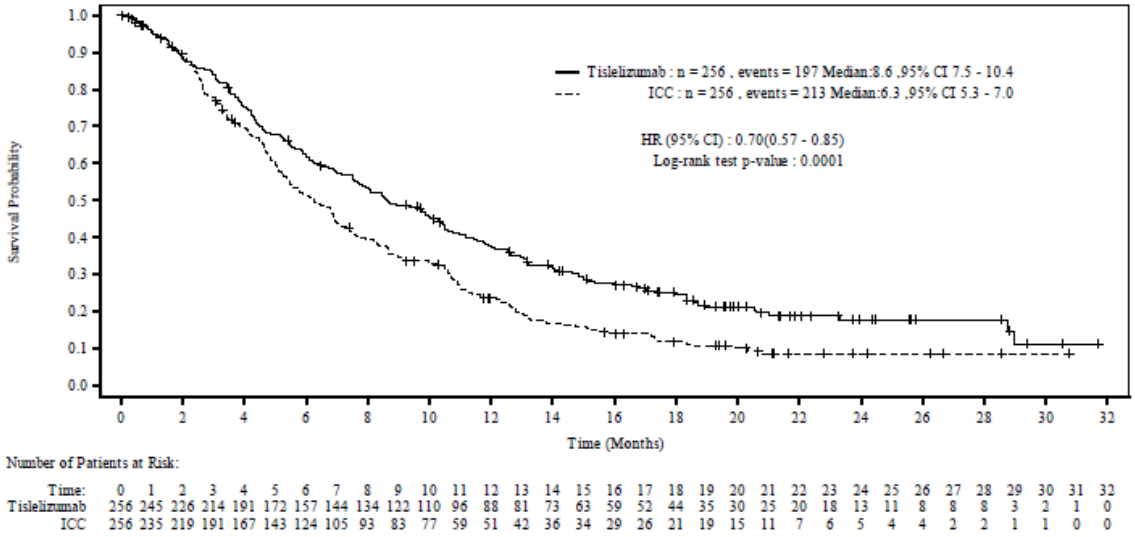
	Tislelizumab (N = 256)	ICC (N = 256)
Number of Patients		
Death, n (%)	197 (77.0)	213 (83.2)
Censored, n (%)	59 (23.0)	43 (16.8)
Ongoing Without Event	54 (21.1)	27 (10.5)
Lost to Follow-up	0 (0.0)	2 (0.8)
Withdrew Consent	5 (2.0)	14 (5.5)
One-Sided Stratified Log-Rank Test P-value [a]	0.0001	
Stratified Hazard Ratio (95% CI) [b]	0.70 (0.57, 0.85)	
Unstratified Hazard Ratio (95% CI) [c]	0.69 (0.57, 0.84)	

Overall Survival (months)		
Median (95% CI)	8.6 (7.5, 10.4)	6.3 (5.3, 7.0)
1st Quartile (95% CI)	4.0 (3.5, 4.6)	3.3 (2.6, 4.0)
3rd Quartile (95% CI)	18.0 (14.7, 21.0)	11.4 (10.6, 12.9)
Overall Survival Rate at, % (95% CI)		
3 Months (95% CI)	84.0 (78.8, 87.9)	78.0 (72.3, 82.7)
6 Months (95% CI)	62.3 (56.0, 67.9)	51.8 (45.3, 57.9)
9 Months (95% CI)	48.7 (42.4, 54.7)	35.0 (29.0, 41.1)
12 Months (95% CI)	37.4 (31.4, 43.4)	23.7 (18.5, 29.3)
Follow-up Time (months)		
Median (95% CI)	20.8 (19.5, 22.4)	21.1 (19.3, 22.8)

Source: Listing 16.2.6.1. Data cutoff: 01DEC2020. Data extraction: 15JAN2021.
Abbreviations: ICC = investigator chosen chemotherapy: paclitaxel vs docetaxel vs irinotecan.
Percentages were based on N.
In absence of death on or before data cut-off, patients will be censored either at the date that the patient was last known to be alive or the date of data cut-off, whichever comes earlier.
Medians and other quartiles were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley.
Overall Survival rates (cumulative probability of OS) were estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula.
Median follow-up time was estimated by the reverse Kaplan-Meier method.
[a] One-sided p-value was estimated from log rank test stratified by ECOG performance status and ICC option.
[b] Hazard ratio (Tislelizumab vs. ICC) was based on Cox regression model including treatment as covariate, and baseline ECOG status and ICC options as strata.
[c] Hazard ratio (Tislelizumab vs. ICC) was based on unstratified Cox regression model only including treatment arm as a factor.
unblind/bgb_a317/bgb_a317_302/csr/dev/pgm/tlfs/t-os.sas 03FEB2021 08:59 t-14-02-01-01-os-itt.rtf

Source: Table 14.2.1.1 CSR Study 302

Figure 3 - 3 - 6 Kaplan-Meier Plot of Overall Survival (OS) (ITT analysis set)



Source: Post-Text Figure 14.2.1.1. Data cutoff: 01DEC2020. Data extraction: 15JAN2021.
One-sided p-value was estimated from log-rank test stratified on ECOG status and ICC option.
Hazard ratio was based on Cox regression model including treatment as covariate stratified by ECOG status and ICC option
unblind/bgb_a317/bgb_a317_302/csr/dev/pgm/intext/f-km.sas 03FEB2021 08:31 f-01-km-os-itt-i.rtf

Source:

Figure 3 CSR Study 302

Progression-Free Survival

Table 3 - 3 - 8 Progression Free Survival (PFS) (ITT analysis set)

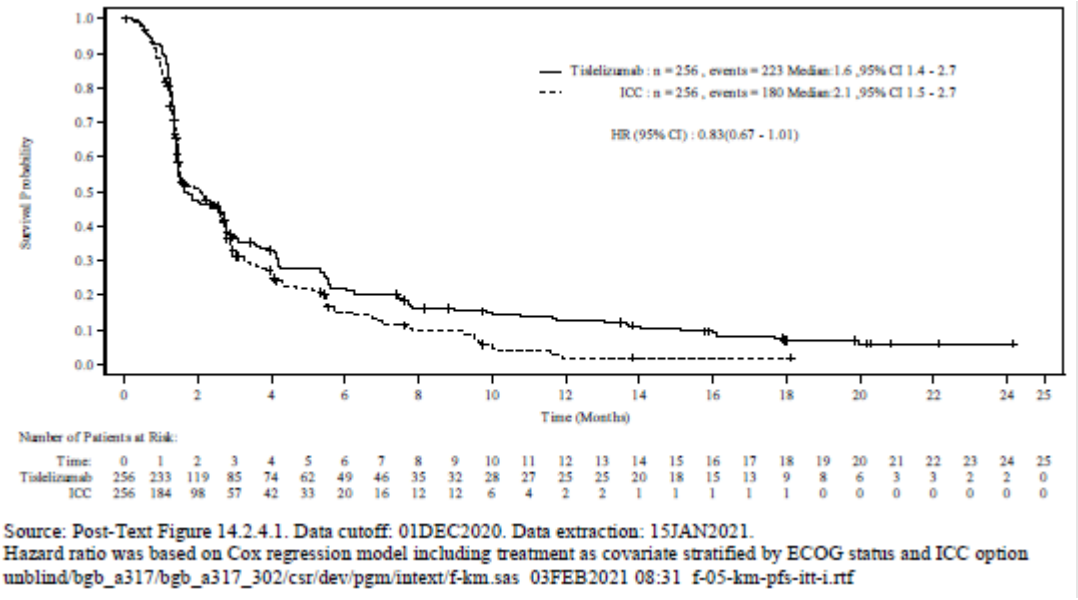
	Tislelizumab (N = 256)	ICC (N = 256)
Progression-Free Survival		
Events, n (%)	223 (87.1)	180 (70.3)
Progressive Disease	191 (74.6)	145 (56.6)
Death	32 (12.5)	35 (13.7)
Censored, n (%)	33 (12.9)	76 (29.7)
No Post-Baseline	3 (1.2)	38 (14.8)
New Anti-Cancer Therapy	12 (4.7)	30 (11.7)
Missed >= 2 Assessments	4 (1.6)	4 (1.6)
No PD/Death *	14 (5.5)	4 (1.6)
Withdrew Consent	1 (0.4)	1 (0.4)
Ongoing Without Event	13 (5.1)	3 (1.2)

One-Sided Stratified Log-Rank Test P-value [b]	0.0292	
Stratified Hazard Ratio (95% CI) [c]	0.83 (0.67, 1.01)	
Unstratified Hazard Ratio (95% CI) [d]	0.83 (0.68, 1.01)	
Progression Free Survival (months)		
Median (95% CI)	1.6 (1.4, 2.7)	2.1 (1.5, 2.7)
1st Quartile (95% CI)	1.3 (1.2, 1.4)	1.2 (1.2, 1.4)
3rd Quartile (95% CI)	5.5 (4.1, 7.4)	4.1 (3.0, 5.5)
Progression Free Survival Rate at, % (95% CI)		
3 Months (95% CI)	36.3 (30.3, 42.2)	33.1 (26.6, 39.7)
6 Months (95% CI)	21.7 (16.7, 27.2)	14.9 (9.9, 20.9)
9 Months (95% CI)	15.8 (11.4, 20.8)	9.6 (5.5, 15.0)
12 Months (95% CI)	12.7 (8.8, 17.5)	1.9 (0.4, 5.8)

Source: Listing 16.2.6.3. Data cutoff: 01DEC2020. Data extraction: 15JAN2021.
Abbreviations: ICC = investigator chosen chemotherapy: paclitaxel vs docetaxel vs irinotecan; PD: Progressive Disease.
Percentages were based on N.
Medians and other quartiles were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley.
Progression free survival rates (cumulative probability of PFS) were estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula.
[a] Patients ongoing without PD and with no Post-baseline assessments are counted in 'No PD/Death Ongoing Without Event' category.
[b] One-sided p-value was estimated from log rank test stratified by ECOG performance status and ICC option, for descriptive purpose only.
[c] Hazard ratio (Tislelizumab vs. ICC) was based on Cox regression model including treatment arm as a factor and stratified by ICC and ECOG performance status.
[d] Hazard ratio (Tislelizumab vs. ICC) was based on unstratified Cox regression model only including treatment arm as a factor.
unblind/bgb_a317/bgb_a317_302/csr/dev/pgm/tlfs/t-pfs.sas 03FEB2021 09:02 t-14-02-03-01-pfs-itt.rtf

Source: Table 14.2.3.1 CSR Study 302

Figure 3 - 3 - 7 Kaplan-Meier Plot of Progression Free Survival (PFS) (ITT analysis set)



Source: Post-Text Figure 14.2.4.1. Data cutoff: 01DEC2020. Data extraction: 15JAN2021.
Hazard ratio was based on Cox regression model including treatment as covariate stratified by ECOG status and ICC option
unblind/bgb_a317/bgb_a317_302/csr/dev/pgm/intext/f-km.sas 03FEB2021 08:31 f-05-km-pfs-itt-i.rtf

Source: Figure 8 CSR Study 302

Objective Response Rate (unconfirmed)

Table 3 - 3 – 11 Unconfirmed Objective Response (ORR) (ITT analysis set)

Response Category	Tislelizumab (N = 256)	ICC (N = 256)
Objective Response Rate (ORR), n	52	25
% (95% CI) [a]	20.3 (15.6, 25.8)	9.8 (6.4, 14.1)
Odds Ratio for ORR, (95% CI) [b]	2.39 (1.42, 4.01)	---
CMH Test P-value [c]	0.0008	---
ORR Difference, % (95% CI) [b]	10.6 (4.5, 16.7)	---
Best Overall Response (BOR), n (%)		
Complete Response (CR)	5 (2.0)	1 (0.4)
Partial Response (PR)	47 (18.4)	24 (9.4)
Stable Disease (SD)	68 (26.6)	82 (32.0)

Progressive Disease (PD)	116 (45.3)	86 (33.6)
Could Not Be Determined [d]	20 (7.8)	63 (24.6)

Source: Post-Text Table 14.2.4.1. Data cutoff: 01DEC2020. Data extraction: 15JAN2021.
Abbreviations: ICC = investigator chosen chemotherapy: paclitaxel vs docetaxel vs irinotecan; CMH test, Cochran-Mantel-Haenszel test.
Percentages were based on N.
[a] Two-sided 95% CI was calculated using Clopper-Pearson method.
[b] Objective response rate, objective response rate differences and odds ratios between arms were calculated using the Cochran-Mantel-Haenszel Chi-square test, stratified by ECOG performance status and ICC option.
[c] CMH test is stratified by ECOG status and ICC option. P-value for descriptive purpose only.
[d] Patients with no post-baseline response assessment (Not Assessable) or assessment as Not Evaluable (NE) per RECIST 1.1.
unblind/bgb_a317/bgb_a317_302/csr/dev/pgm/intext/t-orr-itt.sas 22MAR2021 22:12 t-12-orr-itt-i.rtf

Source: Table 21 CSR Study 302

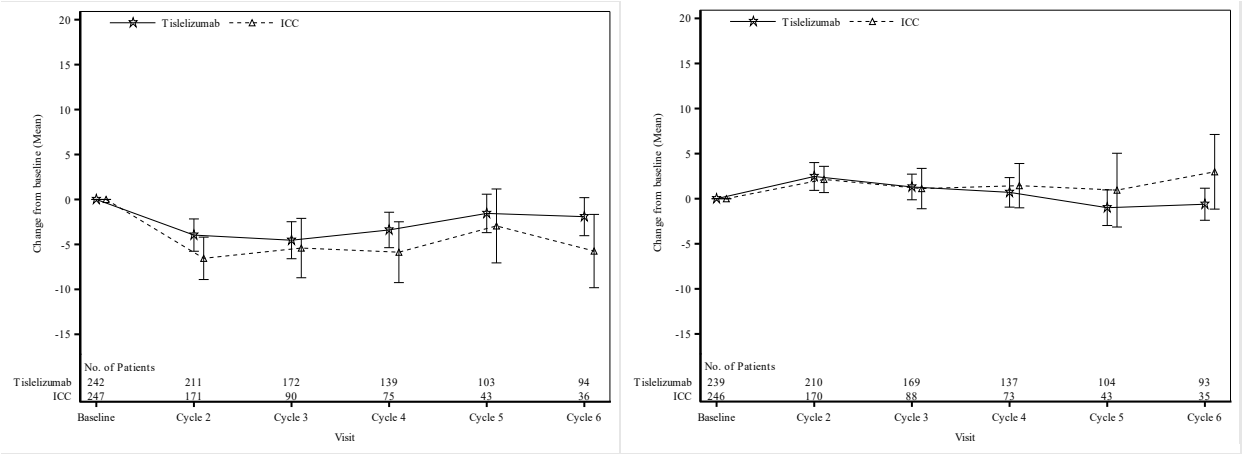
The applicant conducted a post-hoc analysis of **confirmed objective response rates (ORR)**, which revealed slightly lower ORR as compared to the unconfirmed analysis but generally supported unconfirmed ORR results. The confirmed ORR was higher in the Tislelizumab Arm than in the ICC Arm (15.2% [95% CI: 11.1% to 20.2%] versus 6.6% [95% CI: 3.9% to 10.4%], respectively), with an objective response rate difference of 8.6% (95% CI: 3.3% to 13.9%) and an odds ratio of 2.57 (95% CI: 1.40 to 4.71) between the 2 arms.

Health-Related Quality of Life

Changes from baseline to Cycle 6 (mean change [standard deviation]) in HRQoL outcome scores showed a trend in favor of the Tislelizumab Arm versus the ICC Arm:

- A numerically smaller reduction in physical functioning was observed in the Tislelizumab Arm compared with the ICC Arm (Tislelizumab: -1.9 [10.33]; ICC: -5.7 [12.05]) (Figure 3-10, left)
- Global health status (GHS) improved from baseline in the Tislelizumab Arm but worsened in the ICC Arm (Tislelizumab: 1.9 [16.45]; ICC: -6.3 [14.82])
- There were slight numerical improvements in the overall symptoms, as measured by index score of QLQ-OES18, in the Tislelizumab Arm compared with a worsening in the ICC Arm (Tislelizumab: -0.6 [8.63]; ICC: 3.0 [12.05]) (Figure 3-10, right)

Figure 3 - 1 Summary of EORTC QLQ-C30 scores by visit - Physical functioning (left) and Summary of EORTC QLQ-OES18 scores by visit - Index score (right) (ITT analysis set)



Data cutoff: 01DEC2020. Data extraction: 15JAN2021.
Abbreviations: ICC = investigator chosen chemotherapy: paclitaxel vs docetaxel vs irinotecan.
Datapoints represent means and 95% CI.
Increases in scores for physical functioning are improvements for C30. Increases in scores for index score are deteriorations for OES18.

Source: Figure 2-4 and 2-5 SCE

- A numerically lower risk of clinically meaningful worsening was observed in the Tislelizumab Arm compared with the ICC Arm in physical functioning (stratified HR: 0.67 [95% CI: 0.45 to 1.00]) per EORTC QLQ-C30 and overall symptoms of reflux (stratified HR: 0.50 [95% CI: 0.32 to 0.80]), dysphagia (stratified HR: 0.76 [95% CI: 0.53 to 1.07]), and pain (stratified HR: 0.89 [95% CI: 0.59 to 1.35]) per EORTC QLQ-OES18
- Clinically meaningful differences in GHS between the Tislelizumab Arm compared with the ICC Arm were not observed (stratified HR: 0.96 [95% CI: 0.65 to 1.41])

Accounting for the margin of the described differences in HRQoL outcomes, improvements in QoL are not considered clinically meaningful. In addition, the reliability of HRQoL results is hampered by the open-label design of Study 302. As such, patient-reported outcomes are not included in section 5.1 of the SmPC.

Ancillary analyses

Sensitivity analyses

Sensitivity analyses were provided with alternative censoring rules in line with European guidance (EMA/CHMP/27994/2008/Rev.1).

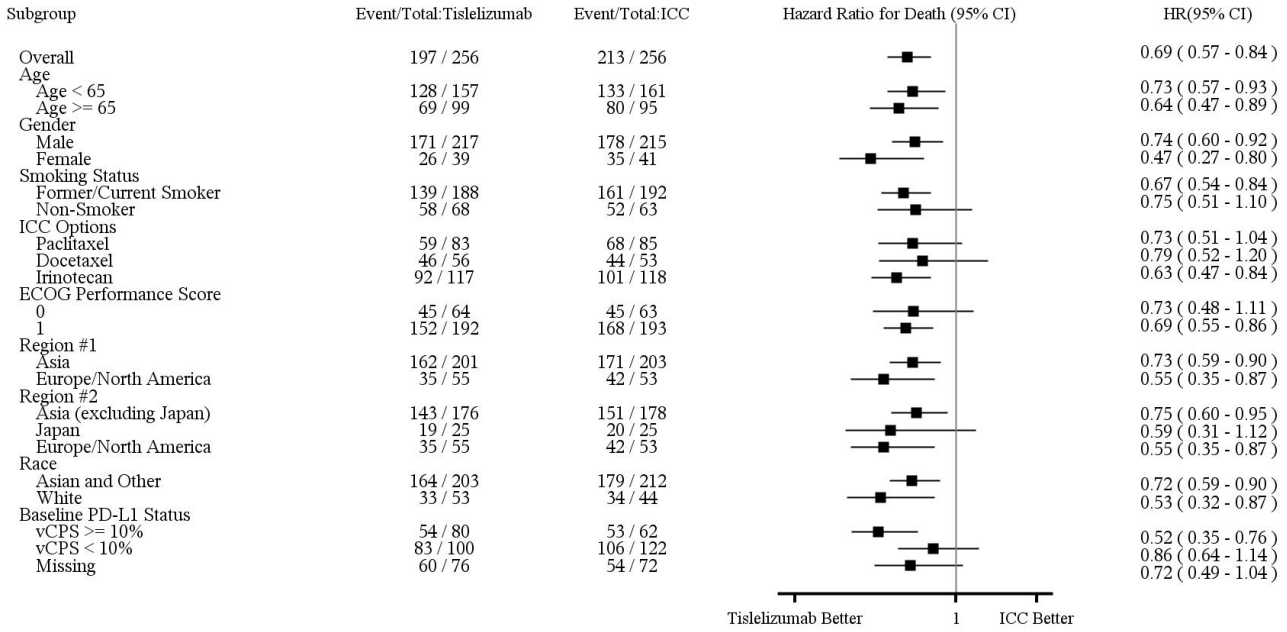
Table 3 - 3 – 10 Progression Free Survival (PFS) – Sensitivity Analysis II (ITT analysis set)

	Tislelizumab (N = 256)	ICC (N = 256)
Progression-Free Survival		
Events, n (%)	230 (89.8)	194 (75.8)
Progressive Disease	191 (74.6)	146 (57.0)
Death	39 (15.2)	48 (18.8)
Censored, n (%)	26 (10.2)	62 (24.2)
No Post-Baseline	0 (0.0)	28 (10.9)
New Anti-Cancer Therapy	12 (4.7)	30 (11.7)
No PD/Death [a]	14 (5.5)	4 (1.6)
Withdrew Consent	1 (0.4)	1 (0.4)
Ongoing Without Event	13 (5.1)	3 (1.2)
One-Sided Stratified Log-Rank Test P-value [b]	0.0510	
Stratified Hazard Ratio (95% CI) [c]	0.85 (0.70, 1.03)	
Unstratified Hazard Ratio (95% CI) [d]	0.84 (0.69, 1.02)	
Progression Free Survival (months)		
Median (95% CI)	1.8 (1.5, 2.7)	2.3 (1.5, 2.7)
1st Quartile (95% CI)	1.3 (1.2, 1.4)	1.3 (1.2, 1.4)
3rd Quartile (95% CI)	5.5 (4.2, 7.4)	4.1 (3.4, 5.5)
Progression Free Survival Rate at, % (95% CI)		
3 Months (95% CI)	37.3 (31.3, 43.2)	36.6 (30.1, 43.1)
6 Months (95% CI)	22.5 (17.5, 27.9)	16.0 (11.1, 21.7)
9 Months (95% CI)	15.5 (11.2, 20.4)	10.2 (6.2, 15.3)
12 Months (95% CI)	12.1 (8.3, 16.7)	3.0 (1.0, 6.8)

Source: Listing 16.2.6.3b. Data cutoff: 01DEC2020. Data extraction: 15JAN2021.
Abbreviations: ICC = investigator chosen chemotherapy: paclitaxel vs docetaxel vs irinotecan; PD: Progressive Disease.
The progression free survival sensitivity analysis II is the same as the primary analysis that is uses the actual reported date of progression or death to define PFS regardless of the progression or death occur after more than one missed tumor assessment visit.
Percentages were based on N.
Medians and other quartiles were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley.
Progression free survival rates (cumulative probability of PFS) were estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula.
[a] Patients ongoing without PD and with no Post-baseline assessments are counted in 'No PD/Death Ongoing Without Event' category.
[b] One-sided p-value was estimated from log rank test stratified by ECOG performance status and ICC option, for descriptive purpose only.
[c] Hazard ratio (Tislelizumab vs. ICC) was based on Cox regression model including treatment arm as a factor and stratified by ICC and ECOG performance status.
[d] Hazard ratio (Tislelizumab vs. ICC) was based on unstratified Cox regression model only including treatment arm as a factor.
unblind/bgb_a317/bgb_a317_302/csr/dev/pgm/tlfs/t-pfs.sas 03FEB2021 09:02 t-14-02-03-04-pfs-2-itt.rtf

Subgroup Analyses for Primary Efficacy Endpoint

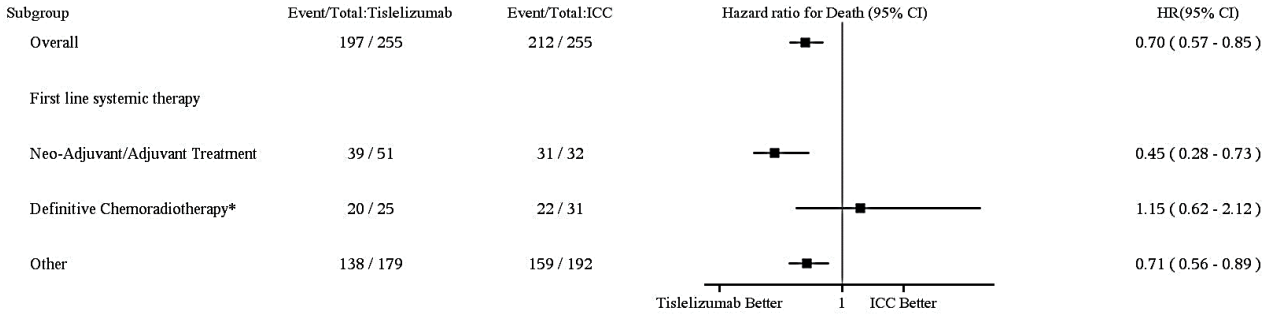
Figure 3 - 3 - 8 Subgroup analysis: Forest Plot of Overall Survival (ITT analysis set)



Data cutoff: 01DEC2020. Data extraction: 15JAN2021.
Abbreviations: ICC = investigator chosen chemotherapy: paclitaxel vs docetaxel vs irinotecan; vCPS: visually-estimated combined positive score. Hazard ratio was based on unstratified Cox regression model including treatment as covariate.
The race subcategory Other includes Black or African American, Not Reported, Unknown and Other.
PD-L1 positive is defined as vCPS ≥ 10%, PD-L1 negative is defined as vCPS < 10%, Missing refers to the patients without sample collection or not evaluable at baseline.

The applicant provided further subgroup analyses splitting patients by prior first-line systemic therapy (neo-adjuvant/adjuvant therapy, definitive chemoradiotherapy and other=palliative chemotherapy), which was considered of interest due to the higher proportion of patients treated with neo-adjuvant therapy in Asia (19.8%) than in Europe/North America (2.8%).

Figure 3 - 3 - 9 Subgroup analysis: Forest Plot of Overall Survival by first-line systemic therapy (ITT analysis set)



Data cutoff: 01DEC2020. Data extraction: 15JAN2021.
Unstratified Hazard ratio was based on Cox regression model including treatment as covariate.
* One patient of each arm was excluded based on protocol deviation of inclusion criteria #4 and exclusion criteria #1 identified in the study.

Subgroups by PD-L1 expression

PD-L1 expression data had to be re-classified after finalization of the CSR for Study 302. In the following, corrected results based on PD-L1 status after reclassification are presented:

Table 3 - 3 – 12 Overview of efficacy results by PD-L1 status (ITT analysis set)

	PD-L1 vCPS ≥ 10%		PD-L1 vCPS < 10%		Missing PD-L1 Status	
	Tislelizumab (N = 80)	**ICC (N = 62)**	**Tislelizumab (N = 100)**	**ICC (N =122)**	**Tislelizumab (N = 76)**	**ICC (N = 72)**
Overall survival						
Stratified HR (95% CI)	0.49 (0.33, 0.74)		0.83 (0.62, 1.12)		0.72 (0.49, 1.06)	
Median OS (95% CI) (months)	10.0 (8.5, 15.1)	5.1 (3.8, 8.2).3)	7.5 (5.5, 8.9)	5.8 (4.8, 6.9)	8.5 (6.2, 12.1)	7.0 (5.8, 8.6)
Progression free survival						
Stratified HR (95% CI)	0.83 (0.54, 1.28)		0.95 (0.70, 1.29)		0.87 (0.58, 1.31)	
Median PFS (95% CI) (months)	2.7 (1.5, 4.2)	2.3 (1.4, 3.0)	1.5 (1.4, 2.6)	1.7 (1.4, 2.7)1	1.5 (1.4, 2.8)	2.1 (1.4, 2.8)
Objective response rate (unconfirmed)						
ORR %, (95% CI)	26.3 (17.0, 37.3)	11.3 (4.7, 21.9)	16.0 (9.4, 24.7)	9.0 (4.6, 15.6)	19.7 (11.5, 30.5)	9.7 (4.0, 19.0)
ORR Difference, % (95% CI)	14.1 (1.7, 26.6)		5.7 (-3.2, 14.6)		10.8 (-0.5, 22.2)	

Source: Excerpt from Tables 14.2.2.1, 14.2.2.1.POST, 14.2.3.2, 14.2.3.2.POST, 14.2.4.2, 14.2.4.2.POST; updated after PD-L1 status reclassification

Figure 2: KM Plot of Overall Survival for vCPS ≥ 10% (PD-L1 positive analysis set)

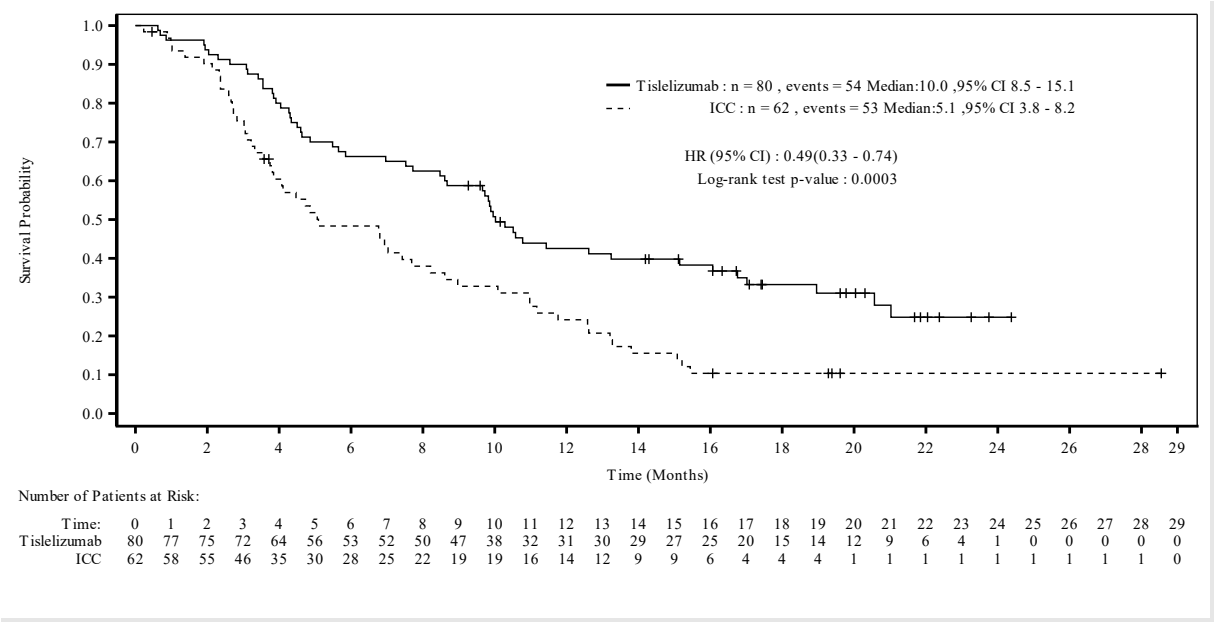
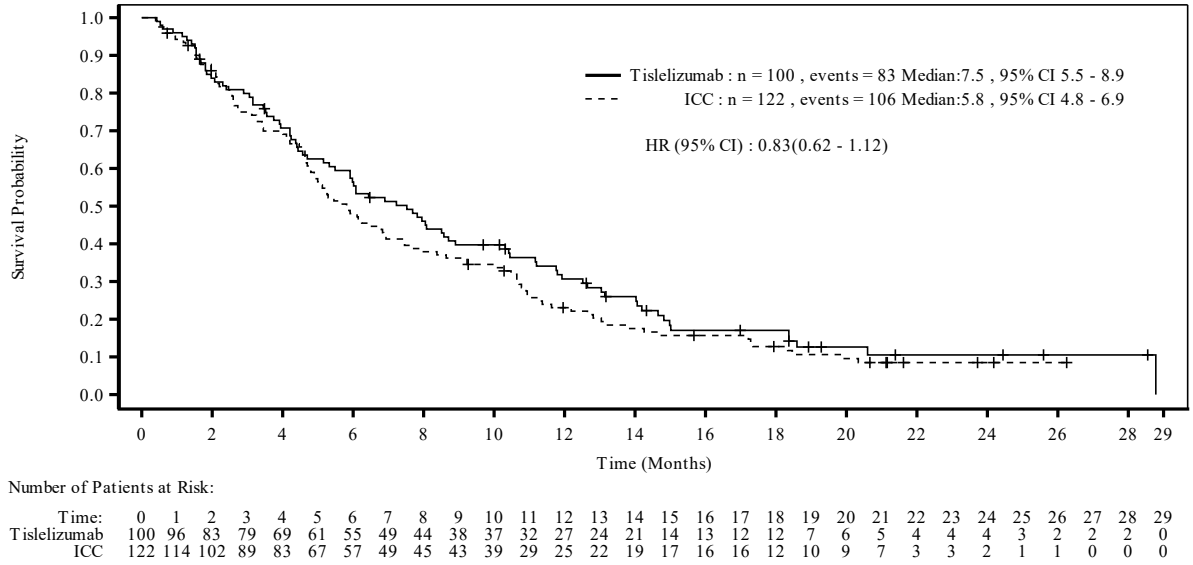


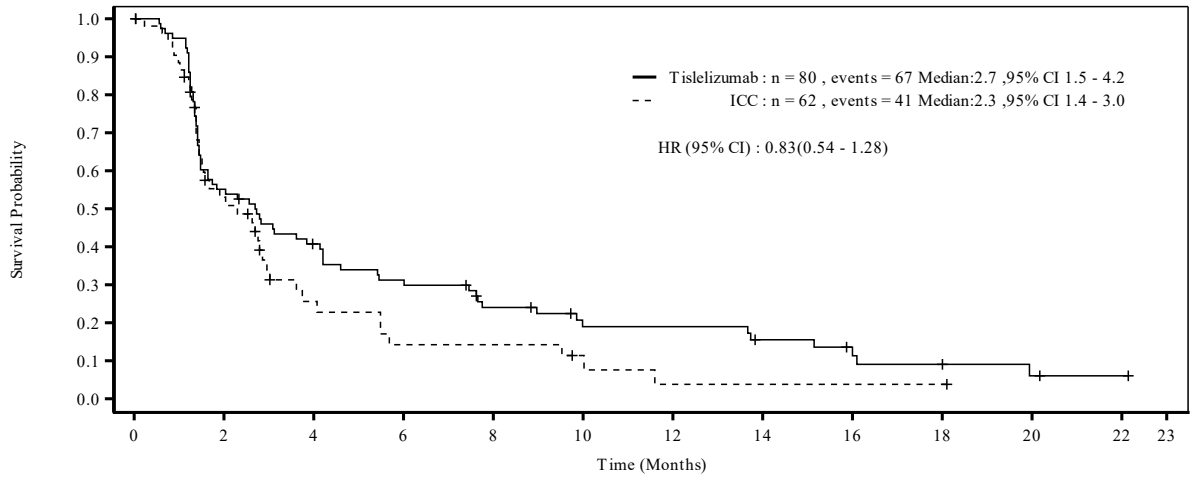
***Figure 3*: KM Plot of Overall Survival for vCPS < 10% (PD-L1 negative patients)**



Number of Patients at Risk:

Time:	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29
Tislelizumab	100	96	83	79	69	61	55	49	44	38	37	32	27	24	21	14	13	12	12	7	6	5	4	4	4	3	2	2	2	0
ICC	122	114	102	89	83	67	57	49	45	43	39	29	25	22	19	17	16	16	12	10	9	7	3	3	2	1	1	0	0	0

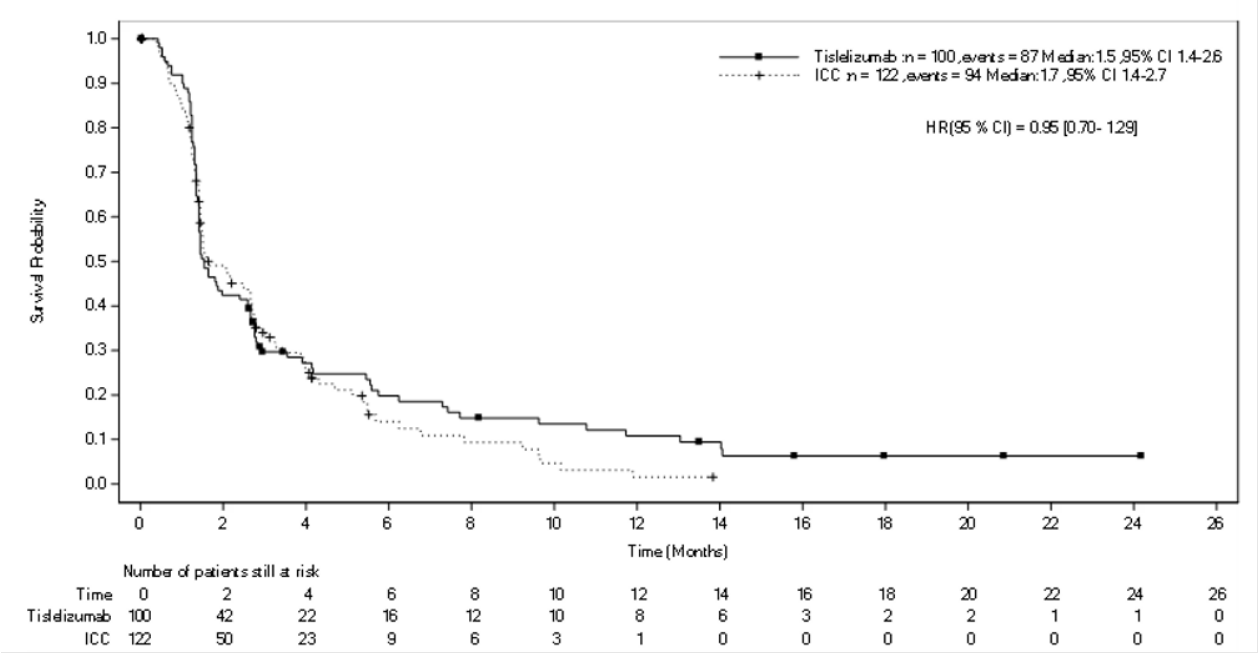
Figure 4:: KM Plot of PFS for vCPS ≥ 10% (PD-L1 positive analysis set)



Number of Patients at Risk:

Time:	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
Tislelizumab	80	74	43	35	30	25	23	22	16	14	11	11	11	11	8	8	6	4	4	3	2	1	1	0
ICC	62	46	24	13	9	8	5	5	5	5	3	2	1	1	1	1	1	1	1	0	0	0	0	0

Figure 5: Figure KM Plot of PFS for vCPS < 10% (PD-L1 negative analysis set)



To further inform on the efficacy of tislelizumab in the PD-L1 negative subgroup, the Applicant provided subgroup analyses by baseline PD-L1 expression status with additional cutoffs (vCPS levels of 25%, 5%, and 1%).

For an overview of efficacy data for the 1%, 5% and 10% cutoffs, please see following excerpts:

OS by baseline PD-L1 status

	vCPS < 1%		vCPS ≥ 1%		vCPS < 5%		vCPS ≥ 5%		vCPS < 10%		vCPS ≥ 10%	
	Tisle	ICC	Tisle	ICC	Tisle	ICC	Tisle	ICC	Tisle	ICC	Tisle	ICC
	N=16	N=23	N=164	N=161	N=56	N=71	N=124	N=113	N=100	N=122	N=80	N=62
Unstratified hazard ratio (95% CI) [a]	1.32 (0.65, 2.70)		0.63 (0.49, 0.80)		0.89 (0.61, 1.30)		0.62 (0.46, 0.83)		0.86 (0.64, 1.14)		0.52 (0.35, 0.76)	
Overall survival (mo)												
Median (95% CI)	5.2 (4.4, 10.4)	7.4 (4.5, 10.6)	8.9 (7.5, 10.6)	5.6 (4.7, 6.9)	5.6 (4.2, 8.1)	5.8 (4.6, 7.5)	10.0 (8.0, 11.8)	5.6 (4.6, 7.4)	7.5 (5.5, 8.9)	5.8 (4.8, 6.9)	10.0 (8.5, 15.1)	5.1 (3.8, 8.2)

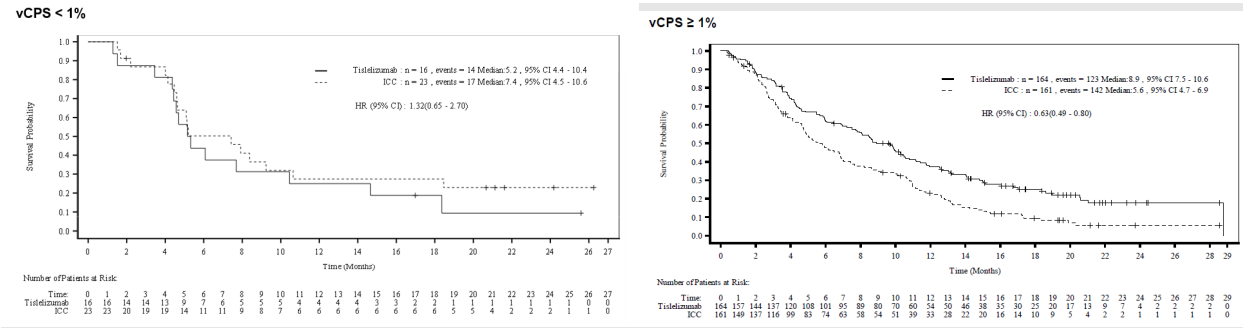
PFS by baseline PD-L1 status

	vCPS < 1%		vCPS ≥ 1%		vCPS < 5%		vCPS ≥ 5%		vCPS < 10%		vCPS ≥ 10%	
	Tisle	ICC	Tisle	ICC	Tisle	ICC	Tisle	ICC	Tisle	ICC	Tisle	ICC
	N=16	N=23	N=164	N=161	N=56	N=71	N=124	N=113	N=100	N=122	N=80	N=62
Unstratified hazard ratio (95% CI) [a]	0.90 (0.44, 1.87)		0.80 (0.62, 1.02)		0.95 (0.65, 1.40)		0.77 (0.57, 1.04)		0.88 (0.66, 1.19)		0.75 (0.50, 1.11)	
Progression-free survival (mo)												
Median (95% CI)	1.4 (1.2, 5.5)	1.4 (1.2, 2.8)	2.0 (1.5, 2.8)	2.2 (1.5, 2.7)	1.4 (1.3, 1.9)	1.6 (1.4, 2.7)	2.6 (1.6, 3.1)	2.2 (1.5, 2.8)	1.5 (1.4, 2.6)	1.7 (1.4, 2.7)	2.7 (1.5, 4.2)	2.3 (1.4, 3.0)

ORR by baseline PD-L1 status

	vCPS < 1%		vCPS ≥ 1%		vCPS < 5%		vCPS ≥ 5%		vCPS < 10%		vCPS ≥ 10%	
	Tisle	ICC	Tisle	ICC	Tisle	ICC	Tisle	ICC	Tisle	ICC	Tisle	ICC
	N=16	N=23	N=164	N=161	N=56	N=71	N=124	N=113	N=100	N=122	N=80	N=62
ORR, n (%)	3 (18.8)	0	27 (16.5)	13 (8.1)	7 (12.5)	4 (5.6)	23 (18.5)	9 (8.0)	14 (14.0)	8 (6.6)	16 (20.0)	5 (8.1)
(95% CI) [a]	(4.0, 45.6)	(0.0, 14.8)	(11.1, 23.0)	(4.4, 13.4)	(5.2, 24.1)	(1.6, 13.8)	(12.1, 26.5)	(3.7, 14.6)	(7.9, 22.4)	(2.9, 12.5)	(11.9, 30.4)	(2.7, 17.8)
Odds ratio, (95% CI) [b]	NE (NE, NE)		2.24 (1.11, 4.52)		2.39 (0.66, 8.63)		2.63 (1.16, 5.96)		1.99 (0.81, 4.90)		2.63 (0.89, 7.72)	
ORR difference, % (95% CI) [b]	18.8 (-0.4, 37.9)		8.4 (1.3, 15.5)		6.9 (-3.3, 17.1)		10.6 (2.1, 19.1)		6.4 (-1.9, 14.7)		10.7 (-0.3, 21.8)	
BOR, n (%)												
CR	1 (6.3)	0	3 (1.8)	0	1 (1.8)	0	3 (2.4)	0	2 (2.0)	0	2 (2.5)	0
PR	2 (12.5)	0	24 (14.6)	13 (8.1)	6 (10.7)	4 (5.6)	20 (16.1)	9 (8.0)	12 (12.0)	8 (6.6)	14 (17.5)	5 (8.1)

OS KM curves



PFS KM curves

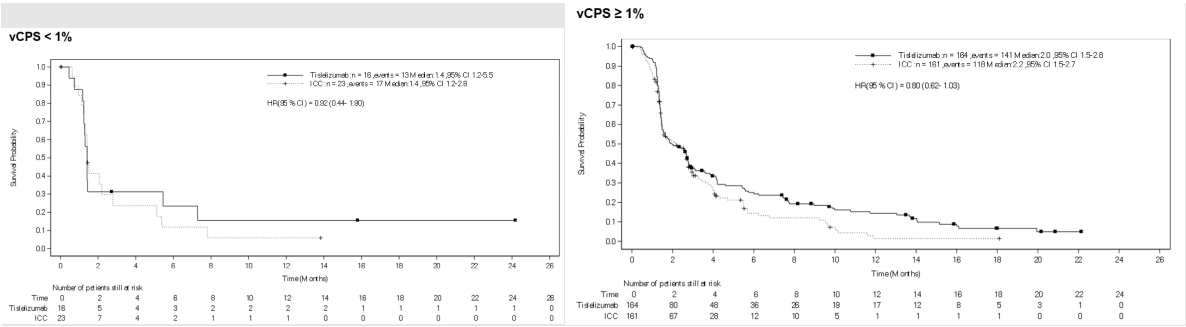
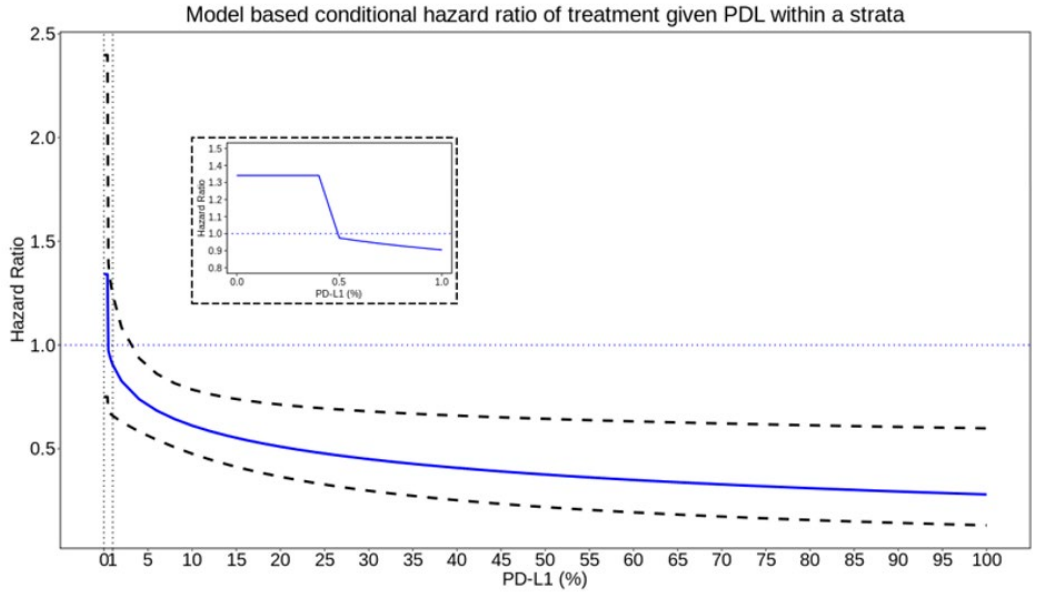


Figure 10- Exploratory OS modelling approach using baseline PD-L1 levels as a continuous variable



Subgroups by region

Table 3 - 3 - 13 Overview of efficacy results by region (ITT analysis set)

	Asia		Europe/North America	
	Tislelizumab (N = 201)	**ICC (N = 203)**	**Tislelizumab (N = 55)**	**ICC (N = 53)**
Overall survival				
Unstratified HR (95% CI)	0.73 (0.59, 0.90)		0.55 (0.35, 0.87)	
Median OS (95% CI) (months)	8.5 (7.1, 10.3)	6.3 (5.3, 7.4)	11.2 (5.9, 14.8)	6.3 (4.6, 7.7)
Progression free survival				
Unstratified HR (95% CI)	0.81 (0.64, 1.02)		0.97 (0.64, 1.47)	
Median PFS (95% CI) (months)	1.5 (1.4, 2.6)	1.7 (1.5, 2.6)	2.3 (1.5, 2.8)	2.7 (1.4, 3.9)
Objective response rate (unconfirmed)				
ORR %, (95% CI)	20.4 (15.1, 26.6)	9.4 (5.7, 14.2)	20.0 (10.4, 33.0)	11.3 (4.3, 23.0)
ORR Difference, % (95% CI)	11.0 (4.2, 17.9)		8.7 (-4.9, 22.3)	
Duration of response				
Unstratified HR (95% CI)	0.42 (0.21, 0.84)		0.42 (0.13, 1.39)	
Median DOR (95% CI) (months)	7.4 (4.1, 12.3)	4.0 (2.6, 8.4)	5.1 (1.6, NE)	2.1 (1.3, 6.3)

Source: Excerpt from tables 14.2.1.1a, 14.2.3.1a, 14.2.4.1a (CSR Study 302)

Subgroups by PD-L1 expression status and region

Table 3 - 3 - 14 Overview of efficacy results by PD-L1 status and region (Study 302, ITT)

	PD-L1 vCPS ≥ 10%		PD-L1 vCPS < 10%		Missing	
	Tislelizumab	**ICC**	**Tislelizumab**	**ICC**	**Tislelizumab**	**ICC**
Asia						
Number of patients, N	58	53	75	87	68	63
Unstratified **HR for OS** (95% CI)	0.52 (0.34, 0.80)		0.97 (0.70, 1.35)		0.70 (0.47, 1.03)	
Median OS, mo (95% CI)	10.4 (8.7, 16.1)	5.1 (3.7, 8.6)	6.1 (4.4, 8.6)	5.9 (4.9, 8.4)	8.1 (6.2, 12.0)	6.9 (5.5, 8.3)
Unstratified **HR for PFS** (95% CI)	0.73 (0.46, 1.15)		0.87 (0.62, 1.24)		0.87 (0.57, 1.31)	
ORR (95% CI)	22.4 (12.5, 35.3)	11.3 (4.3, 23.0)	17.3 (9.6, 27.8)	8.0 (3.3, 15.9)	22.1 (12.9, 33.8)	9.5 (3.6, 19.6)
Europe/North America						
Number of patients, N	22	9	25	35	8	9
Unstratified **HR for OS** (95% CI)	0.47 (0.18, 1.21)		0.55 (0.30, 1.01)		0.55 (0.15, 2.11)	
Median OS, mo (95% CI)	9.2 (3.1, NE)	5.1 (0.2, 7.0)	11.2 (5.9, 13.1)	5.3 (2.6, 7.9)	13.5 (2.0, NE)	10.6 (3.3, NE)
Unstratified **HR for PFS** (95% CI)	0.78 (0.32, 1.88)		0.94 (0.53, 1.67)		1.55 (0.53, 4.54)	
ORR (95% CI)	36.4 (17.2, 59.3)	11.1 (0.3, 48.2)	12.0 (2.5, 31.2)	11.4 (3.2, 26.7)	0.0 (0.0, 36.9)	11.1 (0.3, 48.2)

Table 3 - 3 - 95 Analysis of adjusted Overall Survival by region (ITT analysis set)

Baseline Covariates to Adjust	Unstratified HR (95% CI)		
	Asia	Europe/North America	Overall
ECOG [a]	0.73 (0.59, 0.91)	0.51 (0.32, 0.82)	0.70 (0.57, 0.85)
PD-L1 Expression [b]	0.76 (0.61, 0.94)	0.56 (0.35, 0.89)	0.72 (0.59, 0.88)

Source: ADSL, ADTTE, ADBASE. Data cutoff: 01DEC2020. Data extraction: 15JAN2021.
[a] Hazard ratio (Tislelizumab vs. ICC) was based on Cox regression model including treatment and baseline ECOG (0, 1) as covariate.
[b] Hazard ratio (Tislelizumab vs. ICC) was based on Cox regression model including treatment and vCPS (< 10%, ≥ 10%, missing) as covariate.
unblind/bgb_a317/filing_integration/escc2020_sce/dev/pgm/tlfs/t-tte-adjust.sas 07APR2021 00:19 t-28-tte-adjust-i.rtf [SCE Appendix 1-Table 28]

Source: Table 2-14 SCE

Further post-hoc efficacy analyses in subgroups by PD-L1 expression status and region were conducted (data not shown). Exploratory analyses do not indicate a meaningful impact of the imbalances observed between treatment groups in patients from the Europe/North America subgroup. Overall, efficacy subgroup analyses by region do not raise concerns regarding a differential treatment effect in the European population.

2.6.5.3. Summary of main efficacy results

Table 3 - 3 - 106 Summary of efficacy for Study BGB-A317-302

Title: 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			
Study identifier	Study BGB-A317-302; EudraCT number 2020-004985-21; RATIONAL 302		
Design	Phase III, multicenter, randomized (1:1), open-label study comparing tislelizumab monotherapy versus investigator chose chemotherapy		
	Duration of main phase:		Treatment with tislelizumab or ICC option continued until disease progression, intolerable toxicity, or other treatment discontinuation criteria per protocol were met.
	Duration of Run-in phase:		Not applicable
	Duration of Extension phase:		Not applicable
Hypothesis	Superiority of Tislelizumab over Investigator chosen Chemotherapy (ICC)		
Treatments groups	Tislelizumab		200 mg IV Q3W
	Docetaxel		75 mg/m^2 IV Q3W
	Irinotecan		125 mg/ m^2 Days 1 and 8 Q3W
	Paclitaxel		135-175 mg/m^2 Q3W or 80-100 mg/m2 Weekly in accordance with local/country treatment guidelines
Endpoints and definitions	Primary endpoint	OS	The primary endpoint of the study was overall survival in the ITT Analysis Set, defined as the time from the date of randomization until the date of death due to any cause in all randomized patients.
	Key secondary endpoint	OS	Overall survival in the PD-L1-Positive Analysis Set (PD-L1 expression level of vCPS ⩾ 10%), defined as the time from the date of randomization until the date of death due to any cause in the PD-L1-Positive Analysis Set

	Secondary endpoint	ORR	Objective response rate in the ITT Analysis Set and the PD-L1-Positive Analysis Set, defined as the proportion of patients who had complete response (CR) or partial response (PR) assessed by the investigator per RECIST v1.1
	Secondary endpoint	DOR	Duration of response in the ITT Analysis Set and the PD-L1-Positive Analysis Set, defined as the time from the first determination of an objective response until the first documentation of progression as assessed by the investigator per RECIST v1.1, or death, whichever occurred first.
	Secondary endpoint	PFS	PFS in the ITT Analysis Set and the PD-L1-Positive Analysis Set, defined as the time from the date of randomization to the date of first documentation of disease progression assessed by the investigator per RECIST v1.1, or death, whichever occurred first.
	Secondary endpoint	Health related quality of life assessments (HRQoL)	HRQoL using EORTC QLQ-C-30, EORTC QLQ-OES18, and EQ-5D-5L in the ITT Analysis Set and the PD-L1-Positive Analysis Set.

Database lock	Data cutoff date: 01 December 2020; Data Extraction date: 15 January 2021		
Results and Analysis			
Analysis description	**Primary Analysis Overall Survival in ITT analysis set**		
Analysis population and time point description	Intent to treat (ITT) analysis set includes all randomized patients. The study minimum follow up (last patient randomized to data cutoff) is 9 months.		
Descriptive statistics and estimate variability	Treatment group	Tislelizumab	Investigator chosen Chemotherapy (ICC)
	Number of subjects	256	256
	Death, n (%)	197 (77.0)	213 (83.2)
	Overall Survival ITT analysis set Median (Months) (95% CI)	8.6 (7.5, 10.4)	6.3 (5.3, 7.0)
Effect estimate per comparison	Overall Survival in ITT analysis set	Comparison groups	Tislelizumab vs. ICC
		Stratified Hazard Ratio	0.70
		95% CI	0.57, 0.85
		P-value (log rank test)	0.0001

Analysis description	**Key secondary endpoint Overall Survival in PD-L1 positive analysis set**		
Analysis population and time point description	The PD-L1 positive analysis set includes patients whose PD-L1 expression level of vCPS score $\geqslant$ 10%.		
Descriptive statistics and estimate variability	Treatment group	Tislelizumab	Investigator chosen Chemotherapy (ICC)
	Number of patients	80	62
	Death, n (%)	54 (67.5)	53 (85.5)
	Overall Survival in PD-L1 positive analysis set Median (Months) (95% CI)	10.0 (8.5, 15.1)	5.1 (3.8, 8.2)

Effect estimate per comparison	Overall Survival in PD-L1 positive analysis set	Comparison groups	Tislelizumab vs. ICC
		Stratified HR	0.49
		95% CI	0.33, 0.74
		p-value	0.0003
Notes	p-values are one-sided		
Analysis description	**Secondary endpoint analysis - PFS in ITT**		
Analysis population and time point description	ITT analysis set		
Descriptive statistics and estimate variability	Treatment group	Tislelizumab	Investigator chosen Chemotherapy (ICC)
	ITT		
	Number of patients	256	256
	Events, n(%)	223 (87.1)	180 (70.3)
	Progression free survival (PFS) in ITT Median (Months) (95% CI)	1.6 (1.4, 2.7)	2.1 (1.5, 2.7)
Effect estimate per comparison	**ITT**	Comparison groups	Tislelizumab vs. ICC
		Stratified HR	0.83
		95% CI	0.67, 1.01
		P-value (log rank test), for descriptive purpose only	0.0292
Analysis description	**Secondary endpoint analysis - PFS in ITT – Sensitivity Analysis II**		
Analysis population and time point description	ITT analysis set		
Descriptive statistics and estimate variability	Treatment group	Tislelizumab	Investigator chosen Chemotherapy (ICC)
	ITT		
	Number of patients	256	256
	Events, n(%)	230 (89.8)	194 (75.8)
	Progression free survival (PFS) in ITT Median (Months) (95% CI)	1.8 (1.5, 2.7)	2.3 (1.5, 2.7)
Effect estimate per comparison	**ITT**	Comparison groups	Tislelizumab vs. ICC
		Stratified HR	0.85
		95% CI	0.70, 1.03
		P-value (log rank test), for descriptive purpose only	0.0510
Analysis description	**Secondary endpoint analysis - ORR in ITT**		
Analysis population and time point description	ITT analysis set		
Descriptive statistics and estimate variability	Treatment group	Tislelizumab	Investigator chosen Chemotherapy (ICC)
	ITT		

	Number of patients	256	256
	Unconfirmed objective response rate (ORR) in ITT % (95% CI)	20.3 (15.6, 25.8)	9.8 (6.4, 14.1)
Effect estimate per comparison	Treatment group	Comparison groups	Tislelizumab vs. ICC
	ITT		
	Unconfirmed objective response rate (ORR) in ITT	Stratified Odds Ratio for ORR	2.39
		95% CI	1.42, 4.01
		P-value, for descriptive purpose only	0.0008
Analysis description	**Secondary endpoint analysis - DOR in ITT**		
Analysis population and time point description	ITT analysis set		
Descriptive statistics and estimate variability	Treatment group	Tislelizumab	Investigator chosen Chemotherapy (ICC)
	ITT		
	Number of Responders	52	25
	Duration of response (DOR) Median (Months) (95% CI)	7.1 (4.1, 11.3)	4.0 (2.1, 8.2)
Analysis description	**Secondary endpoint analysis - Health related quality of life assessments (HRQoL)**		
Analysis population and time point description	ITT analysis set		
	Number of patients	256	256
	HRQoL in ITT Changes from baseline to Cycle 6 (n, Mean (standard deviation)) EORTC QLQ-C-30 • Index score • Global health status (GHS) • Physical functioning EORTC QLQ-OES18 • Index score • Eating • Pain • Dysphagia • Reflux	EORTC QLQ-C-30 • 93, 0.2 (8.28) • 94, 1.9 (16.45) • 94, -1.9 (10.33) EORTC QLQ-OES18 • 93, -0.6 (8.63) • 93, -2.5 (15.92) • 93, -1.1 (14.29) • 93, 1.6 (28.50) • 93, 0.2 (14.22)	EORTC QLQ-C-30 • 36, 4.8 (9.38) • 36, -6.3 (14.82) • 36, -5.7 (12.05) EORTC QLQ-OES18 • 35, 3.0 (12.05) • 35, 6.7 (22.94) • 35, 1.9 (15.36) • 35, 2.7 (37.15) • 35, 1.4 (22.28)

2.6.5.4. Clinical studies in special populations

Efficacy by Age

318 patients (62.1%), 166 patients (32.4%), and 28 patients (5.5%) were aged < 65 years, 65 to < 75 years, and ≥ 75 years at baseline, respectively. No further survival analysis was performed for the ≥ 75-year age group as the number of patients was small.

Treatment with tislelizumab was associated with favourable improvements in OS compared with ICC across subgroups of age (< 65 years and ≥ 65 years), with unstratified HRs of 0.75 (95% CI: 0.58 to 0.97) and 0.70 (95% CI: 0.48, 1.03) for patients from Asia and unstratified HRs of 0.58 (95% CI: 0.29 to 1.15) and 0.51 (95% CI: 0.27 to 0.96) for patients from Europe/North America, respectively. Besides, no significant differences in PFS and ORR were observed between the different age groups investigated.

Paediatric population

No data are available for paediatric patients, as these have not been studied in the clinical trials.

Renal and hepatic impairment

Data for patients with severe renal or hepatic impairment are limited. Overall, 5 patients with severe renal impairment and 2 patients with severe hepatic impairment were included in the clinical trials.

2.6.5.5. In vitro biomarker test for patient selection for efficacy

Analytical validation

Ventana PD-L1 (SP263) CDx assay and the algorithm of vCPS measure the total percentage of the tumour area covered by tumour cells with PD-L1 membrane staining and tumour-associated immune cells with PD-L1 staining at any intensity.

Shipping, storage, and handling of archival tumour, fresh tumour, and residual tumour tissue for the assessment of biomarkers were managed through a central laboratory. As confirmed with the responses, the involved sites are CAP/CLIA-certified, which is considered as a sufficient accreditation standard.

Archival tumour tissues were required for central biomarker analysis, such as immunohistochemistry analysis of PD-L1 status, if available. In the absence of available archival tumour tissue samples, the collection of a fresh tumour biopsy at baseline was recommended, if accessible. Tumour tissues collection was not mandatory for eligibility evaluation for enrolment.

As requested, he Applicant provided the analytical validation report for Ventana PD-L1 (SP263) CDx assay that showed that the assay is suitable (i.e. sufficiently analytically validated) to detect PD-L1 expression in in ESCC tissue at the defined cut-off and applying the defined scoring algorithm (i.e. 10% vCPS).

Clinical Validation:

Selection of PD-L1 vCPS ≥ 10% as the cutoff for the key secondary endpoint PD-L1 is expressed in tumour and tumour-infiltrating immune cells in ESCC at a prevalence of 18.4% to 82.8% (Guo et al 2017), which may vary by different detecting antibodies, scoring methods, and cutoffs chosen. PD-L1 expression level showed a trend of correlation with the clinical efficacy of anti-PD-1 treatment in multiple studies, including KEYNOTE-181, ATTRACTION-3, and ESCORT (Kojima et al 2020; Kato et al 2019; Huang et al 2020). In these studies, PD-L1 prevalence for PD-L1 positive population ranged from 40% to 50%.

In this study, overall survival in patients with PD-L1 vCPS ≥ 10% was selected as the key secondary endpoint to explore the predictive role of PD-L1 expression in ESCC. PD-L1 expression of the ESCC

tumour was determined using the Ventana PD-L1 (SP263) CDx assay and the algorithm of vCPS, which measures the total percentage of the tumour area covered by tumour cells with PD-L1 membrane staining and tumour-associated immune cells with PD-L1 staining at any intensity.

A 10% cutoff was selected based on post-hoc analysis of tumours from patients with ESCC who were treated with tislelizumab (ESCC cohort from BGB-A317_Study_001 and BGB-A317-102 studies) based on pathological feasibility, assay reproducibility, assay performance (sensitivity, specificity, positive predictive value, and negative predictive value), and clinical outcomes in patients with PD-L1 vCPS ≥ 10%, as well as PD-L1 positive prevalence. In these phase I/II studies, vCPS ≥ 10% has been analytically validated for ESCC before PD-L1 scoring in Study 302.

Since the terminology (vCPS) may lead to confusion with the IP protected term "CPS" used by Merck, the Applicant is going to change the terminology from "vCPS" to "TAP (Tumour Area Positive) Score". The Applicant confirmed that only the terminology is to be changed, there are no modifications regarding the scoring algorithm or the PD-L1 assay.

Efficacy results by PD-L1 status:

Please refer to "subgroups by PD-L1 expression"

Testing of PD-L1 status – missing data

In the original submission, PD-L1 status was missing for 99 patients (19.3%). As collection of tumour tissue for PD-L1 testing was not an enrolment eligibility criterion, tumour tissue samples were not submitted for 59 patients. Reasons for missing PD-L1 status among the remaining 40 patients included mostly testing failures (n=34) with insufficient or no tumour cells for 21 patients, unacceptable sample types (n=4) and withdrawal of informed consent (n=4).

With the responses, the Applicant informed that further review of PD-L1 expression data after CSR finalization identified the use of unsuitable samples. Based on the sample eligibility criteria specified in the Ventana PD-L1 diagnostic protocol, 49 samples had to be considered invalid for the data analyses. Thus, the proportion of study patients with missing PD-L1 status increased from 19.3% (n=99) to 28.9% (n=148) for the corrected analyses. Reasons for reclassification as "missing" included that cut slide dates were outside of stability window or unknown (n=27), unknown or inappropriate fixative (n=20) and fine needle aspiration (n=3). Both treatment arms were equally affected (numbers of reclassified samples n=24 and n=25, respectively).

The Applicant provided updated results based on reclassified PD-L1 status.

PD-L1 expression was not used as stratification factor, consequently imbalances regarding PD-L1 expression status between the treatment groups in the ITT (vCPS ≥10% in 31.3% patients of the tislelizumab arm vs. 24.2% of patients in the ICC arm) could be seen. The Applicant provided further OS analysis to address this problem, however, in total those imbalances could have an impact on the credibility of the results.

The Applicant was asked to further clarify the rationale for the vCPS ≥10% cut-off selection. A cutoff of CPS ≥10 with the Dako 22C3 antibody was used in KEYNOTE-181 and in KEYNOTE-590, in patients with esophageal cancer. In these studies no clinically meaningful benefit could be demonstrated in the CPS <10 population. The Applicant was asked to further justify his vCPS ≥10% cutoff and clinical validation data were submitted with the responses (derived from Studies 001 and 102). Validation data support the vCPS>=10% cutoff selection.

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

Not applicable.

2.6.5.7. Supportive studies

Study 001

This was a 2-stage open-label study consisting of a Phase 1A dose escalation and dose-finding component to establish the MTD or RP2D(s) followed by a Phase 1B component to investigate efficacy in selected tumour types and to further evaluate safety and tolerability of tislelizumab at RP2D(s).

Study population:

Eligible patients were male or female, ≥ 18 years of age with histologically or cytologically confirmed advanced or metastatic solid tumours for which no effective standard therapy was available, an ECOG PS score ≤ 1, adequate organ function, and ≥ 1 evaluable lesion per RECIST v1.1 without limit to the number of prior treatment lines. Patients who had received prior PD-1 or PD-L1 directed treatment, had active autoimmune disease, had a condition requiring systemic treatment with immunosuppressives, or had a history of interstitial lung disease or non-infectious pneumonitis were excluded.

Treatment:

Patients with ESCC received tislelizumab 5 mg/kg IV Q3W until unacceptable toxicity, withdrawal of informed consent, or no evidence of continued clinical benefit.

Endpoints:

Efficacy was a secondary objective of Phase 1A and the primary objective of Phase 1B. Response to treatment was evaluated by each investigator. Efficacy measures included ORR, defined as the percentage of patients in the study whose best overall response was either CR or PR based on RECIST v1.1, PFS and DCR as assessed by RECIST v1.1, CBR, and DOR for responders.

Study 102

Study 102 was a Phase 1/2 study to investigate the safety, tolerability, PK, and preliminary antitumour activity of tislelizumab in Chinese patients with advanced solid tumours. Once the RP2D was determined in Phase 1, Phase 2 was conducted as an indication-specific expansion study for 11 arms of indications.

Study population:

Eligible patients were ≥ 18 years of age with histologically or cytologically confirmed advanced or metastatic solid tumours whose disease had progressed or who were intolerant to last standard antitumour treatment or had no available standard treatment or had refused standard therapy. Patients had an ECOG PS score ≤ 1, adequate organ function, and ≥ 1 evaluable lesion per RECIST v1.1, with no limit to the number of prior treatment lines. Patients who had received prior PD-1 or PD-L1 directed treatment, had active autoimmune disease, had a condition requiring systemic treatment with immunosuppressives, had a history of interstitial lung disease or non-infectious pneumonitis, or had significant cardiovascular diseases were excluded.

Treatment:

All patients received 200 mg of tislelizumab IV once every 3 weeks. All patients continued to receive tislelizumab until they had no evidence of continued clinical benefit, had unacceptable toxicity, or withdrew informed consent.

Endpoints:

The study included only preliminary assessments of efficacy. The primary efficacy endpoint in Phase 2 was ORR, defined as the percentage of patients in the study with either CR or PR, as assessed by investigators based on RECIST Version 1.1. There was no formal statistical testing for the efficacy endpoints; the efficacy analyses were descriptive only.

Further efficacy endpoints evaluated comprised BOR, ORR, CBR, DCR, PFS, OS, and DOR.

Demographics and Baseline Characteristics (supportive studies 001 and 102)

The demographics and other baseline characteristics of patients with ESCC who were enrolled in Studies 001 and 102 reflected a population that was at a more advanced or metastatic disease stage and that had been heavily treated previously (the majority had received ≥ 2 lines of prior systemic therapy). In Study 001, the median age of the 26 ESCC patients was 61.5 years and 26.9% of patients were ≥ 65 years of age. Most patients were male (65.4%), Asian (73.1%), and had a baseline ECOG PS score of 1 (73.1%). Six patients (23.1%) had never smoked. In Study 102, the median age of the 26 ESCC patients was 62.5 years, and 34.6% of patients were ≥ 65 years of age. Most patients were male (88.5%) and had a baseline ECOG PS score of 1 (88.5%). Ten patients (38.5%) had never smoked.

Efficacy results (supportive studies 001 and 102)

ORR, BOR and DCR

Table 3 - 3 - 17 Objective Response and Disease Control Rate (Studies 001 and 102) (Safety analysis set)

Response Category	001 (N = 26)	102 (N = 26)
Objective Response Rate (ORR) [a], n	5	2
% (95% CI) [b]	19.2 (6.6, 39.4)	7.7 (0.9, 25.1)
Best Overall Response (BOR) - Confirmed, n (%)		
Complete Response (CR)	1 (3.8)	0 (0.0)
Partial Response (PR)	4 (15.4)	2 (7.7)
Stable Disease (SD)	6 (23.1)	7 (26.9)
Progressive Disease (PD)	9 (34.6)	13 (50.0)
Could Not be Determined [c]	6 (23.1)	4 (15.4)
Disease Control Rate (DCR) [a], n	11	9
% (95% CI) [b]	42.3 (23.4, 63.1)	34.6 (17.2, 55.7)

Source: ADRS. Data cutoff: 001-26AUG2020, 102-31MAY2020. Data extraction: 001-26AUG2020, 102-30JUN2020.
Abbreviations: 001 = BGB-A317-Study-001; 102 = BGB-A317-102.
Percentages were based on N.
[a] Objective response rate of study 102 and 001 defined as proportion of number of patients with a confirmed CR or PR (i.e. ORR = CR+PR); Disease control rate of study 102 and 001 defined as proportion of number of patients with a confirmed PR or CR or a SD (i.e. DCR = CR+PR+SD).
[b] Two-sided 95% CI was calculated using Clopper-Pearson method.
[c] Patients with no post-baseline response assessment (Not Assessable) or assessment as Not Evaluable (NE) or Unknown (UNK).
unblind/bgb_a317/filing_integration/escc2020_sce/dev/pgm/tlfs/t-tte-or2.sas 24MAR2021 06:21 t-19-tte-or2-saf-i.rtf [SCE Appendix 1-Table 19]

Source: Table 2-27 SCE

Efficacy results for DOR, PFS and OS in the supportive studies 001 and 102 are summarized in the table below:

Table 3 - 3 - 118 Summarized results for DOR, PFS and OS (Studies 001 and 102) (Safety analysis set)

	001 (N = 26)	**102 (N = 26)**
Duration of Response (months)		
Median (95% CI)	4.2 (2.8, NE)	NR (13.8, NE)
Progression Free Survival (months)		
Median (95% CI)	2.0 (1.3, 4.2)	2.1 (2.0, 4.2)
Overall Survival (months)		
Median (95% CI)	4.7 (1.5, 7.9)	4.8 (3.6, 8.5)

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The application for approval of tislelizumab for the treatment of 2L+ ESCC is based on the open-label, randomized, ICC-controlled single pivotal Phase 3 study BGB-A317-302 conducted in patients with unresectable, locally advanced or metastatic ESCC who progressed on or after prior systemic treatment. Overall, the study design is endorsed. Given the choice of chemotherapies in the comparator arm and considering that OS was selected as primary endpoint, the open-label study design is considered acceptable. Stratification factors for this study were region (Asia [excluding Japan] vs. Japan vs. EU/US), ECOG PS (0 vs. 1), and ICC option (paclitaxel vs. docetaxel vs. irinotecan), which are deemed adequate.

In general, the applied inclusion and exclusion criteria selected an adequate population of patients with advanced or metastatic ESCC eligible for 2nd line treatment, although the population may be considered somewhat selected due to exclusion of patients with ECOG PS ≥ 2. Patients were enrolled regardless of their tumour PD-L1 expression level, which is generally acceptable. However, it would have been beneficial to analyse PD-L1 expression in all patients enrolled and to stratify patients by PD-L1 expression status. Patients with active brain or leptomeningeal metastases, tumour invasion into adjacent organs and prior receipt of anti PD-1/PD-L1 therapy were excluded from the study.

Investigator-chosen chemotherapy was used for the comparator arm and included either paclitaxel, docetaxel or irinotecan monotherapy. These treatment options are considered acceptable as active comparator, since they were standard of care at the time of study initiation and still recommended as preferred options by current ESCC treatment guidelines (2022 NCCN Guidelines, Lordick et al. 2016). The respective treatment regimen was determined by the physicians prior to randomization.

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 dismal prognosis of ESCC patients having failed prior therapy. The selection of OS in the PD-L1-Positive Analysis Set (vCPS ≥ 10%) as key secondary endpoint is considered acceptable, but has been introduced late during the conduct of the study (see below). Other secondary efficacy endpoints (PFS, ORR, DOR, HRQoL, and DCR) 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 study was planned to enrol 500 patients in order to observe 400 deaths. This was expected to provide 82% power to detect an overall survival HR of 0.75 at the 1-sided significance level of α=0.025, corresponding to an improvement in median overall survival from 6 months to 8 months, in the ITT Analysis Set. Assumptions were well justified at the time of planning. It was originally planned to enroll 450 patients and this was amended in a late protocol amendment.

In total, 512 patients were randomized 1:1 to tislelizumab treatment or ICC treatment.

No estimand was defined for this study. The primary endpoint of OS was planned to be compared between tislelizumab and ICC arms in the ITT analysis set, by means of a stratified log-rank test, using a significance level of one-sided 0.025. The ITT set was planned to comprise all randomised subjects. The analysis was planned to be stratified by ECOG performance status (0 vs 1) and ICC option (paclitaxel vs docetaxel vs irinotecan).

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

The key-secondary endpoint OS in the PD-L1 positive analysis set was planned to be tested hierarchically after the primary endpoint. Only OS in the ITT and in the PD-L1 positive analysis sets were planned with multiplicity control, all further analyses are descriptive.

A log-rank test stratified by selected stratification factors (ECOG and ICC option) was planned to be used to descriptively analyse the PFS differences between two treatment arms. Censoring rules are not fully supported, but sensitivity analyses were planned, some of which (sensitivity analysis II) are considered closer to a treatment policy estimand and are preferred.

Recruitment and conduct of the study

Study 302 was a global study which recruited patients from 11 countries/regions, including Asia, Europe and North America. The majority of patients was enrolled in China. In the ITT Analysis Set, a total of 512 patients were randomized 1:1 to receive tislelizumab or ICC. More patients in the ICC arm as compared to the tislelizumab arm were randomized but not treated (6.3% vs. 0.4%) or withdrew from the study (11.3% vs. 2.3%) and more patients in the ICC arm (23.8%) as compared to the tislelizumab arm (11.4%) were exposed to study treatment for less than 1 month. While this is not ideal, tipping-point analyses provided reassurance that even with pessimistic assumptions the interpretation of the study would not have been substantially affected by this imbalance.

At the data cutoff date of 1 December 2020, the median follow-up duration was longer in the tislelizumab as compared to the ICC arm (8.49 months vs. 5.8 months, respectively), which can be explained by patients in the ICC arm having more frequently discontinued the study early (e.g. due to death, withdrawals).

The Applicant committed to provide the final analyses of OS post-authorization. The estimated timeframe for this submission is currently Q3 2024.

There were 4 global amendments of the clinical study protocol for Study 302. The last amendment (Amendment Version 4.0, dated 20 March 2020 that introduced the removal of the interim analysis, an increase in sample size, and the addition of OS in patients with PD-L1 vCPS $\geq$ 10% as key secondary endpoint) was implemented after the last patient was randomized on 4 March 2020. The Applicant clarified the reasons for the late changes. (The Applicant clarified that these decisions were discussed with the Study Steering Committee in Jun-2019. As of 23-May-2019, only 17 patients were randomized in Europe/North America as compared to 330 patients in Asia. Due to concerns that the lack of geographically diverse population would likely not be acceptable for global registrational purposes, the decision was made to remove the interim analysis and to increase the sample size in order to allow enrolment of 100 patients from Ex-Asia. Moreover, the sample size was increased to

accumulate more OS events because the assumption of an OS HR was updated from 0.73 to 0.75 based on KEYNOTE-181 data (published in Jan-2019). Investigators were informed about these changes via a Protocol Communication Letter; however, the implementation of the protocol amendment was delayed because further results from ongoing trials in advanced esophageal carcinoma were awaited to avoid multiple versions of protocol amendments within a limited period. Subgroup results of ATTRACTION-3 and ESCORT studies (published in Sep-2019 and Nov-2019) provided further information on the predictive relevance of PD-L1 expression status that had already been suggested by results from KEYNOTE-181. Following these publications, Protocol Amendment v4.0 was released on 20-Mar-2020 that included the addition of OS in patients with PD-L1 vCPS $\geq$ 10% as a key secondary endpoint together with the removal of the interim analysis and the increase in sample size in the same version of the protocol amendment.

It is clearly not endorsed that the former Sponsor BeiGene implemented changes (removal of interim analysis and increase in sample size) prior to the approval of the respective protocol amendment. However, the above presented rationale that is supported by reasonable documentation ("BeiGene Steering Committee Meeting Minutes" and "Protocol Communication Letter") can be followed and do not raise concerns that the changes have been introduced based on knowledge of BGB-A317-302 study data. The Applicant confirmed that the PD-L1 cutoff selection of vCPS 10% using the Ventana PD-L1 (SP263) assay was based on analyses of response data from ESCC cohorts from Studies_001 and 102 and that PD-L1 expression levels in Study 302 were retrospectively evaluated by central laboratories after implementation of Protocol Amendment 4.). Moreover, the Applicant provided an exploratory OS analysis according to Protocol Amendment v3.0 (dated 08-Nov-2018), i.e. before critical late changes had been introduced with Protocol Amendment v4.0. The results showed that statistical significance would have been also met with this analysis.

Baseline characteristics

The study population included in Study 302 was predominantly male (84.4%) and had a median age of 62.0 years. The majority of patients was recruited at sites in Asia and thus, 79.7% of patients were Asian versus 18.9% being of White or Caucasian race. As the provision of tumour tissue (either archival tissue or fresh biopsy) was not strictly required for enrolment in this study, 19.3% of study participants presented with missing PD-L1 status.

The applicant was seeking approval for tislelizumab for "the treatment of adult patients with unresectable, recurrent, locally advanced or metastatic oesophageal squamous cell carcinoma after prior chemotherapy". Considering that prior treatment with a platinum-based regimen was required for inclusion in Study 302 and that platinum-based therapy was ultimately used in 97.3% of patients, the Applicant agreed to revise the indication wording to read: "Tradename as monotherapy is indicated for the treatment of adult patients with unresectable, locally advanced or metastatic oesophageal squamous cell carcinoma after prior platinum-based chemotherapy".

Only 5% of patients included in Study 302 was diagnosed with locally advanced ESCC, the remaining patients had metastatic disease at the time of study entry. Accounting for the small sample size of patients with locally advanced disease, it is probably not possible to draw reliable conclusions on efficacy results of subgroup analyses, which are therefore not requested. The extrapolation of efficacy results from the metastatic setting is however deemed acceptable and the inclusion of locally advanced disease stage in the indication wording is agreed. Similarly, although no data are available for patients with advanced or metastatic ESCC beyond the 2nd line therapy setting (99.6% of patients included in Study 302 had received exactly 1 prior therapy), the extrapolation of efficacy results from 2nd line ESCC to later lines of therapy is considered acceptable and no strict limitation in the indication wording is warranted.

Several imbalances in baseline characteristics of patients have been identified between treatment groups and specifically in relevant subgroups by region (Asia vs. Europe/North America). In the ITT Analysis Set, the percentage of patients with PD-L1 expression status vCPS ≥10% was higher in the tislelizumab arm (31.3%) as compared to the ICC arm (24.2%). In contrast, PD-L1 expression in the ITT population was < 10% in 39.1% and 47.7% of patients in the tislelizumab and the ICC arm, respectively. Since higher response rates of checkpoint inhibitors have been described in patients with high(er) PD-L1 expression in the past, this imbalance might have biased measures of efficacy, resulting in favouring the tislelizumab over the ICC comparator arm.

Comparing the Asia and Europe/North America population (see Table 3-3-6), patients in the Asia subgroup were younger as compared to those in the Europe/North America subgroup (median age of 61.0 years versus 65.0 years, respectively). In addition, the Asian subgroup of patients included a higher percentage of males (88.9% versus 67.6%), a higher percentage of patients with ECOG PS scores of 1 (79.0% versus 62.0%), a lower percentage of patients with PD-L1 vCPS < 10% (47.5% vs. 59.3%) while the percentage of patients with missing PD-L1 status was equally higher (21.5% vs. 11.1%) and a higher percentage of patients having received neo-/adjuvant prior therapy (19.8% vs. 2.8%) as compared to the Europe/North America subgroup. In general, these imbalances may yield uncertainties as regards to the external validity of the study.

Finally, further imbalances were identified between treatment arms of the Europe/North America subgroup (PD-L1 vCPS ≥ 10%: tislelizumab = 40.0% vs. ICC = 18.9% and ECOG PS 1: tislelizumab = 58.2% vs. ICC = 66.0%), which could have confounded the results in the EU population.

In order to address uncertainties deriving from above discussed imbalances in patients' baseline characteristics, the applicant conducted a variety of subgroup and sensitivity analyses. These suggested a benefit of tislelizumab throughout the different subgroups investigated and mitigate concerns regarding a meaningful confounding impact of imbalances in patient characteristics.

Efficacy data and additional analyses

The primary analysis of **OS in the ITT population** demonstrated a statistically significant benefit of tislelizumab over ICC control with an event rate of 77% and 83.2%, respectively (stratified HR = 0.7 [95% CI: 0.57 – 0.85], p = 0.0001, median OS 8.6 months for tislelizumab vs. 6.3 months for ICC). Given the poor prognosis of patients with advanced or metastatic ESCC, an increase in median OS of 2.3 months can be considered clinically meaningful. Reassurance was provided through tipping-point analyses that study results are robust despite the imbalance regarding drop-outs and withdrawals observed in this open-label study, an OS effect persisted even in very pessimistic scenarios of the tipping-point analysis.

In contrast to the primary OS analysis, no significant benefit could be demonstrated for investigator-assessed **PFS in the ITT population** (stratified HR = 0.83; 95% CI: 0.67 – 1.01; with p = 0.0292). Median PFS was shorter for tislelizumab (1.6 months) than for ICC (2.1 months), but KM curves separated late in favour of tislelizumab. More patients treated with tislelizumab had events of progressive disease (tislelizumab: 74.6% vs. ICC: 56.6%). Based on the number of events in the PFS and OS analyses, it can be concluded that a relevant portion of subjects died, but was censored in PFS analyses. Contingency tables do not support the same interpretation as Kaplan-Meier curves and hazard ratios. It was concluded that an imbalance in (early) censoring may be the reason for the apparent contradiction of time-to-event analyses and contingency tables. Sensitivity analyses investigating the robustness of results from time-to-event analyses against potentially informative (early) censoring provided reassurance. The point estimate for the PFS effect remained positive even in very pessimistic scenarios. However, some uncertainty remains associated with censoring for new

anticancer treatment or missed tumour assessments. When not censoring for either of these, the PFS point estimate was substantially reduced.

In the ITT population, the investigator-assessed **unconfirmed ORR** was higher in the tislelizumab arm as compared to the ICC arm (20.3% vs. 9.8%). A relatively high percentage of patients in the ICC arm (24.6%) with BOR "could not be determined" is noted. Although the high proportion of missing values in the ICC arm is considered unfortunate, the number of patients with indeterminable response in the ICC arm may be explained by the number of patients randomized but not treated or withdrawn from study treatment (N = 45) and by the number of patients exposed to ICC for less than 1 month (N = 57). Sensitivity analyses addressing this imbalance are requested. The applicant further conducted a post-hoc analysis using the confirmed response for assessment of ORR and BOR. Confirmed ORR was slightly lower as compared to unconfirmed ORR (15.2% in the tislelizumab arm vs. 6.6% in the ICC arm with an ORR difference of 8.6%). However, both analyses revealed higher response rates in patients treated with tislelizumab as compared to patients treated with ICC. In section 5.1 of the SmPC, only confirmed ORR is described, which is supported.

Outcomes of HRQoL did not show clinically meaningfully differences between treatment arms in the ITT population. However, results might be confounded by the knowledge of treatment assignment in the open-label study.

Efficacy by region

As discussed above, only 20% of patients in Study 302 were enrolled in Europe/North America. In order to allow an assessment of the adequacy of extrapolation of efficacy data to the EU population, subgroup analyses of the efficacy data in the ITT population by region were provided. For the primary endpoint OS, both the Asia and Europe/North America subgroup favoured the tislelizumab over the ICC arm. Median overall survival in the Asia subgroup was 8.5 months in the tislelizumab arm as compared to 6.3 months in the ICC arm (HR = 0.73, 95% CI: 0.59 - 0.90) and median overall survival in the Europe/North America subgroup was 11.2 months in the tislelizumab arm as compared to 6.3 months in the ICC arm (HR = 0.55, 95% CI: 0.35 - 0.87). Similar results were obtained comparing subgroups of White and Asian race. Although the sample size in the subgroup of White patients or patients from Europe/North America was rather low (N = 44 - 55) and the study was not adequately powered for these subgroup analyses, the results obtained are reassuring and suggest a clinically relevant benefit of tislelizumab vs. ICC also for the EU population primarily relevant for this submission.

Efficacy by PD-L1 status

OS in patients with PD-L1 vCPS $\geq$ 10% was analysed as key secondary endpoint and showed a statistically significant and more pronounced treatment effect of tislelizumab with a stratified HR of 0.49 (p = 0.0003) and a 4.9-month difference in median OS in favour of tislelizumab. Subsequently, post-hoc analyses of OS in patients with PD-L1 vCPS < 10% and missing status were performed. Hazard ratios in both subgroups favoured tislelizumab over ICC; however, the benefit of tislelizumab was apparently lower in the lower PD-L1 expression group (vCPS <10%: HR 0.83; 95% CI 0.62,1.12; missing: HR 0.72; 95% CI 0.49, 1.06). In view of the large sample size of the vCPS < 10% subgroup (62% of PD-L1 evaluable study population), the Applicant was asked to further evaluate the benefit in patients with PD-L1 negative or weak expressing tumours to justify a PD-L1 unrestricted indication.

One of the concerns was related to the high proportion of missing PD-L1 status for 99 patients (19.3%). As collection of tumour tissue for PD-L1 testing (by Ventana PD-L1 SP263 assay) was not part of the eligibility criteria, no tumour tissue samples were submitted for 59 patients. Reasons for missing PD-L1 status among the remaining 40 patients included mostly testing failures.

Further review of PD-L1 expression data after CSR finalization identified the use of additional unsuitable samples. Based on the sample eligibility criteria specified in the Ventana PD-L1 diagnostic

protocol, 49 samples had to be considered invalid for the data analyses. Thus, the proportion of study participants with missing PD-L1 status increased to 28.9% (n=148).

Although retrospective reclassification of tissue samples as unsuitable cannot be endorsed, updated results by corrected PD-L1 expression status did not change meaningfully; thus, conclusions on efficacy by PD-L1 subgroups did not necessarily change. However, it is considered relevant that the numbers in small PD-L1 subgroups diminish further with increasing number of patients with missing data, making any conclusions on small subgroups even less reliable.

Although only a marginal benefit was observed for the subgroup of patients with vCPS <10%, a positive B/R balance can be considered in view of the different and potentially more favourable safety profile as compared to the alternative chemotherapy options. Despite the methodological uncertainties related to cross-trial comparisons, it is notable that the data for the PD-L1 negative population in the pivotal study for nivolumab in 2L OSCC showed a similar outcome (results for PD-L1 TPS <1%: OS HR 0.84; 95% CI 0.62, 1.14; PFS HR 1.3; 95% CI 0.97, 1.73; ORR 14% vs 18% for nivolumab vs chemotherapy control; ATTRACTION-3, Kato et al, Lancet Oncology, 2019). The reported prevalence of both PD-L1 negative populations were in the same range (62% for vCPS <10% in Study 302 based on the Ventana SP263 assay and 52% for TPS <1% in Study ATTRACTION-3 based on the PD-L1 IHC 28-8 pharmDx assay). To further inform on the efficacy of tislelizumab in the PD-L1 negative subgroup, the Applicant provided additional subgroup analyses by baseline PD-L1 expression status with additional cutoffs (including vCPS levels of 5% and 1%).

Tislelizumab data for the < 5% cutoff (OS HR 0.89; 95% CI 0.61, 1.3) could be seen as marginally worse compared to the < 10% cutoff (when comparing the upper 95% CI of the OS HR and the slightly less prominent separation of the OS KM curves) but cannot be considered relevantly different.

In contrary, OS data for patients with a PD-L1 expression level of vCPS <1% indicate a detrimental effect (OS HR 1.32; 95% CI 0.65, 2.70; median OS 5.2 months vs 7.4 months for tislelizumab vs ICC). PFS HR is 0.9 (95% CI 0.44, 1.87) for the vCPS <1% subgroup. PFS KM curves beyond 2 months are minimal in favour of tislelizumab; however, with only very few patients still at risk after 2 months. Of note, there are 3 responses (including 1 CR) in the tislelizumab treatment group vs no response in the ICC group. Nonetheless, the large ORR difference of 18.8% appears to be impacted by the small sample size, considering the smaller ORR differences in the other subgroups (maximal 10.7% for vCPS ≥10%). Drawing satisfactory conclusions on these data is considered difficult.

A detrimental effect in OS as the clinically most relevant endpoint is observed in the subgroup with the lowest PD-L1 expression level. Given the large external evidence of a predictive value of PD-L1 expression status in ESCC, the lack of benefit for patients without PD-L1 expression appears biological plausible. This is considered an important point in favour of a possible restriction of the indication to patients with at least a minimum PD-L1 expression of vCPS ≥ 1%. This would be also supported by the exploratory OS modelling approach which identified a "switch-to-efficacy' point for patients with a PD-L1 expression >0.5%.

On the other hand, there are many factors that make such a decision questionable based on the available dataset. The subgroup of patients with vCPS <1% comprised 7.6% of the PD-L1 evaluable study population (n=16 in the tislelizumab arm vs n=23 in the ICC arm). A similarly low prevalence of 10% has been also observed in the ESCC population of the Phase I/II studies. This is mainly due to the fact that data for the Ventana SP263 assay allowed a further discrimination in subgroups of patients with lowest PD-L1 expression level (as opposed to the PD-L1 IHC 28-8 pharmDx assay used in the pivotal nivolumab study with a prevalence of 52% for the lowest cutoff of CPS <1%). Nonetheless, as already discussed, the number of patients is further diminished as a consequence of deficiencies in the study designs. Given the predictive value of PD-L1 status in this disease setting, mandatory collection of tumour tissue, central testing and stratification for PD-L1 expression would have been appropriate to

ensure adequate results by PD-L1 status. However, PD-L1 expression data were missing for about 30% of the study population.

The number of patients with vCPS <1% are limited to 16 patients in the tislelizumab arm and no reliable conclusions can be drawn. Based on the given study design, PD-L1 status was not a stratification factor, the 1% cutoff was not pre-specified in the protocol, is not analytically validated, and differences in prognostic relevant baseline/disease characteristics are observed between the treatment arms in the vCPS < 1% subgroup which might have had an impact on the OS outcome. While OS data indicated a detrimental outcome, this was not replicated for the secondary endpoint of PFS (HR 0.9; 95% CI 0.44, 1.87) nor for ORR (formally response rates of 18.8% reported with 3 responses in 16 patients). Finally, the different and overall slightly more favourable safety profile of tislelizumab as monotherapy can be taken into account and the fact that the study included an active comparator, even though the activity of chemotherapy seems rather modest in this disease setting (ORR of only 6.6% in the control arm).

Based on the above considerations, a restriction of the indication to exclude patients with vCPS<1% is not appropriate. This refers also to the presented vCPS <5% cutoff, where no detrimental effect was observed. In addition, a positive B/R balance can be considered for the pre-specified vCPS <10 % cutoff considering the different (more favourable) safety profile as compared to the alternative chemotherapy options and the precedent unrestricted indication for nivolumab monotherapy in OSCC.

Further to this, for the sake of improved readability, the term "recurrent" is removed from the initially applied indication wording.

2.6.7. Conclusions on clinical efficacy

A clinically meaningful benefit in overall survival was demonstrated in the intended target population of patients with locally advanced or metastatic OSCC after prior platinum-based therapy.

As Study 302 mainly enrolled patients from China (approx. 80%) and a variety of additional imbalances in baseline characteristics of patients were identified, uncertainties arose regarding the external validity of the study and the applicability of extrapolation of efficacy results to the EU population. However, the provided sensitivity and subgroup analyses within this submission are deemed to have sufficiently addressed these issues. In conclusion, there is currently no evidence of a meaningful differential treatment effect of tislelizumab in the European OSCC population eligible for 2nd line therapy.

2.6.8. Clinical safety

The safety of tislelizumab monotherapy for the treatment of unresectable recurrent locally advanced or metastatic OSCC after prior systemic therapy (abbreviated as "2L+" in the following) is supported by safety data from the following 3 patient populations:

- pivotal Study 302
- previously treated OSCC population (Study 302 as well as early phase studies 102 and 001)
- All Indications population (patients treated with 200 mg Q3W)

ESCC monotherapy pool	**Study 302**		**All patients with OSCC** (Studies 302, 102, and 001	**200 mg Q3W - All Indications** (Studies 302, 102, 001, 303, 208, 204, and 203)
	Tislelizumab	ICC	Tislelizumab	Tislelizumab

	n	n	n	n
Safety analysis Set	255	240	307	1534

Abbreviations: ICC=investigator chosen chemotherapy [paclitaxel, docetaxel or irinotecan]

In addition, some analyses are based on the All Doses All Indications population (n=1972) that also include patients from Study 001 who were treated with tislelizumab monotherapy in different dose regimens (0.5/2/5/10 mg/kg Q2W; 2/5 mg/kg Q2W/Q3W).

The following table describes the studies included in the pooled datasets:

Table 13- Studies providing safety data for tislelizumab 200 mg Q3W

Study	Disease type	Tislelizumab dose	Data cutoff date	Number of treated subjects
302	Previously treated, locally advanced or metastatic ESCC	200 mg Q3W	01-Dec-2020	Tislelizumab: 255 ICC: 240
303	Previously treated NSCLC	200 mg Q3W	10-Aug-2020	Tislelizumab: 534 Docetaxel: 258
208	Previously treated, unresectable HCC	200 mg Q3W	27-Feb-2020	249
204	r/r UBC	200 mg Q3W	16-Sep-2019	113
203	r/r cHL	200 mg Q3W	26-Nov-2018	70
102	Solid tumours	200 mg Q3W	31-May-2020 (Final CSR DCO)	243
		200 mg W1 D1, W5+D1 Q3W (PK substudy)		57
001	Solid tumours	200 mg Q3W	26-Aug-2020 (Final CSR DCO)	13

OSCC: Oesophageal Squamous Cell Carcinoma; HCC: Hepatocellular Carcinoma; NSCLC: Non-Small Cell Lung Cancer; UBC: Urothelial Bladder Cancer; R/R: Relapsed or Refractory; cHL: classical Hodgkin Lymphoma; Q3W: every 3 weeks; W1D1: Week 1Day 1; W5+D1 Q3W: every 3 weeks from Week 5 Day 1.

The supportive phase I Study 001 and the phase I/II Study 102 enrolled patients with advanced solid tumours and enrolled 26 ESCC patients each (included in the ESCC population).

The pivotal Study 302 enrolled patients from 132 sites in 11 countries/regions. At the time of submission, Study 302 was ongoing with a cutoff date of 01 December 2020; randomization was completed on 11 Sep 2019 in Asia and 04 Mar 2020 in Europe/North America. For the tislelizumab arm median study follow-up was 8.49 months versus 5.80 months in the ICC arm. 6.3% (tislelizumab arm) vs. 0.4 % (ICC arm) remained on study treatment at the cutoff date (*Source: CSR Table 9*).

2.6.8.1. Patient exposure

Exposure to tislelizumab and ICC in Study 302

Table 14- Extent of treatment exposure (302 Safety Analysis Set)

	Tislelizumab (N = 255)	ICC (N = 240)
Number of Cycles Received, n (%)		
Mean (SD)	7.1 (7.63)	3.3 (3.22)
Median	4.0	2.0
Q1, Q3	2.0, 8.0	1.0, 4.0
Min, Max	1, 38	1, 28
Duration of Exposure (Months), n (%)		

	Tislelizumab (N = 255)	ICC (N = 240)
< 1 Month	29 (11.4)	57 (23.8)
1 - < 3 Months	118 (46.3)	125 (52.1)
3 - < 6 Months	43 (16.9)	37 (15.4)
6 - < 12 Months	38 (14.9)	20 (8.3)
12 - < 18 Months	13 (5.1)	0 (0.0)
18 - < 24 Months	11 (4.3)	1 (0.4)
≥ 24 Months	3 (1.2)	0 (0.0)
Mean (SD)	5.01 (5.455)	2.48 (2.508)
Median	2.76	1.49
Q1, Q3	1.41, 6.24	1.15, 2.99
Min, Max	0.2, 28.3	0.2, 19.2
Duration of Exposure (Months), n (%)		
≥ 6 Months	65 (25.5)	21 (8.8)
≥ 12 Months	27 (10.6)	1 (0.4)
≥ 18 Months	14 (5.5)	1 (0.4)
≥ 24 Months	3 (1.2)	0 (0.0)
Relative Dose Intensity (RDI) (%) [a]		
Mean (SD)	100.13 (16.635)	87.05 (23.217)
Median	100.00	89.40
Q1, Q3	97.67, 100.00	73.26, 99.54
Min, Max [c]	46.2, 300.0	37.6, 292.4
Patients with Dose Modification [b], n (%)	**88 (34.5)**	**132 (55.0)**
Patients with Infusion Interruption, n (%)	0 (0.0)	8 (3.3)
Patients with Dose Delay [d], n (%)	88 (34.5)	107 (44.6)
Patients with Dose Reduced, n (%)	NA	66 (27.5)

Source SCS Table 1-2 (excerpt)

Exposure to tislelizumab in Study 302 and All Doses All Indication pool

Table 15- Extent of Exposure to Tislelizumab (Study 302 and Tislelizumab 200 mg Q3W - All Indications, Safety Analysis Set [SAS])

	Study 302 N = 255	Tislelizumab – all patients with ESCC N = 307	Tislelizumab 200 mg Q3W – All Indications N = 1534
Number of cycles received, n (%)			
Mean (SD)	7.1 (7.63)	7.1 (8.02)	10.2 (10.14)
Median	4.0	4.0	6.0
Q1, Q3	2.0, 8.0	2.0, 8.0	3.0, 15.0
Min, Max	1, 38	1, 52	1, 56
Duration of exposure (months), n (%)			
< 1 month	29 (11.4)	38 (12.4)	117 (7.6)
1 - < 3 months	118 (46.3)	138 (45.0)	515 (33.6)
3 - < 6 months	43 (16.9)	56 (18.2)	287 (18.7)
6 - < 12 months	38 (14.9)	42 (13.7)	275 (17.9)
12 - < 18 months	13 (5.1)	14 (4.6)	185 (12.1)
18 - < 24 months	11 (4.3)	14 (4.6)	90 (5.9)
≥ 24 months	3 (1.2)	5 (1.6)	65 (4.2)
Mean (SD)	5.01 (5.455)	5.04 (5.753)	7.24 (7.285)
Median	2.76	2.76	4.16
Q1, Q3	1.41, 6.24	1.41, 5.52	2.07, 10.38
Min, Max	0.2, 28.3	0.2, 35.9	0.2, 41.0
Duration of exposure (months), n (%)			

	Study 302	Tislelizumab – all patients with ESCC	Tislelizumab 200 mg Q3W – All Indications
	N = 255	N = 307	N = 1534
≥ 6 months	65 (25.5)	75 (24.4)	615 (40.1)
≥ 12 months	27 (10.6)	33 (10.7)	340 (22.2)
≥ 18 months	14 (5.5)	19 (6.2)	155 (10.1)
≥ 24 months	3 (1.2)	5 (1.6)	65 (4.2)
≥ 30 months	0	1 (0.3)	26 (1.7)
Cumulative dose (mg)			
Mean (SD)	1415.69 (1526.379)	1507.23 (2004.571)	2032.52 (2025.454)
Median	800.00	800.00	1200.00
Q1, Q3	400.00, 1600.00	400.00, 1624.50	600.00, 3000.00
Min, Max	200.0, 7600.0	200.0, 23100.0	200.0, 11200.0

Percentages are based on N, unless otherwise noted.

Analysis of adverse events

In Study 302 all randomized patients having received at least 1 dose of study treatment are included in the Safety Analysis Set (SAS).

All AEs were reported until 30 days after study treatment discontinuation or initiation of a new anticancer therapy, whichever occurred first, with the exception of imAEs that were reported for 90 days after last dose of tislelizumab, regardless of whether or not the patient started a new anticancer therapy.

The following tables are provided for the Safety Analysis Sets described above. Treatment emergent adverse events (TEAE) were coded 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. Dose modification includes either dose interruption or dose delay for tislelizumab and dose interruption or dose delay or dose reduction for ICC. Patients with multiple events for a given PT and SOC were counted only once. For each row category, a patient with two or more adverse events in that category is counted only once.

Summary of AE

Table 16- Overall Summary of treatment-emergent adverse events (TEAEs)

	Study 302			
	Tislelizumab	ICC	Tislelizumab – all patients with ESCC	Tislelizumab 200 mg Q3W – All Indications
	N = 255	N = 240	N = 307	N = 1534
	n (%)	n (%)	n (%)	n (%)
Patients with at least one TEAE	244 (95.7)	236 (98.3)	294 (95.8)	1468 (95.7)
Treatment-related TEAE	187 (73.3)	225 (93.8)	217 (70.7)	1125 (73.3)
Grade ≥ 3 TEAE	118 (46.3)	163 (67.9)	144 (46.9)	668 (43.5)
Treatment-related grade ≥ 3 TEAE	48 (18.8)	134 (55.8)	54 (17.6)	250 (16.3)
Serious TEAE	106 (41.6)	105 (43.8)	128 (41.7)	516 (33.6)
Treatment-related serious TEAE	37 (14.5)	47 (19.6)	40 (13.0)	175 (11.4)
TEAE leading to death	35 (13.7)	28 (11.7)	42 (13.7)	127 (8.3)
Treatment-related TEAE leading to death	7 (2.7)	8 (3.3)	7 (2.3)	20 (1.3)

	Study 302			
	Tislelizumab	ICC	Tislelizumab – all patients with ESCC	Tislelizumab 200 mg Q3W – All Indications
	N = 255	N = 240	N = 307	N = 1534
	n (%)	n (%)	n (%)	n (%)
TEAE leading to treatment discontinuation	49 (19.2)	64 (26.7)	59 (19.2)	190 (12.4)
Treatment-related TEAE leading to treatment discontinuation	17 (6.7)	33 (13.8)	18 (5.9)	85 (5.5)
TEAE leading to dose modification	58 (22.7)	115 (47.9)	71 (23.1)	398 (25.9)
Treatment-related TEAE leading to dose modification	34 (13.3)	106 (44.2)	41 (13.4)	235 (15.3)
Immune-mediated TEAE	57 (22.4)	NA	61 (19.9)	276 (18.0)
Grade ≥ 3 immune-mediated TEAE	12 (4.7)	NA	13 (4.2)	81 (5.3)
Serious immune-mediated TEAE	17 (6.7)	NA	18 (5.9)	90 (5.9)
Immune-mediated TEAE leading to death	1 (0.4)	NA	1 (0.3)	6 (0.4)
Infusion-related reaction	8 (3.1)	11 (4.6)	9 (2.9)	54 (3.5)
Grade ≥ 3 infusion-related reaction	0	0	0	4 (0.3)

Most common Adverse Events

Table 17- Most common TEAEs by PT (≥ 5%) Study 302

Preferred Term	Tislelizumab (N = 255) n (%)	ICC (N = 240) n (%)
Patients with at least one TEAE	**244 (95.7)**	**236 (98.3)**
Anaemia	78 (30.6)	107 (44.6)
Weight decreased	59 (23.1)	45 (18.8)
Cough	43 (16.9)	28 (11.7)
Pyrexia	41 (16.1)	34 (14.2)
Decreased appetite	40 (15.7)	84 (35.0)
Constipation	39 (15.3)	45 (18.8)
Aspartate aminotransferase increased	37 (14.5)	11 (4.6)
Nausea	36 (14.1)	72 (30.0)
Pneumonia	36 (14.1)	27 (11.3)
Hypoalbuminaemia	34 (13.3)	30 (12.5)
Alanine aminotransferase increased	33 (12.9)	18 (7.5)
Fatigue	33 (12.9)	42 (17.5)
Diarrhoea	32 (12.5)	77 (32.1)
Hyponatraemia	32 (12.5)	33 (13.8)
Hypothyroidism	29 (11.4)	1 (0.4)
Dysphagia	28 (11.0)	20 (8.3)
Vomiting	27 (10.6)	48 (20.0)
Asthenia	26 (10.2)	35 (14.6)
Back pain	26 (10.2)	18 (7.5)
Dyspnoea	24 (9.4)	18 (7.5)
Pruritus	23 (9.0)	11 (4.6)
Rash	21 (8.2)	10 (4.2)
Hypokalaemia	20 (7.8)	22 (9.2)
Insomnia	20 (7.8)	17 (7.1)
Productive cough	18 (7.1)	18 (7.5)

Preferred Term	Tislelizumab (N = 255) n (%)	ICC (N = 240) n (%)
Abdominal pain	17 (6.7)	22 (9.2)
Blood alkaline phosphatase increased	17 (6.7)	5 (2.1)
Hyperglycaemia	16 (6.3)	7 (2.9)
Malaise	16 (6.3)	36 (15.0)
Gamma-glutamyltransferase increased	14 (5.5)	8 (3.3)
Gastrooesophageal reflux disease	14 (5.5)	12 (5.0)
Platelet count decreased	14 (5.5)	15 (6.3)
Hypoproteinaemia	13 (5.1)	8 (3.3)
Musculoskeletal pain	13 (5.1)	7 (2.9)
Lymphocyte count decreased	12 (4.7)	22 (9.2)
Dizziness	11 (4.3)	19 (7.9)
Arthralgia	10 (3.9)	13 (5.4)
Abdominal pain upper	9 (3.5)	16 (6.7)
Stomatitis	9 (3.5)	14 (5.8)
White blood cell count decreased	9 (3.5)	98 (40.8)
Leukopenia	8 (3.1)	30 (12.5)
Myalgia	6 (2.4)	14 (5.8)
Neutrophil count decreased	6 (2.4)	94 (39.2)
Neutropenia	2 (0.8)	31 (12.9)
Peripheral sensory neuropathy	2 (0.8)	23 (9.6)
Alopecia	0 (0.0)	42 (17.5)
Febrile neutropenia	0 (0.0)	12 (5.0)

Source SCS table 2-2, SCS 2.7.4.2.1.2.2

Table 18-TEAE by SOC and PT (≥10% patients in any population)

	Study 302			
	Tislelizumab	ICC	Tislelizumab – all patients with ESCC	Tislelizumab 200 mg Q3W – All Indications
System organ class	**N = 255**	**N = 240**	**N = 307**	**N = 1534**
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Patients with at least one TEAE	**244 (95.7)**	**236 (98.3)**	**294 (95.8)**	**1468 (95.7)**
Gastrointestinal disorders	149 (58.4)	171 (71.3)	175 (57.0)	683 (44.5)
Constipation	39 (15.3)	45 (18.8)	45 (14.7)	181 (11.8)
Nausea	36 (14.1)	72 (30.0)	42 (13.7)	151 (9.8)
Diarrhoea	32 (12.5)	77 (32.1)	37 (12.1)	136 (8.9)
Dysphagia	28 (11.0)	20 (8.3)	31 (10.1)	48 (3.1)
Vomiting	27 (10.6)	48 (20.0)	32 (10.4)	115 (7.5)
Investigations	128 (50.2)	166 (69.2)	151 (49.2)	901 (58.7)
Weight decreased	59 (23.1)	45 (18.8)	63 (20.5)	216 (14.1)
Aspartate aminotransferase increased	37 (14.5)	11 (4.6)	41 (13.4)	320 (20.9)
Alanine aminotransferase increased	33 (12.9)	18 (7.5)	40 (13.0)	295 (19.2)
Blood bilirubin increased	9 (3.5)	6 (2.5)	10 (3.3)	153 (10.0)
White blood cell count decreased	9 (3.5)	98 (40.8)	11 (3.6)	101 (6.6)
Neutrophil count decreased	6 (2.4)	94 (39.2)	6 (2.0)	65 (4.2)
Metabolism and nutrition disorders	117 (45.9)	141 (58.8)	138 (45.0)	659 (43.0)
Decreased appetite	40 (15.7)	84 (35.0)	52 (16.9)	221 (14.4)
Hypoalbuminaemia	34 (13.3)	30 (12.5)	36 (11.7)	174 (11.3)
Hyponatraemia	32 (12.5)	33 (13.8)	34 (11.1)	130 (8.5)

	Study 302			
	Tislelizumab	ICC	Tislelizumab – all patients with ESCC	Tislelizumab 200 mg Q3W – All Indications
System organ class	**N = 255**	**N = 240**	**N = 307**	**N = 1534**
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**
General disorders and administration site conditions	116 (45.5)	147 (61.3)	137 (44.6)	646 (42.1)
Pyrexia	41 (16.1)	34 (14.2)	50 (16.3)	236 (15.4)
Fatigue	33 (12.9)	42 (17.5)	38 (12.4)	125 (8.1)
Asthenia	26 (10.2)	35 (14.6)	27 (8.8)	152 (9.9)
Malaise	16 (6.3)	36 (15.0)	20 (6.5)	88 (5.7)
Respiratory, thoracic and mediastinal disorders	104 (40.8)	81 (33.8)	124 (40.4)	558 (36.4)
Cough	43 (16.9)	28 (11.7)	51 (16.6)	237 (15.4)
Blood and lymphatic system disorders	92 (36.1)	139 (57.9)	109 (35.5)	509 (33.2)
Anaemia	78 (30.6)	107 (44.6)	93 (30.3)	422 (27.5)
Leukopenia	8 (3.1)	30 (12.5)	8 (2.6)	44 (2.9)
Neutropenia	2 (0.8)	31 (12.9)	2 (0.7)	25 (1.6)
Infections and infestations	75 (29.4)	75 (31.3)	91 (29.6)	472 (30.8)
Pneumonia	36 (14.1)	27 (11.3)	44 (14.3)	142 (9.3)
Musculoskeletal and connective tissue disorders	66 (25.9)	61 (25.4)	82 (26.7)	408 (26.6)
Back pain	26 (10.2)	18 (7.5)	33 (10.7)	112 (7.3)
Skin and subcutaneous tissue disorders	59 (23.1)	67 (27.9)	66 (21.5)	370 (24.1)
Pruritus	23 (9.0)	11 (4.6)	25 (8.1)	154 (10.0)
Alopecia	0	42 (17.5)	1 (0.3)	6 (0.4)
Endocrine disorders	39 (15.3)	2 (0.8)	49 (16.0)	243 (15.8)
Hypothyroidism	29 (11.4)	1 (0.4)	38 (12.4)	184 (12.0)

Most common related AEs

Table 19- Most common treatment-related TEAEs ≥5% by SOC and PT, Study 302 (SAS)

	Study 302	
	Tislelizumab	ICC
System organ class	**N = 255**	**N = 240**
Preferred term	**n (%)**	**n (%)**
Patients with at least one treatment-related TEAE	**187 (73.3)**	**225 (93.8)**
Investigations	81 (31.8)	151 (62.9)
Aspartate aminotransferase increased	29 (11.4)	9 (3.8)
Alanine aminotransferase increased	25 (9.8)	18 (7.5)
Platelet count decreased	11 (4.3)	15 (6.3)
Weight decreased	8 (3.1)	25 (10.4)
Lymphocyte count decreased	7 (2.7)	19 (7.9)
White blood cell count decreased	5 (2.0)	98 (40.8)
Neutrophil count decreased	3 (1.2)	94 (39.2)
General disorders and administration site conditions	51 (20.0)	108 (45.0)
Fatigue	19 (7.5)	33 (13.8)
Asthenia	12 (4.7)	28 (11.7)
Malaise	10 (3.9)	35 (14.6)
Pyrexia	10 (3.9)	12 (5.0)

	Study 302	
	Tislelizumab	ICC
System organ class	**N = 255**	**N = 240**
Preferred term	**n (%)**	**n (%)**
Metabolism and nutrition disorders	47 (18.4)	103 (42.9)
Decreased appetite	16 (6.3)	75 (31.3)
Hyponatraemia	8 (3.1)	21 (8.8)
Hypoalbuminaemia	7 (2.7)	15 (6.3)
Hypokalaemia	1 (0.4)	15 (6.3)
Skin and subcutaneous tissue disorders	45 (17.6)	61 (25.4)
Rash	19 (7.5)	8 (3.3)
Pruritus	15 (5.9)	8 (3.3)
Alopecia	0	42 (17.5)
Blood and lymphatic system disorders	39 (15.3)	119 (49.6)
Anaemia	28 (11.0)	83 (34.6)
Leukopenia	7 (2.7)	30 (12.5)
Neutropenia	2 (0.8)	31 (12.9)
Febrile neutropenia	0	12 (5.0)
Gastrointestinal disorders	39 (15.3)	132 (55.0)
Diarrhoea	14 (5.5)	66 (27.5)
Nausea	7 (2.7)	66 (27.5)
Constipation	4 (1.6)	25 (10.4)
Stomatitis	4 (1.6)	14 (5.8)
Vomiting	4 (1.6)	43 (17.9)
Abdominal pain	2 (0.8)	12 (5.0)
Endocrine disorders	35 (13.7)	0
Hypothyroidism	26 (10.2)	0
Musculoskeletal and connective tissue disorders	22 (8.6)	33 (13.8)
Myalgia	2 (0.8)	14 (5.8)
Nervous system disorders	9 (3.5)	48 (20.0)
Peripheral sensory neuropathy	2 (0.8)	22 (9.2)
Dizziness	1 (0.4)	13 (5.4)

Treatment-related TEAE in Study 302 is defined as a TEAE that is assessed by the investigator as causally related to study drug or with missing causal relationship.

Table 20- Examples of all-cause and related PTs, Study 302

Preferred Term	**All-cause**		**Related**	
	Tislelizumab (N = 255) n (%)	**ICC (N = 240) n (%)**	**Tislelizumab (N = 255) n (%)**	**ICC (N = 240) n (%)**
Constipation	39 (15.3)	45 (18.8)	4 (1.6)	25 (10.4)
Nausea	36 (14.1)	72 (30.0)	7 (2.7)	66 (27.5)
Diarrhoe	32 (12.5)	77 (32.1)	14 (5.5)	66 (27.5)
Weight decreased	59 (23.1)	45 (18.8)	8 (3.1)	25 (10.4)
Decreased appetite	40 (15.7)	84 (35.0)	16 (6.3)	75 (31.3)
Anaemia	78 (30.6)	107 (44.6)	28 (11.0)	83 (34.6)
Fatigue	33 (12.9)	42 (17.5)	19 (7.5)	33 (13.8)

Source: excerpts from CSR Table 26, 27 and Table 14.3.1.2.3.4

Grade ≥ 3 TEAEs, all cause

Table 21-Grade ≥3 TEAEs (PT ≥ 1% in Study 302)

Preferred Term	Tislelizumab (N = 255) n (%)	ICC (N = 240) n (%)
Patients with at least one Grade 3 or Higher TEAE	**118 (46.3)**	**163 (67.9)**
Dysphagia	16 (6.3)	7 (2.9)
Anaemia	15 (5.9)	26 (10.8)
Hyponatraemia	14 (5.5)	10 (4.2)
Pneumonia	12 (4.7)	17 (7.1)
Dyspnoea	6 (2.4)	3 (1.3)
Lymphocyte count decreased	6 (2.4)	18 (7.5)
Hypertension	5 (2.0)	0 (0.0)
Oesophageal obstruction	4 (1.6)	1 (0.4)
Oesophageal stenosis	4 (1.6)	1 (0.4)
Pneumonitis	4 (1.6)	2 (0.8)
Pulmonary embolism	4 (1.6)	1 (0.4)
Upper gastrointestinal haemorrhage	4 (1.6)	4 (1.7)
Aspartate aminotransferase increased	3 (1.2)	1 (0.4)
Diarrhoea	3 (1.2)	15 (6.3)
Gamma-glutamyltransferase increased	3 (1.2)	3 (1.3)
General physical health deterioration	3 (1.2)	5 (2.1)
Hypoglycaemia	3 (1.2)	0 (0.0)
Hypophosphataemia	3 (1.2)	0 (0.0)
Multiple organ dysfunction syndrome	3 (1.2)	1 (0.4)
Oesophageal fistula	3 (1.2)	1 (0.4)
Pleural effusion	3 (1.2)	2 (0.8)
Pneumonia aspiration	3 (1.2)	2 (0.8)
Syncope	3 (1.2)	2 (0.8)
Tumour pain	3 (1.2)	1 (0.4)
Weight decreased	3 (1.2)	0 (0.0)
Acquired tracheo-oesophageal fistula	2 (0.8)	4 (1.7)
Alanine aminotransferase increased	2 (0.8)	4 (1.7)
Asthenia	2 (0.8)	5 (2.1)
Death	2 (0.8)	4 (1.7)
Decreased appetite	2 (0.8)	10 (4.2)
Fatigue	2 (0.8)	6 (2.5)
Hypokalaemia	2 (0.8)	6 (2.5)
Malaise	2 (0.8)	4 (1.7)
Vomiting	2 (0.8)	9 (3.8)
Nausea	1 (0.4)	8 (3.3)
Neutropenia	1 (0.4)	16 (6.7)
Septic shock	1 (0.4)	4 (1.7)
White blood cell count decreased	1 (0.4)	48 (20.0)
Febrile neutropenia	0 (0.0)	11 (4.6)
Leukopenia	0 (0.0)	17 (7.1)
Neutrophil count decreased	0 (0.0)	63 (26.3)

Source SCS Table 2-3

Table 22-Grade ≥ 3 TEAEs occurring in ≥ 1% of patients by SOC and pT (All Indications, SAS)

	Study 302			
	Tislelizumab	**ICC**	**Tislelizumab – all patients with ESCC**	**Tislelizumab 200 mg Q3W – All Indications**
System organ class	**N = 255**	**N = 240**	**N = 307**	**N = 1534**
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**

Patients with at least one grade ≥ 3 TEAE	**118 (46.3)**	**163 (67.9)**	144 (46.9)	668 (43.5)
Gastrointestinal disorders	38 (14.9)	45 (18.8)	43 (14.0)	115 (7.5)
Dysphagia	16 (6.3)	7 (2.9)	17 (5.5)	21 (1.4)
Oesophageal obstruction	4 (1.6)	1 (0.4)	5 (1.6)	4 (0.3)
Oesophageal stenosis	4 (1.6)	1 (0.4)	4 (1.3)	4 (0.3)
Upper gastrointestinal haemorrhage	4 (1.6)	4 (1.7)	6 (2.0)	13 (0.8)
Diarrhoea	3 (1.2)	15 (6.3)	3 (1.0)	12 (0.8)
Oesophageal fistula	3 (1.2)	1 (0.4)	3 (1.0)	3 (0.2)
Vomiting	2 (0.8)	9 (3.8)	2 (0.7)	9 (0.6)
Nausea	1 (0.4)	8 (3.3)	1 (0.3)	3 (0.2)
Ascites	0	0	0	18 (1.2)
Metabolism and nutrition disorders	27 (10.6)	31 (12.9)	33 (10.7)	129 (8.4)
Hyponatraemia	14 (5.5)	10 (4.2)	16 (5.2)	39 (2.5)
Hypoglycaemia	3 (1.2)	0	3 (1.0)	8 (0.5)
Hypophosphataemia	3 (1.2)	0	3 (1.0)	5 (0.3)
Decreased appetite	2 (0.8)	10 (4.2)	3 (1.0)	15 (1.0)
Hypokalaemia	2 (0.8)	6 (2.5)	3 (1.0)	23 (1.5)
Hypercalcaemia	2 (0.8)	1 (0.4)	3 (1.0)	14 (0.9)
Hyperglycaemia	0	1 (0.4)	0	16 (1.0)
Investigations	25 (9.8)	90 (37.5)	26 (8.5)	174 (11.3)
Lymphocyte count decreased	6 (2.4)	18 (7.5)	6 (2.0)	16 (1.0)
Aspartate aminotransferase increased	3 (1.2)	1 (0.4)	3 (1.0)	40 (2.6)
Gamma-glutamyltransferase increased	3 (1.2)	3 (1.3)	3 (1.0)	32 (2.1)
Weight decreased	3 (1.2)	0	3 (1.0)	10 (0.7)
Alanine aminotransferase increased	2 (0.8)	4 (1.7)	2 (0.7)	22 (1.4)
Blood alkaline phosphatase increased	2 (0.8)	0	2 (0.7)	17 (1.1)
Blood bilirubin increased	2 (0.8)	1 (0.4)	2 (0.7)	21 (1.4)
White blood cell count decreased	1 (0.4)	48 (20.0)	1 (0.3)	8 (0.5)
Neutrophil count decreased	0	63 (26.3)	0	11 (0.7)
Respiratory, thoracic and mediastinal disorders	25 (9.8)	18 (7.5)	30 (9.8)	105 (6.8)
Dyspnoea	6 (2.4)	3 (1.3)	7 (2.3)	19 (1.2)
Pneumonitis	4 (1.6)	2 (0.8)	5 (1.6)	16 (1.0)
Pulmonary embolism	4 (1.6)	1 (0.4)	4 (1.3)	11 (0.7)
Pleural effusion	3 (1.2)	2 (0.8)	3 (1.0)	8 (0.5)
Pneumonia aspiration	3 (1.2)	2 (0.8)	4 (1.3)	3 (0.2)
Acquired tracheo-oesophageal fistula	2 (0.8)	4 (1.7)	2 (0.7)	2 (0.1)
Infections and infestations	20 (7.8)	31 (12.9)	28 (9.1)	125 (8.1)
Pneumonia	12 (4.7)	17 (7.1)	18 (5.9)	72 (4.7)
Sepsis	2 (0.8)	1 (0.4)	3 (1.0)	5 (0.3)
Septic shock	1 (0.4)	4 (1.7)	1 (0.3)	2 (0.1)
Blood and lymphatic system disorders	18 (7.1)	56 (23.3)	23 (7.5)	96 (6.3)
Anaemia	15 (5.9)	26 (10.8)	19 (6.2)	75 (4.9)

Neutropenia	1 (0.4)	16 (6.7)	1 (0.3)	8 (0.5)
Febrile neutropenia	0	11 (4.6)	0	0
Leukopenia	0	17 (7.1)	0	3 (0.2)
General disorders and administration site conditions	15 (5.9)	25 (10.4)	18 (5.9)	76 (5.0)
General physical health deterioration	3 (1.2)	5 (2.1)	3 (1.0)	11 (0.7)
Multiple organ dysfunction syndrome	3 (1.2)	1 (0.4)	3 (1.0)	8 (0.5)
Asthenia	2 (0.8)	5 (2.1)	2 (0.7)	13 (0.8)
Death	2 (0.8)	4 (1.7)	3 (1.0)	15 (1.0)
Fatigue	2 (0.8)	6 (2.5)	3 (1.0)	10 (0.7)
Malaise	2 (0.8)	4 (1.7)	3 (1.0)	8 (0.5)
Vascular disorders	9 (3.5)	0	9 (2.9)	40 (2.6)
Hypertension	5 (2.0)	0	5 (1.6)	28 (1.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	8 (3.1)	5 (2.1)	10 (3.3)	25 (1.6)
Tumour pain	3 (1.2)	1 (0.4)	3 (1.0)	7 (0.5)
Nervous system disorders	6 (2.4)	9 (3.8)	8 (2.6)	39 (2.5)
Syncope	3 (1.2)	2 (0.8)	3 (1.0)	6 (0.4)

Grade ≥ 3 AEs (related)

Table 23- Treatment-related TEAEs ≥ Grade 3 by SOC and PT (≥ 1%) all populations

	Study 302			
	Tislelizumab	**ICC**	**Tislelizumab – all patients with ESCC**	**Tislelizumab 200 mg Q3W – All Indications**
System organ class	**N = 255**	**N = 240**	**N = 307**	**N = 1534**
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Patients with at least one grade ≥ 3 treatment-related TEAE	**48 (18.8)**	**134 (55.8)**	**54 (17.6)**	**250 (16.3)**
Investigations	17 (6.7)	90 (37.5)	17 (5.5)	79 (5.1)
Lymphocyte count decreased	4 (1.6)	16 (6.7)	4 (1.3)	8 (0.5)
Gamma-glutamyltransferase increased	3 (1.2)	2 (0.8)	3 (1.0)	12 (0.8)
Aspartate aminotransferase increased	2 (0.8)	1 (0.4)	2 (0.7)	22 (1.4)
Alanine aminotransferase increased	0	4 (1.7)	0	15 (1.0)
Neutrophil count decreased	0	63 (26.3)	0	6 (0.4)
White blood cell count decreased	0	48 (20.0)	0	4 (0.3)
Metabolism and nutrition disorders	10 (3.9)	21 (8.8)	11 (3.6)	27 (1.8)
Hyponatraemia	5 (2.0)	7 (2.9)	5 (1.6)	8 (0.5)
Decreased appetite	0	7 (2.9)	0	3 (0.2)
Hypokalaemia	0	5 (2.1)	0	2 (0.1)
Blood and lymphatic system disorders	7 (2.7)	48 (20.0)	9 (2.9)	30 (2.0)
Anaemia	6 (2.4)	17 (7.1)	8 (2.6)	21 (1.4)
Neutropenia	1 (0.4)	16 (6.7)	1 (0.3)	5 (0.3)
Febrile neutropenia	0	11 (4.6)	0	0
Leukopenia	0	17 (7.1)	0	2 (0.1)

	Study 302			
	Tislelizumab	ICC	Tislelizumab – all patients with ESCC	Tislelizumab 200 mg Q3W – All Indications
System organ class	**N = 255**	**N = 240**	**N = 307**	**N = 1534**
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Respiratory, thoracic and mediastinal disorders	7 (2.7)	2 (0.8)	9 (2.9)	44 (2.9)
Pneumonitis	4 (1.6)	1 (0.4)	5 (1.6)	16 (1.0)
Infections and infestations	5 (2.0)	11 (4.6)	5 (1.6)	18 (1.2)
Pneumonia	4 (1.6)	5 (2.1)	4 (1.3)	13 (0.8)
Septic shock	0	4 (1.7)	0	0
Gastrointestinal disorders	4 (1.6)	31 (12.9)	5 (1.6)	23 (1.5)
Diarrhoea	0	15 (6.3)	0	6 (0.4)
Nausea	0	7 (2.9)	0	1 (0.1)
Vomiting	0	8 (3.3)	0	1 (0.1)
General disorders and administration site conditions	2 (0.8)	14 (5.8)	3 (1.0)	15 (1.0)
Malaise	1 (0.4)	4 (1.7)	2 (0.7)	5 (0.3)
Asthenia	0	4 (1.7)	0	1 (0.1)
Fatigue	0	3 (1.3)	0	3 (0.2)

Source SCS Appendix 1, Table 2.7.4.2.1.3.2

Table 24- Grade ≥ 3 TEAEs occurring in ≥ 1% of patients by SOC and pT (All Indications, SAS)

	Study 302			
	Tislelizumab	ICC	Tislelizumab – all patients with ESCC	Tislelizumab 200 mg Q3W – All Indications
System organ class	**N = 255**	**N = 240**	**N = 307**	**N = 1534**
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Patients with at least one grade ≥ 3 TEAE	**118 (46.3)**	**163 (67.9)**	144 (46.9)	668 (43.5)
Gastrointestinal disorders	38 (14.9)	45 (18.8)	43 (14.0)	115 (7.5)
Dysphagia	16 (6.3)	7 (2.9)	17 (5.5)	21 (1.4)
Oesophageal obstruction	4 (1.6)	1 (0.4)	5 (1.6)	4 (0.3)
Oesophageal stenosis	4 (1.6)	1 (0.4)	4 (1.3)	4 (0.3)
Upper gastrointestinal haemorrhage	4 (1.6)	4 (1.7)	6 (2.0)	13 (0.8)
Diarrhoea	3 (1.2)	15 (6.3)	3 (1.0)	12 (0.8)
Oesophageal fistula	3 (1.2)	1 (0.4)	3 (1.0)	3 (0.2)
Vomiting	2 (0.8)	9 (3.8)	2 (0.7)	9 (0.6)
Nausea	1 (0.4)	8 (3.3)	1 (0.3)	3 (0.2)
Ascites	0	0	0	18 (1.2)
Metabolism and nutrition disorders	27 (10.6)	31 (12.9)	33 (10.7)	129 (8.4)
Hyponatraemia	14 (5.5)	10 (4.2)	16 (5.2)	39 (2.5)
Hypoglycaemia	3 (1.2)	0	3 (1.0)	8 (0.5)
Hypophosphataemia	3 (1.2)	0	3 (1.0)	5 (0.3)
Decreased appetite	2 (0.8)	10 (4.2)	3 (1.0)	15 (1.0)
Hypokalaemia	2 (0.8)	6 (2.5)	3 (1.0)	23 (1.5)

Hypercalcaemia	2 (0.8)	1 (0.4)	3 (1.0)	14 (0.9)
Hyperglycaemia	0	1 (0.4)	0	16 (1.0)
Investigations	25 (9.8)	90 (37.5)	26 (8.5)	174 (11.3)
Lymphocyte count decreased	6 (2.4)	18 (7.5)	6 (2.0)	16 (1.0)
Aspartate aminotransferase increased	3 (1.2)	1 (0.4)	3 (1.0)	40 (2.6)
Gamma-glutamyltransferase increased	3 (1.2)	3 (1.3)	3 (1.0)	32 (2.1)
Weight decreased	3 (1.2)	0	3 (1.0)	10 (0.7)
Alanine aminotransferase increased	2 (0.8)	4 (1.7)	2 (0.7)	22 (1.4)
Blood alkaline phosphatase increased	2 (0.8)	0	2 (0.7)	17 (1.1)
Blood bilirubin increased	2 (0.8)	1 (0.4)	2 (0.7)	21 (1.4)
White blood cell count decreased	1 (0.4)	48 (20.0)	1 (0.3)	8 (0.5)
Neutrophil count decreased	0	63 (26.3)	0	11 (0.7)
Respiratory, thoracic and mediastinal disorders	25 (9.8)	18 (7.5)	30 (9.8)	105 (6.8)
Dyspnoea	6 (2.4)	3 (1.3)	7 (2.3)	19 (1.2)
Pneumonitis	4 (1.6)	2 (0.8)	5 (1.6)	16 (1.0)
Pulmonary embolism	4 (1.6)	1 (0.4)	4 (1.3)	11 (0.7)
Pleural effusion	3 (1.2)	2 (0.8)	3 (1.0)	8 (0.5)
Pneumonia aspiration	3 (1.2)	2 (0.8)	4 (1.3)	3 (0.2)
Acquired tracheo-oesophageal fistula	2 (0.8)	4 (1.7)	2 (0.7)	2 (0.1)
Infections and infestations	20 (7.8)	31 (12.9)	28 (9.1)	125 (8.1)
Pneumonia	12 (4.7)	17 (7.1)	18 (5.9)	72 (4.7)
Sepsis	2 (0.8)	1 (0.4)	3 (1.0)	5 (0.3)
Septic shock	1 (0.4)	4 (1.7)	1 (0.3)	2 (0.1)
Blood and lymphatic system disorders	18 (7.1)	56 (23.3)	23 (7.5)	96 (6.3)
Anaemia	15 (5.9)	26 (10.8)	19 (6.2)	75 (4.9)
Neutropenia	1 (0.4)	16 (6.7)	1 (0.3)	8 (0.5)
Febrile neutropenia	0	11 (4.6)	0	0
Leukopenia	0	17 (7.1)	0	3 (0.2)
General disorders and administration site conditions	15 (5.9)	25 (10.4)	18 (5.9)	76 (5.0)
General physical health deterioration	3 (1.2)	5 (2.1)	3 (1.0)	11 (0.7)
Multiple organ dysfunction syndrome	3 (1.2)	1 (0.4)	3 (1.0)	8 (0.5)
Asthenia	2 (0.8)	5 (2.1)	2 (0.7)	13 (0.8)
Death	2 (0.8)	4 (1.7)	3 (1.0)	15 (1.0)
Fatigue	2 (0.8)	6 (2.5)	3 (1.0)	10 (0.7)
Malaise	2 (0.8)	4 (1.7)	3 (1.0)	8 (0.5)
Vascular disorders	9 (3.5)	0	9 (2.9)	40 (2.6)
Hypertension	5 (2.0)	0	5 (1.6)	28 (1.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	8 (3.1)	5 (2.1)	10 (3.3)	25 (1.6)
Tumour pain	3 (1.2)	1 (0.4)	3 (1.0)	7 (0.5)
Nervous system disorders	6 (2.4)	9 (3.8)	8 (2.6)	39 (2.5)
Syncope	3 (1.2)	2 (0.8)	3 (1.0)	6 (0.4)

Adverse drug 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 include 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 are 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 Quantative Safety groups.

- Numerical screening rule to identify other non-pre-qualified ADR candidates

Other ADR candidates are 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 randomized 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.

Frequency of ADRs

ADRs identified with tislelizumab in the monotherapy pool are shown in the following table.

***Table 25*- Frequency of ADRs by SOC and PT (SAS)**

	Tislelizumab 200 mg Q3W – All Indications N = 1534		
Adverse drug reaction	**Any grade n (%)**	**Grade 3-4 n (%)**	**Frequency category (All grades)**
Infections and infestations			
Pneumonia [1]	148 (9.6)	64 (4.2)	Common
Blood and lymphatic system disorders			
Anaemia [2]	448 (29.2)	77 (5.0)	Very common
Thrombocytopaenia [3]	136 (8.9)	16 (1.0)	Common
Neutropaenia [4]	85 (5.5)	19 (1.2)	Common
Lymphopaenia [5]	69 (4.5)	17 (1.1)	Common
Endocrine disorders			
Hypothyroidism [6]	204 (13.3)	1 (0.07)	Very common
Hyperthyroidism [7]	85 (5.5)	0	Common
Thyroiditis [8]	17 (1.1)	0	Common
Adrenal insufficiency [9]	7 (0.5)	3 (0.2)	Uncommon
Hypophysitis [10]	1 (0.07)	0	Rare
Metabolism and nutrition disorders			
Hyperglycaemia [11]	143 (9.3)	23 (1.5)	Common
Hyponatraemia [12]	140 (9.1)	42 (2.7)	Common
Hypokalaemia [13]	113 (7.4)	23 (1.5)	Common
Diabetes mellitus [14]	11 (0.7)	5 (0.3)	Uncommon
Nervous system disorders			
Guillain-Barré syndrome	-	-	Uncommon **
Eye disorders			
Uveitis [15]	4 (0.3)	0	Uncommon
Cardiac disorders			
Myocarditis [16]	12 (0.8)	4 (0.3)	Uncommon
Pericarditis	1 (0.07)	0	Rare
Vascular disorders			
Hypertension [17]	73 (4.8)	29 (1.9)	Common
Respiratory, thoracic and mediastinal disorders			
Cough	237 (15.4)	5 (0.3)	Very common
Dyspnoea	113 (7.4)	18 (1.2)	Common
Pneumonitis [18]	80 (5.2)	31 (2.0)	Common
Gastrointestinal disorders			
Nausea	151 (9.8)	3 (0.2)	Common
Diarrhoea [19]	137 (8.9)	12 (0.8)	Common
Stomatitis [20]	46 (3.0)	5 (0.3)	Common
Pancreatitis [21]	15 (1.0)	8 (0.5)	Uncommon
Colitis [22]	5 (0.3)	0	Uncommon
Hepatobiliary disorders			
Hepatitis [23]	40 (2.6)	18 (1.2)	Common
Skin and subcutaneous tissue disorders			
Rash [24]	221 (14.4)	15 (1.0)	Very common
Pruritus	154 (10.0)	0	Very common
Severe skin reaction [25]	1 (0.07)	0	Rare
Musculoskeletal and connective tissue disorders			
Arthralgia	132 (8.6)	4 (0.3)	Common

	Tislelizumab 200 mg Q3W – All Indications		
	N = 1534		
	Any grade	Grade 3-4	Frequency category
Adverse drug reaction	**n (%)**	**n (%)**	**(All grades)**
Myalgia	24 (1.6)	0	Common
Myositis [26]	14 (0.9)	4 (0.3)	Uncommon
Arthritis [27]	6 (0.4)	0	Uncommon
Renal and urinary disorders			
Nephritis [28]	3 (0.2)	1 (0.07)	Uncommon
General disorders and administration site conditions			
Fatigue [29]	352 (22.9)	30 (2.0)	Very common
Decreased appetite	221 (14.4)	14 (0.9)	Very common
Investigations			
Aspartate aminotransferase increased	320 (20.9)	40 (2.6)	Very common
Alanine aminotransferase increased	295 (19.2)	22 (1.4)	Very common
Blood bilirubin increased [30]	183 (11.9)	30 (2.0)	Very common
Blood alkaline phosphatase increased	111 (7.2)	17 (1.1)	Common
Blood creatinine increased	79 (5.1)	2 (0.1)	Common
Injury, poisoning and procedural complications			
Infusion-related reaction [31]	3 (0.2)	1 (0.07)	Uncommon

Source: Table EU_D180_ADR_Table_4-1_mono

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 4.03 for all studies except for Studies 304 and 307 (version 5.0), 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 (≥ 1/1000 to < 1/100); rare (≥ 1/10000 to < 1/1000); very rare (< 1/10000).

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.

[1] Pneumonia includes PTs of pneumonia, lower respiratory tract infection, lower respiratory tract infection bacterial, pneumonia bacterial, pneumonia fungal, and pneumocystis jirovecii pneumonia.

[2] Anaemia includes PTs of anaemia and haemoglobin decreased.

[3] Thrombocytopaenia includes PTs of platelet count decreased and thrombocytopaenia.

[4] Neutropaenia includes PTs of neutrophil count decreased and neutropaenia.

[5] Lymphopaenia includes PTs of lymphocyte count decreased, lymphopaenia, and lymphocyte percentage decreased.

[6] Hypothyroidism includes PTs of hypothyroidism, thyroxine free decreased, tri-iodothyronine free decreased, tri-iodothyronine decreased, primary hypothyroidism, and thyroxine decreased.

[7] Hyperthyroidism includes PTs of hyperthyroidism, blood thyroid stimulating hormone decreased, tri iodothyronine free increased, thyroxine free increased, thyroxine increased, and tri iodothyronine increased.

[8] Thyroiditis includes PTs of thyroiditis, autoimmune thyroiditis and thyroiditis subacute.

[9] Adrenal insufficiency includes PTs of adrenal insufficiency and secondary adrenocortical insufficiency.

[10] Hypophysitis includes PTs of hypopituitarism.

[11] Hyperglycaemia includes PTs of hyperglycaemia and blood glucose increased.

[12] Hyponatraemia includes PTs of hyponatraemia and blood sodium decreased.

[13] Hypokalaemia includes PTs of hypokalaemia and blood potassium decreased.

[14] Diabetes mellitus includes PTs of diabetes mellitus, type 1 diabetes mellitus, and latent autoimmune diabetes in adults.

[15] Uveitis includes PTs of uveitis and iritis.

[16] Myocarditis includes PTs of myocarditis, immune-mediated myocarditis, and autoimmune myocarditis.

[17] Hypertension includes PTs of hypertension, blood pressure increased, and essential hypertension.

	Tislelizumab 200 mg Q3W – All Indications		
	N = 1534		
	Any grade	Grade 3-4	Frequency category
Adverse drug reaction	**n (%)**	**n (%)**	**(All grades)**

[18] Pneumonitis includes PTs of pneumonitis, immune-mediated lung disease, interstitial lung disease, and organising pneumonia.

[19] Diarrhoea includes PTs of diarrhoea and frequent bowel movements.

[20] Stomatitis includes PTs of stomatitis, mouth ulceration, and aphthous ulcer.

[21] Pancreatitis includes PTs of amylase increased, lipase increased, pancreatitis, and pancreatitis acute.

[22] Colitis includes PTs of colitis and immune-mediated enterocolitis.

[23] Hepatitis includes PTs of hepatitis, hepatitis function abnormal, immune-mediated hepatitis, and liver injury and autoimmune hepatitis.

[24] Rash includes PTs of rash, rash maculo-papular, eczema, rash erythematous, dermatitis, dermatitis allergic, rash papular, urticaria, erythema, skin exfoliation, drug eruption, rash macular, psoriasis, rash pustular, dermatitis acneiform, rash pruritic, lichenoid keratosis, hand dermatitis, immune-mediated dermatitis, rash follicular, acute febrile neutrophilic dermatosis, erythema nodosum, and pemphigoid.

[25] Severe skin reaction includes erythema multiforme.

[26] Myositis includes PTs of myositis and immune-mediated myositis.

[27] Arthritis includes PTs of arthritis and immune-mediated arthritis.

[28] Nephritis includes PTs of nephritis, focal segmental glomerulosclerosis, and immune-mediated nephritis.

[29] Fatigue includes PTs of fatigue, asthenia, malaise, and lethargy.

[30] Blood bilirubin increased includes PTs of blood bilirubin increased, bilirubin conjugated increased, blood bilirubin unconjugated increased, and hyperbilirubinaemia.

[31] Infusion-related reaction includes PTs of IRR and infusion-related hypersensitivity reaction.

** Frequency based on studies outside the monotherapy pool.

2.6.8.2. Serious adverse events, deaths, and other significant events

SAEs, all-cause

Table 26 -Serious TEAE by PT (≥ 1% for tislelizumab) in Study 302

Preferred Term	Tislelizumab (N = 255) n (%)	ICC (N = 240) n (%)
Patients with at least one Serious TEAE	**105 (41.2)**	**105 (43.8)**
Pneumonia	18 (7.1)	17 (7.1)
Dysphagia	12 (4.7)	4 (1.7)
Oesophageal obstruction	5 (2.0)	1 (0.4)
Pneumonitis	5 (2.0)	2 (0.8)
Hyponatraemia	4 (1.6)	0 (0.0)
Upper gastrointestinal haemorrhage	4 (1.6)	4 (1.7)
Dyspnoea	3 (1.2)	1 (0.4)
General physical health deterioration	3 (1.2)	4 (1.7)
Immune-mediated pneumonitis	3 (1.2)	0 (0.0)
Multiple organ dysfunction syndrome	3 (1.2)	1 (0.4)
Oesophageal stenosis	3 (1.2)	0 (0.0)
Pleural effusion	3 (1.2)	4 (1.7)
Pneumonia aspiration	3 (1.2)	1 (0.4)

Source SCS Table 2-7 (excerpt)

Table 27- Serious TEAE by SOC and PT (≥ 1%) in all populations

	Study 302			
	Tislelizumab	**ICC**	**Tislelizumab – all patients with ESCC**	**Tislelizumab 200 mg Q3W – All Indications**
System organ class	**N = 255**	**N = 240**	**N = 307**	**N = 1534**
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Patients with at least one serious TEAE	**106 (41.6)**	**105 (43.8)**	**128 (41.7)**	**516 (33.6)**
Gastrointestinal disorders	36 (14.1)	30 (12.5)	40 (13.0)	95 (6.2)
Dysphagia	12 (4.7)	4 (1.7)	13 (4.2)	16 (1.0)
Oesophageal obstruction	5 (2.0)	1 (0.4)	6 (2.0)	5 (0.3)
Upper gastrointestinal haemorrhage	4 (1.6)	4 (1.7)	6 (2.0)	13 (0.8)
Oesophageal stenosis	3 (1.2)	0	3 (1.0)	3 (0.2)
Vomiting	2 (0.8)	3 (1.3)	2 (0.7)	8 (0.5)
Diarrhoea	0	8 (3.3)	0	5 (0.3)
Nausea	0	4 (1.7)	0	4 (0.3)
Respiratory, thoracic and mediastinal disorders	29 (11.4)	19 (7.9)	32 (10.4)	128 (8.3)
Pneumonitis	5 (2.0)	2 (0.8)	6 (2.0)	24 (1.6)
Dyspnoea	3 (1.2)	1 (0.4)	3 (1.0)	16 (1.0)
Immune-mediated pneumonitis	3 (1.2)	0	3 (1.0)	12 (0.8)
Pleural effusion	3 (1.2)	4 (1.7)	3 (1.0)	13 (0.8)
Pneumonia aspiration	3 (1.2)	1 (0.4)	3 (1.0)	3 (0.2)
Acquired tracheo-oesophageal fistula	1 (0.4)	4 (1.7)	1 (0.3)	1 (0.1)
Infections and infestations	25 (9.8)	31 (12.9)	34 (11.1)	112 (7.3)
Pneumonia	18 (7.1)	17 (7.1)	24 (7.8)	75 (4.9)
Sepsis	2 (0.8)	1 (0.4)	3 (1.0)	5 (0.3)
Septic shock	1 (0.4)	4 (1.7)	1 (0.3)	2 (0.1)
General disorders and administration site conditions	13 (5.1)	14 (5.8)	15 (4.9)	64 (4.2)
General physical health deterioration	3 (1.2)	4 (1.7)	3 (1.0)	10 (0.7)
Multiple organ dysfunction syndrome	3 (1.2)	1 (0.4)	3 (1.0)	8 (0.5)
Death	2 (0.8)	4 (1.7)	3 (1.0)	15 (1.0)
Pyrexia	2 (0.8)	2 (0.8)	3 (1.0)	15 (1.0)
Metabolism and nutrition disorders	10 (3.9)	6 (2.5)	13 (4.2)	44 (2.9)
Hyponatraemia	4 (1.6)	0	4 (1.3)	5 (0.3)
Hypercalcaemia	2 (0.8)	0	3 (1.0)	6 (0.4)
Decreased appetite	1 (0.4)	6 (2.5)	2 (0.7)	10 (0.7)
Blood and lymphatic system disorders	1 (0.4)	19 (7.9)	2 (0.7)	11 (0.7)
Anaemia	1 (0.4)	3 (1.3)	1 (0.3)	4 (0.3)
Febrile neutropenia	0	8 (3.3)	0	0
Leukopenia	0	4 (1.7)	0	0
Investigations	1 (0.4)	13 (5.4)	2 (0.7)	20 (1.3)
Neutrophil count decreased	0	10 (4.2)	0	0
White blood cell count decreased	0	8 (3.3)	0	0

Treatment-related SAEs

Table 28-Treatment-Related SAEs by SOC and PT (≥ 1%) All Populations

	Study 302			
	Tislelizumab	ICC	Tislelizumab – all patients with ESCC	Tislelizumab 200 mg Q3W – All Indications
System organ class	**N = 255**	**N = 240**	**N = 307**	**N = 1534**
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Patients with at least one treatment-related serious TEAE	**37 (14.5)**	**47 (19.6)**	**40 (13.0)**	**175 (11.4)**
Respiratory, thoracic and mediastinal disorders	12 (4.7)	2 (0.8)	14 (4.6)	61 (4.0)
Pneumonitis	5 (2.0)	1 (0.4)	6 (2.0)	23 (1.5)
Immune-mediated pneumonitis	3 (1.2)	0	3 (1.0)	12 (0.8)
Infections and infestations	8 (3.1)	11 (4.6)	8 (2.6)	18 (1.2)
Pneumonia	7 (2.7)	5 (2.1)	7 (2.3)	16 (1.0)
Septic shock	0	4 (1.7)	0	0
Gastrointestinal disorders	5 (2.0)	20 (8.3)	5 (1.6)	21 (1.4)
Vomiting	1 (0.4)	3 (1.3)	1 (0.3)	4 (0.3)
Diarrhoea	0	8 (3.3)	0	5 (0.3)
Nausea	0	4 (1.7)	0	3 (0.2)
Metabolism and nutrition disorders	5 (2.0)	3 (1.3)	6 (2.0)	15 (1.0)
Decreased appetite	0	3 (1.3)	0	2 (0.1)
Blood and lymphatic system disorders	1 (0.4)	16 (6.7)	1 (0.3)	6 (0.4)
Febrile neutropenia	0	8 (3.3)	0	0
Leukopenia	0	4 (1.7)	0	0
Investigations	1 (0.4)	13 (5.4)	1 (0.3)	13 (0.8)
Neutrophil count decreased	0	10 (4.2)	0	0
White blood cell count decreased	0	8 (3.3)	0	0

Source SCS appendix 1, Table 2.7.4.2.1.4.2 excerpts

Deaths

Table 29-TEAE leading to death and Treatment-related TEAE leading to death; Study 302

	Study 302			
System Organ Class Preferred Term	**Tislelizumab (N = 255) n (%)**	**ICC (N = 240) n (%)**	**Tislelizumab (N = 255) n (%)**	**ICC (N = 240) n (%)**
	Patients with at least one TEAE Leading to Death		Patients with at least one **Treatment-related** TEAE Leading to Death	
	35 (13.7)	**28 (11.7)**	**7 (2.7)**	**8 (3.3)**
Respiratory, thoracic and mediastinal disorders	**10 (3.9)**	**3 (1.3)**	2 (0.8)	0 (0.0)
Acute respiratory failure	1 (0.4)	0 (0.0)		
Bronchiectasis	1 (0.4)	0 (0.0)		
Dyspnoea	1 (0.4)	0 (0.0)		
Haemoptysis	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)
Lung disorder	1 (0.4)	0 (0.0)		
Oesophagobronchial fistula	1 (0.4)	0 (0.0)		
Pulmonary arterial hypertension	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)
Pulmonary embolism	1 (0.4)	0 (0.0)		

Pulmonary haemorrhage	1 (0.4)	0 (0.0)		
Respiratory failure	1 (0.4)	1 (0.4)		
Acquired tracheo-oesophageal fistula	0 (0.0)	1 (0.4)		
Pneumothorax	0 (0.0)	1 (0.4)		
General disorders and administration site conditions	9 (3.5)	10 (4.2)	1 (0.4)	3 (1.3)
General physical health deterioration	3 (1.2)	4 (1.7)	0 (0.0)	1 (0.4)
Multiple organ dysfunction syndrome	3 (1.2)	1 (0.4)	1 (0.4)	1 (0.4)
Death	2 (0.8)	4 (1.7)	0 (0.0)	1 (0.4)
Sudden death	1 (0.4)	1 (0.4)		
Infections and infestations	6 (2.4)	8 (3.3)	1 (0.4)	4 (1.7)
Pneumonia	4 (1.6)	3 (1.3)	1 (0.4)	1 (0.4)
Bronchitis	1 (0.4)	0 (0.0)		
Sepsis	1 (0.4)	1 (0.4)		
COVID-19	0 (0.0)	1 (0.4)		
Septic shock	0 (0.0)	3 (1.3)	0 (0.0)	3 (1.3)
Gastrointestinal disorders	4 (1.6)	3 (1.3)	2 (0.8)	0 (0.0)
Upper gastrointestinal haemorrhage	3 (1.2)	1 (0.4)	1 (0.4)	0 (0.0)
Oesophageal obstruction	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)
Intestinal ischaemia	0 (0.0)	1 (0.4)		
Oesophageal fistula	0 (0.0)	1 (0.4)		
Neoplasms benign, malignant and unspecified	2 (0.8)	1 (0.4)		
Metastases to liver	1 (0.4)	0 (0.0)		
Tumour fistulisation	1 (0.4)	0 (0.0)		
Tumour haemorrhage	0 (0.0)	1 (0.4)		
Cardiac disorders	1 (0.4)	1 (0.4)		
Cardio-respiratory arrest	1 (0.4)	0 (0.0)		
Cardiac arrest	0 (0.0)	1 (0.4)		
Investigations	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)
Platelet count decreased	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)
Metabolism and nutrition disorders	1 (0.4)	0 (0.0)		
Decreased appetite	1 (0.4)	0 (0.0)		
Musculoskeletal and connective tissue disorders	1 (0.4)	0 (0.0)		
Muscular weakness	1 (0.4)	0 (0.0)		
Nervous system disorders	1 (0.4)	1 (0.4)		
Depressed level of consciousness	1 (0.4)	1 (0.4)		
Blood and lymphatic system disorders	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.4)
Febrile neutropenia	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.4)

Source SCS Appendix 1 Table 2.14 and 2.15 merged

Other significant events (imAEs, AESI)

Methodology to determine imAEs / AESI

- Methodology to determine immune-related AEs **(imAEs)** – **Study 302**

All reported immune-mediated treatment-emergent adverse events (imAEs) in Study 302 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 etiologies 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.

- Methodology to determine **imAEs** in **supportive studies**

The process for immune-mediated adverse event identification that was followed in Study 302 was different from the process followed for individual CSRs for supportive Studies 102, 001, 208, 204, and 203. This difference derives mainly from different guidelines being used for identification in Step 1. Grade 1 and 2 events, AE considered as unrelated by investigator and most events not treated with corticosteroids were excluded.

- Methodology to determine adverse events of special interest (**AESI**) – **Study 302**

The term 'adverse events of special interest' is used for both treatment arms to report 'potential' immune-mediated adverse event cases (corresponding to the above described Step 1). This is opposed to reported imAEs outputs which include only 'confirmed' (or 'adjudicated') immune-mediated adverse event cases that include the above described Step 2 and are reported only for the tislelizumab arm.

In addition, infusion-related reactions are reported as adverse events of special interest.

Immune-related AEs (imAEs) - Frequency

Table 30- Overall Summary of immune-mediated TEAE (Tislelizumab populations)

	Study 302		
	Tislelizumab	**Tislelizumab – all patients with ESCC**	**Tislelizumab 200 mg Q3W – All Indications**
	N = 255	**N = 307**	**N = 1534**
	n (%)	**n (%)**	**n (%)**
Patients with at least one im TEAE	**57 (22.4)**	**61 (19.9)**	**276 (18.0)**
Grade ≥ 3 immune-mediated TEAE	**12 (4.7)**	**13 (4.2)**	**81 (5.3)**

Serious immune-mediated TEAE	**17 (6.7)**	**18 (5.9)**	**90 (5.9)**
Im TEAE leading to treatment modification	**19 (7.5)**	**21 (6.8)**	**89 (5.8)**
Im TEAE leading to treatment discontinuation	**9 (3.5)**	**9 (2.9)**	**53 (3.5)**
Im TEAE leading to death	**1 (0.4)**	**1 (0.3)**	**6 (0.4)**

Table 31-Immune-Mediated TEAE by Category (Tislelizumab populations)

	Study 302 Tislelizumab	**Tislelizumab – all patients with ESCC**	**Tislelizumab 200 mg Q3W – All Indications**
Category	**N = 255**	**N = 307**	**N = 1534**
Preferred term	**n (%)**	**n (%)**	**n (%)**
Patients with at least one immune-mediated TEAE	**57 (22.4)**	**61 (19.9)**	**276 (18.0)**
Immune-mediated hypothyroidism	23 (9.0)	24 (7.8)	116 (7.6)
Immune-mediated pneumonitis	18 (7.1)	19 (6.2)	66 (4.3)
Immune-mediated skin adverse reaction	5 (2.0)	5 (1.6)	27 (1.8)
Immune-mediated colitis	3 (1.2)	4 (1.3)	11 (0.7)
Immune-mediated hepatitis	3 (1.2)	4 (1.3)	26 (1.7)
Immune-mediated myositis/rhabdomyolysis	3 (1.2)	3 (1.0)	14 (0.9)
Immune-mediated type 1 diabetes mellitus	3 (1.2)	3 (1.0)	6 (0.4)
Immune-mediated adrenal insufficiency	2 (0.8)	2 (0.7)	4 (0.3)
Immune-mediated myocarditis	2 (0.8)	2 (0.7)	7 (0.5)
Immune-mediated pituitary dysfunction	1 (0.4)	1 (0.3)	1 (0.1)
Immune-mediated hyperthyroidism	0	0	5 (0.3)
Immune-mediated nephritis and renal dysfunction	0	0	10 (0.7)
Immune-mediated pancreatitis	0	0	1 (0.1)
Immune-mediated thyroiditis	0	0	12 (0.8)
Other immune-mediated reactions	0	0	4 (0.3)
Arthritis	0	0	2 (0.1)
Immune-mediated arthritis	0	0	1 (0.1)
Pericarditis	0	0	1 (0.1)

Table 32- Immune-Mediated TEAEs by Category** (severity and treatment) **(302 SAS)

	Study 302 Tislelizumab (N = 255)						
	n (%)						
Category	**Any grade**	**Grade ≥ 3**	**Leading to treatment discont-inuation**	**Resulted in death**	**Received systemic cortico-steroids[a]**	**Received immuno-suppressive drug[a]**	**Received hormone therapy[a]**
Patients with at least one Immune-mediated TEAE	**57 (22.4)**	**12 (4.7)**	**9 (3.5)**	**1 (0.4)**	**35 (61.4)**	**0**	**26 (45.6)**
Immune-mediated hypothyroidism	23 (9.0)	1 (0.4)	0	0	0	0	23 (100.0)

	Study 302 Tislelizumab (N = 255)						
	n (%)						
Category	Any grade	Grade ≥ 3	Leading to treatment discont-inuation	Resulted in death	Received systemic cortico-steroids[a]	Received immuno-suppressive drug[a]	Received hormone therapy[a]
Immune-mediated pneumonitis	18 (7.1)	4 (1.6)	5 (2.0)	1 (0.4)	18 (100.0)	0	0
Immune-mediated skin adverse reaction	5 (2.0)	0	0	0	5 (100.0)	0	0
Immune-mediated colitis	3 (1.2)	0	0	0	3 (100.0)	0	0
Immune-mediated hepatitis	3 (1.2)	2 (0.8)	0	0	3 (100.0)	0	0
Immune-mediated myositis/rhabdomyolysis	3 (1.2)	2 (0.8)	2 (0.8)	0	3 (100.0)	0	0
Immune-mediated type 1 diabetes mellitus	3 (1.2)	2 (0.8)	1 (0.4)	0	0	0	3 (100.0)
Immune-mediated adrenal insufficiency	2 (0.8)	0	0	0	2 (100.0)	0	0
Immune-mediated myocarditis	2 (0.8)	1 (0.4)	1 (0.4)	0	2 (100.0)	0	0
Immune-mediated pituitary dysfunction	1 (0.4)	0	0	0	1 (100.0)	0	0

[a] Percentages are based on the number of patients with at least one immune-mediated TEAE under any category for the first row and under each category for all other rows.

Table 33- Overview of time-to-onset of imTEAEs (Study 302, Safety Analysis Set)

imAE category	Number of events in category	< 3 months	3 to < 6 months	6 to < 9 months	9 to < 12 months	≥ 12 months
		Events (%)	Events (%)	Events (%)	Events (%)	Events (%)
Immune-mediated hypothyroidism	23	13 (56.5)	6 (26.1)	1 (4.3)	1 (4.3)	2 (8.7)
Immune-mediated pneumonitis	19	12 (63.2)	3 (15.8)	1 (5.3)	2 (10.5)	1 (5.3)
Immune-mediated skin adverse reaction	6	4 (66.7)	1 (16.7)	1 (16.7)	0	0
Immune-mediated hepatitis	5	3 (60.0)	2 (40.0)	0	0	0
Immune-mediated myositis/rhabdomyolysis	4	3 (75.0)	0	0	1 (25.0)	0
Immune-mediated colitis	3	2 (66.7)	0	1 (33.3)	0	0
Immune-mediated type 1 diabetes mellitus	3	2 (66.7)	0	0	0	1 (33.3)
Immune-mediated adrenal insufficiency	2	1 (50.0)	0	0	1 (50.0)	0
Immune-mediated myocarditis	2	2 (100.0)	0	0	0	0
Immune-mediated pituitary dysfunction	1	0	0	0	1 (100.0)	0

Source Response to List of Questions, Table 2-7

Table 34- Im TEAEs by outcome - Percentage of imAE events resolved and resolving by imAE category (Tislelizumab 200 mg Q3W – All Indications, SAS)

	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)

	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

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.

Although the majority of imAE were observed within the first three months, there is a relevant proportion of events occurring later (with onset of single events even beyond 1 year after the first dose of treatment). Overall, 36.8% of imAEs had resolved in Study 302 at the time of data cutoff. In the all Doses All Indications populations, for 45.7% of patients at least one imAE category resolved (i.e. concurrent imAEs of other imAE categories might be ongoing), and in 39.1% of patients all imAEs resolved.

Table 35- Immune-mediated pneumonitis by prior radiotherapy

	Study 302 Tislelizumab N = 255		Tislelizumab 200 mg Q3W – All Indications N = 1534		
	With prior radiotherapy	Without prior radiotherapy	With prior radiotherapy	Without prior radiotherapy	Missing
	N = 168	N = 87	N = 615	N = 861	N = 58
	n (%)	n (%)	n (%)	n (%)	n (%)
Any grade	14 (8.3)	4 (4.6)	39 (6.3)	24 (2.8)	3 (5.2)
Grade ≥ 3	4 (2.4)	0	17 (2.8)	11 (1.3)	3 (5.2)
Leading to treatment discontinuation	4 (2.4)	1 (1.1)	16 (2.6)	10 (1.2)	2 (3.4)
Resulted in death	1 (0.6)	0	2 (0.3)	1 (0.1)	0
Received systemic corticosteroids	14 (8.3)	4 (4.6)	39 (6.3)	24 (2.8)	3 (5.2)
Received immunosuppressive drug	0	0	1 (0.2)	0	0
Received hormone therapy	0	0	0	0	0

Prior radiotherapy is associated with an increased incidence of 'immune-mediated pneumonitis' in both Study 302 and the All Doses All Indications population. This information has been included in section 4.8 of the SmPC.

Adverse events of special interest (AESI) - Frequency

AESI were analysed post-hoc for the tislelizumab and ICC arms of Study 302:

***Table 36*-Treatment-Emergent AESI by Safety Topic excluding IRR and Grade* (302 SAS)**

	Tislelizumab N=255			ICC N=240		
	Any grade	Grade 3/4	Grade 5	Any grade	Grade 3/4	Grade 5
Safety topic	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Patients with at least one AESI	**65 (25.5)**	**13 (5.1)**	**4 (1.6)**	**13 (5.4)**	**4 (1.7)**	**3 (1.3)**
Immune-mediated hypothyroidism	23 (9.0)	1 (0.4)	0	0	0	0
Immune-mediated pneumonitis	22 (8.6)	3 (1.2)	4 (1.6)	8 (3.3)	3 (1.3)	3 (1.3)
Immune-mediated skin adverse reaction	7 (2.7)	0	0	3 (1.3)	0	0
Immune-mediated hepatitis	5 (2.0)	4 (1.6)	0	0	0	0
Immune-mediated type 1 diabetes mellitus	4 (1.6)	2 (0.8)	0	1 (0.4)	1 (0.4)	0
Immune-mediated colitis	3 (1.2)	0	0	0	0	0
Immune-mediated myositis/rhabdomyolysis	3 (1.2)	2 (0.8)	0	0	0	0
Immune-mediated adrenal insufficiency	2 (0.8)	0	0	0	0	0
Immune-mediated myocarditis	2 (0.8)	1 (0.4)	0	0	0	0
Immune-mediated pituitary dysfunction	1 (0.4)	0	0	0	0	0
Immune-mediated hyperthyroidism	0	0	0	2 (0.8)		

Source Response to List of Questions, Table 2-10

Infusion-related reactions (IRR)

Table 37- Overall summary of infusion-related reactions (IRR)

	Study 302			
	Tislelizumab	ICC	Tislelizumab – all patients with ESCC	Tislelizumab 200 mg Q3W – All Indications
	N = 255	N = 240	N = 307	N = 1534
Category	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Patients with at least one IRR	8 (3.1)	11 (4.6)	9 (2.9)	54 (3.5)
IRR with grade ≥ 3	0	0	0	4 (0.3)
IRR leading to dose modification	0	3 (1.3)	0	7 (0.5)
IRR leading to treatment discontinuation	0	0	0	2 (0.1)
Resolved IRR [a, b]	7 (87.5)	11 (100.0)	8 (88.9)	51 (94.4)
Treated with corticosteroids [b]	2 (25.0)	5 (45.5)	2 (22.2)	14 (25.9)

[a] A patient was considered as resolved if all the events were resolved.

[b] Denominator for % = number of patients with IRR.

2.6.8.3. Laboratory findings

Table 38-Worsening laboratory abnormalities from baseline (≥ 5%, all grades and grade ≥3)

	Study 302					
	Tislelizumab		ICC		Tislelizumab 200 mg Q3W – All Indications	
	N = 255		N = 240		N = 1534	
Laboratory category	**All grades**	**Grade 3-4**	**All grades**	**Grade 3-4**	**All grades**	**Grade 3-4**
Laboratory test (direction)	**n/m (%)**	**n/m (%)**	**n/m (%)**	**n/m (%)**	**n/m (%)**	**n/m (%)**
Patients with at least one shift from baseline	**216/236 (91.5)**	**65/236 (27.5)**	**204/213 (95.8)**	**114/213 (53.5)**	**1416/1495 (94.7)**	**411/1495 (27.5)**
Hematology						
Hemoglobin (low)	103/236 (43.6)	13/236 (5.5)	128/212 (60.4)	20/212 (9.4)	563/1494 (37.7)	66/1494 (4.4)
Lymphocytes (low)	92/231 (39.8)	25/231 (10.8)	125/211 (59.2)	59/211 (28.0)	577/1475 (39.1)	126/1475 (8.5)
Platelets (low)	26/236 (11.0)	3/236 (1.3)	24/212 (11.3)	2/212 (0.9)	202/1495 (13.5)	17/1495 (1.1)
Leukocytes (low)	23/236 (9.7)	2/236 (0.8)	139/212 (65.6)	66/212 (31.1)	216/1494 (14.5)	13/1494 (0.9)
Neutrophils (low)	11/231 (4.8)	2/231 (0.9)	117/211 (55.5)	64/211 (30.3)	163/1476 (11.0)	25/1476 (1.7)
Biochemistry						
Glucose (high)	105/236 (44.5)	6/236 (2.5)	81/209 (38.8)	3/209 (1.4)	642/1485 (43.2)	54/1485 (3.6)
Sodium (low)	76/235 (32.3)	21/235 (8.9)	73/209 (34.9)	16/209 (7.7)	494/1486 (33.2)	84/1486 (5.7)
Albumin (low)	75/236 (31.8)	2/236 (0.8)	77/209 (36.8)	2/209 (1.0)	465/1491 (31.2)	6/1491 (0.4)
Alkaline phosphatase (high)	71/236 (30.1)	6/236 (2.5)	31/209 (14.8)	1/209 (0.5)	437/1490 (29.3)	34/1490 (2.3)
AST (high)	62/236 (26.3)	2/236 (0.8)	25/210 (11.9)	1/210 (0.5)	471/1491 (31.6)	48/1491 (3.2)
ALT (high)	52/236 (22.0)	2/236 (0.8)	31/210 (14.8)	3/210 (1.4)	434/1491 (29.1)	30/1491 (2.0)
Potassium (low)	30/235 (12.8)	3/235 (1.3)	31/209 (14.8)	7/209 (3.3)	210/1486 (14.1)	33/1486 (2.2)
Creatine kinase (high)	26/205 (12.7)	3/205 (1.5)	3/136 (2.2)	0/136	165/894 (18.5)	18/894 (2.0)
Bilirubin (high)	26/231 (11.3)	4/231 (1.7)	15/205 (7.3)	1/205 (0.5)	280/1486 (18.8)	32/1486 (2.2)
Glucose (low)	23/236 (9.7)	1/236 (0.4)	20/209 (9.6)	1/209 (0.5)	129/1485 (8.7)	5/1485 (0.3)
Potassium (high)	21/235 (8.9)	3/235 (1.3)	10/209 (4.8)	2/209 (1.0)	143/1486 (9.6)	13/1486 (0.9)
Creatinine (high)	11/236 (4.7)	0/236	5/209 (2.4)	0/209	180/1491 (12.1)	13/1491 (0.9)
Sodium (high)	9/235 (3.8)	0/235	8/209 (3.8)	0/209	99/1486 (6.7)	1/1486 (0.1)

n is the number of patients with worsen toxicity grade compared with baseline. m is the number of patients with baseline assessment and at least one post-baseline assessment.
Laboratory data are reported up to 30 days after the last dose of study treatment.

2.6.8.4. In vitro biomarker test for patient selection for safety

Not applicable

2.6.8.5. Safety in special populations

Overall, no consistent, clinically meaningful differences could be observed by analyses of subgroups across age, gender, body weight, and mild/moderate renal or hepatic impairment; however, interpretation of safety data by gender and hepatic impairment is hampered by the small proportions of subgroups with females (15.3%) and patients with hepatic impairment (9%) (please see clinical AR for additional tables of TEAEs by subgroups).

TEAE by age

Table 39-Overview of controlled and non-controlled studies by age group (All Doses All Indications)

	Age category			
	< 65 years	**65 to < 75 years**	**75 to < 85 years**	**≥ 85 years**
	n (%)	**n (%)**	**n (%)**	**n (%)**
Controlled studies				
Study 302 (N=495)	306 (61.8)	162 (32.7)	27 (5.5)	0
Tislelizumab (N=255)	157 (61.6)	85 (33.3)	13 (5.1)	0
ICC (N=240)	149 (62.1)	77 (32.1)	14 (5.8)	0
Study 303 (N=792)	535 (67.6)	231 (29.2)	25 (3.2)	1 (0.1)
Tislelizumab (N=534)	364 (68.2)	155 (29.0)	14 (2.6)	1 (0.2)
Docetaxel (N=258)	171 (66.3)	76 (29.5)	11 (4.3)	0
Non-controlled studies				
Study_001 (N=451)	285 (63.2)	126 (27.9)	40 (8.9)	0
Study 102 (N=300)	223 (74.3)	72 (24.0)	5 (1.7)	0
Study 203 (N=70)	66 (94.3)	4 (5.7)	0	0
Study 204 (N=113)	69 (61.1)	38 (33.6)	6 (5.3)	0
Study 208 (N=249)	149 (59.8)	75 (30.1)	24 (9.6)	1 (0.4)

Source Response to D120 LoQ Table 2-23

Table 40- TEAE ≥ 5% by Age, SOC and PT (Study 302)

	Tislelizumab			
System Organ Class Preferred Term	**< 65 (N = 157) n (%)**	**≥ 65 - < 75 (N = 85) n (%)**	**≥ 75 (N = 13) n (%)**	**All (N = 255) n (%)**
Patients with at least one TEAE	**154 (98.1)**	**78 (91.8)**	**12 (92.3)**	**244 (95.7)**
Gastrointestinal disorders	93 (59.2)	48 (56.5)	8 (61.5)	149 (58.4)
Constipation	26 (16.6)	9 (10.6)	4 (30.8)	39 (15.3)
Nausea	24 (15.3)	9 (10.6)	3 (23.1)	36 (14.1)
Diarrhoea	14 (8.9)	14 (16.5)	4 (30.8)	32 (12.5)
Dysphagia	14 (8.9)	13 (15.3)	1 (7.7)	28 (11.0)
Vomiting	21 (13.4)	4 (4.7)	2 (15.4)	27 (10.6)
Abdominal pain	10 (6.4)	7 (8.2)	0 (0.0)	17 (6.7)
Gastrooesophageal reflux disease	8 (5.1)	5 (5.9)	1 (7.7)	14 (5.5)
Investigations	79 (50.3)	45 (52.9)	4 (30.8)	128 (50.2)
Weight decreased	37 (23.6)	20 (23.5)	2 (15.4)	59 (23.1)
Aspartate aminotransferase increased	29 (18.5)	8 (9.4)	0 (0.0)	37 (14.5)
Alanine aminotransferase increased	26 (16.6)	7 (8.2)	0 (0.0)	33 (12.9)
Blood alkaline phosphatase increased	14 (8.9)	3 (3.5)	0 (0.0)	17 (6.7)
Gamma-glutamyltransferase increased	10 (6.4)	4 (4.7)	0 (0.0)	14 (5.5)
Platelet count decreased	6 (3.8)	7 (8.2)	1 (7.7)	14 (5.5)
General disorders and administration site conditions	61 (38.9)	47 (55.3)	8 (61.5)	116 (45.5)
Pyrexia	20 (12.7)	17 (20.0)	4 (30.8)	41 (16.1)
Fatigue	17 (10.8)	13 (15.3)	3 (23.1)	33 (12.9)
Asthenia	14 (8.9)	10 (11.8)	2 (15.4)	26 (10.2)
Malaise	7 (4.5)	8 (9.4)	1 (7.7)	16 (6.3)
Metabolism and nutrition disorders	75 (47.8)	38 (44.7)	3 (23.1)	116 (45.5)
Decreased appetite	30 (19.1)	9 (10.6)	1 (7.7)	40 (15.7)
Hypoalbuminaemia	22 (14.0)	12 (14.1)	0 (0.0)	34 (13.3)
Hyponatraemia	22 (14.0)	10 (11.8)	0 (0.0)	32 (12.5)
Hypokalaemia	11 (7.0)	8 (9.4)	1 (7.7)	20 (7.8)

Hyperglycaemia	10 (6.4)	6 (7.1)	0 (0.0)	16 (6.3)
Hypoproteinaemia	10 (6.4)	3 (3.5)	0 (0.0)	13 (5.1)
Respiratory, thoracic and mediastinal disorders	64 (40.8)	35 (41.2)	5 (38.5)	104 (40.8)
Cough	28 (17.8)	13 (15.3)	2 (15.4)	43 (16.9)
Dyspnoea	11 (7.0)	11 (12.9)	2 (15.4)	24 (9.4)
Productive cough	12 (7.6)	5 (5.9)	1 (7.7)	18 (7.1)
Blood and lymphatic system disorders	61 (38.9)	29 (34.1)	2 (15.4)	92 (36.1)
Anaemia	50 (31.8)	26 (30.6)	2 (15.4)	78 (30.6)
Infections and infestations	49 (31.2)	22 (25.9)	4 (30.8)	75 (29.4)
Pneumonia	26 (16.6)	8 (9.4)	2 (15.4)	36 (14.1)
Musculoskeletal and connective tissue disorders	44 (28.0)	17 (20.0)	5 (38.5)	66 (25.9)
Back pain	20 (12.7)	5 (5.9)	1 (7.7)	26 (10.2)
Musculoskeletal pain	8 (5.1)	5 (5.9)	0 (0.0)	13 (5.1)
Skin and subcutaneous tissue disorders	35 (22.3)	21 (24.7)	3 (23.1)	59 (23.1)
Pruritus	14 (8.9)	7 (8.2)	2 (15.4)	23 (9.0)
Rash	14 (8.9)	6 (7.1)	1 (7.7)	21 (8.2)
Endocrine disorders	26 (16.6)	12 (14.1)	1 (7.7)	39 (15.3)
Hypothyroidism	20 (12.7)	9 (10.6)	0 (0.0)	29 (11.4)
Psychiatric disorders	16 (10.2)	8 (9.4)	2 (15.4)	26 (10.2)
Insomnia	13 (8.3)	6 (7.1)	1 (7.7)	20 (7.8)

Source SCS Table 5-1

Table 41-Safety in special populations (All Doses All Indications, Safety Analysis Set)

	Tislelizumab N=1972			
	< 65 years N=1313	**65 – 74 years N=555**	**75 – 84 years N=102**	**≥ 85 years N=2**
MedDRA terms	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Total AEs	1262 (96.1)	528 (95.1)	99 (97.1)	2 (100.0)
Grade ≥ 3 AEs	558 (42.5)	268 (48.3)	46 (45.1)	1 (50.0)
Serious AEs – total	432 (32.9)	212 (38.2)	37 (36.3)	1 (50.0)
Fatal	88 (6.7)	45 (8.1)	6 (5.9)	1 (50.0)
Hospitalization/prolong existing hospitalization	408 (31.1)	200 (36.0)	32 (31.4)	1 (50.0)
Life-threatening	32 (2.4)	17 (3.1)	1 (1.0)	0
Disability/incapacity	2 (0.2)	3 (0.5)	0	0
Other (medically significant)	18 (1.4)	15 (2.7)	3 (2.9)	1 (50.0)
AE leading to treatment discontinuation	136 (10.4)	78 (14.1)	15 (14.7)	0
Psychiatric disorders	106 (8.1)	57 (10.3)	8 (7.8)	0
Nervous system disorders	190 (14.5)	96 (17.3)	21 (20.6)	0
Accidents and injuries	0	0	0	0
Cardiac disorders	103 (7.8)	59 (10.6)	7 (6.9)	0
Vascular disorders	88 (6.7)	62 (11.2)	7 (6.9)	0
Cerebrovascular disorders	0	0	0	0
Infections and infestations	432 (32.9)	179 (32.3)	31 (30.4)	2 (100.0)
Anticholinergic syndrome	0	0	0	0
Quality of life decreased	0	0	0	0
Impaired quality of life	0	0	0	0
Quality of life decreased	0	0	0	0

	Tislelizumab N=1972			
	< 65 years N=1313	65 – 74 years N=555	75 – 84 years N=102	≥ 85 years N=2
MedDRA terms	**n (%)**	**n (%)**	**n (%)**	**n (%)**
CMQ sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	126 (9.6)	85 (15.3)	13 (12.7)	0
<other appearing more frequently in older patients>				
Eye disorders	101 (7.7)	57 (10.3)	13 (12.7)	1 (50.0)
General disorders and administration site conditions	555 (42.3)	248 (44.7)	49 (48.0)	0
Hepatobiliary disorders	69 (5.3)	39 (7.0)	12 (11.8)	1 (50.0)
Metabolism and nutrition disorders	515 (39.2)	260 (46.8)	33 (32.4)	1 (50.0)
Musculoskeletal and connective tissue disorders	385 (29.3)	159 (28.6)	35 (34.3)	0
Skin and subcutaneous disorders	312 (23.8)	165 (29.7)	44 (43.1)	1 (50.0)

TEAE by Race

Table 42- Subgroup Analysis: TEAE ≥5% by Race, SOC and PT (302 Safety Analysis Set)

	Tislelizumab			
System Organ Class	**Asian (N = 201)**	**White (N = 52)**	**Other (N = 2)**	**All (N = 255)**
Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Patients with at least one TEAE	192 (95.5)	50 (96.2)	2 (100.0)	244 (95.7)
Gastrointestinal disorders	108 (53.7)	39 (75.0)	2 (100.0)	149 (58.4)
Constipation	30 (14.9)	9 (17.3)	0 (0.0)	39 (15.3)
Nausea	25 (12.4)	11 (21.2)	0 (0.0)	36 (14.1)
Diarrhoea	16 (8.0)	15 (28.8)	1 (50.0)	32 (12.5)
Dysphagia	15 (7.5)	13 (25.0)	0 (0.0)	28 (11.0)
Vomiting	21 (10.4)	6 (11.5)	0 (0.0)	27 (10.6)
Abdominal pain	12 (6.0)	5 (9.6)	0 (0.0)	17 (6.7)
Gastrooesophageal reflux disease	13 (6.5)	1 (1.9)	0 (0.0)	14 (5.5)
Investigations	117 (58.2)	11 (21.2)	0 (0.0)	128 (50.2)
Weight decreased	56 (27.9)	3 (5.8)	0 (0.0)	59 (23.1)
Aspartate aminotransferase increased	34 (16.9)	3 (5.8)	0 (0.0)	37 (14.5)
Alanine aminotransferase increased	31 (15.4)	2 (3.8)	0 (0.0)	33 (12.9)
Blood alkaline phosphatase increased	16 (8.0)	1 (1.9)	0 (0.0)	17 (6.7)
Gamma-glutamyltransferase increased	14 (7.0)	0 (0.0)	0 (0.0)	14 (5.5)
Platelet count decreased	13 (6.5)	1 (1.9)	0 (0.0)	14 (5.5)
General disorders and administration site conditions	77 (38.3)	39 (75.0)	0 (0.0)	116 (45.5)
Pyrexia	30 (14.9)	11 (21.2)	0 (0.0)	41 (16.1)
Fatigue	19 (9.5)	14 (26.9)	0 (0.0)	33 (12.9)
Asthenia	10 (5.0)	16 (30.8)	0 (0.0)	26 (10.2)
Malaise	16 (8.0)	0 (0.0)	0 (0.0)	16 (6.3)
Metabolism and nutrition disorders	95 (47.3)	20 (38.5)	1 (50.0)	116 (45.5)
Decreased appetite	29 (14.4)	11 (21.2)	0 (0.0)	40 (15.7)
Hypoalbuminaemia	32 (15.9)	2 (3.8)	0 (0.0)	34 (13.3)
Hyponatraemia	30 (14.9)	1 (1.9)	1 (50.0)	32 (12.5)
Hypokalaemia	17 (8.5)	3 (5.8)	0 (0.0)	20 (7.8)

Hyperglycaemia	14 (7.0)	2 (3.8)	0 (0.0)	16 (6.3)
Hypoproteinaemia	13 (6.5)	0 (0.0)	0 (0.0)	13 (5.1)
Respiratory, thoracic and mediastinal disorders	79 (39.3)	24 (46.2)	1 (50.0)	104 (40.8)
Cough	36 (17.9)	7 (13.5)	0 (0.0)	43 (16.9)
Dyspnoea	18 (9.0)	6 (11.5)	0 (0.0)	24 (9.4)
Productive cough	16 (8.0)	2 (3.8)	0 (0.0)	18 (7.1)
Blood and lymphatic system disorders	75 (37.3)	16 (30.8)	1 (50.0)	92 (36.1)
Anaemia	62 (30.8)	15 (28.8)	1 (50.0)	78 (30.6)
Infections and infestations	59 (29.4)	15 (28.8)	1 (50.0)	75 (29.4)
Pneumonia	33 (16.4)	3 (5.8)	0 (0.0)	36 (14.1)
Musculoskeletal and connective tissue disorders	46 (22.9)	19 (36.5)	1 (50.0)	66 (25.9)
Back pain	17 (8.5)	8 (15.4)	1 (50.0)	26 (10.2)
Musculoskeletal pain	10 (5.0)	3 (5.8)	0 (0.0)	13 (5.1)
Skin and subcutaneous tissue disorders	45 (22.4)	14 (26.9)	0 (0.0)	59 (23.1)
Pruritus	21 (10.4)	2 (3.8)	0 (0.0)	23 (9.0)
Rash	18 (9.0)	3 (5.8)	0 (0.0)	21 (8.2)
Endocrine disorders	32 (15.9)	7 (13.5)	0 (0.0)	39 (15.3)
Hypothyroidism	24 (11.9)	5 (9.6)	0 (0.0)	29 (11.4)
Psychiatric disorders	18 (9.0)	8 (15.4)	0 (0.0)	26 (10.2)
Insomnia	14 (7.0)	6 (11.5)	0 (0.0)	20 (7.8)

Notes: N = Number of patients in each subgroup. Percentages are based on N, unless otherwise noted. The 'Other' category includes American Indian or Alaska Native, Black or African American, Native Hawaiian or Other Pacific Islander, and patients whose race was reported as 'Other' or 'Not Reported' or 'Unknown'.
Only preferred terms with an incidence ≥ 5% in the 'Tislelizumab/All' column are reported.
Source SCS Table 5-3

The majority of patients was Asian (about 80% in Study 302 and 70% in the All Doses All Indications Group). Numerically higher incidences of laboratory-related adverse events were reported in the Asian subgroup than in the White subgroup (incidence of investigations 58.2% for Asian vs. 21.1% for White in the tislelizumab arm of Study 302).

TEAE by region

More patients in Study 302 were enrolled in Asia compared with Europe/North America (78.8% versus 21.2%); The two subgroups by region, Asia and Europe/North America*, were almost identical to the two subgroups by race, Asian and white. The findings for adverse events by region were very similar with that by race (please see clinical AR for Tables). ** 1 patient enrolled in NA*

2.6.8.6. 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 3.3.1.2 for a detailed assessment of immunogenicity.

2.6.8.7. 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 metabolized 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.

2.6.8.8. Discontinuation due to adverse events

Table 43-TEAE Leading to Treatment Discontinuation (≥ 1%) by PT (Study 302 SAS)

Preferred Term	Tislelizumab (N = 255) n (%)	ICC (N = 240) n (%)
Patients with ≥ 1 AE Leading to Treatment Discontinuation	**49 (19.2)**	**64 (26.7)**
Pneumonia	5 (2.0)	4 (1.7)
Immune-mediated pneumonitis	3 (1.2)	0 (0.0)
Pneumonitis	3 (1.2)	2 (0.8)
Upper gastrointestinal haemorrhage	3 (1.2)	3 (1.3)
General physical health deterioration	2 (0.8)	3 (1.3)
Acquired tracheo-oesophageal fistula	1 (0.4)	3 (1.3)
Asthenia	1 (0.4)	4 (1.7)
Decreased appetite	1 (0.4)	3 (1.3)
Diarrhoea	1 (0.4)	5 (2.1)
Malaise	1 (0.4)	3 (1.3)
Febrile neutropenia	0 (0.0)	4 (1.7)
Pleural effusion	0 (0.0)	3 (1.3)
Septic shock	0 (0.0)	3 (1.3)

Source SCS Table 2-8

Table 44- Related AEs leading to Treatment Discontinuation by SOC and PT (≥ 1%)

System Organ Class Preferred Term	Tislelizumab (N = 255) n (%)	ICC (N = 240) n (%)
Patients With ≥ 1 Treatment-Related TEAE Leading to Treatment Discontinuation	**17 (6.7)**	**33 (13.8)**
Respiratory, thoracic and mediastinal disorders	8 (3.1)	2 (0.8)
Immune-mediated pneumonitis	3 (1.2)	0 (0.0)
Pneumonitis	3 (1.2)	2 (0.8)
Gastrointestinal disorders	2 (0.8)	8 (3.3)
Diarrhoea	1 (0.4)	5 (2.1)
Infections and infestations	2 (0.8)	4 (1.7)
Septic shock	0 (0.0)	3 (1.3)
General disorders and administration site conditions	1 (0.4)	5 (2.1)
Malaise	1 (0.4)	3 (1.3)
Blood and lymphatic system disorders	0 (0.0)	6 (2.5)
Febrile neutropenia	0 (0.0)	4 (1.7)

Source CSR Table 33

2.6.8.9. Post marketing experience

Tislelizumab is registered in China for the treatment of several cancers. The first marketing authorization 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.

2.6.9. Discussion on clinical safety

The **safety data** to support the MAA for tislelizumab monotherapy in locally advanced or metastatic esophageal squamous cell carcinoma (ESCC) are based on the randomized, controlled, open-label Study 302. The pivotal study evaluated tislelizumab versus investigator´s choice of chemotherapy (ICC: paclitaxel, docetaxel or irinotecan) in patients after 1 line of prior systemic therapy. Safety data are available from 255 patients in the tislelizumab arm and 240 patients in the ICC arm. 2L ESCC data are further complemented by 52 previously treated ESCC patients from two phase 1/2 studies (n=307 2L+ ESCC in total) and a pooled safety dataset from patients treated with tislelizumab monotherapy in different dosing regimens and across different indications (n=1972; including ESCC, NSCLC, HCC, UC und r/r cHL). Of these 1534 patients were treated with tislelizumab in the dose regimen of 200 mg Q3W, the 200 mg Q3W All Indications pool that form the basis for most of the presented safety analysis.

In principle, this amount of safety data can be considered adequate to describe the toxicity profile of tislelizumab. It is however noted that the pivotal Study 302 mainly recruited Asian patients (about 80%) and did not enrol patients with more than one prior line of systemic chemotherapy (whereas the proposed 2L+ ESCC indication refers to patients after prior chemotherapy without restricting the use of tislelizumab to 2L).
Median **exposure** to tislelizumab in Study 302 was longer than exposure to ICC (2.76 months vs. 1.49 months, respectively). A notably higher number of patients received treatment for less than 1 month in the ICC arm (24%) compared to 11% in the tislelizumab arm. Reasons for treatment discontinuation during the first month were disease progression/deterioration, AEs and withdrawal by subject, all higher in the ICC arm.

The safety of the medicinal product as monotherapy is based on pooled data in 1 534 patients across multiple tumour types who received 200 mg tislelizumab every 3 weeks. 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%). 1.17% 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.

Most common AEs in the tislelizumab monotherapy group of Study 302 (≥ 15%) were anemia (31%), weight decreased (23%), cough (17%), pyrexia (16%), decreased appetite (16%), and constipation (15%). Lower incidences (difference ≥ 10%) compared to the ICC arm were reported for decreased appetite, nausea, diarrhoea, alopecia and haematological toxicities.

The safety profile was overall **comparable between** the **tislelizumab monotherapy groups** (in Study 302, the 2L+ ESCC pool and the All Indications pools; differences reported in the All Indications population could be attributed to the different tumour types (e.g. lower rates for gastrointestinal disorders, but higher rates in renal and urinary disorders in the All Indications Population).

Grade ≥ 3 AEs were reported at lower incidences for tislelizumab than for ICC (46% vs 68%), mainly driven by lower rates of haematological toxicities. Dysphagia was the most common severe events in the tislelizumab arm (6.3%) and occurred at a higher rate than in the ICC arm (2.9%); similarly, other less frequent oesophageal PTs, such as oesophageal obstruction / stenosis and fistula were numerically higher in the tislelizumab arm than the ICC arm. However, as outlined in the responses to the LoQ, imbalances in baseline/disease characteristics might have impacted the frequencies of dysphagia and related esophageal PTs.

Serious adverse events were reported at similar incidences between both treatment arms (42% and 44%). Most common serious AEs for tislelizumab were pneumonia (7.1%), dysphagia (4.7%), oesophageal obstruction and pneumonitis (each 2.0%). Pneumonia occurred at the same frequency across both arms. Numerical higher incidences for tislelizumab compared to ICC were observed in the SOC of respiratory, thoracic and mediastinal disorders (11.4% vs 7.9% of patients) with differences driven by pneumonitis and immune-mediated pneumonitis (together 3.2% vs 0.8%), and dyspnoea and pneumonia aspiration (both 1.2% vs 0.4%); in addition, dysphagia (4.7% vs. 1.7%) and oesophageal obstruction / stenosis (together 3.2% vs. 0.4%) were observed at higher rates in the tislelizumab compared to the ICC arm. As expected for the ICC arm, higher incidences compared to the tislelizumab arm were mainly reported for serious haematological events.

In Study 302, AEs leading to treatment **discontinuation** were reported at a lower rate in the tislelizumab arm than in the ICC arm (19.2% vs 26.7%). The most frequent AEs in the tislelizumab arm were pneumonia (2.0%), pneumonitis, immune-mediated pneumonitis, and upper gastrointestinal haemorrhage (each 1.2%). Dose modifications occurred also less frequent in the tislelizumab arm (23%) than in the ICC arm (48%).

TEAE leading to death were reported for 13.7% of patients in the tislelizumab arm and for 11.7% in the ICC arm (including AEs related to disease progression); in about 6% of patients in both arms an adverse event was reported as primary cause of death. Grade 5 AEs in at least 2 patients in the tislelizumab arm were pneumonia, upper gastrointestinal haemorrhage, general physical health deterioration, multiple organ dysfunction and death. Only a low proportion of approximately 3% of AEs leading to death were considered related by the investigators in both treatment arms.

The incidences of **related AEs** are lower in the tislelizumab group of Study 302 compared to ICC across all categories (with the exception of related AEs leading to death that were reported with similar rates). Overall, tislelizumab related AEs in Study 302 reflected the AEs that were observed regardless of treatment relationship; however, there appeared to be a trend for investigators to consider AEs to be more frequently related to chemotherapy as opposed to tislelizumab. With the responses, the Applicant discussed that the 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.

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 same posology of tislelizumab, a pooled analysis across suitable studies is usually considered to provide the best estimate of frequency and thus, this approach can be considered acceptable.

The methodology to determine ADRs (as described in the dossier) and the final selection of ADRs cis considered acceptable.

In general, **laboratory** findings in Study 302 reflected the known safety profiles of each drug; haematological toxicities were reported more frequently for patients treated with chemotherapy, while increases in liver enzymes (AST, ALT, ALP), CK and creatinine were more common for tislelizumab treated patients.

Immune-related AEs

Incidences of imAE

22.4% of the patients in the tislelizumab group of Study 302 had an immune-mediated TEAE (18% in the pooled 200 mg Q3W dataset across indications). The most common imAEs (≥ 2%) in the tislelizumab arm of Study 302 were hypothyroidism (9%), pneumonitis (7.1%) and skin adverse

reactions (2%). For 6.7% of patients imAEs were serious. 4.7% of patients experienced Grade ≥ 3 imAEs (pneumonitis 1.6%, hepatitis and myositis/rhabdomyolysis each 0.8% and myocarditis and hypothyroidism each 0.4%). No imAE was fatal. ImAEs led to discontinuation of tislelizumab in 3.5%, in most patients ([20% of discontinuations]) due to pneumonitis; further reasons were myositis/rhabdomyolysis and myocarditis.

As per the Applicant´s definition, all patients with immune-mediated hypothyroidism were treated with hormone therapy. All other patients with imAEs were treated with corticosteroids, none received an immunosuppressant. Among the 54 patients who experienced immune-mediated adverse events in the tislelizumab arm of Study 302, the events had resolved in 21 patients (38.9%) at the data cutoff date; similarly, for 39.1% of patients in the All Indication pool all imAEs resolved.

Immune-related adverse reactions have been reported, including fatal cases, during treatment with tislelizumab (see section 4.8). 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.

For suspected immune-related adverse reactions, adequate evaluation to confirm aetiology or exclude alternative aetiologies, including infection, should be ensured. Based on the severity of the adverse reaction, tislelizumab should be withheld and corticosteroids administered (see section 4.2 of the SmPC). Based on limited data from clinical studies, administration of other systemic immunosuppressants can be considered in patients whose immune-related adverse reactions are not controlled with corticosteroid use (see sections 4.2 and 4.8 of the SmPC). Upon improvement to grade ≤1, corticosteroid taper should be initiated and continued over at least 1 month.

Immune-related pneumonitis, including fatal cases, has been reported in patients receiving tislelizumab. Patients should be monitored for signs and symptoms of pneumonitis. Patients with suspected pneumonitis should be evaluated with radiographic imaging and infectious or disease-related aetiologies should be ruled out.

Patients with immune-related pneumonitis should be managed according to the treatment modifications as recommended in Table 1-see section 4.2 of the SmPC.

Immune-related hepatitis, including fatal cases, has been reported in patients treated with tislelizumab. Patients should be monitored for signs and symptoms of hepatitis and changes in liver function. Liver function tests should be performed at baseline and periodically during treatment.

Patients with immune-related hepatitis should be managed according to the treatment modifications as recommended in Table 1 -see section 4.2 of the SmPC.

Immune-related skin rash or dermatitis have been reported in patients receiving tislelizumab. Patients should be monitored for suspected skin reactions and other causes should be excluded. Based on the severity of the skin adverse reactions, tislelizumab should be withheld or permanently discontinued as recommended in Table 1 -see section 4.2 of the SmPC.

Cases of severe cutaneous adverse reactions (SCARs) have been reported in patients receiving tislelizumab. Patients should be monitored for signs or symptoms of SCARs (e.g. a prodrome of fever, flu-like symptoms, mucosal lesions or progressive skin rash) and other causes should be excluded. For suspected SCARs (including severe erythema multiforme [EM], SJS or TEN), tislelizumab should be withheld and the patient should be referred to specialised care for assessment and treatment. If SCARs, including SJS or TEN, is confirmed, tislelizumab should be permanently discontinued (see section 4.2 of the SmPC).

Immune-related colitis, frequently associated with diarrhoea, has been reported in patients treated with tislelizumab. Patients should be monitored for signs and symptoms of colitis. Infectious and disease-related aetiologies should be ruled out.

Patients with immune-related colitis should be managed according to the treatment modifications as recommended in Table 1 -see section 4.2 of the SmPC.

Immune-related endocrinopathies, including thyroid disorders, adrenal insufficiency, hypophysitis and type 1 diabetes mellitus, have been reported in patients treated with tislelizumab. These may require supportive treatment depending on the specific endocrine disorder. Long-term hormone replacement therapy (HRT) may be necessary in cases of immune-related endocrinopathies.

Patients with immune-related endocrinopathies should be managed according to the treatment modifications as recommended in Table 1 -see section 4.2 of the SmPC.

Thyroid disorders, including thyroiditis, hypothyroidism and hyperthyroidism, have been reported in patients treated with tislelizumab. Patients should be monitored (at the start of treatment, periodically during treatment and as indicated based on clinical evaluation) for changes in thyroid function and clinical signs and symptoms of thyroid disorders. Hypothyroidism may be managed with HRT without treatment interruption and without corticosteroids. Hyperthyroidism may be managed symptomatically (see section 4.2 of the SmPC).

Adrenal insufficiency has been reported in patients treated with tislelizumab. Patients should be monitored for signs and symptoms of adrenal insufficiency. Monitoring of adrenal function and hormone levels should be considered. Corticosteroids and HRT should be administered as clinically indicated (see section 4.2 of the SmPC).

Hypophysitis has been reported in patients treated with tislelizumab. Patients should be monitored for signs and symptoms of hypophysitis/hypopituitarism. Monitoring of pituitary function and hormone levels should be considered. Corticosteroids and HRT should be administered as clinically indicated (see section 4.2 of the SmPC).

Type 1 diabetes mellitus, including diabetic ketoacidosis, has been reported in patients treated with tislelizumab. Patients should be monitored for hyperglycaemia and other signs and symptoms of diabetes. Insulin should be administered for type 1 diabetes. In patients with severe hyperglycaemia or ketoacidosis (grade ≥3), tislelizumab should be withheld and anti-hyperglycaemic treatment should be administered (see section 4.2 of the SmPC). Treatment with tislelizumab may be resumed when metabolic control is achieved

Immune-related nephritis with renal dysfunction has been reported in patients treated with tislelizumab. Patients should be monitored for changes in renal function (elevated serum creatinine), and other causes of renal dysfunction should be excluded.

Patients with immune-related nephritis with renal dysfunction should be managed according to the treatment modifications as recommended in Table 1 -see section 4.2 of the SmPC.

Other clinically important immune-related adverse reactions were reported with tislelizumab: myositis, myocarditis, arthritis, polymyalgia rheumatica, pericarditis and Guillain-Barré syndrome (see section 4.8 of the SmPC).

Patients with other immune-related adverse reactions should be managed according to the treatment modifications as recommended in Table 1 -see section 4.2 of the SmPC.

Solid organ transplant rejection has been reported in the post-marketing setting in patients treated with PD-1 inhibitors. Treatment with tislelizumab may increase the risk of rejection in solid organ

transplant recipients. The benefit of treatment with tislelizumab versus the risk of possible organ rejection should be considered in these patients.

Severe infusion-related reactions (grade 3 or higher) have been reported in patients receiving tislelizumab as a single agent (see section 4.8). Patients should be monitored for signs and symptoms of infusion-related reactions.

Infusion-related reactions should be managed as recommended in Table 1 -see section 4.2 of the SmPC.

Patients with any of the following conditions were excluded from clinical studies: baseline ECOG performance score greater than or equal to 2; active brain or leptomeningeal metastases; active autoimmune disease or history of autoimmune disease that may relapse; any condition requiring systemic treatment with either corticosteroids (>10 mg/day prednisone or equivalent) or other immunosuppressants within the 14 days prior to study treatment; active or untreated HIV; untreated hepatitis B or hepatitis C carriers; history of interstitial lung disease; administration of live vaccine within the 14 days prior to study treatment; infection requiring systemic therapy within the 14 days prior to study treatment; history of severe hypersensitivity to another monoclonal antibody. In the absence of data, tislelizumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

Methodology to determine imAEs

Above reported incidences of immune-mediated TEAEs were confirmed events based on a 2-step process. Potential imAEs were identified by a prespecified list of MedDRA PT but were only taken into further consideration and forwarded to medical review if the TEAEs were treated with systemic corticosteroids, other immunosuppressants or endocrine therapy. Potential imAEs underwent a medical review to assess possible alternate aetiology in a second step.

Deficiencies in the algorithm that were used to select potential imAEs were identified. Insulin was inadvertently not included as endocrine therapy in Step 1 and, as a result, cases of diabetes treated with insulin were not captured. Moreover, fatal (grade 5) events which were not treated were not captured. Finally, events treated more than 30 days after the start date were not captured in Step 1 nor were events where concomitant medication was administered prior to the event start date. The Applicant performed a targeted re-adjudication to correct the above identified gaps and provided updated results.

The methodology of the determination of imAEs itself remained unchanged despite the corrections. The Applicant plans to implement a revised single, global methodology for tislelizumab imAE identification that will be based on a fully automated algorithmic methodology. This would address many of the concerns raised during the assessment of the imAEs. Applying this approach, all grade imAE were identified in about 30% of patients in the tislelizumab monotherapy pool in contrary to 17% with the currently used methodology (the proportion of patients with serious imAEs remained similar).

Different approaches are currently used for the identification of imAEs across different ICIs with the consequence of partially relevant differences across imAE frequencies. Thus, an adaption of the methodology with the aim to identify imAEs more correctly (and ideally more consistently) is endorsed. It is however considered acceptable that the currently submitted imAE data are based on the original methodology, acknowledging that this approach has been also accepted for other ICIs approved in the EU.

Safety in special populations

Overall, no consistent, clinically meaningful differences could be observed by analyses of subgroups across age, gender, body weight, and mild/moderate renal or hepatic impairment; however, interpretation of safety data by gender and hepatic impairment is hampered by the small proportions of subgroups with females (15.3%) and patients with hepatic impairment (9%). Overall, it can be agreed that the safety profile of tislelizumab monotherapy does not appear to be significantly different between patients aged < 65 years and patients aged between 65 and 74 years. However the safety data for tislelizumab monotherapy in patients ≥ 75 years are limited (n=104 of 1972 patients in the All Doses All Indications monotherapy pool). This has been reflected in the SmPC.

Race and region: The majority of patients treated with tislelizumab monotherapy was Asian (about 80% in Study 302 and 70% in the All Doses All Indications Group). Higher incidences of laboratory-related adverse events were reported in the Asian subgroup than in the White subgroup (incidence of investigations 58.2% for Asian vs. 21.1% for White in the tislelizumab arm of Study 302). A similar trend was observed in patients treated with chemotherapy and in the pooled dataset across indications. The Applicant was asked to discuss possible reasons such as worse tolerability of Asian patients or a possible underreporting in the White subgroup. As outlined in the responses, 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 mainly in Asian patients derived results would not be applicable to European patients.

2.7. Conclusions on clinical safety

Safety data for tislelizumab for the treatment of patients with esophageal squamous cell carcinoma (ESCC) generally reflect the known toxicity profile of checkpoint inhibitors as monotherapy. No new safety issues have been identified.

2.8. Risk Management Plan

2.8.1. Safety concerns

Table 45-Part II SVIII.1: Summary of safety concerns

Important identified risks	• Immune-mediated adverse reactions
Important potential risks	• Reproductive and developmental toxicity
Missing information	• None

2.8.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.8.3. Risk minimisation measures

Table 46-Summary of pharmacovigilance activities and risk minimization activities by safety concerns

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important identified risk		
Immune-mediated adverse reactions	**Routine risk minimization 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 (ADRs) 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. Legal status: Restricted medical prescription **Additional risk minimization measures:** Patient Card	**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 minimization measures:** SmPC Section 4.6 where advice is provided regarding the need for women of child-bearing potential to avoid getting pregnant and for lactating women to avoid breastfeeding infants while taking tislelizumab and that, women of child-bearing 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. Legal status: Restricted medical prescription **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Missing Information		
None		

2.8.4. Conclusion

The CHMP considers that the risk management plan version 1.0 is acceptable.

2.9. Pharmacovigilance

2.9.1. 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.

2.9.2. Periodic Safety Update Reports submission requirements

The active substance is not included in the EURD list and a new entry will be required. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 26-Dec-1019. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.10. Product information

2.10.1. 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.*

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Tevimbra (tislelizumab) is included in the additional monitoring list as:

-it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU;

-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

3.1.1. Disease or condition

Approved indication: Tevimbra as monotherapy is indicated for the treatment of adult patients with unresectable, locally advanced or metastatic oesophageal squamous cell carcinoma after prior platinum-based chemotherapy.

*O*esophageal cancer (OC) is the eighth most common cancer and the sixth most common cause of cancer-related death worldwide, with an estimated 604,100 new cases and 544,076 deaths (5.5% of all cancer mortality) observed in 2020 (GLOBOCAN 2020, accessed 04 March 2021). ECs are divided in two major histological subtypes: oesophageal squamous cell carcinoma (OSCC) or oesophageal adenocarcinoma (OAC). Although ESCC accounts for ~90% of cases of oesophageal cancer worldwide

(Abnet et al. 2018), mortality rates associated with EAC are rising and have surpassed those of OSCC in several regions in the EU (Castro et al. Ann Oncol 2014). Oesophageal carcinoma is rare in young people, while the incidence peaks in the seventh and eighth decades of life. The main risk factors for OSCC in Western countries include tobacco and alcohol consumption.

Patients are often diagnosed late in the disease course and as such, most patients present with advanced or metastatic disease at the time of diagnosis. The 5-year survival for localized disease is 32.0% but drops to 24.0% for regional disease and 6.1% for patients with distant metastases. Patients diagnosed or treated once OSCC has progressed face a very poor prognosis (Abraham et al 2020) and patients with advanced and/or metastatic disease having failed initial therapy are solely treated with palliative intent.

3.1.2. Available therapies and unmet medical need

Platinum-based doublet chemotherapy (cisplatin/oxaliplatin/carboplatin plus fluoropyrimidines or taxanes) is usually offered as first-line palliative therapy aiming at an extension of survival (Lordick et al. 2016, Muro et al. 2019, NCCN 2020) of patients with good performance status. Unfit patients (ECOG PS > 1) are treated with best supportive care.

In the 2nd line disease setting, single-agent palliative chemotherapy (taxanes, irinotecan) was commonly used in medical practice for patients with PS scores 0 - 1 (NCCN 2017) in the past. Response rates were however low with less than 20% of patients responding to treatment and median OS ranging from 3 to 7 months. Recently, nivolumab was approved (October 2020) as monotherapy for the treatment of patients with unresectable advanced, recurrent or metastatic OSCC after prior fluoropyrimidine- and platinum-based combination chemotherapy.

3.1.3. Main clinical studies

The open-label study BGB-A317-302 randomly assigned 512 patients with advanced unresectable or metastatic OSCC who had previously received platinum-based chemotherapy in a 1:1 ratio to receive either tislelizumab or investigator's choice chemotherapy (paclitaxel, docetaxel, or irinotecan). All patients had received 1 prior standard of care chemotherapy regimens.

3.2. Favourable effects

The primary analysis of **OS in the ITT population** demonstrated a statistically significant benefit of tislelizumab over ICC control with an event rate of 77% and 83.2%, respectively (stratified HR = 0.7 [95% CI: 0.57 – 0.85], p = 0.0001, median OS 8.6 months for tislelizumab vs. 6.3 months for ICC).

OS in in PD-L1 positive analysis set vCPS ≥10% was analysed as key secondary endpoint and showed a statistically significant and more pronounced treatment effect of tislelizumab with a stratified HR of 0.49 (95% CI: 0.33 – 0.74; p = 0.0003) and a 4.9-month difference in median OS in favour of tislelizumab.

A subgroup analysis of OS in the Europe/North America subgroup favoured the tislelizumab over the ICC arm with a median overall survival of 11.2 months in the tislelizumab arm compared to 6.3 months in the ICC arm (HR = 0.55, 95% CI: 0.35 - 0.87).

3.3. Uncertainties and limitations about favourable effects

In the PD-L1 negative subgroup (PD-L1 score <10%), the magnitude of effect was lower compared to PD-L1 positive subgroup with a stratified HR for OS of 0.83 (95% CI: 0.62 to 1.12), and a median overall survival of 7.5 months (95% CI: 5.5 to 8.9 months) and 5.8 months (95% CI: 4.8 to 6.9 months) for the tislelizumab and ICC arms, respectively. This was reflected in section 5.1 of the SmPC.

3.4. Unfavourable effects

The incidences of treatment-related AEs (73.3% vs 93.8%), all cause and treatment-related Grade ≥ 3 AEs (46.3% vs 67.9% and 18.8% vs. 55.8%), treatment-related SAEs (14.5% vs 19.6%) and AEs leading to treatment discontinuations or dose modification (19.2% vs 26.7% and 22.7% vs 47.9%) were less frequent in the tislelizumab arm of Study 302 than in the investigator´s choice of chemotherapy (ICC) arm. Similar frequencies in both treatment arms were reported for all cause SAEs (41.6% vs 43.8%) and AEs leading to death (13.7% vs 11.7%).

Most common AEs in the tislelizumab group of Study 302 (≥ 15%) were anaemia (30.6%), weight decreased (23.1%), cough (16.9%), pyrexia (16.1%), decreased appetite (15.7%) and constipation (15.3%).

22.4% of patients in the tislelizumab arm of Study 302 had an immune-mediated TEAE. The most common imAEs (≥ 2%) in the tislelizumab arm were hypothyroidism (9%), pneumonitis (7.1%) and skin adverse reactions (2%). For 6.7% of patients imAEs were serious. 4.7% of patients experienced Grade ≥ 3 imAEs (pneumonitis 1.6%, hepatitis and myositis/rhabdomyolysis each 0.8% and myocarditis and hypothyroidism each 0.4%). No imAE was fatal. ImAEs led to discontinuation of tislelizumab in 3.5%. In the tislelizumab arm of Study 302, the events had resolved in 38.9% at the data cutoff date; similarly, for 39.1% of patients in the All Indication pool all imAEs resolved.

3.5. Uncertainties and limitations about unfavourable effects

No safety data are available for tislelizumab in patients with ECOG PS >1 and after more than 1 prior line of therapy in Study 302 (see section 5.1 of the SmPC).

There are only limited safety data in patients with ≥ 75 years (see section 4.8 of the SmPC).

3.6. Effects Table

Table 47: Effects Table for tislelizumab for the treatment of patients with locally advanced or metastatic ESCC after prior chemotherapy (data cut-off: 01-Dec-2020)

Effect	Short Description	Unit	Tislelizumab	ICC	Uncertainties/ Strength of evidence
Favourable Effects in ITT population					
OS, median	Time from randomization until death	months	8.6	6.3	
		HR, 95% CI	0.7 (0.57 - 0.85)		
PFS, median	Time from randomization	months	1.6	2.1	

Effect	Short Description	Unit	Tislelizumab	ICC	Uncertainties/ Strength of evidence
	until progression or death	HR, 95% CI	0.83 (0.67, 1.01)		
ORR	Confirmed CR or PR, as assessed by investigator per RECIST v1.1.	%	15.2	6.6	
		Difference, months	8.6		

Effect	Short Description	Unit	Tislelizumab	ICC	Uncertainties/ Strength of evidence
Unfavourable Effects					
Tolerability					
	All cause AE • *drug related*	%	96 *73*	98 *94*	Study 302 enrolled 80% of patients in Asia;
	Grade ≥3 AE • *drug related*	%	46 *19*	68 *56*	
	Serious AE • *drug related*	%	42 *15*	44 *20*	
	AE leading to death • *drug related*	%	13.7 *2.7*	11.7 *3.3*	
	AE leading to discont. • *drug related*	%	19 *7*	27 *14*	
Immune-mediated AE					
	All cause imAE • *Grade ≥ 3* • *serious*	%	22.4 *4.7* *6.7*	NR	
Most frequent imAE (in ≥ 1% of patients)					
	Hypothyroidism	%	9.0	NR	
	Pneumonitis	%	7.1	NR	
	Skin adverse reactions	%	2.0	NR	
	Colitis	%	1.2	NR	
	Hepatitis	%	1.2	NR	
	Myositis/rhabdomyolysis	%	1.2	NR	

Abbreviations: ESCC: esophageal oesophageal carcinoma; HR=Hazard ratio, ICC=investigator's choice chemotherapy, CR=complete response, PR=partial response
Note: Above safety results are as submitted with the initial dossier.

3.7. Benefit-risk assessment and discussion

3.8. Importance of favourable and unfavourable effects

Study BGB-A317-302 demonstrated a statistically significant and clinically meaningful improvement in overall survival for tislelizumab compared to treatment with investigator's choice chemotherapy in the overall study population of advanced or metastatic ESCC patients after prior platinum-based therapy. The benefit of tislelizumab is correlated with PD-L1 expression status; nonetheless a favourable B/R can be accepted in a PD-L1 unrestricted indication considering the different and potentially more favourable safety profile in comparison to the chemotherapy options in this disease setting.

The described safety profile of tislelizumab monotherapy in the sought indication was as expected for PD-1 inhibitors without new safety concerns.

3.8.1. Balance of benefits and risks

In view of the improvement in overall survival in the overall study population, the benefit of treatment with tislelizumab is considered to outweigh its associated risks.

3.8.2. Additional considerations on the benefit-risk balance

Prior regulatory decisions and evaluations of B/R balance in this disease setting are considered relevant for this procedure.

3.9. Conclusions

The overall benefit /risk balance of Tevimbra as monotherapy in the treatment of adult patients with unresectable, locally advanced or metastatic oesophageal squamous cell carcinoma after prior platinum-based chemotherapy is considered positive.

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 Tevimbra is favourable in the following indication:

Tevimbra as monotherapy is indicated for the treatment of adult patients with unresectable, locally advanced or metastatic oesophageal squamous cell carcinoma after prior platinum-based chemotherapy.

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 Tevimbra 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 Tevimbra. 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 Tevimbra is marketed, all healthcare professionals and patients/carers who are expected to prescribe and use Tevimbra 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 Tevimbra.
- A reminder that all known or suspected adverse drug reactions (ADRs) can also be reported to local regulatory authorities.
- The contact details of their Tevimbra 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 CHMP review of the available data, the CHMP considers that tislelizumab is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.