EU RISK MANAGEMENT PLAN

TEVIMBRA (TISLELIZUMAB)

Risk Management Plan (RMP) Version to be Assessed as Part of This Application:

RMP Version number: 2.0

Data Lock Point for This RMP	Clinical data: 01 December 2020 Global Safety Database: 25 December 2022 Postmarketing exposure data: 25 December 2022	Version number	2.0
Date of Final Sign Off	05 March 2024		

Rationale for Submitting an Updated RMP:

This European Union (EU) RMP is prepared as a consolidation of the 2 existing approved tislelizumab RMPs (Tevimbra EU RMP [Version 1.0] and Tizveni EU RMP [Version 1.0]) to combine the indications of oesophageal squamous cell carcinoma (OSCC) and non-small cell lung cancer (NSCLC) under a single Tevimbra RMP (Version 2.0).

Summary of Significant Changes in This RMP:

The key changes for this Tevimbra EU RMP (Version 2.0) compared with the Tevimbra EU RMP Version 1.0 are provided below:

- Addition of a new indication for the treatment of NSCLC in adults (≥ 18 years of age) using tislelizumab in combination and as monotherapy:
  - Tevimbra, in combination with pemetrexed and platinum-containing chemotherapy, is indicated for the first-line treatment of adult patients with non-squamous NSCLC whose tumours have programmed cell death ligand-1 (PD-L1) expression on ≥ 50% of tumour cells [TCs] with no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) positive mutations and who have: locally advanced NSCLC and are not candidates for surgical resection or platinum-based chemoradiation, or metastatic NSCLC.
  - Tevimbra, in combination with carboplatin and either paclitaxel or nab-paclitaxel (nab-PC), is indicated for the first-line treatment of adult patients with squamous

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

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

- Addition of data from NSCLC combination therapy studies, including the 2 pivotal Studies BGB-A317-304 and BGB-A317-307, as well as the supportive Study BGB-A317-206.

Part	Module/Annex	Significant Changes in Each Module
Part I Product overview		Updated Marketing Authorisation Holder name and information from Novartis Europharm Ltd to BeiGene Ireland Ltd. Indications in the European Economic Area (EEA) updated to include NSCLC and to align with the proposed Summary of Product Characteristics (SmPC). Added dosage for Tevimbra as part of combination therapy for NSCLC.
Part II Safety specification	Module SI Epidemiology of the indication(s) and target population(s)	Updated to include epidemiology and target population information for the NSCLC indication.
	Module SII Nonclinical part of the safety specification	No updates.
	Module SIII Clinical study exposure	NSCLC indication wording and exposure data was added. Monotherapy study BGB-A317-303, and combination therapy studies BGB-A317-304 BGB-A317-307 were added as pivotal studies. Combination therapy study BGB-A317-206 was added as a supportive study. Description of the Safety Analysis Set used for the NSCLC indication was added.
	Module SIV Populations not studied in clinical studies	No updates.
	Module SV Post-authorisation experience	No updates.

Part	Module/Annex	Significant Changes in Each Module
	Module SVI Additional EU requirements for the safety specification	No updates.
	Module SVII Identified and potential risks	Updated to include data from the combination therapy studies (Studies BGB-A317-206, BGB-A317-304, and BGB-A317-307).
	Module SVIII Summary of the safety concerns	No updates
Part III Pharmacovigilance plan (including post-authorisation safety studies)		No updates.
Part IV Plan for post-authorisation efficacy studies		No updates.
Part V Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)		No updates.
Part VI Summary of Risk Management Plan for TEVIMBRA (tislelizumab)		Updated to reflect the addition of the NSCLC indication.
Part VII Annexes	**ANNEX 1** Eudravigilance interface	No updates.
	ANNEX 2 Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme	No updates.
	ANNEX 3 Protocols for proposed, ongoing and completed studies in the pharmacovigilance plan	No updates.
	ANNEX 4 Specific adverse drug reaction follow-up forms	No updates.

Part	Module/Annex	Significant Changes in Each Module
	ANNEX 5 Protocols for proposed and ongoing studies in RMP Part IV	No updates.
	ANNEX 6 Details of proposed additional risk minimisation activities (if applicable)	Updated to include the information that "the Patient Card reminds patients about key symptoms that need to be reported immediately to the physician".
	ANNEX 7 Other supporting data (including referenced material)	Added references related to the NSCLC indication.
	ANNEX 8 Summary of changes to the RMP over time	Summary of changes table was added.

Other RMP Versions Under Evaluation:

CCI [redacted]

Details of the Currently Approved RMP:

RMP Version Number	Approved With Procedure	Date of Approval (Opinion Date)
1.0	EMEA/H/C/5919	20 July 2023

Qualified Person Responsible for Pharmacovigilance (QPPV) Name: Dr Olaf Schickling

QPPV Signature:

Dr Olaf Schickling PD 05-Mar-2024 | 05:18:18 PST Date

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LIST OF ABBREVIATIONS FOR ALL PARTS/MODULES

ADA	antidrug antibody
AE	adverse event
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CSS	cancer-specific survival
CTLA4	cytotoxic T lymphocyte-associated protein 4
dCRT	definitive chemoradiation
EEA	European Economic Area
EGFR	epidermal growth factor receptor
EPAR	European Public Assessment Report
EU	European Union
FDA	Food and Drug Administration
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCP	healthcare professional
HCV	hepatitis C virus
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICI	immune checkpoint inhibitor
imAE	immune-mediated adverse event
INN	Invented name
IR	incidence rate
IRR	infusion-related reaction
LC	lung cancer
mAb	monoclonal antibody
nab-PC	nab-paclitaxel

NCCN	National Comprehensive Cancer Network
NSCLC	non-small cell lung cancer
OC	oesophageal carcinoma
OS	overall survival
OSCC	oesophageal squamous cell carcinoma
PD	programmed cell death protein
PD-L	programmed cell death ligand
PFS	progression-free survival
PK	pharmacokinetic(s)
PL	Product Label
PT	Preferred Term
QPPV	Qualified Person Responsible for Pharmacovigilance
RMP	Risk Management Plan
RS	relative survival
RSR	relative survival rate
SEER	Surveillance, Epidemiology, and End Results
SJS	Stevens-Johnson syndrome
SmPC	Summary of Product Characteristics
TC	tumour cell
TEAE	treatment-emergent adverse event
TEN	toxic epidermal necrolysis
UK	United Kingdom
ULN	upper limit of normal
US	United States

PART I PRODUCT(S) OVERVIEW

Table Part I-1: Product Overview

Active Substance(s) (INN or Common Name)	Tislelizumab
Pharmacotherapeutic Group(s) (ATC Code)	L01FF09
Marketing Authorisation Holder	BeiGene Ireland, Ltd. 10 Earlsfort Terrace Dublin 2 D02 T380 Ireland
Medicinal Products to Which This RMP Refers	1
Invented Name(s) in the EEA	Tevimbra
Marketing Authorisation Procedure	Centralised procedure
Brief Description of the Product	Chemical Class: Tislelizumab is a humanised immunoglobulin G4 variant monoclonal antibody (mAb).
	Summary of Mode of Action: Tislelizumab binds to the extracellular domain of human programmed cell death protein (PD)-1 with high specificity and affinity. Tislelizumab competitively blocks the binding of both PD-L1 and PD-L2, thus inhibiting PD-1 mediated negative signalling and enhancing the functional activity in T-cells at the site of the tumour.
	Important Information about its Composition: Concentrate for solution for infusion. The solution has a pH of approximately 6.5 and an osmolality of approximately 270 to 330 mOsm/kg. Tislelizumab is produced in Chinese hamster ovary cells by recombinant DNA technology.
Hyperlink to the Product Information	Tislelizumab SmPC
Indication(s) in the EEA	Current: Tevimbra, as monotherapy, is indicated for the treatment of adult patients with unresectable, locally advanced or metastatic oesophageal squamous cell carcinoma (OSCC) after prior platinum-based chemotherapy. Tevimbra in combination with pemetrexed and platinum-containing chemotherapy is indicated for the first-line treatment of adult patients with nonsquamous non-small cell lung cancer whose tumours have

	PD-L1 expression on ≥ 50% of tumour cells with no EGFR or ALK positive mutations and who have: • locally advanced NSCLC and are not candidates for surgical resection or platinum-based chemoradiation, or • metastatic NSCLC. Tevimbra in combination with carboplatin and either paclitaxel or nab-paclitaxel, is indicated for the first-line treatment of adult patients with squamous non-small cell lung cancer who have: • locally advanced NSCLC and are not candidates for surgical resection or platinum-based chemoradiation, or • metastatic NSCLC. Tevimbra as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer after prior platinum-based therapy. Patients with EGFR mutant or ALK positive NSCLC should also have received targeted therapies before receiving tislelizumab.
	Additional Indication Proposed: No changes.
Dosage in the EEA	Current: **Tevimbra as monotherapy:** 200 mg administered by intravenous infusion once every 3 weeks. **Tevimbra combination therapy:** The recommended dose of Tevimbra is 200 mg administered by intravenous infusion once every 3 weeks, in combination with chemotherapy. When Tevimbra and chemotherapy are administered on the same day, Tevimbra should be administered before chemotherapy. The SmPC for the chemotherapy product should be referred to for dosing as well as for recommendations on corticosteroid use as premedication for the prevention of chemotherapy-related adverse reactions.
	Proposed: No changes.
Pharmaceutical Form(s) and Strengths	Current: 100 mg/10 mL (10 mg/mL) concentrate for solution for infusion.
	Proposed: No changes.
Is/will the Product be Subject to Additional Monitoring in the EU?	Yes

PART II SAFETY SPECIFICATION

PART II: MODULE SI EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

Oesophageal Squamous Cell Carcinoma

Indication

Oesophageal carcinoma (OC) was the seventh most common cancer worldwide in 2020, with an estimated 604,000 new cases (3.1% of all cancers), and the sixth leading cause of all cancer deaths, with 544,000 deaths (5.5% of all cancer mortality), based on the GLOBOCAN 2020 database (Sung et al 2021). OSCC is the predominant type of EC accounting for approximately 87% of all OC cases globally (Uhlenhopp et al 2020). The geographic distribution of OSCC however, varies greatly, with more than 10-fold differences between countries. Over the last 40 years there have been large changes in the incidence in the different types of oesophageal cancers, and these trends are region specific. In the United States (US), Europe, Australia, and many other Western countries, the incidence of OSCC had been decreasing for several decades, whereas the incidence of oesophageal adenocarcinoma has increased. In Eastern Europe, Japan, and South America, OSCC still predominates. In most of Asia and Sub-Saharan Africa, OCs occur almost exclusively as OSCCs (Abnet et al 2018).

Incidence

In Europe, the age-adjusted incidence rate (IR) of OC as estimated from the GLOBOCAN database, was 3.3 per 100,000 in 2020 (Ferlay et al 2020). In a publication also using the GLOBOCAN database, the age-adjusted IRs of OSCC per 100,000 in 2018 by European region, were as follows: Eastern Europe 2.5, Western Europe 2.3, Northern Europe 1.8, Southern Europe 1.3 (Arnold et al 2020). Additionally, Rumgay et al (2021a) used the Cancer Incidence in Five Continents Plus database of population-based cancer registry data and multiple subnational cancer registries, to examine OC subtype incidence patterns in 27 countries. In European countries, for years 2003 to 2012, the age-standardised IR of OSCC ranged from 0.9 to 3.0 per 100,000, the highest being within Eastern and Central Europe in Slovakia (3.0 per 100,000) and the lowest within Northern Europe in Norway (0.9 per 100,000). The proportion of OSCC cases of total OC in that European country ranged from 30% to 77% with the highest in Slovakia (77%), followed by Slovenia (70%) and the lowest, within the EU27, in The Netherlands (31%), followed by Norway (37%). Table Part II: Module SI-1 shows the OSCC cases, the proportion of total OC cases, and the OSCC age-adjusted IR per 100,000 persons by population from 2003 to 2012 (Rumgay et al 2021b). Additionally, based on the analysis of data from Czech National Cancer Registry, Kroupa et al (2020) reported an age-adjusted IR of OSCC as 1.67 per 100,000 from 2013 to 2017.

Table Part II: Module SI-1: Oesophageal Squamous Cell Carcinoma Cases, Proportion of Total Oesophageal Carcinoma Cases, Oesophageal Squamous Cell Carcinoma Age-standardised Incidence Rate per 100,000 by Population From 2003 to 2012

Oesophageal Squamous Cell Carcinoma			
Population	**Cases**	**Proportion of Total OC Cases (%)**	**ASR per 100,000**
North America			
Canada[a]	418	33	0.9
US Black[a]	100	65	2.6
US White[a]	280	21	0.8
Central and Eastern Europe			
Czechia	275	50	1.6
Slovakia	221	77	3.0
Northern Europe			
Denmark	192	44	1.9
Ireland	147	40	2.3
Lithuania	109	59	2.1
Norway	80	37	0.9
UK - England[a]	1978	30	1.9
UK - Northern Ireland	54	30	1.7
UK - Scotland	302	36	2.8
Southern Europe			
Croatia	112	51	1.5
Italy[a]	142	60	1.4
Slovenia	61	70	1.7
Spain[a]	273	63	2.1
Western Europe			
Austria	178	45	1.3
France (Metropolitan)[a]	284	65	3.0
Germany[a]	117	47	2.2
Switzerland[a]	78	57	2.5
The Netherlands	558	31	1.9

Abbreviations: ASR, age-standardised incidence rate; OC, oesophageal cancer; SEER, Surveillance, Epidemiology, and End Results; UK, United Kingdom; US, United States.

[a] Country-level aggregates compiled from the following regional registries:
Canada - Alberta, British Columbia, Manitoba, New Brunswick, Newfoundland and Labrador, Northwest Territories, Nova Scotia, Ontario, Prince Edward Island, Saskatchewan.
US - Georgia, Greater California, Idaho, Kentucky, Louisiana, Massachusetts, New York, Utah, Wisconsin (SEER-9).
UK - England - East Midlands, East of England, London, North East, North West, South East, South West, West Midlands, Yorkshire.
Italy - Modena, Parma, Ragusa, Romagna, Veneto.
Spain - Albacete, Basque Country, Canary-Islands, Cuenca, Girona, Granada, Murcia, Navarra, Tarragona.
France - Bas-Rhin, Calvados, Doubs, Haut-Rhin, Herault, Isere, Somme.
Germany - Hamburg, Saarland; Switzerland - Geneva, Neuchatel, St Gall-Appenzell, Vaud.

In the US, a recent, retrospective analyses of Surveillance, Epidemiology, and End Results (SEER) database for the period 2004 to 2015, identified 13,919 OSCC cases with an age-adjusted IR of 1.9 per 100,000 (Then et al 2020). In Canada, a nationwide population-based study conducted in 1992 to 2010 identified 9115 OSCC cases with a reported annual age-adjusted IR of 1.04 per 100,000 (Cattelan et al 2020). This is slightly higher than the age-adjusted IR of 0.9 per 100,000 later reported by Rumgay et al (2021a) based on regional registry data from 2003 to 2012.

In the rest of the world, a recent analysis of the Cancer Incidence in Five Continents Plus Volume X database estimated the age-adjusted IR per 100,000 for Eastern-, South-Central- and Western Asian countries for 15 to 30 years. The highest age-adjusted IR was reported in Japan as 5.6 for the years 1988 to 2010, followed by India as 3.6 for 1983 to 2012, China as 3.0 for 1998 to 2012, Republic of Korea as 2.5 for 1998 to 2012 and Turkey as 1.1 for 1998 to 2012 (Rumgay et al 2021b).

Prevalence

Published population-based studies on the prevalence of OSCC are lacking.

Only 1 study in the US was identified, reporting a 40-year prevalence of OSCC of 911 (95% CI: 853 to 972) as of 01 January 2015. The study was based on the analysis of the SEER database from 1973 to 2015 (He et al 2020). In Table Part II: Module SI-2, estimates of OC prevalence proportion and counts in the year 2020, worldwide, EU27 and for Europe, as the 39 countries that comprise the European population defined by the International Agency for Research on Cancer/World Health Organization, are presented (Ferlay et al 2020).

Table Part II: Module SI-2: Oesophageal Carcinoma 5-year Prevalence Count and Proportion per 10,000 Persons, Worldwide, in Europe and in 4 European Regions

Region	Prevalence Count (5-year duration)	Prevalence Proportion (5-year duration per 10,000 persons)
Worldwide	666,388	0.85
Europe	70,575	0.76
Central and Eastern Europe	18,106	0.62
Northern Europe	3509	0.92
+ United Kingdom	15,650	1.48

Table Part II: Module SI-2: Oesophageal Carcinoma 5-year Prevalence Count and Proportion per 10,000 Persons, Worldwide, in Europe and in 4 European Regions

Region	Prevalence Count (5-year duration)	Prevalence Proportion (5-year duration per 10,000 persons)
Southern Europe	7451	0.50
Western Europe	22,854	1.17
EU27	37,360	0.84

Abbreviations: EU, European Union.

The worldwide 5-year prevalence proportion of OC was 0.85 per 10,000. The EU27 prevalence proportion was 0.84 per 10,000 (Ferlay et al 2020). Prevalence was lowest in Southern Europe (0.50 per 10,000) and Central/Eastern Europe (0.62 per 10,000) while the highest was in Western Europe (1.17 per 10,000) followed by Northern Europe (0.92 per 10,000). These differences partially reflect differences in the underlying incidence of OC, but also reflect differences in risk factor prevalence (and shifts in risk factor prevalence), relative changes in the incidence of squamous cell carcinomas relative to adenocarcinomas, as well as access to and types of health care interventions and other factors that in turn impact survivorship.

Demographics of the Population in the Authorised Indication – Sex, Age, Racial and/or Ethnic Origin, Geographic Distribution, and Risk Factors for the Disease

The mean age of OSCC was 66.3 ± 10 years based on SEER data of 13,919 OSCC patients between 2004 and 2015 (Then et al 2020). Similarly, the mean age at diagnosis was reported as 68.3 ± 1.1 years in a nationwide Canadian study conducted between 1992 and 2010. In that study, the age-adjusted IR of OSCC increased with age: for age < 30 years the incidence was 0.0 per 100,000, increasing gradually until ages 60 to 69 (4.2 per 100,000) and peaking at ages 70 to 79 (7.1 per 100,000) (Cattelan et al 2020).

Globally, the IRs of OSCC are higher in men as compared to women. In 2012, the IR of OSCC was 7.7 per 100,000 in men and 2.8 per 100,000 in women. The global male to female ratio was reported as 2.7 per 100,000 with substantial geographical variations; it was highest in Eastern Europe (7.8 per 100,000) and lowest in Northern Africa and Western Asia (1.2 per 100,000). The estimates were based on a study by Arnold et al (2015) analysing data from Cancer Incidence in Five Continents Vol. X and GLOBOCAN 2012.

It has been reported that the frequency of OSCC varies substantially depending on race/ethnicity and geographical region. About 80% of the global OSCC cases (corresponding to 315,000 cases) occurred in the Central and South-East Asian region. China alone contributed more than half of the global cases (53% or 210,000 cases). The reported age-adjusted IR per 100,000 was the highest in Eastern/South-East Asia at 13.6 per 100,000 in men and 4.3 per 100,000 in women, followed by sub-Saharan Africa and Central Asia. Using the same data source, Malhotra et al (2017) reported the highest OSCC age-adjusted IR per 100,000 in Asia (9.6 in men and 4.4 in women) and the lowest age-adjusted IR per 100,000 in North America (1.2 in men and 0.8 in women). Europe and Oceania reported the same low incidence among women as North America (0.8 per 100,000).

Regarding risk factors, smoking, and alcohol consumption and particularly their synergistic effect, are well established risk factors for OSCC. The adjusted odds ratio for current smokers and ever drinkers was reported as 2.2 (95% CI: 1.6 to 2.92); p value of interaction = 0.003 (Yang et al 2017). Other risk factors include age (OSCC incidence increases with age, mean age at diagnosis in the US is 68 years), sex (males have higher incidence than females), race (Blacks have higher incidence than Caucasians), low socio-economic status and rural area, consumption of very hot beverages/foods and exposure to nitrosamines (Uhlenhopp et al 2020). A recent meta-analysis of studies investigating cooking fuel and OSCC among 16,189 participants, reported that use of biomass fuel for cooking and or heating increased the risk of OSCC (pooled odds ratio 3.02; 95% CI: 2.2 to 4.1) (Okello et al 2019).

Main Existing Treatment Options

Neoadjuvant chemoradiation in combination with surgery is recommended for patients with resectable tumours, and definitive chemoradiation (dCRT) is recommended for patients who decline surgery or have unresectable locally advanced tumours. Patients with advanced (metastatic, non-resectable, or recurrent) OSCC are treated with palliative chemotherapy and/or localised treatments, such as radiotherapy or stents (Lordick et al 2016). Platinum-based chemotherapy is the most frequently recommended first-line palliative treatment (Lordick et al 2016; Muro et al 2019; National Comprehensive Cancer Network [NCCN] 2020) and has overall response rate of 30% to 57% and median overall survival (OS) of 10 to 13.5 months (Kato et al 2020; Lee et al 2015; Liu et al 2016).

Second-line OSCC systemic therapy is recommended for patients with good performance status (0 to 1). Barbetta et al (2019) observed significantly worse survival among OSCC patients with recurrence within 6 months of chemoradiation followed by surgery. Patients relapsing after platinum-based chemotherapy, during adjuvant/neo-adjuvant treatment, or within 6 months of dCRT are treated with single-agent docetaxel, paclitaxel, or irinotecan (NCCN 2020). The treatment benefit from these agents is typically less than 6 months, with median OS of 5 to 7 months.

Table Part II: Module SI-3 outlines some of the references to the studies conducted for the second-line chemotherapy for OSCC.

Table Part II: Module SI-3 Second-line Chemotherapy for Oesophageal Squamous Cell Carcinoma

Agent	Study Design and Patient Population	Sample Size by Histology (N)	Regimen	Median OS (mo)	Median PFS (mo)
Paclitaxel (Shirakawa et al 2014)	Retrospective in Japanese patients	OSCC (n = 31)	100 mg/m^2 weekly x 6, 1-week rest	6.1	2.5
Paclitaxel (Mizota et al 2011)	Retrospective in Japanese patients	OSCC (n = 35) OAC (n = 3)	80 to 100 mg/m^2 Day 1, 8, 15 every 28 days	7.2[a]	3.5[a]
Paclitaxel (Ilson et al 2007)	Multicentre, collaborative study in US patients	OSCC (n = 32) OAC (n = 63)	80 mg/m^2 weekly	9.0[a]	3.1[a]

Table Part II: Module SI-3 Second-line Chemotherapy for Oesophageal Squamous Cell Carcinoma

Agent	Study Design and Patient Population	Sample Size by Histology (N)	Regimen	Median OS (mo)	Median PFS (mo)
Docetaxel (Shirakawa et al 2014)	Retrospective in Japanese patients	OSCC (n = 132)	70 mg/m^2 Q3W	5.5	2.3
Docetaxel (Mizota et al 2011)	Retrospective study in Japanese patients	OSCC (n = 84) OAC (n = 2)	60 to 70 mg/m^2 Q3W	6.1[a]	2.1[a]
Docetaxel (Song and Zhang 2014)	Retrospective study in Chinese patients	OSCC (n = 41)	Not specified	5.2	3.2
Docetaxel (Albertsson et al 2007)	Prospective study in Scandinavian patients	OSCC (n = 39) OAC (n = 13)	Docetaxel alone: 100 mg/m^2 Q3W	NA[b]	NA[b]
Irinotecan (Burkart et al 2007)	Single arm, Phase II study in German patients	OSCC (n = 7) OAC (n = 7)	100 mg/m^2 weekly x 3 every 4 weeks	5[a]	2[a]

Abbreviations: CR, complete response; mo, month; NA, not applicable; OAC, oesophageal adenocarcinoma; OS, overall survival; OSCC, oesophageal squamous cell carcinoma; PFS, progression-free survival; PR, partial response; Q3W, once every 3 weeks; US, United States.

[a] Combined OSCC and OAC histology (and first- and second-line combined, [Ilson et al 2007]).

[b] Study I: CR, 5%; PR, 26%.

Chemotherapy has significant toxicity with substantial morbidity and mortality for patients and frequent treatment interruptions, delays, and dose reductions that increase the risk of disease progression. Docetaxel is associated with Grade 3 or 4 neutropenia (32.6 to 48.8%), febrile neutropenia (6.1 to 20.9%), anaemia (2.3 to 9.1%), anorexia (3.0 to 4.7%), and pneumonia (4.5%) (Shirakawa et al 2014, Mizota et al 2011). Grade 3 or 4 adverse events (AEs) with paclitaxel include neutropenia (52.8%), leukopenia (45.3%), anorexia (9.4%), fatigue (9.4%), constipation (7.5%), pneumonia (7.5%), and sensory neuropathy (5.7%). Sensory neuropathy of any grade is observed in 81.1% of patients treated with paclitaxel and often is debilitating (Muro et al 2004, Kato et al 2011). Irinotecan often results in neutropenia (21.4%), anaemia (28.6%), and diarrhoea (57.1%) (Burkart et al 2007). Chemotherapy-related toxicities can severely limit patient function and often result in emergency room visits, hospitalisations, and death.

More recently immune checkpoint inhibitors (ICI) targeting the PD-1/PD-L1 axis have further shaped the treatment landscape for patients with OSCC. PD-1 inhibitors have demonstrated survival improvement over chemotherapy in advanced or metastatic OSCC patients with disease progression after prior systemic therapies (Kato et al 2019; Kojima et al 2019). Pembrolizumab was approved by the Food and Drug Administration (FDA) in July 2019 for the treatment of recurrent, locally advanced or metastatic OSCC but only in patients whose tumours express PD-L1 (Combined Positive Score ≥ 10) as determined by an FDA-approved test with disease progression after 1 or more prior lines of systemic therapy. Nivolumab was approved by the European Medicines Agency and FDA, in November 2020 and June 2020, respectively, for the

treatment of patients with unresectable advanced, recurrent, or metastatic OSCC after prior fluoropyrimidine- and platinum-based chemotherapy regardless of PD-L1 level. Nivolumab was approved by European Medicines Agency and FDA in July 2021 and May 2021, respectively, for adjuvant treatment of completely resected oesophageal or gastroesophageal junction cancer with residual pathologic disease in patients who have received neoadjuvant chemoradiotherapy.

Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity

OSCC is characterised by a poor prognosis from the time of diagnosis, despite advances in treatments (Uhlenhopp et al 2020).

In Europe, the 1-year relative survival (RS) was reported to be 33.9% (95% CI: 33.3 to 34.6) and the 5-year RS was reported at 10.1% (95% CI: 9.7 to 10.6), based on a study that utilised cancer survival data for patients diagnosed in 1995 to 1999 with follow-up to the end of 2003, collected from 66 cancer registries in 24 European countries based on EUROCARE-4 data (Gavin et al 2012).

Among 13,919 patients with OSCC, the most common stage of presentation (about 27% of patients) was Stage IV. The 1-year cancer-specific survival (CSS) was reported to be 43.8% and the 5-year CSS was 18.9%, with a median survival time of 10 months. Significant predictors for worse outcomes were African American race, location of lesions in the lower oesophagus, tumour Grade 3 and tumour Stage IV and lack of surgery treatment, based on SEER data during 2004 to 2015 (Then et al 2020). Another recent US study based on SEER data identified 6890 OSCC patients from 2007 to 2015. It was reported that OS differed by sex, with a higher 5-year OS in females (19.2%) compared with males (12.9%). The median survival time was longer for females (12 months) than for males (9 months). However, in OSCC patients ≥ 80 years, 5-year OS did not differ by sex (Li et al 2021).

A nationwide population-based study in Sweden evaluated the prognosis of OSCC among patients who underwent surgery, and in those who did not, from 1990 to 2013. In patients who did not undergo surgery, the 1-year and 5-year OS and RS improved during the study period; the 5-year OS increased from 2% (95% CI: 1.0 to 3.0) in the period 1990 to 1994 up to 5% (95% CI: 3.0 to 7.0) in the period 2010 to 2013. An improvement was also reported for 5-year RS from 3% (95% CI: 1.0 to 4.0) in 1990 to 1994 to 6% (95% CI: 4.0 to 8.0) in 2010 to 2013 (Kauppila et al 2018).

Table Part II: Module SI-4 outlines details on OS and RS across calendar periods.

Table Part II: Module SI-4: Overall and Relative 1-year and 5-year Survivals

	Overall Survival in % (95% CI)		Relative Survival in % (95% CI)	
Calendar Period	**1-Year**	**5-Year**	**1-Year**	**5-Year**
1990-1994	19 (16-22)	2 (1-3)	20 (17-23)	3 (1-4)
1995-1999	19 (17-22)	4 (2-5)	21 (18-24)	5 (3-6)
2000-2004	25 (22-28)	3 (2-5)	26 (23-29)	4 (2-5)
2005-2009	23 (20-26)	4 (3-6)	24 (21-27)	5 (3-7)

Table Part II: Module SI-4: Overall and Relative 1-year and 5-year Survivals

	Overall Survival in % (95% CI)		Relative Survival in % (95% CI)	
2010-2013	24 (20-27)	5 (3-7)	25 (21-29)	6 (4-8)

Source: Adapted from Kauppila et al (2018).

Important Comorbidities

Zhao et al (2021) evaluated the clinicopathological features of 503 OSCC patients with median age 62 years (range: 56 to 67), who underwent oesophagectomy in a tertiary centre in Japan between 2005 and 2015. Comorbidities were identified by a physician during the pre-operative evaluation. The identified comorbidities included history of hypertension (34.4%), history of diabetes (24.3%), history of chronic obstructive pulmonary disease (COPD) (11.5%), history of hepatitis (14.9%), history of cardiovascular disease (16.1%). It was reported that renal comorbidities were too rare, therefore, they were excluded from the statistical analysis.

A population-based study aimed to compare the comorbidity distribution in oesophageal and gastric carcinoma patients in The Netherlands between 1993 to 2001. There were 13.6% OSCC patients (N = 479) with mean age of 64 years (range: 27 to 97) among a total of 3533 included patients. The prevalence estimates of comorbidities among OSCC patients were as follows: cardiovascular disease (17%), hypertension (15%), previous cancers (13%), COPD (11%), ulcerative disease (9%), diabetes (6%), cerebrovascular disease (5%) and liver disease (3%) (Koppert et al 2004).

Non-small Cell Lung Cancer

Indication

Lung cancer (LC) is one of the most common cancers worldwide with approximately 2.2 million cases diagnosed annually (11.4% of all cancers), and had, along with breast cancer, the highest incidence among all cancers in 2020. Further, LC accounts for the most cancer related deaths, causing 1.8 million deaths in 2020 based on GLOBOCAN data (International Agency for Research on Cancer Lung Cancer Fact Sheet 2020). NSCLC is the predominant subtype, accounting for approximately 85% of all LC (Lungevity 2021). In the EUROCARE5 study on lung and pleural cancer from 87 European cancer registries in 28 countries in Europe, squamous cell carcinoma, adenocarcinoma and large cell carcinoma were the 3 main histological subtypes of NSCLC representing 51% of male and 43% of female cases (Francisci et al 2015).

Incidence

Published population-based studies on NSCLC are sparse.

In Europe, the estimated number of patients diagnosed with LC was 477,534 with an age-standardised IR of 29.4 per 100,000 in 2020, according to GLOBOCAN 2020 (Ferlay et al 2020). Based on the assumption that 85% of LC is NSCLC, the estimated IR of NSCLC is approximately 25.0 per 100,000. Based on the European Centre for Information System, there were 318,327 new cases of LC diagnosed in the 27 member states of the EU in 2020, with an associated IR of 67.3 per 100,000 and an estimated IR of NSCLC of 57.2 per 1,000,000 (Table Part II: Module SI-5).

Table Part II: Module SI-5: Estimated Number of New LC and NSCLC Cases and IR per 100,000 by EU27 Region and Country in 2020 Based on the European Cancer Information System

Country/Region	Estimated Incidence of LC in 2020		Estimated Incidence of NSCLC in 2020 [a]	
	Number of New Cases	Rate per 100,000	Number of New Cases	Rate per 100,000
EU-27	318,327	67.3	270,578	57.2
France	48,299	71.0	41,054	60.4
Germany	64,804	67.7	55,083	57.5
Italy	41,963	59.3	35,669	50.4
Spain	29,188	61.2	24,810	52.0
United Kingdom	51,983	81.2	44,186	69.0
EU-27	318,327	67.3	270,578	57.2

Abbreviations: EU, European Union; IR, incidence rate; LC, lung cancer; NSCLC, non-small cell lung cancer.
[a] NSCLC incidence estimation was calculated assuming that the NSCLC accounts for 85% of LC cases (Lungevity 2021).

Ryska et al (2018) published results of a survey conducted among expert pathologists of the Central European Cooperative Oncology Group, encompassing 10 countries of Central and Southeastern Europe estimating the annual mean age-adjusted IR of NSCLC to be 53.4 per 100,000 in 2017. The highest IR was reported in Hungary (110 per 100,000), followed by Serbia (76.4 per 100,000) and Croatia (65.1 per 100,000), and the lowest IR in Bulgaria (31.1 per 100,000), Czech Republic (42.9 per 100,000) and Romania (44.7 per 100,000).

Table Part II: Module SI-6 presents the results of this study by number of new cases and the IR per 100,000 of NSCLC in the included countries from highest to lowest IR.

Table Part II: Module SI-6: Annual Incidence of NSCLC in Central and Southeastern Europe

Country	New Cases in 2017	Annual IR per 100,000
Hungary	11,000	110.0
Serbia	5500	76.4
Croatia	2800	65.1
Slovenia	1100	55.0
Austria	4000	47.1
Poland	18,000	46.8
Slovakia	2500	46.3
Romania	8500	44.7
Czech Republic	4500	42.9

Table Part II: Module SI-6: Annual Incidence of NSCLC in Central and Southeastern Europe

Country	New Cases in 2017	Annual IR per 100,000
Bulgaria	2300	31.1
Total	**60,200**	**53.4**

Abbreviations: IR, incidence rate; NSCLC, non-small cell lung cancer.
Source: Adapted from Ryska et al 2018.

In the US, the age-standardised IR of LC in 2020 was 33.1 per 100,000 based on estimates from GLOBOCAN 2020 (Ferlay et al 2020). Based on the assumption that 85% of LC is NSCLC, the estimated IR of NSCLC is approximately 28.1 per 100,000. The annual age-adjusted IR per 100,000 was reported to have decreased across 3 decades, from 1983 to 2012. The IR per each decade was as follows: 44.6 in 1983 to 1992, 41.3 in 1993 to 2002 and 34.8 in 2003 to 2012, based on the SEER data of 293,471 NSCLC patients (Wang et al 2017).

Prevalence

No publications were identified that reported the prevalence of NSCLC.

Table Part II: Module SI-7 presents the estimated prevalence of NSCLC in all age groups for all world regions based on GLOBOCAN 2020 data (highest to lowest proportions per 100,000). The estimates for NSCLC were calculated based on the assumption that NSCLC constitutes approximately 85% of all LC cases (Lungevity 2021). Worldwide, the estimated NSCLC prevalence was 28.4 per 100,000. The highest estimated NSCLC prevalence was reported in Northern America at 75.7 per 100,000, followed by Europe at 66.1 per 100,000, and the lowest prevalence was reported in Africa at 3.1 per 100,000. Among 5 European countries, the highest estimated NSCLC prevalence was in Germany at 85.9 per 100,000, followed by United Kingdom (UK) at 82.4 per 100,000 and the lowest in Spain with 65.0 per 100,000.

Table Part II: Module SI-7: Estimated 5-year Prevalence of LC and NSCLC and Proportion per 100,000 by Country or Region in GLOBOCAN 2020

Country/Region	Estimated 5-year Prevalence of LC		Estimated 5-year Prevalence of NSCLC[a]	
	Number	Proportion per 100,000	Number	Proportion per 100,000
Worldwide	2,604,791	33.4	2,214,072	28.4
Northern America	328,224	89.0	278,990	75.7
Europe	582,924	77.8	495,485	66.1
France	59,708	91.5	50,752	77.8
Germany	84,586	101.0	71,898	85.9
Italy	49,423	81.7	42,010	69.4
Spain	35,729	76.4	30,370	65.0

Table Part II: Module SI-7: Estimated 5-year Prevalence of LC and NSCLC and Proportion per 100,000 by Country or Region in GLOBOCAN 2020

Country/Region	Estimated 5-year Prevalence of LC		Estimated 5-year Prevalence of NSCLC[a]	
	Number	Proportion per 100,000	Number	Proportion per 100,000
United Kingdom	65,836	97.0	55,960	82.5
Oceania	21,677	50.8	18,425	43.2
Asia	1,515,321	32.7	1,288,022	27.8
Latin America and the Caribbean	106,459	16.3	90,490	13.9
Africa	50,186	3.7	42,658	3.1

Abbreviations: LC, lung cancer; NSCLC, non-small cell lung cancer.
[a] Prevalence of NSCLC is calculated assuming that the NSCLC accounts for 85% of LC cases (Lungevity 2021).

Demographics of the Population in the Authorised Indication – Sex, Age, Racial and/or Ethnic Origin, Geographic Distribution, and Risk Factors for the Disease

In a multinational, multicentre, observational study conducted in 8 European countries, the median age (range) of diagnosis for NSCLC was 65 (22 to 91) years of age (Carrato et al 2014). Most patients are male (52% to 78%), with a male to female ratio of 3.5:1 (Carrato et al 2014; Morgan et al 2021).

One study reported the differences in annual age-adjusted IR per 100,000 of NSCLC between Asians and Whites, based on the California Cancer Registry between 1988 and 2003. In this study, Asians had a lower IR of NSCLC (29.8 per 100,000) compared with Whites (57.7 per 100,000), South Asians had markedly low rates of NSCLC (12.0 per 100,000), and foreign-born Asians had an approximately 35% higher rate of NSCLC than US-born Asians (Raz et al 2008).

Risk factors for NSCLC include cigarette smoking as the main cause of LC in the 20th century. This risk is also inclusive of passive or second-hand smoking; the relative risk in people who never smoked but who lived with a smoker varies from 1.1 to 5.2. Other known risk factors are exposure to occupational and environmental carcinogens (such as asbestos, arsenic, radon and polycyclic aromatic hydrocarbons), alcohol consumption (people who consume at least 30 g/day of alcohol have a slightly higher risk of NSCLC than those who abstained from alcohol), and genetic factors (an increased risk of LC was found in the carriers of TP53 gene) (Molina et al 2008).

Main Existing Treatment Options

First-line Treatment of NSCLC Without Actionable Oncogenic Driver

ICI therapy is the standard of care for the first-line treatment of metastatic NSCLC without actionable oncogenic driver. ICI monotherapy is approved for the patients with tumour expressing PD-L1 ≥ 1% with the approval restricted to PD-L1 above 50% in the EU, whereas ICI in combination with platinum-based chemotherapy can be administrated irrespective of

PD-L1 expression. For patients who are not suitable to receive ICI therapy due to underlying medical condition or other reasons, chemotherapy with platinum doublets should remain as the standard treatment option for these patients. In the EU, a recently published study of real-world treatment patterns of metastatic NSCLC in (data collected between Quarter 3 2018 and Quarter 3 2019 from Germany, France, Italy, Spain, and the UK) reported that chemotherapy alone was still the most common first-line therapy in NSCLC patients with PD-L1 expression below 50%, being prescribed for 93% of patients with PD-L1 < 1% and 84% of patients with PD-L1 1% to 49% (versus 12% of patients with PD-L1 ≥ 50%) (Janowicz et al 2020). In another analysis of EU real-world data using the same dataset, the treatment sequence of first-line chemotherapy to second-line immunotherapy was prescribed to 60 to 81% of patients with PD-L1 < 1% and 73 to 91% of patients with PD-L1 1% to 49% (Gower et al 2021). Similar finding was observed from a Novartis internal real-world analysis using ConcertAI electronic health records. In the US in 2020, 66.1% of patients received an ICI (either as monotherapy or in combination with chemotherapy) and 20.4% of patients received chemotherapy alone as first-line treatment for an advanced NSCLC population without EGFR, ALK, or ROS mutation. Of those administered chemotherapy alone as first-line treatment, 54.2%, 25.3%, and 20.5% of patients had PD-L1 expression as negative, unknown, and positive, respectively; 81.9% of patients did not have a contraindication to immunotherapy. Therefore, chemotherapy remains a treatment option in first-line NSCLC, especially for PD-L1 low and PD-L1 negative patients.

Pembrolizumab is considered a standard first-line option for patients with advanced NSCLC with PD-L1 expression either ≥ 1% or ≥ 50% (depending on the country approval label) who do not otherwise have contraindications to use of immunotherapy (Keytruda [pembrolizumab] European Public Assessment Report [EPAR] 2020; Planchard et al 2018). The Phase III KEYNOTE024 study has established the role for pembrolizumab as first-line treatment in patients with untreated, advanced NSCLC and tumour characterised by PD-L1 expression ≥ 50% in absence of EGFR mutation or ALK translocations (Reck et al 2016). In this study, the median OS doubled in patients who received pembrolizumab compared with chemotherapy (30 versus 14 months) (Planchard et al 2018). In the subsequent KEYNOTE042 study, pembrolizumab monotherapy also demonstrated efficacy expanding the patients to PD-L1 ≥ 1% (Mok et al 2019), although this expansion was only approved in the US but not in the EU (Keytruda [pembrolizumab] United States Prescribing Information 2021, Keytruda [pembrolizumab] EPAR 2020). Additionally, atezolizumab represents another first-line treatment option in patients with PD-L1 selected NSCLC. In the Phase III IMpower110 study, patients were randomised 1:1 to receive atezolizumab, 1200 mg or platinum-based chemotherapy (for 4 or 6 cycles) once every 3 weeks (Spigel et al 2019). In an interim analysis, atezolizumab monotherapy improved OS compared with platinum-based chemotherapy as a first-line treatment of patients with wildtype NSCLC who had ≥ 50% expression of PD-L1 on TC3 or ≥ 10% expression on tumour infiltrating immune cells (IC3). Atezolizumab monotherapy improved OS by 7.1 months compared with chemotherapy alone. More recently, cemiplimab (Libtayo [cemiplimab] EPAR 2019) monotherapy has been approved for the first-line treatment of adult patients with locally advanced (not candidate for dCRT) or metastatic NSCLC expressing PD-L1 (in ≥ 50% TCs), with no EGFR, ALK, or receptor tyrosine kinase 1 aberration, based on EMPOWER Lung 1 study that showed statistically significant improvement in OS for patients randomised to cemiplimab as compared with chemotherapy (Sezer et al 2021).

Combinations of platinum-based chemotherapy and anti-PD-(L)1 inhibitors have reproducibly demonstrated superiority to standard platinum-based chemotherapy. Pembrolizumab, in combination with pemetrexed and platinum chemotherapy, is currently indicated for the first-line treatment of metastatic nonsquamous NSCLC in adults whose tumours have no EGFR or ALK positive mutations; and in combination with carboplatin and either paclitaxel or nab-PC for the first-line treatment of metastatic squamous NSCLC in adults (Keytruda [pembrolizumab] EPAR 2020). Nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy is indicated for the first-line treatment of metastatic NSCLC in adults whose tumours have no sensitising EGFR mutation or ALK translocation (Opdivo [nivolumab] EPAR 2021). Atezolizumab in combination with bevacizumab, paclitaxel and carboplatin, is indicated for the first-line treatment of adult patients with metastatic nonsquamous NSCLC. In patients with EGFR mutant or ALK-positive NSCLC it is indicated only after failure of appropriate targeted therapies (Tecentriq [atezolizumab] EPAR 2021). In the absence of contraindications and conditioned by the registration and accessibility of anti-PD(L1) combination with platinum-based chemotherapy, this strategy is preferred to platinum-based chemotherapy in patients with ECOG PS 0 to 1 and PD-L1 < 50% (Planchard et al 2018).

Platinum-based doublets are the recommended chemotherapy option in all Stage IV NSCLC patients with no contraindications to platinum compounds and an ECOG PS of 0 to 2. Platinum-based doublets with a third-generation cytotoxic agent (gemcitabine, vinorelbine, taxanes) are recommended in advanced squamous cell carcinoma patients without major comorbidities and ECOG PS 0 to 2. Pemetrexed based combination chemotherapy is preferred to gemcitabine or docetaxel-based combinations in patients with nonsquamous tumours. Pemetrexed use is restricted to nonsquamous cell carcinoma in any line of treatment in advanced disease. Bevacizumab might be considered with platinum-based regimens beyond paclitaxel/carboplatin in the absence of contraindications. Treatment with bevacizumab has shown encouraging efficacy and acceptable safety in patients with nonsquamous cell carcinoma and asymptomatic, untreated brain metastases (Planchard et al 2018).

Second-line Treatment of NSCLC Without Actionable Oncogenic Driver

Three ICI therapies have been approved by the European Medicines Agency in the second-line setting. The 3 approved therapies in the immunotherapy-naive, second-line setting include nivolumab, pembrolizumab and atezolizumab (Opdivo [nivolumab] EPAR 2021; Keytruda [pembrolizumab] EPAR 2020; Tecentriq [atezolizumab] EPAR 2021). Each has been approved based on Phase III studies demonstrating improved OS in comparison with docetaxel. Overall, there are no major differences in terms of efficacy or safety among these 3 therapies to inform a single optimal choice, and no comparative studies have been conducted. Nivolumab and atezolizumab are approved in patients with previously treated, advanced NSCLC irrespective of PD-L1 expression, while pembrolizumab is approved only in patients with PD-L1 ≥ 1% (Planchard et al 2018). In patients with progression after first-line immunotherapy with pembrolizumab monotherapy, platinum-based chemotherapy is recommended as second-line treatment option.

With the increasing adoption of ICI as the first-line therapy for advanced NSCLC, the number of patients who are not eligible for immunotherapy as the second-line option is also increasing given ICI is only approved in the immunotherapy-naive population. For those patients who are not immunotherapy-naive along with patients who are not suitable for immunotherapy due to

underlying medical conditions, chemotherapy remains the recommended treatment option. Docetaxel and pemetrexed (for nonsquamous cell only) are standard treatment options in second-line chemotherapy, with comparable efficacy. Moreover, docetaxel in combination either with ramucirumab or nintedanib is a treatment option in patients with NSCLC progressing after first-line chemotherapy or immunotherapy. In the REVEL study, ramucirumab, an antivascular endothelial growth factor receptor-2 antibody, in combination with docetaxel, showed a superior OS (median OS 10.5 versus 9.1 months, HR = 0.86, 95% CI 0.75 to 0.98, p = 0.032) and progression-free survival (PFS; modified PFS 4.5 versus 3 months, p < 0.0001) compared with docetaxel and placebo regardless of histology and represents a treatment option in patients with NSCLC progressing after first-line chemotherapy with ECOG PS 0 to 2. Nintedanib, an oral angiokinase inhibitor, improved PFS in combination with docetaxel compared with chemotherapy alone in the LUME1 study (modified PFS 3.4 versus 2.7 months, HR = 0.79, 95% CI 0.68 to 0.92, p = 0.0019) and represents a treatment option for patients with adenocarcinoma progressing after previous chemotherapy.

Erlotinib represents a potential second-, third-line treatment option, in particular for patients not suitable for immunotherapy or second-line chemotherapy in unknown EGFR status or EGFR wildtype tumours.

In patients with advanced squamous cell carcinoma with ECOG PS 0 to 2 unfit for chemotherapy or immunotherapy, afatinib is a potential option with unknown EGFR status or EGFR wildtype patients (Planchard et al 2018).

Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity

NSCLC originates from the epithelial cells of the lung and it is further divided into 3 main histological subtypes: adenocarcinoma, squamous cell carcinoma, and large cell carcinoma, among which adenocarcinoma constitutes around 40% of all NSCLC cases (Lungevity 2021).

NSCLC is associated with a relatively poor prognosis. Approximately 79.90% of NSCLC patients who die within the first 6 years of diagnoses, do so from the disease itself rather than comorbidities (Janssen-Heijnen et al 2015). In Europe, a multinational prospective cohort study including 3508 NSCLC patients enrolled consecutively from 01 January 2009 to 31 July 2009 were followed up for 12 months or until death, reported 1-year OS by disease stage at diagnosis and by histological subtype. The 1-year OS was the lowest for advanced stages, from 45% with a median OS time of 10.8 months for Stage IV, to 61% with a median OS time of 14.3 month for Stage IIIb, and the highest for first disease stages: 90% for Stage IIa, to 95% for Stage Ia. Among the histologic NSCLC subtypes, large cell carcinoma had a lower 1 year OS (48%) and a shorter OS time (median 11.9 months) compared with adenocarcinoma (58%, median OS time 14.4 months), squamous cell carcinoma (65%, median OS time > 15 months), and other histologies (64%, median OS time > 15 months) (Carrato et al 2014). Based on data from 21 cancer registries of 7 countries (as part of ICBP SURVMARK2 project), the 1 year and 3-year age-standardised net survival (alternative terms: disease-specific survival/CSS) were estimated for a total of 262,040 NSCLC patients, diagnosed during 2010 to 2014 and followed until 2015. For the included European countries, the 1-year CSS was highest for Norway (50.3%; 95% CI: 49.0 to 51.6), Denmark (49.4%; 95% CI: 48.3 to 50.4), Ireland (47.4%; 95% CI: 45.9 to 48.9) and slightly lower for the UK (44.3%; 95% CI: 43.9 to 44.7). The 3-year CSS showed a

similar pattern: highest for Norway (28.0%; 95% CI: 26.8 to 29.2), Denmark (26.2%; 95% CI: 25.2 to 27.1), Ireland (25.7%; 95% CI: 24.4 to 26.9) and slightly lower for UK (22.2%; 95% CI: 21.8 to 22.5). In Canada the 1-year CSS was reported as 53.0% (95% CI: 52.4 to 53.5) and 3-year CSS was 31.8% (95% CI: 31.2 to 32.3). For Australia, the 1-year CSS was 52.4% (95% CI: 51.6 to 53.2) and the 3-year CSS was 29.0% (95% CI: 28.3 to 29.8). For New Zealand, the 1-year CSS was 45.2% (95% CI: 43.6 to 46.7) and the 3-year CSS was 23.1 (95% CI: 21.7 to 24.4) (Morgan et al 2021).

In the US, Wang et al (2017) analysed the relative survival rate (RSR) in each decade between 1983 and 2012, in 573,987 NSCLC patients identified from the SEER registries. The 1-year RSR improved slightly from 39.7% (years: 1983 to 1992) to 40.9% (years: 1993 to 2002) to 45.5% (years: 2003 to 2012). The 5-year RSR improved slightly but remained very low across 3 decades, from 14.3% (years: 1983 to 1992), to 15.5% (years: 1993 to 2002) and to 18.4% (years: 2003 to 2012).

Important Comorbidities

In a retrospective medical record review of 9640 adults diagnosed with Stage I to III NSCLC treated with definitive resection in 2006 to 2007 and randomly selected from hospital based cancer registries participating in the US National Cancer Database, approximately two-thirds of the patients had at least 1 comorbidity (Wong et al 2018). The medical records from 30 days before surgery and up to 90 days after surgery indicated that the following comorbidities were present in at least 5% of patients: COPD (40.4%), coronary artery disease (20.8%), diabetes (15.4%), peripheral vascular disease (8.4%), and congestive heart failure (5.7%). Major comorbidities such as chronic obstructive pulmonary disease and cardiovascular diseases are highly prevalent in patients with LC, due to the strong association with cigarette smoking and ageing.

A secondary analysis of data from a Phase III study comparing 2 chemotherapy regimens for Stage IIIb or Stage IV NSCLC evaluated the association between severe comorbidities and skeletal muscle density (Grønberg et al 2019). Patients enrolled in the study had to have adequate bone marrow, kidney, and liver function, but other comorbidities were allowed. The mean age of the 263 patients was 65.5 years and 92% of patients were current or former smokers. Approximately half of the patients (48%) had severe comorbidities, defined as at least 1 organ system comorbidity with a Grade 3 (severe) or 4 (extremely severe) rating on the Cumulative Illness Rating Scale for Geriatrics. The most common Grade 3 or 4 ratings were for the respiratory (26%), heart (10%), and vascular (7%) systems.

PART II: MODULE SII NONCLINICAL PART OF THE SAFETY SPECIFICATION

Key safety findings from nonclinical studies and relevance to human use are shown in Table Part II: Module SII-1.

Table Part II: Module SII-1: Key Safety Findings From Nonclinical Studies

Key Safety Findings	Relevance to Human Usage
Toxicity	
Single- and Repeat Dose Toxicity No mortality or apparent toxicity was noted at single doses up to 100 mg/kg in mice or cynomolgus monkeys. No apparent toxicity and/or treatment-related changes were observed in cynomolgus monkeys after intravenous infusion at doses of 3, 10, 30 or 60 mg/kg once every 2 weeks for 13 weeks (7 dose administrations). At 60 mg/kg, there were treatment-related changes observed consistent with immunogenicity (antidrug antibodies [ADAs]) against tislelizumab and immune complex disease.	The risk of acute toxicities in patients is considered minimal. Immunogenicity-related changes in nonclinical species are not predictive for humans.
Reproductive/Developmental Toxicity	
No apparent treatment-related histopathological changes in tissues or organs, including male and female reproductive systems, were noted in the 13-week toxicity study in cynomolgus monkeys. However, not all animals were sexually mature in these studies. A literature-based assessment of effects on embryofoetal toxicity demonstrated that the pharmacologically mediated blockade of PD-1/PD-L1 interaction in animal models can result in foetal loss (Guleria et al 2005). This is due to disrupting immune tolerance to a foetus as there is a role played by the PD-1/PD-L1 pathway in the maintenance of tolerance to the foetus (Tripathi and Guleria 2015). The PD-1 binding to the abundantly expressed PD-L1 in tumours is analogous to the PD-1 binding to a highly expressed PD-L1 at the uteroplacental interface (Guleria et al 2005; Habicht et al 2007; Petroff and Perchellet 2010).	Based on the mechanism of action and published literature, tislelizumab may cause harm to the foetus. Women of childbearing potential should be advised to use effective methods of contraception and avoid pregnancy while taking tislelizumab and for at least 4 months after the last dose.
Genotoxicity	
Genotoxicity studies have not been conducted with tislelizumab since the range and type of genotoxicity studies routinely conducted for pharmaceuticals are not applicable to biotechnology-derived pharmaceuticals (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [ICH] S6[R1] 2011).	Not applicable.

Table Part II: Module SII-1: Key Safety Findings From Nonclinical Studies

Key Safety Findings	Relevance to Human Usage
Carcinogenicity	
Carcinogenicity studies have not been conducted with tislelizumab since they are not warranted to support marketing for therapeutics intended to treat patients with advanced cancer (ICH S9 2010).	Not applicable.
Cardiovascular, Nervous, and Respiratory Systems	
No specific concerns were identified on vital functions, including cardiovascular system, central nervous system (CNS), or respiratory system.	Based on nonclinical data, a direct impact on the functions of the cardiovascular, respiratory, and CNS systems is not expected.
Mechanisms for Drug Interactions	
No studies were conducted in line with ICH S6(R1) (2011).	The potential for drug-drug interaction between tislelizumab and small molecule drug products is very low, given that tislelizumab is a therapeutic mAb and is expected to be degraded into amino acids via catabolism; therefore, it is unlikely to influence drug metabolising enzymes or transporters.
Other Toxicity-related Information or Data	
Tislelizumab did not induce cytokine release in the human whole blood and peripheral blood mononuclear cell assays.	The risk of acute cytokine release syndrome is considered to be low.

PART II: MODULE SIII CLINICAL STUDY EXPOSURE

Overview of Clinical Development

Tislelizumab was studied in 4 indications as mentioned below:

- Tislelizumab as monotherapy is indicated for the treatment of adult patients with unresectable, locally advanced or metastatic OSCC after prior platinum-based chemotherapy.
- Tislelizumab in combination with pemetrexed and platinum-containing chemotherapy is indicated for the first-line treatment of adult patients with nonsquamous NSCLC whose tumours have PD-L1 expression on ≥ 50% of TCs with no EGFR or ALK positive mutations and who have:
  - locally advanced NSCLC and are not candidates for surgical resection or platinum-based chemoradiation, or
  - metastatic NSCLC.
- Tislelizumab in combination with carboplatin and either paclitaxel or nab-PC is indicated for the first-line treatment of adult patients with squamous NSCLC who have:
  - locally advanced NSCLC and are not candidates for surgical resection or platinum-based chemoradiation, or
  - metastatic NSCLC.
- Tislelizumab as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic NSCLC after prior platinum-based therapy. Patients with EGFR mutant or ALK positive NSCLC should also have received targeted therapies before receiving tislelizumab.

Pivotal Phase III Study in OSCC

The safety analysis of patients receiving tislelizumab is based primarily on the pivotal study, BGB-A317-302 (Study 302; Table Part II: Module SIII-1), which compared tislelizumab with chemotherapy in patients with OSCC. Safety data from the use of tislelizumab in patients with OSCC in other clinical studies and safety data from clinical studies evaluating tislelizumab in multiple tumour types are provided as supportive information.

The pivotal Study 302 population includes OSCC patients who received ≥ 1 dose of either tislelizumab 200 mg once every 3 weeks (tislelizumab arm – 255 patients) or investigator-chosen chemotherapy (ICC arm - 240 patients). The safety analysis results of the investigator-chosen chemotherapy patient population are not discussed in the RMP. The study population included patients with advanced unresectable or metastatic OSCC that had progressed during or after prior systemic therapy, and patients whose disease progressed during treatment of or within 6 months of cessation of neo-adjuvant/adjuvant chemotherapy or dCRT. This patient population was eligible for treatment with single-agent chemotherapy.

Pivotal Phase III Studies in NSCLC

Three ongoing pivotal Phase III studies contribute to the key safety data in this submission. In these studies, tislelizumab is being investigated for:

- Second- (or third-) line treatment of tislelizumab monotherapy in patients with previously treated locally advanced or metastatic NSCLC (Study BGB-A317-303) (Table Part II: Module SIII-1).
- First-line treatment in combination with chemotherapy of patients with locally advanced or metastatic nonsquamous NSCLC (Study BGB-A317-304) and squamous NSCLC (Study BGB-A317-307) (Table Part II: Module SIII-2).

Studies Providing Supportive Safety Data

Several supportive studies with tislelizumab in OSCC, NSCLC, and other cancers provided supportive safety data in this submission.

- Safety data from Studies BGB-A317-001, BGB-A317-102, BGB-A317-203, BGB-A317-204, BGB-A317-208, and BGB-A317-303 were supportive to BGB-A317-302 in the second- (or third-) line treatment of patients with advanced unresectable or metastatic OSCC. In all of these studies, tislelizumab was given as monotherapy; these studies form the tislelizumab monotherapy safety pool (Table Part II: Module SIII-1).
- Safety data from Studies BGB-A317-001, BGB-A317-102, BGB-A317-302, BGB-A317-208, BGB-A317-204 and BGB-A317-203 were supportive to Study BGB-A317-303 in second- (or third-) line treatment of patients with previously treated locally advanced or metastatic NSCLC. In all abovementioned studies, tislelizumab was given as monotherapy.
- Study BGB-A317-206 with the combination of tislelizumab and chemotherapy was supportive to Studies BGB-A317-307 and BGB-A317-304 for first-line treatment of patients with locally advanced or metastatic squamous or nonsquamous NSCLC. All 3 studies used tislelizumab in combination with chemotherapy (Table Part II: Module SIII-2). Study 206 also included a cohort of 17 small cell LC patients which were excluded from this analysis of safety in NSCLC patients (Table Part II: Module SIII-2).

All analyses were performed in the Tislelizumab Safety Analysis Set. The Tislelizumab Safety Analysis Set includes all patients who received at least 1 dose of tislelizumab, either as monotherapy or in combination with other study drug. Patients in the tislelizumab + chemotherapy arms in Studies BGB-A317-304, BGB-A317-307 who crossed over to receive tislelizumab were excluded from the analysis sets.

Table Part II: Module SIII-1 and Table Part II: Module SIII-2, below, present a summary of the monotherapy and combination therapy studies, respectively, included in assessments of efficacy and safety.

Table Part II: Module SIII-1: Details of Tislelizumab Monotherapy Studies

Study Numbers (Disease Type; Location)	Data Cutoff Dates	Tislelizumab Dose	Number of Patients who Received Tislelizumab
Pivotal Studies			
BGB-A317-302 (Advanced unresectable or metastatic OSCC, with disease progression during or after 1L systemic therapy; Global) A randomized, controlled, open-label, global Phase III study comparing the efficacy of the anti-PD-1 antibody tislelizumab versus chemotherapy as second-line treatment in patients with advanced unresectable/metastatic esophageal squamous cell carcinoma (hereafter referred to as Study 302).	01 December 2020	200 mg Q3W	255
BGB-A317-303 (NSCLC in the second- or third-line setting; Global) A Phase III, open-label, multicenter, randomized study to investigate the efficacy and safety of tislelizumab (anti-PD-1 antibody) compared with docetaxel in patients with NSCLC who have progressed on a prior platinum-containing regimen (hereafter referred to as Study 303).	10 August 2020	200 mg Q3W	534
Supporting Studies			
BGB-A317_Study_001 (Advanced tumours; Global) A Phase Ia/Ib, open label, multiple-dose, dose escalation and expansion study to investigate the safety, pharmacokinetics (PK) and antitumor activities of the anti-PD-1 mAb, tislelizumab, in patients with advanced tumors (hereafter referred to as Study 001).	26 August 2020	0.5, 2, 5 or 10 mg/kg Q2W 2 or 5 mg/kg Q3W 200 mg Q3W	451

Table Part II: Module SIII-1: Details of Tislelizumab Monotherapy Studies

Study Numbers (Disease Type; Location)	Data Cutoff Dates	Tislelizumab Dose	Number of Patients who Received Tislelizumab
BGB-A317-102 (Advanced solid tumours; China) A Phase I/II study investigating safety, tolerability, PK, and preliminary antitumor activities of anti-PD-1 mAb, tislelizumab, in patients with advanced solid tumors (hereafter referred to as Study 102).	31 May 2020	200 mg Q3W; 200 mg W1D1, W5D1, then Q3W	300
BGB-A317-203 (Relapsed or refractory classical Hodgkin lymphoma; China) A single arm, multicenter, Phase II study of tislelizumab as monotherapy in relapsed or refractory classical Hodgkin lymphoma (hereafter referred to as Study 203).	26 November 2018	200 mg Q3W	70
BGB-A317-204 (PD-L1+ locally advanced or metastatic urothelial cancer; China and South Korea) A single-arm, multicenter, Phase II study of tislelizumab in patients with previously treated PD-L1+ locally advanced or metastatic urothelial cancer (hereafter referred to as Study 204).	16 September 2019	200 mg Q3W	113
BGB-A317-208 (Previously treated hepatocellular unresectable carcinoma; Global) A Phase II, open-label, multicenter study to investigate the efficacy, safety, and PK of the anti-PD-1 mAb, tislelizumab, in patients with previously treated hepatocellular unresectable carcinoma (hereafter referred to as Study 208).	27 February 2020	200 mg Q3W	249
Total Patients who Received Tislelizumab as Monotherapy			**1972**

Abbreviations: 1L, first-line; mAb, monoclonal antibody; NSCLC, non-small cell lung cancer; OSCC, oesophageal squamous cell carcinoma; PD-1, programmed cell death protein-1; PD-L1, programmed cell death ligand-1; PK, pharmacokinetic(s); QxW, every x weeks; WxDy, Week x Day y.

Table Part II: Module SIII-2: Details of Tislelizumab Chemotherapy Combination Therapy Studies

Study Numbers (Disease Type; Location)	Data Cutoff Dates	Tislelizumab Dose	Number of Patients who Received Tislelizumab
Pivotal Studies			
BGB-A317-304[a] (NSQ NSCLC; China) A Phase III, randomized, open-label study enrolling patients with untreated locally advanced or metastatic (Stage IIIB or IV) non-squamous NSCLC (hereafter referred to as Study 304).	26 October 2020	Induction Phase: *Arm T + PP* Tislelizumab 200 mg IV D1 Q3W Cisplatin 75 mg/m^2 or Carboplatin AUC 5 Pemetrexed 500 mg/m^2 (Chemotherapy administered 4-6 cycles Q3W) *Arm PP* Cisplatin 75 mg/m^2 or Carboplatin AUC 5 Pemetrexed 500 mg/m^2 (Chemotherapy administered 4-6 cycles Q3W) Maintenance Phase: *Arm T + PP* Tislelizumab 200 mg IV D1 Q3W Pemetrexed 500 mg/m^2 *Arm PP*[b] Pemetrexed 500 mg/m^2	222

Table Part II: Module SIII-2: Details of Tislelizumab Chemotherapy Combination Therapy Studies

Study Numbers (Disease Type; Location)	Data Cutoff Dates	Tislelizumab Dose	Number of Patients who Received Tislelizumab
BGB-A317-307[a] (SQ NSCLC; China) A Phase III, multicenter, randomized, open-label study to compare the efficacy and safety of tislelizumab combined with paclitaxel plus carboplatin or nab-PC plus carboplatin versus paclitaxel plus carboplatin alone as first-line treatment for untreated advanced squamous NSCLC (hereafter referred to as Study 307).	30 September 2020	*Arm T + PC* Tislelizumab 200 mg IV D1 Q3W Paclitaxel 175 mg/m^2 D1 Q3W Carboplatin AUC 5 D1 Q3W (Paclitaxel and carboplatin administered 4-6 cycles) *Arm T + nab-PC* Tislelizumab 200 mg IV D1 Q3W nab-PC 100 mg/m^2 D1, 8, 15 Q3W Carboplatin AUC 5 D1 Q3W (nab-PC and carboplatin administered 4-6 cycles) *Arm PC*[b] Paclitaxel 175 mg/m^2 D1 Carboplatin AUC 5 D1 (Q3W for 4 to 6 cycles)	238
Supporting Study			
BGB-A317-206[c] (NSQ NSCLC, SQ NSCLC, SCLC; China) A Phase II, multi-cohort study of tislelizumab in combination with standard chemotherapy as first-line treatment in Chinese patients with locally advanced or metastatic LC to evaluate the antitumor activity of	31 December 2019	<u>NSQ:</u> *Arm T + PP* Tislelizumab + pemetrexed + cisplatin (or carboplatin) Q3W 4 cycles, followed by tislelizumab Q3W + pemetrexed Q3W <u>SQ-A:</u>	37 NSCLC patients

Table Part II: Module SIII-2: Details of Tislelizumab Chemotherapy Combination Therapy Studies

Study Numbers (Disease Type; Location)	Data Cutoff Dates	Tislelizumab Dose	Number of Patients who Received Tislelizumab
tislelizumab in combination with platinum-containing doublet chemotherapy (hereafter referred to as Study 206).		*Arm T + PC* Tislelizumab + paclitaxel + cisplatin (or carboplatin) Q3W 4-6 cycles, followed by tislelizumab Q3W SQ-B: *Arm T + GC* Tislelizumab + gemcitabine + cisplatin (or carboplatin) Q3W 4-6 cycles, followed by tislelizumab Q3W SCLC: Tislelizumab + etoposide + cisplatin (or carboplatin) Q3W 4-6 cycles, followed by tislelizumab Q3W	
Total Patients who Received Tislelizumab as Combination Therapy			**497**

Abbreviations: AUC, area under the curve; D, day; GC, gemcitabine + cisplatin/carboplatin; IV, intravenous; LC, lung cancer; nab-PC, nab-paclitaxel; NSCLC, non-small cell lung cancer; NSQ, nonsquamous; PC, paclitaxel + carboplatin/carboplatin; PP, pemetrexed + platinum; SCLC, small cell lung cancer; SQ, squamous; Q3W, every 3 weeks; T, tislelizumab.

[a] Tislelizumab treated patients who switched from the chemotherapy control arms in Studies 304 and 307 were not included.

[b] Optional crossover to receive tislelizumab 200 mg IV upon disease progression.

[c] 17 patients from SCLC cohort in Study 206 were not included.

Extent of Exposure

Exposure to tislelizumab in clinical studies is summarised in Table Part II: Module SIII-3 through Table Part II: Module SIII-6 by duration of exposure, by age group and sex, by dose, and by race, including ethnic origin.

Table Part II: Module SIII-3: Duration of Tislelizumab Exposure (All Tislelizumab Treated Population)

Duration of Exposure	Patients n (%)	Person Time
Total Population		
< 1 month	189 (7.7)	126.53
1 - < 3 months	758 (30.7)	1536.42
3 - < 6 months	460 (18.6)	2049.65
6 - < 12 months	472 (19.1)	4003.25
12 - < 18 months	301 (12.2)	4483.57
18 - < 24 months	176 (7.1)	3589.13
> 24 months	113 (4.6)	3501.70
Total	**2469 (100.0)**	**19,290.25**
OSCC		
< 1 month	38 (12.4)	24.18
1 - < 3 months	138 (45.0)	286.78
3 - < 6 months	56 (18.2)	245.36
6 - < 12 months	42 (13.7)	358.31
12 - < 18 months	14 (4.6)	203.10
18 - < 24 months	14 (4.6)	290.50
> 24 months	5 (1.6)	139.40
Total	**307 (100.0)**	**1547.63**
1L SQ NSCLC		
< 1 month	14 (5.4)	9.63
1 - < 3 months	28 (10.8)	53.94
3 - < 6 months	44 (16.9)	223.54
6 - < 12 months	72 (27.7)	664.03
12 - < 18 months	49 (18.8)	758.64
18 - < 24 months	45 (17.3)	923.45
> 24 months	8 (3.1)	202.12
Total	**260 (100.0)**	**2835.35**

Table Part II: Module SIII-3: Duration of Tislelizumab Exposure (All Tislelizumab Treated Population)

Duration of Exposure	Patients n (%)	Person Time
1L NSQ NSCLC		
< 1 month	14 (5.8)	9.66
1 - < 3 months	27 (11.3)	63.54
3 - < 6 months	45 (18.8)	210.04
6 - < 12 months	67 (27.9)	561.07
12 - < 18 months	52 (21.7)	818.94
18 - < 24 months	31 (12.9)	637.59
> 24 months	4 (1.7)	105.53
Total	**240 (100.0)**	**2406.37**
2L+ NSCLC		
< 1 month	44 (6.9)	28.06
1 - < 3 months	177 (27.8)	359.52
3 - < 6 months	136 (21.4)	595.61
6 - < 12 months	140 (22.0)	1173.75
12 - < 18 months	69 (10.8)	1004.91
18 - < 24 months	35 (5.5)	719.54
> 24 months	35 (5.5)	1059.06
Total	**636 (100.0)**	**4940.45**

Abbreviations: 1L, first-line; 2L+, second-line onwards; NSCLC, non-small cell lung cancer; NSQ, nonsquamous; OSCC, oesophageal squamous cell carcinoma; SCLC, small cell lung cancer; SQ, squamous.
Source data: Annex 7 Table 1.1 and Annex 7 Table 1.2.
The statistical outputs for tislelizumab were generated to support 2 indications – NSCLC and OSCC. Hence, the footnote of all exposure tables in Annex 7 refers to data from both monotherapy studies (302, 303, 001, 102, 203, 204, 208) and combination therapy studies (304, 307, 206). However, as detailed in Part II Module SIII Clinical Study Exposure, the data for OSCC population is derived from monotherapy studies (302, 303, 001, 102, 203, 204, 208) only.
Tislelizumab treated patients who switched from the chemotherapy control arms in Studies 304 and 307 were not included. Patients from SCLC cohort in Study 206 were not included.
Person time is sum of treatment duration (months) for all patients in the row.
Percentages are based on the number of patients who received at least a dose of tislelizumab.

Table Part II: Module SIII-4: Exposure of Tislelizumab by Age Group and Sex (All Tislelizumab Treated Population)

Age Group	Sex			
	Male		Female	
	Persons n (%)	Person Time	Persons n (%)	Person Time
OSCC				
≥ 18 and < 55 years	58 (18.9)	213.42	13 (4.2)	59.04
≥ 55 and < 65 years	110 (35.8)	616.48	12 (3.9)	27.76
≥ 65 and < 75 years	76 (24.8)	450.27	22 (7.2)	118.28
≥ 75 years	12 (3.9)	47.28	4 (1.3)	15.11
Total	**256 (83.4)**	**1327.44**	**51 (16.6)**	**220.19**
1L SQ NSCLC				
≥ 18 and < 55 years	37 (14.2)	430.53	10 (3.8)	116.87
≥ 55 and < 65 years	109 (41.9)	1132.74	7 (2.7)	78.29
≥ 65 and < 75 years	91 (35.0)	1003.48	6 (2.3)	73.44
≥ 75 years	0 (0.0)	0	0 (0.0)	0
Total	**237 (91.2)**	**2566.75**	**23 (8.8)**	**268.60**
1L NSQ NSCLC				
≥ 18 and < 55 years	35 (14.6)	362.07	22 (9.2)	217.46
≥ 55 and < 65 years	89 (37.1)	892.50	27 (11.3)	298.86
≥ 65 and < 75 years	49 (20.4)	480.28	13 (5.4)	111.31
≥ 75 years	5 (2.1)	43.90	0 (0.0)	0
Total	**178 (74.2)**	**1778.74**	**62 (25.8)**	**627.63**
2L+ NSCLC				
≥ 18 and < 55 years	108 (17.0)	942.09	59 (9.3)	373.06
≥ 55 and < 65 years	208 (32.7)	1551.74	58 (9.1)	394.45
≥ 65 and < 75 years	151 (23.7)	1275.79	35 (5.5)	296.38
≥ 75 years	13 (2.0)	83.94	4 (0.6)	23.00
Total	**480 (75.5)**	**3853.57**	**156 (24.5)**	**1086.88**

Abbreviations: 1L, first-line; 2L+, second-line onwards; NSCLC, non-small cell lung cancer; NSQ, nonsquamous; OSCC, oesophageal squamous cell carcinoma; SCLC, small cell lung cancer; SQ, squamous.
Source data: Annex 7 Table 1.5.
The statistical outputs for tislelizumab were generated to support 2 indications – NSCLC and OSCC. Hence, the footnote of all exposure tables in Annex 7 refers to data from both monotherapy studies (302, 303, 001, 102, 203, 204, 208) and combination therapy studies (304, 307, 206). However, as detailed in Part II Module SIII Clinical Study Exposure, the data for OSCC population is derived from monotherapy studies (302, 303, 001, 102, 203, 204, 208) only.

Tislelizumab treated patients who switched from the chemotherapy control arms in Studies 304 and 307 were not included. Patients from SCLC cohort in Study 206 were not included.
Person time is sum of treatment duration (months) for all patients in the row.
Percentages are based on the number of patients who received at least a dose of tislelizumab.

Table Part II: Module SIII-5: Exposure of Tislelizumab by Dose (All Tislelizumab Treated Population)

Dose Level of Exposure	Persons n (%)	Person Time
OSCC		
200 mg Q3W	281 (91.5)	1417.20
5.0 mg/kg Q3W	26 (8.5)	130.43
2.0 mg/kg Q3W	0 (0.0)	0
10.0 mg/kg Q2W	0 (0.0)	0
5.0 mg/kg Q2W	0 (0.0)	0
2.0 mg/kg Q2W	0 (0.0)	0
0.5 mg/kg Q2W	0 (0.0)	0
Total	**307 (100.0)**	**1547.63**
1L SQ NSCLC		
200 mg Q3W	260 (100.0)	2835.35
5.0 mg/kg Q3W	0 (0.0)	0
2.0 mg/kg Q3W	0 (0.0)	0
10.0 mg/kg Q2W	0 (0.0)	0
5.0 mg/kg Q2W	0 (0.0)	0
2.0 mg/kg Q2W	0 (0.0)	0
0.5 mg/kg Q2W	0 (0.0)	0
Total	**260 (100.0)**	**2835.35**
1L NSQ NSCLC		
200 mg Q3W	238 (99.2)	2397.34
5.0 mg/kg Q3W	2 (0.8)	9.03
2.0 mg/kg Q3W	0 (0.0)	0
10.0 mg/kg Q2W	0 (0.0)	0
5.0 mg/kg Q2W	0 (0.0)	0
2.0 mg/kg Q2W	0 (0.0)	0
0.5 mg/kg Q2W	0 (0.0)	0
Total	**240 (100.0)**	**2406.37**

Table Part II: Module SIII-5: Exposure of Tislelizumab by Dose (All Tislelizumab Treated Population)

Dose Level of Exposure	Persons n (%)	Person Time
2L+ NSCLC		
200 mg Q3W	589 (92.6)	4531.45
5.0 mg/kg Q3W	47 (7.4)	409.00
2.0 mg/kg Q3W	0 (0.0)	0
10.0 mg/kg Q2W	0 (0.0)	0
5.0 mg/kg Q2W	0 (0.0)	0
2.0 mg/kg Q2W	0 (0.0)	0
0.5 mg/kg Q2W	0 (0.0)	0
Total	**636 (100.0)**	**4940.45**

Abbreviations: 1L, first-line; 2L+, second-line onwards; NSCLC, non-small cell lung cancer; NSQ, nonsquamous; OSCC, oesophageal squamous cell carcinoma; QxW, every x weeks; SCLC, small cell lung cancer; SQ, squamous.
Source data: Annex 7 Table 1.3.
The statistical outputs for tislelizumab were generated to support 2 indications – NSCLC and OSCC. Hence, the footnote of all exposure tables in Annex 7 refers to data from both monotherapy studies (302, 303, 001, 102, 203, 204, 208) and combination therapy studies (304, 307, 206). However, as detailed in Part II Module SIII Clinical Study Exposure, the data for OSCC population is derived from monotherapy studies (302, 303, 001, 102, 203, 204, 208) only.
Tislelizumab treated patients who switched from the chemotherapy control arms in Studies 304 and 307 were not included. Patients from SCLC cohort in Study 206 were not included.
Person time is sum of treatment duration (months) for all patients in the row.
Percentages are based on the number of patients who received at least a dose of tislelizumab.

Table Part II: Module SIII-6: Exposure of Tislelizumab by Race (All Tislelizumab Treated Population)

Race	Persons n (%)	Person Time
OSCC		
American Indian or Alaska Native	0 (0.0)	0
Asian	246 (80.1)	1265.51
Black or African American	1 (0.3)	0.16
Native Hawaiian or Other Pacific Islander	0 (0.0)	0
White	58 (18.9)	279.26
Other	0 (0.0)	0
Not Reported	2 (0.7)	2.69
Total	**307 (100.0)**	**1547.63**

Table Part II: Module SIII-6: Exposure of Tislelizumab by Race (All Tislelizumab Treated Population)

Race	Persons n (%)	Person Time
1L SQ NSCLC		
American Indian or Alaska Native	0 (0.0)	0
Asian	260 (100.0)	2835.35
Black or African American	0 (0.0)	0
Native Hawaiian or Other Pacific Islander	0 (0.0)	0
White	0 (0.0)	0
Other	0 (0.0)	0
Not Reported	0 (0.0)	0
Total	**260 (100.0)**	**2835.35**
1L NSQ NSCLC		
American Indian or Alaska Native	0 (0.0)	0
Asian	238 (99.2)	2397.34
Black or African American	0 (0.0)	0
Native Hawaiian or Other Pacific Islander	0 (0.0)	0
White	2 (0.8)	9.03
Other	0 (0.0)	0
Not Reported	0 (0.0)	0
Total	**240 (100.0)**	**2406.37**
2L+ NSCLC		
American Indian or Alaska Native	12 (1.9)	70.11
Asian	499 (78.5)	3956.57
Black or African American	2 (0.3)	8.31
Native Hawaiian or Other Pacific Islander	4 (0.6)	47.74
White	115 (18.1)	844.75
Other	4 (0.6)	12.98
Not Reported	0 (0.0)	0
Total	**636 (100.0)**	**4940.45**

Abbreviations: 1L, first-line; 2L+, second-line onwards; NSCLC, non-small cell lung cancer; NSQ, nonsquamous; OSCC, oesophageal squamous cell carcinoma; SCLC, small cell lung cancer; SQ, squamous.
Source data: Annex 7 Table 1.9.
The statistical outputs for tislelizumab were generated to support 2 indications – NSCLC and OSCC. H Hence, the footnote of all exposure tables in Annex 7 refers to data from both monotherapy studies (302, 303, 001, 102, 203, 204, 208) and combination therapy studies (304, 307, 206). However, as detailed in Part II Module SIII Clinical

Study Exposure, the data for OSCC population is derived from monotherapy studies (302, 303, 001, 102, 203, 204, 208) only.
Tislelizumab treated patients who switched from the chemotherapy control arms in Studies 304 and 307 were not included. Patients from SCLC cohort in Study 206 were not included.
Person time is sum of treatment duration (months) for all patients in the row.
Percentages are based on the number of patients who received at least a dose of tislelizumab.
Annex 7 Table 1.8 provides the information regarding ethnic origin (Hispanic or Latino [0.5%], Not Hispanic or Latino [93.5%], Not reported [6.0%], for any of the indications).

PART II: MODULE SIV POPULATIONS NOT STUDIED IN CLINICAL STUDIES

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Table Part II: Module SIV-1: Important Exclusion Criteria in Pivotal Clinical Studies Across the Development Programme

Active Autoimmune Diseases or History of Autoimmune Diseases. Patients with the Following Autoimmune Diseases were Allowed: Controlled Type 1 Diabetes, Hypothyroidism Managed with Hormone Replacement Therapy only, Controlled Celiac Disease, Skin Diseases not Requiring Systemic Treatment (such as vitiligo, psoriasis or alopecia), or Diseases not Expected to Recur in the Absence of External Triggering Factors.	
Reason for Being an Exclusion Criterion	By disrupting PD-1-mediated signalling, tislelizumab acts to restore antitumour immunity and halt progression of tumour growth. This restoration of immune function may result in immune-mediated adverse reactions involving one or more body systems, which can be life-threatening or fatal in rare cases. Patients with active or history of autoimmune diseases that may relapse were excluded from clinical studies as it is unknown if the use of tislelizumab in these patients may worsen the existing autoimmune condition based on the mechanism of action of tislelizumab.
Considered to be Included as Missing Information	No
Rationale (if not included as missing information)	Tislelizumab has not been specifically studied in patients with active autoimmune diseases or history of autoimmune diseases; however, patients with autoimmune diseases have been included in clinical studies. Additionally, the treating physician would be expected to evaluate the benefit and risks in individual patients and follow patients closely for any evidence of immune-mediated adverse events (imAEs) and intervene promptly (SmPC). Routine monitoring of reports of patients with active autoimmune diseases or history of autoimmune diseases in context of Periodic Reporting appears to adequately contribute to further characterisation.
Prior Active Malignancy Within 2 to 3 Years, or Active Leptomeningeal Disease, or Uncontrolled and Untreated Brain Metastases. (In Studies 302, 303, 304, 307, 309, patients with a history of treated and, at the time of screening, asymptomatic CNS metastases were eligible, provided they met the specified criteria in the protocol.)	
Reason for Being an Exclusion Criterion	The studies were conducted in specific patient populations. Other malignant cancer or the local treatment for CNS metastasis may impact the interpretation of study results.
Considered to be Included as Missing Information	No
Rationale (if not included as missing information)	These patients were excluded from the studies and there is no expectation that the safety profile would be different. However, the treating physician would be expected to evaluate the benefits and risks in individual patients as the additional pharmacotherapy needed

Table Part II: Module SIV-1: Important Exclusion Criteria in Pivotal Clinical Studies Across the Development Programme

	to treat other malignancy or local treatment for CNS metastasis can confound efficacy and safety assessment.
Conditions Requiring Systemic Treatment With Corticosteroids or Other Immunosuppressive Medications.	
Reason for Being an Exclusion Criterion	Immunosuppressive medications may attenuate the effects of anti-PD-1 treatment. Such conditions may impact the interpretation of study results.
Considered to be Included as Missing Information	No
Rationale (if not included as missing information)	Prior to starting tislelizumab, corticosteroids and other immunosuppressants should be avoided because of their potential interference with the pharmacodynamic activity of tislelizumab. For the same reason, these patients were excluded in the clinical studies. However, systemic corticosteroids and other immunosuppressants can be used after starting tislelizumab to treat immune-mediated adverse reactions, in the postmarketing setting.
History of Interstitial Lung Disease, Noninfectious Pneumonitis or Uncontrolled Systemic Diseases, Including Diabetes, Hypertension, Pulmonary Fibrosis, Acute Lung Diseases.	
Reason for Being an Exclusion Criterion	Such conditions may impact the interpretation of study results.
Considered to be Included as Missing Information	No
Rationale (if not included as missing information)	These patients may benefit from treatment with tislelizumab; however, such conditions and associated therapies may confound efficacy and safety assessment of the study and were therefore excluded. The treating physician would be expected to evaluate the benefits and risks in individual patients.
History of Severe Hypersensitivity Reactions to mAbs.	
Reason for Being an Exclusion Criterion	To reduce the risk of a patient experiencing hypersensitivity to tislelizumab.
Considered to be Included as Missing Information	No
Rationale (if not included as missing information)	Hypersensitivity to tislelizumab is listed as a contraindication in the EU SmPC.
Prior Therapy Targeting PD-1 or PD-L1.	
Reason for Being an Exclusion Criterion	Prior therapy targeting PD-1 or PD-L1 may impact the interpretation of study results.
Considered to be Included as Missing Information	No
Rationale (if not included as missing information)	The target population is intended to be naive to treatment with anti-PD-1/PD-L1 therapy.

Table Part II: Module SIV-1: Important Exclusion Criteria in Pivotal Clinical Studies Across the Development Programme

Use of Live or Attenuated Vaccines Within 4 Weeks.	
Reason for Being an Exclusion Criterion	Use of live or attenuated vaccines within 4 weeks may impact the interpretation of study results.
Considered to be Included as Missing Information	No
Rationale (if not included as missing information)	Live vaccines are not recommended for patients who are receiving immune-oncology therapies (Cancer Research UK 2019). Accordingly, patients who received live vaccines within 4 weeks from the start of treatment were excluded from clinical studies for tislelizumab.
Prior Chemotherapy, Radiation Therapy, Immunotherapy Within ≤ 28 Days or ≤ 5 Half-lives, Whichever is Shorter.	
Reason for Being an Exclusion Criterion	Carryover of the effect from prior chemotherapy, radiation therapy, immunotherapy within 2 weeks may impact the interpretation of study results.
Considered to be Included as Missing Information	No
Rationale (if not included as missing information)	These patients may benefit from treatment with tislelizumab; however, to avoid carryover effects, patients were required to wait 2 weeks after discontinuation of prior therapy before enrolling in the study. There is no expectation that the tislelizumab safety profile would be different. However, in the postmarketing setting the treating physician would be expected to evaluate the benefits and risks in individual patients.
Prior Allogeneic or Solid Organ Transplantation.	
Reason for Being an Exclusion Criterion	Prior allogeneic or solid organ transplantation may impact the interpretation of study results. Treatment with PD-1 blocking antibodies may increase the risk of rejection in solid organ transplant recipients and increase the risk of postallogeneic haematopoietic stem cell transplantation complications.
Considered to be Included as Missing Information	No
Rationale (if not included as missing information)	The treating physician would be expected to evaluate the benefit and risks in individual patients and follow patients closely for evidence of transplant-related complications and intervene promptly (SmPC).
Clinically Important Cardiovascular Impairment. (eg, heart failure of New York Heart Association cardiac disease Class III or greater, myocardial infarction, unstable arrhythmias, or unstable angina.)	
Reason for Being an Exclusion Criterion	Cardiovascular impairment may also impact the interpretation of study results; however, the risk of affecting patients' cardiovascular function is considered to be low since no apparent effects on cardiovascular function were identified in nonclinical studies.

Table Part II: Module SIV-1: Important Exclusion Criteria in Pivotal Clinical Studies Across the Development Programme

Considered to be Included as Missing Information	No
Rationale (if not included as missing information)	As discussed in Table Part II: Module SII-1, no apparent effects on cardiovascular function were identified in nonclinical studies.
Severe Hepatic Impairment. (eg, serum total bilirubin ≥ 1.5 x upper limit of normal [ULN], or serum total bilirubin ≥ 34.2 µmol/L [2 mg/dL] for patients with hepatocellular carcinoma [HCC]; aspartate aminotransferase [AST] and alanine aminotransferase [ALT] ≥ 2.5 x ULN, or AST and ALT ≥ 5 x ULN for patients with liver metastases or HCC.)	
Reason for Being an Exclusion Criterion	Severe hepatic impairment may impact the interpretation of study results.
Considered to be Included as Missing Information	No
Rationale (if not included as missing information)	Tislelizumab is a mAb and unlikely to be metabolised by the liver. As such, formal pharmacokinetic (PK) interaction studies have not been conducted and are not warranted.
Severe Renal Impairment. (eg, estimated glomerular filtration rate < 30 mL/min/1.73 m^2 by Chronic Kidney Disease Epidemiology Collaboration Equation [Levey et al 2009; Stevens and Levin 2013].)	
Reason for Being an Exclusion Criterion	Severe renal impairment may impact the interpretation of study results.
Considered to be Included as Missing Information	No
Rationale (if not included as missing information)	Tislelizumab is a mAb and unlikely to be metabolised by the kidneys. As such, formal PK interaction studies have not been conducted and are not warranted.
Severe Chronic or Active Infections Requiring Systemic Therapy.	
Reason for Being an Exclusion Criterion	Infection may impact the interpretation of study results.
Considered to be Included as Missing Information	No
Rationale (if not included as missing information)	There is no evidence that tislelizumab worsens bacterial infections. These patients may benefit from treatment. The treating physician would be expected to evaluate the benefits and risks in individual patients.
Untreated Chronic Hepatitis B Virus (HBV) or Chronic HBV Carriers with HBV DNA ≥ 200 to 500 IU/mL (1000 to 2500 copies/mL), or Active Hepatitis C Virus (HCV), or HIV Infection. (Active HCV and major surgery within 28 days were exclusion criteria for non-HCC indications only.)	
Reason for Being an Exclusion Criterion	Infection may impact the interpretation of study results.
Considered to be Included as Missing Information	No

Table Part II: Module SIV-1: Important Exclusion Criteria in Pivotal Clinical Studies Across the Development Programme

Rationale (if not included as missing information)	Patients with HCV and HBV have been included in clinical studies investigating the use of tislelizumab. There is no evidence that tislelizumab worsens viral infections. These patients may benefit from treatment. The treating physician would be expected to evaluate the benefits and risks in individual patients.
Patients Aged < 18 Years.	
Reason for Being an Exclusion Criterion	Paediatric patients were not included in the clinical development programme.
Considered to be Included as Missing Information	No
Rationale (if not included as missing information)	Use in paediatric patients is not recommended and is also not expected considering the indications' incidence/prevalence in this age group.
Use During Pregnancy or Lactation.	
Reason for Being an Exclusion Criterion	The blockade of the PD-1/PD-L1 pathway in inducing foetal loss/abortion has been shown in murine models of allogeneic pregnancy. Therefore, the potential risks of administering tislelizumab during pregnancy include increased rates of abortion or stillbirth and women of childbearing potential should be advised to avoid pregnancy and breastfeed while taking tislelizumab.
Considered to be Included as Missing Information	No
Rationale (if not included as missing information)	There is no available human data regarding the risk of embryofoetal toxicity. Women of childbearing potential should be advised to use effective contraception during treatment with tislelizumab and for 4 months after the last dose (SmPC). This topic is covered within the important potential risk of reproductive and developmental toxicity.
Uncontrollable Pleural Effusion, Pericardial Effusion, or Ascites Requiring Repeated Drainage.	
Reason for Being an Exclusion Criterion	Such conditions may impact the interpretation of study results.
Considered to be Included as Missing Information	No
Rationale (if not included as missing information)	General exclusion criterion to ensure patient safety in clinical studies not associated with specific safety concerns for tislelizumab. These patients may benefit from treatment with tislelizumab. In the postmarketing setting, the treating physician would be expected to evaluate the benefits and risks in individual patients.
Major Surgery Within 28 Days. (Active HCV and major surgery within 28 days were exclusion criteria for non-HCC indications only.)	
Reason for Being an Exclusion Criterion	To ensure patient safety. Major surgery within 4 weeks of entering the study may impact the interpretation of study results.

Table Part II: Module SIV-1: Important Exclusion Criteria in Pivotal Clinical Studies Across the Development Programme

Considered to be Included as Missing Information	No
Rationale (if not included as missing information)	These patients may benefit from treatment with tislelizumab; however, major surgery may confound efficacy and safety assessment of the study. In the postmarketing setting, it is expected that the treating physician will evaluate when the individual patient has recovered enough from major surgery to receive new anticancer therapy.

SIV.2 Limitations to Detect Adverse Reactions in the Tislelizumab Clinical Study Development Programme

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Study Development Programmes

Table Part II: Module SIV-2: Exposure of Special Populations Included or Not in Clinical Study Development Programmes

Type of Special Population	Exposure
Pregnant Women	Not included in the clinical development programme.
Breastfeeding Women	Not included in the clinical development programme.
Patients with Relevant Comorbidities:	
Patients with Renal Impairment (Defined as estimated glomerular filtration rate 60 to 89 mL/min/1.73 m^2, mild; 30 to 59 mL/min/1.73 m^2, moderate; and 15 to 29 mL/min/1.73 m^2, severe; using the Chronic Kidney Disease Epidemiology Collaboration Equation [Levey et al 2009; Stevens and Levin 2013].)	Renal impairment was reported in 1053/2469 (42.6%) patients (8709.16 person time; person time is sum of treatment duration [months]) who received tislelizumab as monotherapy in Study 001, Study 102, Study 203, Study 204, Study 208, Study 302, and Study 303 and as combination therapy from Study 206, Study 304, and Study 307. Normal renal function was reported in 1416 (57.4%) patients (10,581.09 person time) (Annex 7 Table 2.1). Based on a population PK analysis, no dose adjustment of tislelizumab is recommended for patients with mild to moderate renal impairment (creatinine clearance ≥ 30 mL/min). Specific PK studies in patients with renal impairment are not warranted.
Patients with Hepatic Impairment (Defined as AST > ULN; serum total bilirubin > 1 to 1.5 x ULN, mild; > 1.5 to 3 x ULN, moderate; and > 3 x ULN, severe.)	Hepatic impairment was reported in 411/2469 (16.6%) patients (2303.06 person time) who received tislelizumab as monotherapy in Study 001, Study 102, Study 203, Study 204, Study 208, Study 302, and Study 303 and as combination therapy from Study 206, Study 304, and Study 307. Normal hepatic function was reported in 2052 (83.1%) patients (16,949.67 person time). In 6 (0.2%) patients, information on hepatic impairment at baseline was missing (Annex 7 Table 2.1). Based on a population PK analysis, no dose adjustment of tislelizumab is recommended for patients with mild to moderate hepatic impairment hepatic impairment (total bilirubin ≤ 3 times ULN and any AST). Specific PK studies in patients with hepatic impairment are not warranted.
Patients with Cardiovascular Impairment (eg, heart failure of New York Heart Association cardiac disease Class III or greater, myocardial infarction, unstable arrhythmias, or unstable angina.)	Not included in the clinical development programme.
Immunocompromised Patients	Not included in the clinical development programme.
Patients With a Disease Severity Different from Inclusion Criteria in Clinical Studies	Not included in the clinical development programme.
Population With Relevant Different Ethnic Origin	Clinical study exposure data on race including ethnicity is presented in Table Part II: Module SIII-6.

Table Part II: Module SIV-2: Exposure of Special Populations Included or Not in Clinical Study Development Programmes

Type of Special Population	Exposure
Subpopulations Carrying Relevant Genetic Polymorphisms.	Patients with known EGFR sensitising or driver mutation or ALK-gene translocation were excluded from Study 303, Study 304, and Study 307. However, screening prior to enrolment for EGFR was only mandatory for patients in Study 304 or with nonsquamous histology in Study 303. Additionally, although patients with known ALK-fusion oncogene were excluded, patients (nonsquamous or squamous histology in 3 studies) with unknown ALK-fusion oncogene status were not required to be tested at screening.

Table Part II: Module SIV-3: Exposure of Tislelizumab by Special Population (All Tislelizumab Treated Population)

	Persons n (%)	Person Time
Renal Impairment Status at Baseline		
Normal	1416 (57.4)	10,581.09
Impairment	1053 (42.6)	8709.16
Hepatic Impairment Status at Baseline		
Normal	2052 (83.1)	16,949.67
Impairment	411 (16.6)	2303.06
Missing	6 (0.2)	37.52

Abbreviations: AST, aspartate aminotransferase; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; SCLC, small cell lung cancer; ULN, upper limit of normal.
Source data: Annex 7 Table 2.1.
Studies include monotherapy studies (Studies 001, 102, 203, 204, 208, 302, 303) and combination studies (Studies 206, 304, 307).
Tislelizumab treated patients who switched from the chemotherapy control arms in Studies 304 and 307 were not included. Patients from SCLC cohort in Study 206 were not included.
Person time is sum of treatment duration (months) for all patients in the row.
Percentages are based on the number of patients who received at least a dose of tislelizumab.
The hepatic impairment status at baseline was determined by the baseline total bilirubin and AST value according to the criterion below. Patients with missing baseline total bilirubin or AST (if any) would be considered and reported as “Missing” for hepatic impairment status.
Total bilirubin: Normal ≤ ULN; Mild (Scenario 1): ≤ ULN, Mild (Scenario 2): > 1 to 1.5 x ULN; Moderate: > 1.5 to 3 x ULN; Severe: > 3 x ULN.
Aspartate aminotransferase: Normal ≤ ULN; Mild Scenario 1: > ULN, Mild Scenario 2: Any; Moderate: Any; Severe: Any.
The renal impairment status at baseline was determined by the eGFR (ml/min) according to the criterion below. The eGFR was calculated using the CKD-EPI equation with serum creatinine at baseline, sex, race, and age at baseline for patients in the Tislelizumab Monotherapy Safety Analysis Set and the Cockcroft-Gault equation with serum creatinine, age, and weight at baseline for patients in the Tislelizumab Combination Therapy Safety Analysis Set. Patients with missing serum creatinine at baseline (if any) would be considered and reported as “Missing” for renal impairment status.
Renal Impairment status (eGFR [mL/min or mL/min/1.73 m^2]):

Normal: ≥ 90; Mild impairment: 60 to < 90; Moderate impairment: 30 to < 60; Severe impairment: 15 to < 30; End state: < 15.

PART II: MODULE SV POST-AUTHORISATION EXPERIENCE

Tislelizumab was first authorised in China on 26 December 2019 for the treatment of Hodgkin's lymphoma and has since then been registered for the treatment of several other cancers in this country: locally advanced or metastatic urothelial carcinoma (09 April 2020), first-line, unresectable, locally advanced or metastatic squamous NSCLC (12 January 2021), first-line unresectable, locally advanced or metastatic nonsquamous NSCLC (22 June 2021), second-/third-line HCC that has been previously treated with at least one systemic therapy (22 June 2021), locally advanced or metastatic NSCLC that has progressed after prior platinum-based chemotherapy or where platinum-based chemotherapy was intolerable (31 December 2021), advanced unresectable or metastatic high microsatellite instability or deficient mismatch repair solid tumours (08 March 2022), first-line locally advanced or metastatic OSCC (08 April 2022), and first-line recurrent or metastatic nasopharyngeal cancer (07 June 2022).

SV.1 Post-authorisation Exposure

As of Periodic Benefit-Risk Evaluation Report data lock point (25 December 2022), CCI [redacted]

SV.1.1 Method Used to Calculate Exposure

Sales data were used for patient exposure calculations, which may overestimate patient exposure due to the holding of drug stocks at pharmacies/distributors.

The number of doses supplied is defined as mg CCI [redacted] The patient years of exposure is defined as doses supplied/17.3.

SV.1.2 Exposure

Table Part II: Module SV-1: Cumulative Exposure From Marketing Experience

Channel		Sales and Sample Volume Data (China)	Estimated Number of Infusions (China)
Ex-factory sales units (vials)	Total units sold to distributors	CCI [redacted]	CCI [redacted]
Samples (vials)	Total units delivered to charities in China	CCI [redacted]	CCI [redacted]
Total		CCI [redacted]	CCI [redacted]

Periodic Benefit-Risk Evaluation Report data lock point: 25 December 2022.

PART II: MODULE SVI ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for Misuse for Illegal Purposes

Commonly misused classes of prescription drugs include opioid pain relievers, stimulants, and CNS depressants (sedatives and tranquilisers). There is minimal potential for misuse for illegal purposes as tislelizumab is an infused product only administered by a healthcare professional (HCP) in a healthcare setting.

Tislelizumab does not share characteristics with drugs that have recognised misuse potential and is not deemed to have misuse potential.

PART II: MODULE SVII IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Reason for Not Including an Identified or Potential Risk in the List of Safety Concerns in the RMP:

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

- None

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

- None

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered to by prescribers (eg, actions being part of standard clinical practice in each EU Member state where the product is authorised):

- **Infusion-Related Reaction**

  Infusion-related reactions (IRRs) are commonly observed with mAb therapy, and temporally related to drug administration. Information in the label is considered sufficient to prevent or mitigate such events.

  IRR was reported in 83 (4.2%) of the 1972 patients who received tislelizumab as monotherapy in Study 001, Study 102, Study 203, Study 204, Study 208, Study 302, and Study 303. In these studies, 7 (0.4%) patients experienced serious infusion-related AE, of which the outcome was recovered/resolved in all 7 (0.4%) patients. AEs related to IRR led to treatment discontinuation for 5 (0.3%) patients and dose interruption for 18 (0.9%) patients (Annex 7 Table 3.1.2.1, Annex 7 Table 3.2.2.1, Annex 7 Table 3.3.2.1).

  In combination therapy, IRR was reported in 14 (2.8%) patients of the 497 patients from Study 206, Study 304, and Study 307. AEs related to IRR led to dose interruption for 1 (0.2%) patient. No serious events of IRR were reported in the combination therapy from these studies (Annex 7 Table 3.1.2.2, Annex 7 Table 3.2.2.2, Annex 7 Table 3.3.2.2).

Known risks that do not impact the risk-benefit profile:

- None

Other reasons for considering the risks not important:

- **Hypersensitivity Events (by immunogenicity) in ADA-positive Patients**

  There was no evidence of relevant hypersensitivity reactions known to be triggered by patients' ADA positivity.

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Reason for Classification as an Important Identified Risk:

- **Immune-Mediated Adverse Reactions**

  Immune-mediated adverse reactions, which include immune-mediated pneumonitis, immune-mediated hepatitis, immune-mediated skin adverse reaction, immune-mediated colitis, immune-mediated myositis/rhabdomyolysis, immune-mediated endocrinopathies, immune-mediated nephritis, and renal dysfunction, immune-mediated myocarditis, immune-mediated nervous system disorder, immune-mediated pancreatitis, and other immune-mediated reactions have been reported in patients receiving tislelizumab, including fatal cases.

  Immune-mediated adverse reactions were reported in 335 (17%) of the 1972 patients who received tislelizumab as monotherapy.

  In combination therapy, immune-mediated adverse reactions were reported in 127 (25.6%) of the 497 patients.

  Immune-Mediated Pneumonitis: Immune-mediated pneumonitis, including fatal cases, has been observed in patients receiving tislelizumab.

  Data from monotherapy studies (Study 001, Study 102, Study 203, Study 204, Study 208, Study 302, and Study 303): Immune-mediated pneumonitis was reported for 77 (3.9%) of the 1972 patients who received tislelizumab as monotherapy. In these studies, 55 patients (2.8%) experienced a serious event of immune-mediated pneumonitis, of which the outcomes were death in 4 patients (0.2%), recovered/resolved for 25 (1.3%) patients, recovered/resolved with sequelae for 1 patient (0.1%), recovering/resolving for 12 (0.6%) patients, and not recovered/not resolved for 14 patients (0.7%). Immune-mediated pneumonitis led to treatment discontinuation for 36 (1.8%) patients and dose modification in 29 (1.5%) patients.

  Data from combination therapy studies (Study 206, Study 304, and Study 307): Immune-mediated pneumonitis was reported in 45 (9.1%) of the 497 patients. In these studies, 33 (6.6%) patients experienced a serious event of immune-mediated pneumonitis, of which the outcomes were death in 3 patients (0.6%), recovered/resolved in 13 patients (2.6%), recovering/resolving in 10 patients (2.0%), and not recovered/not resolved in 6 patients (1.2%). The outcome for the serious AEs, interstitial lung disease, in 1 (0.2%) patient was unknown. Immune-mediated pneumonitis led to treatment discontinuation for 20 (4.0%) patients and dose modification in 21 (4.2%) patients.

  Immune-Mediated Hepatitis: Immune-mediated hepatitis has been reported in patients receiving tislelizumab, including fatal cases.

  Data from monotherapy studies (Study 001, Study 102, Study 203, Study 204, Study 208, Study 302, and Study 303): Immune-mediated hepatitis was reported in 36 (1.8%) of the 1972 patients who received tislelizumab as monotherapy. In these studies, 12 patients (0.6%) experienced serious immune-mediated hepatitis, of which

the outcomes were death in 2 patients (0.1%), recovered/resolved in 7 patients (0.4%), recovering/resolving in 2 patients (0.1%), and not recovered/not resolved in 1 (0.1%) patient. Immune-mediated hepatitis led to treatment discontinuation for 9 patients (0.5%) and treatment dose modification in 21 patients (1.1%).

Data from combination therapy studies (Study 206, Study 304, and Study 307): Immune-mediated hepatitis was reported in 8 patients (1.6%) of the 497 patients. In these studies, 3 patients (0.6%) experienced a serious event of immune-mediated hepatitis, of which the outcomes were death in 1 patient (0.2%) and recovered/resolved for 2 patients (0.4%). Immune-mediated hepatitis led to treatment discontinuation in 3 patients (0.6%) and dose modification in 4 patients (0.8%).

Immune-Mediated Skin Adverse Reaction: Immune-mediated skin adverse reaction have been observed in patients receiving tislelizumab.

Data from monotherapy studies (Study 001, Study 102, Study 203, Study 204, Study 208, Study 302, and Study 303): Immune-mediated skin adverse reaction was reported for 32 (1.6%) of the 1972 patients who received tislelizumab as monotherapy. In these studies, 6 patients (0.3%) experienced a serious event of immune-mediated skin adverse reaction, of which the outcomes were recovered/resolved for 4 patients (0.2%), recovering/resolving for 1 patient (0.1%), and not recovered/not resolved in 1 patient (0.1%). Immune-mediated skin adverse reaction led to treatment discontinuation for 5 patients (0.3%) and dose modification in 11 (0.6%) patients.

Data from combination therapy studies (Study 206, Study 304, and Study 307): Immune-mediated skin adverse reaction was reported in 19 patients (3.8%) of the 497 patients. In these studies, 5 patients (1.0%) experienced a serious event of immune-mediated skin adverse reaction, in whom, the outcome was recovered/resolved in 4 patients (0.8%) and recovering/resolving in 1 patient (0.2%). Immune-mediated skin adverse reaction led to treatment discontinuation for 2 (0.4%) patients and dose modification in 9 (1.8%) patients.

Immune-Mediated Colitis: Immune-mediated colitis, which may present as diarrhoea, has been observed in patients receiving tislelizumab.

Data from monotherapy studies (Study 001, Study 102, Study 203, Study 204, Study 208, Study 302, and Study 303): Immune-mediated colitis was reported in 19 (1.0%) of the 1972 patients who received tislelizumab as monotherapy. In these studies, 11 patients (0.6%) experienced a serious event of immune-mediated colitis, of which the outcomes were recovered/resolved for 8 patients (0.4%), recovered/resolved with sequelae for 2 patients (0.1%), and not recovered/not resolved for 1 patient (0.1%). Immune-mediated colitis led to treatment discontinuation for 3 (0.2%) patients and dose modification in 12 patients (0.6%).

Data from combination therapy studies (Study 206, Study 304, and Study 307): Immune-mediated colitis was reported in 7 (1.4%) of the 497 patients. In these studies, 4 patients (0.8%) experienced a serious event of immune-mediated colitis, of which the outcomes were recovered/resolved for 2 patients (0.4%),

recovering/resolving for 1 patient (0.2%), and not recovered/not resolved for 1 patient (0.2%). Immune-mediated colitis led to treatment discontinuation for 3 (0.6%) patients and dose modification in 3 (0.6%) patients.

Immune-Mediated Myositis/Rhabdomyolysis: Immune-mediated myositis/rhabdomyolysis has been reported in patients receiving tislelizumab.

Data from monotherapy studies (Study 001, Study 102, Study 203, Study 204, Study 208, Study 302, and Study 303): Immune-mediated myositis/rhabdomyolysis was reported for 14 (0.7%) of the 1972 patients who received tislelizumab as monotherapy. In these studies, 7 patients (0.4%) experienced a serious event of immune-mediated myositis/rhabdomyolysis of which the outcomes were recovered/resolved in 3 patients (0.2%) and not recovered/not resolved for 4 patients (0.2%). Immune-mediated myositis/rhabdomyolysis led to treatment discontinuation for 3 patients (0.2%) and dose modification in 10 patients (0.5%).

Data from combination therapy studies (Study 206, Study 304, and Study 307): Immune-mediated myositis/rhabdomyolysis was reported in 6 (1.2%) of the 497 patients. In these studies, 4 patients (0.8%) experienced a serious event of immune-mediated myositis/rhabdomyolysis, of which the outcomes were death for 1 patient (0.2%) and recovered/resolved in 3 patients (0.6%). Immune-mediated myositis led to treatment discontinuation for 5 (1.0%) patients and dose modification in 3 (0.6%) patients.

Immune-Mediated Endocrinopathies: Immune-mediated endocrinopathies have been reported in patients receiving tislelizumab, which may require supportive treatment depending on the specific endocrine disorder.

Hypothyroidism

Data from monotherapy studies (Study 001, Study 102, Study 203, Study 204, Study 208, Study 302, and Study 303): Immune-mediated hypothyroidism was reported for 133 (6.7%) of the 1972 patients who received tislelizumab as monotherapy. In these studies, 1 patient (0.1%) experienced a serious event of immune-mediated hypothyroidism, of which the outcome was recovered/resolved. AE of hypothyroidism led to dose modification in 6 (0.3%) patients.

Data from combination therapy studies (Study 206, Study 304, and Study 307): Immune-mediated hypothyroidism was reported in 45 (9.1%) of the 497 patients. In these studies, there were no serious events of immune-mediated hypothyroidism. However, AE of hypothyroidism was reported in 4 patients (0.8%) leading to discontinuation and dose modification was reported in 19 (3.8%) patients.

Hyperthyroidism

Data from monotherapy studies (Study 001, Study 102, Study 203, Study 204, Study 208, Study 302, and Study 303): Immune-mediated hyperthyroidism was reported for 12 (0.6%) of the 1972 patients who received tislelizumab as monotherapy. In these studies, there were no serious events of immune-mediated hyperthyroidism. One AE (hyperthyroidism; Grade 3) was reported in a patient leading to discontinuation and dose modification was reported in 1 patient (0.1%).

Data from combination therapy studies (Study 206, Study 304, and Study 307): Immune-mediated hyperthyroidism was reported in 3 (0.6%) of the 497 patients. In these studies, there were no serious events of immune-mediated hyperthyroidism. Dose modification was reported in 1 patient (0.2%).

Thyroiditis

Data from monotherapy studies (Study 001, Study 102, Study 203, Study 204, Study 208, Study 302, and Study 303): Immune-mediated thyroiditis was reported for 13 (0.7%) of the 1972 patients who received tislelizumab as monotherapy. In these studies, there were no serious events of immune-mediated thyroiditis. Dose modification was reported in 2 patients (0.1%).

Data from combination therapy studies (Study 206, Study 304, and Study 307): Immune-mediated thyroiditis was reported in 2 (0.4%) of the 497 patients. In these studies, 1 patient (0.2%) experienced a serious event of immune-mediated thyroiditis which was recovered/resolved.

Adrenal Insufficiency

Data from monotherapy studies (Study 001, Study 102, Study 203, Study 204, Study 208, Study 302, and Study 303): Immune-mediated adrenal insufficiency was reported for 6 (0.3%) of the 1972 patients who received tislelizumab as monotherapy. In these studies, 2 patients (0.1%) experienced serious immune-mediated adrenal insufficiency, of which the outcomes were recovered/resolved and recovering/resolving for 1 patient (0.1%) each. Immune-mediated adrenal insufficiency led to dose modification in 5 (0.3%) patients.

Data from combination therapy studies (Study 206, Study 304, and Study 307): No events of immune-mediated adrenal insufficiency were reported.

Pituitary Dysfunction

Data from monotherapy studies (Study 001, Study 102, Study 203, Study 204, Study 208, Study 302, and Study 303): Pituitary dysfunction was reported for 1 (0.1%) of the 1972 patients who received tislelizumab as monotherapy. In these studies, there were no serious events of pituitary dysfunction.

Data from combination therapy studies (Study 206, Study 304, and Study 307): No events of pituitary dysfunction were reported.

Type 1 Diabetes Mellitus

Data from monotherapy studies (Study 001, Study 102, Study 203, Study 204, Study 208, Study 302, and Study 303): Immune-mediated type 1 diabetes mellitus was reported for 8 (0.4%) of the 1972 patients who received tislelizumab as monotherapy. In these studies, 6 patients (0.3%) experienced serious type 1 diabetes mellitus, of which the outcomes were recovered/resolved in 2 (0.1%), recovered/resolved with sequelae in 1 patient (0.1%), recovering/resolving for 2 patients (0.1%), and not recovered/not resolved in 4 (0.2%) patients. Immune-mediated type 1 diabetes mellitus led to dose discontinuation in 3 (0.2%) patients and dose modification in 2 (0.1%) patients.

Data from combination therapy studies (Study 206, Study 304, and Study 307): immune-mediated type 1 diabetes mellitus was reported in 5 (1.0%) of the 497 patients. In these studies, serious events of immune-mediated type 1 diabetes mellitus were reported in 2 patients (0.4%). Immune-mediated type 1 diabetes mellitus led to dose modification in 3 patients (0.6%).

Immune-Mediated Nephritis and Renal Dysfunction: Immune-mediated nephritis and renal dysfunction has been observed in patients receiving tislelizumab including a fatal case.

Data from monotherapy studies (Study 001, Study 102, Study 203, Study 204, Study 208, Study 302, and Study 303): Immune-mediated nephritis and renal dysfunction was reported in 10 (0.5%) of the 1972 patients who received tislelizumab as monotherapy. In these studies, 5 patients (0.3%) experienced a serious event of immune-mediated nephritis and renal dysfunction, of which the outcomes were death in 1 patient (0.1%), recovered/resolved and recovering/resolving in 1 patient (0.1%) each, and recovered/resolved with sequelae for 2 patients (0.1%). Immune-mediated nephritis and renal dysfunction led to treatment discontinuation for 4 patients (0.2%) and dose modification for 4 (0.2%) patients.

Data from combination therapy studies (Study 206, Study 304, and Study 307): Immune-mediated nephritis and renal dysfunction was reported in 5 (1.0%) of the 497 patients. In these studies, 2 patients (0.4%) experienced a serious event of immune-mediated nephritis and renal dysfunction, of which the outcomes were recovered/resolved and recovering/resolving in 1 patient (0.2%), each. No treatment discontinuation was reported; however, dose modification was reported in 5 (1.0%) patients.

Immune-Mediated Myocarditis: Immune-mediated myocarditis has been reported in patients receiving tislelizumab, including fatal cases.

Data from monotherapy studies (Study 001, Study 102, Study 203, Study 204, Study 208, Study 302, and Study 303): Immune-mediated myocarditis was reported in 7 patients (0.4%) who received tislelizumab as monotherapy. In these studies, 7 (0.4%) of the 1972 patients experienced a serious event of immune-mediated myocarditis, of which the outcomes were recovered/resolved in 4 patients (0.2%), recovering/resolving in 1 patient (0.1%), and not recovered/not resolved in 2 patients (0.1%). Immune-mediated myocarditis led to treatment discontinuation in 5 (0.3%) patients and dose modification in 3 (0.2%) patients.

Data from combination therapy studies (Study 206, Study 304, and Study 307): Immune-mediated myocarditis was reported in 7 (1.4%) of the 497 patients. In these studies, 5 patients (1.0%) experienced a serious event of immune-mediated myocarditis, of which the outcomes were death in 2 patients (0.4%), recovered/resolved in 2 patients (0.4%), and recovering/resolving in 1 patient (0.2%). Immune-mediated myocarditis led to treatment discontinuation for 6 (1.2%) patients and dose modification in 2 (0.4%) patients.

Immune-Mediated Nervous System Disorders: Immune-mediated nervous system disorders have been reported in patients receiving tislelizumab.

Data from monotherapy studies (Study 001, Study 102, Study 203, Study 204, Study 208, Study 302, and Study 303): No AEs related to immune-mediated nervous disorders were reported.

Data from combination therapy studies (Study 206, Study 304, and Study 307): Immune-mediated nervous system disorder was reported in 2 (0.4%) of the 497 patients. In these studies, 2 patients (0.4%) experienced a serious event of immune-mediated nervous system disorders, of which the outcomes were recovered/resolved in 1 patient (0.2%) and not recovered/not resolved in 1 patient (0.2%). Immune-mediated nervous system disorders led to treatment discontinuation and dose modification in 1 patient (0.2%) each.

Immune-Mediated Pancreatitis: Immune-mediated pancreatitis has been reported in patients receiving tislelizumab.

Data from monotherapy studies (Study 001, Study 102, Study 203, Study 204, Study 208, Study 302, and Study 303): Immune-mediated pancreatitis was reported in 1 patient (0.1%) who received tislelizumab as monotherapy. In these studies, 1 (0.1%) of the 1972 patients experienced a serious event of immune-mediated pancreatitis, the outcome of which was recovered/resolved. Immune-mediated pancreatitis led to dose modification in 1 patient (0.1%).

Data from combination therapy studies (Study 206, Study 304, and Study 307): No AEs related to immune-mediated pancreatitis were reported.

Other Immune-Mediated Reactions: Other immune-mediated reactions including arthritis, immune-mediated arthritis, pericarditis, and polymyalgia rheumatica have been reported in patients receiving tislelizumab. The details are presented below.

Data from monotherapy studies (Study 001, Study 102, Study 203, Study 204, Study 208, Study 302, and Study 303): Other immune-mediated reactions (Preferred Terms [PTs]: Arthritis, [n = 4], Immune-mediated arthritis [n = 1], Pericarditis [n = 1], and Polymyalgia rheumatica [n = 1]) were reported in 7 (0.4%) of the 1972 patients who received tislelizumab as monotherapy. Out of these 7 patients, 2 patients (0.1%) experienced a serious event of other immune-mediated reactions (PT: Arthritis), of which the outcome was recovered/resolved. Dose discontinuation in 1 patient (0.1%) and dose modification in 2 patients (0.1%) were reported.

Data from combination therapy studies (Study 206, Study 304, and Study 307): No events of other immune-mediated reactions were reported.

By disrupting PD-1-mediated signalling, tislelizumab acts to restore antitumour immunity and halt progression of tumour growth. This restoration of immune system activity may result in immune-mediated adverse reactions involving one or more body systems, which can be life-threatening or fatal in rare cases (SmPC). The risk should be managed by the guidance listed in the tislelizumab SmPC.

Overall, the benefit-risk balance is positive given the clinical efficacy associated with the use of the product and the severity of the diseases. The risk should be managed by the guidance listed in the tislelizumab SmPC.

Additional information is provided in Part II: Module SVII.3.1.

Reason for Classification as an Important Potential Risk:

- **Reproductive and Developmental Toxicity**

  No events of reproductive and developmental toxicity were reported from the monotherapy studies (Study 001, Study 102, Study 203, Study 204, Study 208, Study 302, and Study 303) and combination therapy studies (Study 206, Study 304, and Study 307).

  Based on the mechanism of action, the administration of tislelizumab during pregnancy could cause harm to the foetus (SmPC). Pregnant women should be advised of the potential risk to the foetus. Women of childbearing potential should use effective contraception during treatment with tislelizumab and for at least 4 months after the last dose of tislelizumab.

  Additional information is provided in Part II: Module SVII.3.1.

Table Part II: Module SVII-1: Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Summary of Safety Concerns	
Important Identified Risks	Immune-mediated adverse reactions
Important Potential Risks	Reproductive and developmental toxicity
Missing Information	None

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

There are no new safety concerns and/or reclassification.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

The data presented in this EU RMP are based on a population of 1972 patients treated with tislelizumab monotherapy in Study 001, Study 102, Study 203, Study 204, Study 208, Study 302, and Study 303, and 497 patients from Study 304, Study 307, and Study 206 in chemotherapy combination therapy. As discussed in Part II Module SIII – Clinical Study Exposure, the total person time of exposure to date for all patients for OSCC indication who have received tislelizumab is 1547.63 patient-months, and the total person time of exposure to date for all patients who have received tislelizumab is 19,290.25 patient-months.

For the immune-mediated identified and potential risks, the Medical Dictionary for Regulatory Activities PTs listed in Annex 7 Listing 1.1 were used to identify potential immune-mediated events. The methodology for diagnostic evaluation and management of imAEs was based on American Society of Clinical Oncology and European Society for Medical Oncology guidelines (Brahmer et al 2018; Haanen et al 2017). Potential imAEs included treatment-emergent AEs (TEAEs) that started on or after the first dose of tislelizumab and required treatment with systemic corticosteroids or other immunosuppressant treatment or endocrine therapy for hyperthyroidism and hypothyroidism events. Additionally, in order to determine which TEAEs are imAEs, medical reviewers performed an adjudication to rule out clear alternative aetiologies of potential imAE cases.

Important Identified Risk:

Immune-Mediated Adverse Reactions:

Potential Mechanisms:

The use of mAbs that block coinhibitory immune checkpoint molecules, such as tislelizumab, may serve to increase a baseline T-cell-specific immune response that enhances the immune antitumour response. However, disruption of the functioning of immune checkpoint molecules can lead to imbalances in immunologic tolerance that result in an unchecked immune response. This may clinically manifest as autoimmune-like/inflammatory side-effects, which cause collateral damage to normal organ systems and tissues (Naidoo et al 2015). However, the exact pathogenesis of immune toxicity is not clear, and many other inflammatory cells, such as Th17 and other types of cells, are reported to be involved (Puzanov et al 2017).

Evidence Source(s) and Strength of Evidence:

Review of tislelizumab clinical study data, postmarketing experience and literature regarding immune-mediated adverse reactions (including immune-mediated pneumonitis, immune-mediated hepatitis, immune-mediated skin adverse reaction, immune-mediated colitis, immune-mediated myositis/rhabdomyolysis, immune-mediated endocrinopathies, immune-mediated nephritis and renal dysfunction, immune-mediated myocarditis, immune-mediated nervous system disorder, immune-mediated pancreatitis, and other immune-mediated reactions) represent sufficient evidence of a causal association with tislelizumab exposure.

Immune-Mediated Pneumonitis

Nonclinical data: No treatment-related inflammation in the lungs was observed in cynomolgus monkeys after intravenous infusion at doses of 3, 10, 30 mg/kg or 60 mg/kg (once every 2 weeks, 7 doses) for 13 weeks.

Clinical data: The most common lung toxicity observed in patients receiving ICI treatment is pneumonitis. Reports of pneumonitis were documented in 2% to 4% of patients, with 1% to 2% of patients having Grade ≥ 3 events, frequency of fatal pneumonitis in 0.2% of patients, and discontinuation due to pneumonitis in 0.2% to 4% of patients (Haanen et al 2017). Patients with NSCLC were significantly more likely to experience any grade pneumonitis and Grade 3 or higher pneumonitis compared with other tumour types (Ma et al 2018).

Immune-Mediated Hepatitis

Nonclinical data: No treatment-related hepatic inflammation was observed in cynomolgus monkeys after intravenous infusion at doses of 3, 10, 30 mg/kg or 60 mg/kg (once every 2 weeks, 7 doses) for 13 weeks.

Clinical data: Although infrequently observed, the occurrence of immune-mediated hepatitis is well established in patients treated with ICIs. These patients are typically asymptomatic, and diagnosis is made based on elevated liver enzymes such as ALT and/or AST, and occasionally hyperbilirubinemia. The median onset of transaminase elevation is approximately 6 to 14 weeks after starting ICI treatment, and the incidence of developing immune-mediated hepatitis in patients treated with ICIs is approximately 5% (Puzanov et al 2017).

Immune-Mediated Skin Adverse Reaction

Nonclinical data: No treatment-related skin rash was observed in cynomolgus monkeys after intravenous infusion at doses of 3, 10, 30 mg/kg or 60 mg/kg (once every 2 weeks, 7 doses) for 13 weeks.

Clinical data: Skin AEs are among the most frequent AEs observed in patients treated with mAbs inhibiting either immune checkpoints cytotoxic T lymphocyte-associated protein 4 (CTLA4; ipilimumab in 43% to 45% of the patients) or PD-(L)1 (nivolumab and pembrolizumab in approximately 34% of the patients). However, serious skin AEs are rare and do not usually require dose reductions or treatment discontinuation (Haanen et al 2017).

Immune-Mediated Colitis

Nonclinical data: No treatment-related diarrhoea or gastrointestinal tract inflammation was observed in cynomolgus monkeys after intravenous infusion at doses of 3, 10, 30 mg/kg or 60 mg/kg (once every 2 weeks, 7 doses) for 13 weeks.

Clinical data: Diarrhoea and colitis are more frequent with anti-CTLA4 agents (eg, ipilimumab) than with anti-PD-(L)1 targeted agents, including nivolumab or pembrolizumab, with Grade 3 to 4 AEs occurring in 1% to 2% of cases (Haanen et al 2017). The presence of diarrhoea in conjunction with abdominal pain, rectal bleeding, mucus in the stool, and fever should alert the clinician to the possibility of colitis, a potentially serious or even life-threatening gastrointestinal complication of ICI therapy (Puzanov et al 2017).

Immune-Mediated Myositis/Rhabdomyolysis

Nonclinical data: No treatment-related inflammation in muscle was observed in cynomolgus monkeys after intravenous infusion at doses of 3, 10, 30 mg/kg or 60 mg/kg (once every 2 weeks, 7 doses) for 13 weeks.

Clinical data: Immune-mediated myositis/rhabdomyolysis occur uncommonly in cancer patients treated with ICIs (Abdel-Rahman et al 2017). Recognising musculoskeletal imAEs in the oncology setting is challenging due to the broad range of potential presenting symptoms and the prevalence of musculoskeletal complaints in the general population.

Immune-Mediated Endocrinopathies (Hypothyroidism, Hyperthyroidism, Thyroiditis, Adrenal Insufficiency, Pituitary Dysfunction, Type 1 Diabetes Mellitus)

Nonclinical data: No treatment-related thyroid inflammation was observed in cynomolgus monkeys after intravenous infusion at doses of 3, 10, 30 mg/kg or 60 mg/kg (once every 2 weeks, 7 doses) for 13 weeks.

Clinical data: Thyroid disease or abnormalities in thyroid function tests (primary hypothyroidism and thyroiditis) is one of the most common endocrine imAEs. Thyroid dysfunction (hypothyroidism, hyperthyroidism, and thyroiditis) was reported in 6 to 20% of patients in large Phase III clinical studies (Puzanov et al 2017). Pituitary dysfunction is a rare condition which occurs in 0.5 to 1% of patients treated with anti-PD-1/PD-L1 monotherapy and up to 10% with combination CTLA4/PD-1 blockade. In contrast to thyroid disorders, most patients with pituitary dysfunction present with clinical symptoms commonly related to neuro-compression or, more often, to secondary adrenal insufficiency including fatigue and nausea. Primary adrenal insufficiency is a rare complication of ICI therapy. Diabetes Mellitus after treatment with ICIs occurs in slightly less than 1% of patients; approximately 97% of all reported cases have arisen with anti-PD-1/PD-L1 monotherapy or combination treated patients (Wright et al 2021).

Immune-Mediated Nephritis and Renal Dysfunction

Nonclinical data: No treatment-related inflammation in the kidneys was observed in cynomolgus monkeys after intravenous infusion at doses of 3, 10, 30 mg/kg or 60 mg/kg (once every 2 weeks, 7 doses) for 13 weeks. Secondary renal changes were observed at 60 mg/kg due to immunogenicity against tislelizumab (ADAs).

Clinical data: In the published literature, renal immune-mediated AEs are considered rare. Most reports document isolated cases of interstitial nephritis with specific agents and regimens, such as anti-PD-(L)1 monotherapy, and combination anti-CTLA4/PD-1 treatment in melanoma (Puzanov et al 2017).

Immune-Mediated Myocarditis

Nonclinical data: No treatment-related inflammation of the heart was observed in cynomolgus monkeys after intravenous infusion at doses of 3, 10, 30 mg/kg or 60 mg/kg (once every 2 weeks, 7 doses) for 13 weeks.

Clinical data: Myocarditis and cardiac dysfunction due to ICIs are rare and the true incidence is unknown; current estimates suggest this incidence is < 1% of patients. Cardiac immune-mediated AEs due to ICIs may present with nonspecific symptoms such as fatigue and weakness. However, more typical cardiac symptoms of chest pain, shortness of breath, pulmonary or lower

extremity oedema, palpitations, irregular heartbeat, rapid onset of heart failure symptoms, or new heart block on electrocardiogram can occur at any time, more frequently within the first few months of treatment, and may lead to death (Puzanov et al 2017).

Immune-Mediated Nervous System Disorders

Nonclinical data: No treatment-related inflammation in the brain was observed in cynomolgus monkeys after intravenous infusion at doses of 3, 10, 30 mg/kg or 60 mg/kg (once every 2 weeks, 7 doses) for 13 weeks.

Clinical data: Neurologic immune-related AEs are uncommon with an overall incidence up to 6% with anti-PD-(L)1 antibodies and include autoimmune encephalitis, myasthenic syndrome, and Guillain-Barre syndrome (Puzanov et al 2017).

Immune-Mediated Pancreatitis

Nonclinical data: No treatment-related inflammation in the pancreas was observed in cynomolgus monkeys after intravenous infusion at doses of 3, 10, 30 mg/kg or 60 mg/kg (once every 2 weeks, 7 doses) for 13 weeks.

Clinical data: Acute pancreatitis has been reported but is rare in cancer patients treated with ICIs (Puzanov et al 2017); asymptomatic elevation of lipase and amylase are more common.

Other Immune-Mediated Reactions

Nonclinical data: No other immune-mediated reactions were observed in cynomolgus monkeys after intravenous infusion at doses of 3, 10, 30 mg/kg or 60 mg/kg (once every 2 weeks, 7 doses) for 13 weeks.

Clinical data: Immune-related AEs can affect any organ system (Puzanov et al 2017), including haematological, ocular, or rheumatological manifestations (Haanen et al 2017).

Characterisation of the Risk - Data:

The clinical study data including incidence, severity and nature of risk, SAEs, and outcome of SAEs are summarised in Table Part II: Module SVII-2.

Table Part II: Module SVII-2: Clinical Study Data of Immune-Mediated Adverse Reactions

	Monotherapy (N = 1972) n (%) (95% CI)[a]	**Combination therapy (N = 497) n (%) (95% CI)[a]**
Immune-Mediated Pneumonitis		
Incidence		
Patients with at least one AE	77 (3.9) (3.1, 4.9)	45 (9.1) (6.7, 11.9)
Pneumonitis	44 (2.2)	33 (6.6)
Immune-mediated pneumonitis	13 (0.7)	8 (1.6)
Interstitial lung disease	12 (0.6)	4 (0.8)
Pneumonia	6 (0.3)	2 (0.4)
Organising pneumonia	2 (0.1)	0 (0.0)
Severity and Nature of Risk		
Patients with worst Grade 3 AE	29 (1.5)	15 (3.0)
Pneumonitis	17 (0.9)	11 (2.2)
Interstitial lung disease	6 (0.3)	0 (0.0)
Immune-mediated pneumonitis	3 (0.2)	4 (0.8)
Organising pneumonia	2 (0.1)	0 (0.0)
Pneumonia	1 (0.1)	0 (0.0)
Patients with worst Grade 4 AE	5 (0.3)	2 (0.4)
Immune-mediated pneumonitis	2 (0.1)	0 (0.0)
Interstitial lung disease	2 (0.1)	1 (0.2)

Table Part II: Module SVII-2: Clinical Study Data of Immune-Mediated Adverse Reactions

	Monotherapy (N = 1972) n (%) (95% CI)[a]	**Combination therapy (N = 497) n (%) (95% CI)[a]**
Pneumonitis	1 (0.1)	1 (0.2)
Patients with worst Grade 5 AE	4 (0.2)	3 (0.6)
Pneumonitis	2 (0.1)	3 (0.6)
Pneumonia	2 (0.1)	0 (0.0)
Patients with at least one AE leading to discontinuation of tislelizumab	36 (1.8)	20 (4.0)
Pneumonitis	21 (1.1)	15 (3.0)
Immune-mediated pneumonitis	7 (0.4)	3 (0.6)
Interstitial lung disease	6 (0.3)	2 (0.4)
Organising pneumonia	1 (0.1)	0 (0.0)
Pneumonia	1 (0.1)	0 (0.0)
Patients with at least one immune-mediated AE leading to dose modification of tislelizumab	29 (1.5)	21 (4.2)
Pneumonitis	16 (0.8)	15 (3.0)
Pneumonia	2 (0.1)	1 (0.2)
Immune-mediated pneumonitis	5 (0.3)	3 (0.6)
Interstitial lung disease	5 (0.3)	2 (0.4)
Organising pneumonia	1 (0.1)	0 (0.0)
Patients with at least one SAE	55 (2.8) (2.1, 3.6)	33 (6.6) (4.6, 9.2)
Pneumonitis	28 (1.4)	26 (5.2)

Table Part II: Module SVII-2: Clinical Study Data of Immune-Mediated Adverse Reactions

	Monotherapy (N = 1972) n (%) (95% CI)[a]	**Combination therapy (N = 497) n (%) (95% CI)[a]**
Immune-mediated pneumonitis	11 (0.6)	4 (0.8)
Interstitial lung disease	9 (0.5)	3 (0.6)
Pneumonia	5 (0.3)	0 (0.0)
Organising pneumonia	2 (0.1)	0 (0.0)
Outcome (of SAEs)		
Death	4 (0.2)	3 (0.6)
Pneumonitis	2 (0.1)	3 (0.6)
Pneumonia	2 (0.1)	0 (0.0)
Recovered/resolved	25 (1.3)	13 (2.6)
Pneumonitis	12 (0.6)	10 (2.0)
Immune-mediated pneumonitis	6 (0.3)	3 (0.6)
Pneumonia	3 (0.2)	0 (0.0)
Interstitial lung disease	3 (0.2)	0 (0.0)
Organising pneumonia	1 (0.1)	0 (0.0)
Recovered/resolved with sequelae	1 (0.1)	0 (0.0)
Organising pneumonia	1 (0.1)	0 (0.0)
Recovering/resolving	12 (0.6)	10 (2.0)
Pneumonitis	5 (0.3)	7 (1.4)

Table Part II: Module SVII-2: Clinical Study Data of Immune-Mediated Adverse Reactions

	Monotherapy (N = 1972) n (%) (95% CI)[a]	**Combination therapy (N = 497) n (%) (95% CI)[a]**
Interstitial lung disease	4 (0.2)	2 (0.4)
Immune-mediated pneumonitis	3 (0.2)	1 (0.2)
Not recovered/not resolved	14 (0.7)	6 (1.2)
Pneumonitis	9 (0.5)	6 (1.2)
Immune-mediated pneumonitis	2 (0.1)	0 (0.0)
Interstitial lung disease	2 (0.1)	0 (0.0)
Pneumonia	1 (0.1)	0 (0.0)
Unknown	0 (0.0)	1 (0.2)
Interstitial lung disease	0 (0.0)	1 (0.2)
Immune-Mediated Hepatitis		
Incidence		
Patients with at least one AE	36 (1.8) (1.3, 2.5)	8 (1.6) (0.7, 3.1)
Alanine aminotransferase increased	12 (0.6)	1 (0.2)
Aspartate aminotransferase increased	9 (0.5)	1 (0.2)
Hepatitis	8 (0.4)	0 (0.0)
Immune-mediated hepatitis	6 (0.3)	3 (0.6)
Blood bilirubin increased	2 (0.1)	2 (0.4)
Hepatic failure	2 (0.1)	1 (0.2)

Table Part II: Module SVII-2: Clinical Study Data of Immune-Mediated Adverse Reactions

	Monotherapy (N = 1972) n (%) (95% CI)[a]	Combination therapy (N = 497) n (%) (95% CI)[a]
Hepatocellular injury	2 (0.1)	0 (0.0)
Liver injury	2 (0.1)	1 (0.2)
Autoimmune hepatitis	1 (0.1)	0 (0.0)
Bilirubin conjugated increased	1 (0.1)	1 (0.2)
Drug-induced liver injury	1 (0.1)	0 (0.0)
Gamma-glutamyltransferase increased	1 (0.1)	1 (0.2)
Transaminases increased	1 (0.1)	0 (0.0)
Severity and Nature of Risk		
Patients with worst Grade 3 AE	20 (1.0)	6 (1.2)
Alanine aminotransferase increased	5 (0.3)	1 (0.2)
Aspartate aminotransferase increased	5 (0.3)	0 (0.0)
Hepatitis	5 (0.3)	0 (0.0)
Hepatocellular injury	2 (0.1)	0 (0.0)
Immune-mediated hepatitis	2 (0.1)	3 (0.6)
Liver injury	2 (0.1)	0 (0.0)
Drug-induced liver injury	1 (0.1)	0 (0.0)
Gamma-glutamyltransferase increased	1 (0.1)	1 (0.2)
Transaminases increased	1 (0.1)	0 (0.0)

Table Part II: Module SVII-2: Clinical Study Data of Immune-Mediated Adverse Reactions

	Monotherapy (N = 1972) n (%) (95% CI)[a]	Combination therapy (N = 497) n (%) (95% CI)[a]
Bilirubin conjugated increased	0 (0.0)	1 (0.2)
Patients with worst Grade 4 AE	1 (0.1)	0 (0.0)
Immune-mediated hepatitis	1 (0.1)	0 (0.0)
Patients with worst Grade 5 AE	2 (0.1)	1 (0.2)
Hepatic failure	2 (0.1)	1 (0.2)
Patients with at least one AE leading to discontinuation of tislelizumab	9 (0.5)	3 (0.6)
Alanine aminotransferase increased	2 (0.1)	0 (0.0)
Aspartate aminotransferase increased	2 (0.1)	0 (0.0)
Hepatitis	2 (0.1)	0 (0.0)
Drug-induced liver injury	1 (0.1)	0 (0.0)
Hepatic failure	1 (0.1)	1 (0.2)
Hepatocellular injury	1 (0.1)	0 (0.0)
Liver injury	1 (0.1)	0 (0.0)
Transaminases increased	1 (0.1)	0 (0.0)
Bilirubin conjugated increased	0 (0.0)	1 (0.2)
Immune-mediated hepatitis	0 (0.0)	1 (0.2)
Patients with at least one immune-mediated AE leading to dose modification of tislelizumab	21 (1.1)	4 (0.8)
Alanine aminotransferase increased	9 (0.5)	1 (0.2)

Table Part II: Module SVII-2: Clinical Study Data of Immune-Mediated Adverse Reactions

	Monotherapy (N = 1972) n (%) (95% CI)[a]	**Combination therapy (N = 497) n (%) (95% CI)[a]**
Aspartate aminotransferase increased	6 (0.3)	1 (0.2)
Immune-mediated hepatitis	4 (0.2)	2 (0.4)
Autoimmune hepatitis	1 (0.1)	0 (0.0)
Blood bilirubin increased	1 (0.1)	1 (0.2)
Hepatitis	4 (0.2)	0 (0.0)
Hepatocellular injury	2 (0.1)	0 (0.0)
Transaminases increased	1 (0.1)	0 (0.0)
Liver injury	0 (0.0)	1 (0.2)
Patients with at least one SAE	12 (0.6) (0.3, 1.1)	3 (0.6) (0.1, 1.8)
Hepatitis	3 (0.2)	0 (0.0)
Alanine aminotransferase increased	2 (0.1)	0 (0.0)
Aspartate aminotransferase increased	2 (0.1)	0 (0.0)
Hepatic failure	2 (0.1)	1 (0.2)
Immune-mediated hepatitis	2 (0.1)	2 (0.4)
Drug-induced liver injury	1 (0.1)	0 (0.0)
Liver injury	1 (0.1)	0 (0.0)
Transaminases increased	1 (0.1)	0 (0.0)

Table Part II: Module SVII-2: Clinical Study Data of Immune-Mediated Adverse Reactions

	Monotherapy (N = 1972) n (%) (95% CI)[a]	**Combination therapy (N = 497) n (%) (95% CI)[a]**
Outcome (of SAEs)		
Death	2 (0.1)	1 (0.2)
Hepatic failure	2 (0.1)	1 (0.2)
Recovered/resolved	7 (0.4)	2 (0.4)
Hepatitis	3 (0.2)	0 (0.0)
Alanine aminotransferase increased	2 (0.1)	0 (0.0)
Aspartate aminotransferase increased	2 (0.1)	0 (0.0)
Drug-induced liver injury	1 (0.1)	0 (0.0)
Immune-mediated hepatitis	1 (0.1)	2 (0.4)
Recovering/resolving	2 (0.1)	0 (0.0)
Liver injury	1 (0.1)	0 (0.0)
Transaminases increased	1 (0.1)	0 (0.0)
Not recovered/not resolved	1 (0.1)	0 (0.0)
Immune-mediated hepatitis	1 (0.1)	0 (0.0)
Immune-Mediated Skin Adverse Reaction		
Incidence		
Patients with at least one AE	32 (1.6) (1.1, 2.3)	19 (3.8) (2.3, 5.9)
Rash	15 (0.8)	13 (2.6)

Table Part II: Module SVII-2: Clinical Study Data of Immune-Mediated Adverse Reactions

	Monotherapy (N = 1972) n (%) (95% CI)[a]	Combination therapy (N = 497) n (%) (95% CI)[a]
Drug eruption	5 (0.3)	3 (0.6)
Pruritus	4 (0.2)	0 (0.0)
Rash maculo-papular	2 (0.1)	0 (0.0)
Acute febrile neutrophilic dermatosis	1 (0.1)	0 (0.0)
Dermatitis	1 (0.1)	0 (0.0)
Dermatitis allergic	1 (0.1)	0 (0.0)
Erythema multiforme	1 (0.1)	0 (0.0)
Rash macular	1 (0.1)	0 (0.0)
Rash papular	1 (0.1)	0 (0.0)
Rash pruritic	1 (0.1)	0 (0.0)
Vitiligo	1 (0.1)	0 (0.0)
Rash erythematous	0 (0.0)	1 (0.2)
Rash pustular	0 (0.0)	2 (0.4)
Severity and Nature of Risk		
Patients with worst Grade 3 AE	8 (0.4)	11 (2.2)
Rash	3 (0.2)	7 (1.4)
Rash maculo-papular	2 (0.1)	0 (0.0)
Dermatitis	1 (0.1)	0 (0.0)

Table Part II: Module SVII-2: Clinical Study Data of Immune-Mediated Adverse Reactions

	Monotherapy (N = 1972) n (%) (95% CI)[a]	Combination therapy (N = 497) n (%) (95% CI)[a]
Drug eruption	1 (0.1)	2 (0.4)
Rash macular	1 (0.1)	0 (0.0)
Rash papular	1 (0.1)	1 (0.2)
Rash erythematous	0 (0.0)	1 (0.2)
Patients with worst Grade 4 AE	4 (0.2)	0 (0.0)
Drug eruption	3 (0.2)	0 (0.0)
Rash	1 (0.1)	0 (0.0)
Patients with worst Grade 5 AE	0 (0.0)	0 (0.0)
Patients with at least one AE leading to discontinuation of tislelizumab	5 (0.3)	2 (0.4)
Drug eruption	4 (0.2)	0 (0.0)
Rash	1 (0.1)	1 (0.2)
Rash pustular	0 (0.0)	1 (0.2)
Patients with at least one immune-mediated AE leading to dose modification of tislelizumab	11 (0.6)	9 (1.8)
Acute febrile neutrophilic dermatosis	1 (0.1)	0 (0.0)
Dermatitis	1 (0.1)	0 (0.0)
Dermatitis allergic	1 (0.1)	0 (0.0)
Drug eruption	1 (0.1)	1 (0.2)
Pruritus	1 (0.1)	0 (0.0)

Table Part II: Module SVII-2: Clinical Study Data of Immune-Mediated Adverse Reactions

	Monotherapy (N = 1972) n (%) (95% CI)[a]	**Combination therapy (N = 497) n (%) (95% CI)[a]**
Rash	4 (0.2)	7 (1.4)
Rash macular	1 (0.1)	0 (0.0)
Rash maculo-papular	2 (0.1)	0 (0.0)
Rash erythematous	0 (0.0)	1 (0.2)
Patients with at least one SAE	6 (0.3) (0.1, 0.7)	5 (1.0) (0.3, 2.3)
Drug eruption	4 (0.2)	1 (0.2)
Dermatitis	1 (0.1)	0 (0.0)
Dermatitis allergic	1 (0.1)	0 (0.0)
Rash	0 (0.0)	2 (0.4)
Rash erythematous	0 (0.0)	1 (0.2)
Rash pustular	0 (0.0)	1 (0.2)
Outcome (of SAEs)		
Death	0 (0.0)	0 (0.0)
Recovered/resolved	4 (0.2)	4 (0.8)
Drug eruption	2 (0.1)	1 (0.2)
Dermatitis	1 (0.1)	0 (0.0)
Dermatitis allergic	1 (0.1)	0 (0.0)
Rash	0 (0.0)	2 (0.4)

Table Part II: Module SVII-2: Clinical Study Data of Immune-Mediated Adverse Reactions

	Monotherapy (N = 1972) n (%) (95% CI)[a]	**Combination therapy (N = 497) n (%) (95% CI)[a]**
Rash erythematous	0 (0.0)	1 (0.2)
Recovering/resolving	1 (0.1)	1 (0.2)
Drug eruption	1 (0.1)	0 (0.0)
Rash pustular	0 (0.0)	1 (0.2)
Not recovered/not resolved	1 (0.1)	0 (0.0)
Drug eruption	1 (0.1)	0 (0.0)
Immune-Mediated Colitis		
Incidence		
Patients with at least one AE	19 (1.0) (0.6, 1.5)	7 (1.4) (0.6, 2.9)
Diarrhoea	9 (0.5)	2 (0.4)
Colitis	8 (0.4)	1 (0.2)
Immune-mediated enterocolitis	2 (0.1)	4 (0.8)
Colitis ulcerative	1 (0.1)	0 (0.0)
Rectal haemorrhage	1 (0.1)	0 (0.0)
Severity and Nature of Risk		
Patients with worst Grade 3 AE	7 (0.4)	3 (0.6)
Diarrhoea	4 (0.2)	0 (0.0)
Colitis	3 (0.2)	1 (0.2)

Table Part II: Module SVII-2: Clinical Study Data of Immune-Mediated Adverse Reactions

	Monotherapy (N = 1972) n (%) (95% CI)[a]	Combination therapy (N = 497) n (%) (95% CI)[a]
Immune-mediated enterocolitis	1 (0.1)	2 (0.4)
Patients with worst Grade 4 AE	0 (0.0)	0 (0.0)
Patients with worst Grade 5 AE	0 (0.0)	0 (0.0)
Patients with at least one AE leading to discontinuation of tislelizumab	3 (0.2)	3 (0.6)
Colitis	2 (0.1)	0 (0.0)
Immune-mediated enterocolitis	1 (0.1)	3 (0.6)
Patients with at least one immune-mediated AE leading to dose modification of tislelizumab	12 (0.6)	3 (0.6)
Colitis	3 (0.2)	1 (0.2)
Diarrhoea	6 (0.3)	1 (0.2)
Colitis ulcerative	1 (0.1)	0 (0.0)
Immune-mediated enterocolitis	2 (0.1)	1 (0.2)
Patients with at least one SAE	11 (0.6) (0.3, 1.0)	4 (0.8) (0.2, 2.0)
Colitis	6 (0.3)	1 (0.2)
Diarrhoea	4 (0.2)	0 (0.0)
Immune-mediated enterocolitis	1 (0.1)	3 (0.6)
Outcome (of SAEs)		
Death	0 (0.0)	0 (0.0)
Recovered/resolved	8 (0.4)	2 (0.4)

Table Part II: Module SVII-2: Clinical Study Data of Immune-Mediated Adverse Reactions

	Monotherapy (N = 1972) n (%) (95% CI)[a]	**Combination therapy (N = 497) n (%) (95% CI)[a]**
Colitis	4 (0.2)	1 (0.2)
Diarrhoea	4 (0.2)	0 (0.0)
Immune-mediated enterocolitis	0 (0.0)	1 (0.2)
Recovered/resolved with sequelae	2 (0.1)	0 (0.0)
Colitis	2 (0.1)	0 (0.0)
Recovering/resolving	0 (0.0)	1 (0.2)
Immune-mediated enterocolitis	0 (0.0)	1 (0.2)
Not recovered/not resolved	1 (0.1)	1 (0.2)
Immune-mediated enterocolitis	1 (0.1)	1 (0.2)
Immune-Mediated Myositis/Rhabdomyolysis		
Incidence		
Patients with at least one AE	14 (0.7) (0.4, 1.2)	6 (1.2) (0.4, 2.6)
Blood creatine phosphokinase increased	7 (0.4)	4 (0.8)
Myositis	5 (0.3)	1 (0.2)
Immune-mediated myositis	3 (0.2)	0 (0.0)
Rhabdomyolysis	0 (0.0)	1 (0.2)
Severity and Nature of Risk		
Patients with worst Grade 3 AE	5 (0.3)	3 (0.6)

Table Part II: Module SVII-2: Clinical Study Data of Immune-Mediated Adverse Reactions

	Monotherapy (N = 1972) n (%) (95% CI)[a]	**Combination therapy (N = 497) n (%) (95% CI)[a]**
Blood creatine phosphokinase increased	2 (0.1)	2 (0.4)
Immune-mediated myositis	2 (0.1)	0 (0.0)
Myositis	2 (0.1)	1 (0.2)
Patients with worst Grade 4 AE	1 (0.1)	1 (0.2)
Blood creatine phosphokinase increased	1 (0.1)	1 (0.2)
Patients with worst Grade 5 AE	0 (0.0)	1 (0.2)
Rhabdomyolysis	0 (0.0)	1 (0.2)
Patients with at least one AE leading to discontinuation of tislelizumab	3 (0.2)	5 (1.0)
Immune-mediated myositis	2 (0.1)	0 (0.0)
Myositis	1 (0.1)	1 (0.2)
Blood creatine phosphokinase increased	0 (0.0)	3 (0.6)
Rhabdomyolysis	0 (0.0)	1 (0.2)
Patients with at least one immune-mediated AE leading to dose modification of tislelizumab	10 (0.5)	3 (0.6)
Immune-mediated myositis	2 (0.1)	0 (0.0)
Blood creatine phosphokinase increased	5 (0.3)	3 (0.6)
Myositis	3 (0.2)	0 (0.0)
Patients with at least one SAE	7 (0.4) (0.1, 0.7)	4 (0.8) (0.2, 2.0)
Myositis	4 (0.2)	1 (0.2)

Table Part II: Module SVII-2: Clinical Study Data of Immune-Mediated Adverse Reactions

	Monotherapy (N = 1972) n (%) (95% CI)[a]	**Combination therapy (N = 497) n (%) (95% CI)[a]**
Immune-mediated myositis	2 (0.1)	0 (0.0)
Blood creatine phosphokinase increased	1 (0.1)	2 (0.4)
Rhabdomyolysis	0 (0.0)	1 (0.2)
Outcome (for SAEs)		
Death	0 (0.0)	1 (0.2)
Rhabdomyolysis	0 (0.0)	1 (0.2)
Recovered/resolved	3 (0.2)	3 (0.6)
Blood creatine phosphokinase increased	1 (0.1)	2 (0.4)
Immune-mediated myositis	1 (0.1)	0 (0.0)
Myositis	1 (0.1)	1 (0.2)
Not recovered/not resolved	4 (0.2)	0 (0.0)
Myositis	3 (0.2)	0 (0.0)
Immune-mediated myositis	1 (0.1)	0 (0.0)
Immune-Mediated Endocrinopathies (Hypothyroidism, Hyperthyroidism, Thyroiditis, Adrenal Insufficiency, Pituitary Dysfunction, Type 1 Diabetes Mellitus)		
Immune-Mediated Adrenal Insufficiency		
Incidence		
Patients with at least one AE	6 (0.3) (0.1, 0.7)	0 (0.0)
Adrenal insufficiency	6 (0.3)	0 (0.0)

Table Part II: Module SVII-2: Clinical Study Data of Immune-Mediated Adverse Reactions

	Monotherapy (N = 1972) n (%) (95% CI)[a]	**Combination therapy (N = 497) n (%) (95% CI)[a]**
Severity and Nature of Risk		
Patients with worst Grade 3 AE	1 (0.1)	0 (0.0)
Adrenal insufficiency	1 (0.1)	0 (0.0)
Patients with worst Grade 4 AE	1 (0.1)	0 (0.0)
Adrenal insufficiency	1 (0.1)	0 (0.0)
Patients with worst Grade 5 AE	0 (0.0)	0 (0.0)
Patients with at least one AE leading to discontinuation of tislelizumab	0 (0.0)	0 (0.0)
Patients with at least one immune-mediated AE leading to dose modification of tislelizumab	5 (0.3)	0 (0.0)
Adrenal insufficiency	5 (0.3)	0 (0.0)
Patients with at least one SAE	2 (0.1) (0.0, 0.4)	0 (0.0)
Adrenal insufficiency	2 (0.1)	0 (0.0)
Outcome (for SAEs)		
Death	0 (0.0)	0 (0.0)
Recovered/resolved	1 (0.1)	0 (0.0)
Adrenal insufficiency	1 (0.1)	0 (0.0)
Recovering/resolving	1 (0.1)	0 (0.0)
Adrenal insufficiency	1 (0.1)	0 (0.0)

Table Part II: Module SVII-2: Clinical Study Data of Immune-Mediated Adverse Reactions

	Monotherapy (N = 1972) n (%) (95% CI)[a]	**Combination therapy (N = 497) n (%) (95% CI)[a]**
Immune-Mediated Thyroiditis		
Incidence		
Patients with at least one AE	13 (0.7) (0.4, 1.1)	2 (0.4) (0.0, 1.4)
Thyroiditis	6 (0.3)	0 (0.0)
Autoimmune thyroiditis	5 (0.3)	1 (0.2)
Thyroiditis subacute	1 (0.1)	0 (0.0)
Thyroid function test abnormal	1 (0.1)	1 (0.2)
Severity and Nature of Risk		
Patients with worst Grade 3 AE	0 (0.0)	1 (0.2)
Autoimmune thyroiditis	0 (0.0)	1 (0.2)
Patients with worst Grade 4 AE	0 (0.0)	0 (0.0)
Patients with worst Grade 5 AE	0 (0.0)	0 (0.0)
Patients with at least one AE leading to discontinuation of tislelizumab	0 (0.0)	0 (0.0)
Patients with at least one immune-mediated AE leading to dose modification of tislelizumab	2 (0.1)	0 (0.0)
Thyroiditis	1 (0.1)	0 (0.0)
Thyroiditis subacute	1 (0.1)	0 (0.0)
Patients with at least one SAE	0 (0.0)	1 (0.2) (0.0, 1.1)
Autoimmune thyroiditis	0 (0.0)	1 (0.2)

Table Part II: Module SVII-2: Clinical Study Data of Immune-Mediated Adverse Reactions

	Monotherapy (N = 1972) n (%) (95% CI)[a]	**Combination therapy (N = 497) n (%) (95% CI)[a]**
Outcome (for SAEs)		
Death	0 (0.0)	0 (0.0)
Recovered/resolved	0 (0.0)	1 (0.2)
Autoimmune thyroiditis	0 (0.0)	1 (0.2)
Immune-Mediated Hyperthyroidism		
Incidence		
Patients with at least one AE	12 (0.6) (0.3, 1.1)	3 (0.6) (0.1, 1.8)
Hyperthyroidism	12 (0.6)	2 (0.4)
Thyroxine free increased	0 (0.0)	1 (0.2)
Severity and Nature of Risk		
Patients with worst Grade 3 AE	1 (0.1)	0 (0.0)
Hyperthyroidism	1 (0.1)	0 (0.0)
Patients with worst Grade 4 AE	0 (0.0)	0 (0.0)
Patients with worst Grade 5 AE	0 (0.0)	0 (0.0)
Patients with at least one AE leading to discontinuation of tislelizumab	1 (0.1)	0 (0.0)
Hyperthyroidism	1 (0.1)	0 (0.0)
Patients with at least one immune-mediated AE leading to dose modification of tislelizumab	1 (0.1)	1 (0.2)
Hyperthyroidism	1 (0.1)	1 (0.2)

Table Part II: Module SVII-2: Clinical Study Data of Immune-Mediated Adverse Reactions

	Monotherapy (N = 1972) n (%) (95% CI)[a]	**Combination therapy (N = 497) n (%) (95% CI)[a]**
Patients with at least one SAE	0 (0.0)	0 (0.0)
Outcome (for SAEs)		
Death	0 (0.0)	0 (0.0)
Recovered/resolved	0 (0.0)	0 (0.0)
Immune-Mediated Hypothyroidism		
Incidence		
Patients with at least one AE	133 (6.7) (5.7, 7.9)	45 (9.1) (6.7, 11.9)
Hypothyroidism	131 (6.6)	45 (9.1)
Tri-iodothyronine free decreased	2 (0.1)	1 (0.2)
Triiodothyronine decreased	1 (0.1)	1 (0.2)
Primary hypothyroidism	1 (0.1)	0 (0.0)
Thyroxine free decreased	1 (0.1)	0 (0.0)
Severity and Nature of Risk		
Patients with worst Grade 3 AE	0 (0.0)	0 (0.0)
Patients with worst Grade 4 AE	1 (0.1)	0 (0.0)
Hypothyroidism	1 (0.1)	0 (0.0)
Patients with worst Grade 5 AE	0 (0.0)	0 (0.0)
Patients with at least one AE leading to discontinuation of tislelizumab	0 (0.0)	4 (0.8)

Table Part II: Module SVII-2: Clinical Study Data of Immune-Mediated Adverse Reactions

	Monotherapy (N = 1972) n (%) (95% CI)[a]	**Combination therapy (N = 497) n (%) (95% CI)[a]**
Hypothyroidism	0 (0.0)	4 (0.8)
Patients with at least one immune-mediated AE leading to dose modification of tislelizumab	6 (0.3)	19 (3.8)
Hypothyroidism	6 (0.3)	19 (3.8)
Patients with at least one SAE	1 (0.1) (0.0, 0.3)	0 (0.0)
Hypothyroidism	1 (0.1)	0 (0.0)
Outcome (for SAEs)		
Death	0 (0.0)	0 (0.0)
Recovered/resolved	1 (0.1)	0 (0.0)
Hypothyroidism	1 (0.1)	0 (0.0)
Immune-Mediated Type 1 Diabetes Mellitus		
Incidence		
Patients with at least one AE	8 (0.4) (0.2, 0.8)	5 (1.0) (0.3, 2.3)
Type 1 diabetes mellitus	5 (0.3)	1 (0.1)
Hyperglycaemia	3 (0.2)	2 (0.4)
Diabetic ketoacidosis	2 (0.1)	0 (0.0)
Latent autoimmune diabetes in adults	1 (0.1)	0 (0.0)
Diabetes mellitus	0 (0.0)	2 (0.4)

Table Part II: Module SVII-2: Clinical Study Data of Immune-Mediated Adverse Reactions

	Monotherapy (N = 1972) n (%) (95% CI)[a]	**Combination therapy (N = 497) n (%) (95% CI)[a]**
Severity and Nature of Risk		
Patients with worst Grade 3 AE	6 (0.3)	3 (0.6)
Type 1 diabetes mellitus	4 (0.2)	0 (0.0)
Hyperglycaemia	2 (0.1)	2 (0.4)
Diabetic ketoacidosis	1 (0.1)	0 (0.0)
Latent autoimmune diabetes in adults	1 (0.1)	0 (0.0)
Diabetes mellitus	0 (0.0)	1 (0.2)
Patients with worst Grade 4 AE	1 (0.1)	2 (0.4)
Diabetic ketoacidosis	1 (0.1)	0 (0.0)
Type 1 diabetes mellitus	1 (0.1)	1 (0.2)
Diabetes mellitus	0 (0.0)	1 (0.2)
Patients with worst Grade 5 AE	0 (0.0)	0 (0.0)
Patients with at least one AE leading to discontinuation of tislelizumab	3 (0.2)	0 (0.0)
Diabetic ketoacidosis	1 (0.1)	0 (0.0)
Hyperglycaemia	1 (0.1)	0 (0.0)
Type 1 diabetes mellitus	1 (0.1)	0 (0.0)
Patients with at least one immune-mediated AE leading to dose modification of tislelizumab	2 (0.1)	3 (0.6)
Type 1 diabetes mellitus	1 (0.1)	1 (0.2)

Table Part II: Module SVII-2: Clinical Study Data of Immune-Mediated Adverse Reactions

	Monotherapy (N = 1972) n (%) (95% CI)[a]	**Combination therapy (N = 497) n (%) (95% CI)[a]**
Hyperglycaemia	1 (0.1)	1 (0.2)
Latent autoimmune diabetes in adults	1 (0.1)	0 (0.0)
Diabetes mellitus	0 (0.0)	1 (0.2)
Patients with at least one SAE	6 (0.3) (0.1, 0.7)	2 (0.4) (0.0, 1.4)
Type 1 diabetes mellitus	4 (0.2)	1 (0.2)
Diabetic ketoacidosis	2 (0.1)	0 (0.0)
Hyperglycaemia	2 (0.1)	0 (0.0)
Latent autoimmune diabetes in adults	1 (0.1)	0 (0.0)
Diabetes mellitus	0 (0.0)	1 (0.2)
Outcome (for SAEs)		
Death	0 (0.0)	0 (0.0)
Recovered/resolved	2 (0.1)	0 (0.0)
Diabetic ketoacidosis	1 (0.1)	0 (0.0)
Hyperglycaemia	1 (0.1)	0 (0.0)
Recovered/resolved with sequelae	1 (0.1)	0 (0.0)
Diabetic ketoacidosis	1 (0.1)	0 (0.0)
Recovering/resolving	2 (0.1)	1 (0.2)
Hyperglycaemia	1 (0.1)	0 (0.0)

Table Part II: Module SVII-2: Clinical Study Data of Immune-Mediated Adverse Reactions

	Monotherapy (N = 1972) n (%) (95% CI)[a]	**Combination therapy (N = 497) n (%) (95% CI)[a]**
Type 1 diabetes mellitus	1 (0.1)	1 (0.2)
Not recovered/not resolved	4 (0.2)	1 (0.2)
Type 1 diabetes mellitus	3 (0.2)	0 (0.0)
Latent autoimmune diabetes in adults	1 (0.1)	0 (0.0)
Diabetes mellitus	0 (0.0)	1 (0.2)
Immune-Mediated Pituitary Dysfunction		
Incidence		
Patients with at least one AE	1 (0.1) (0.0, 0.3)	0 (0.0)
Hypopituitarism	1 (0.1)	0 (0.0)
Severity and Nature of Risk	0 (0.0)	0 (0.0)
Patients with worst Grade 3 AE	0 (0.0)	0 (0.0)
Patients with worst Grade 4 AE	0 (0.0)	0 (0.0)
Patients with worst Grade 5 AE	0 (0.0)	0 (0.0)
Patients with at least one AE leading to discontinuation of tislelizumab	0 (0.0)	0 (0.0)
Patients with at least one AE leading to dose modification of tislelizumab	0 (0.0)	0 (0.0)
Patients with at least one SAE	0 (0.0)	0 (0.0)
Outcome (for SAEs)		
Death	0 (0.0)	0 (0.0)

Table Part II: Module SVII-2: Clinical Study Data of Immune-Mediated Adverse Reactions

	Monotherapy (N = 1972) n (%) (95% CI)[a]	**Combination therapy (N = 497) n (%) (95% CI)[a]**
Recovered/resolved	0 (0.0)	0 (0.0)
Immune-Mediated Nephritis and Renal Dysfunction		
Incidence		
Patients with at least one AE	10 (0.5) (0.2, 0.9)	5 (1.0) (0.3, 2.3)
Renal failure	2 (0.1)	0 (0.0)
Blood creatinine increased	2 (0.1)	2 (0.4)
Renal impairment	2 (0.1)	0 (0.0)
Acute kidney injury	1 (0.1)	1 (0.2)
Focal segmental glomerulosclerosis	1 (0.1)	0 (0.0)
Immune-mediated nephritis	1 (0.1)	0 (0.0)
Nephritis	1 (0.1)	2 (0.4)
Renal injury	0 (0.0)	1 (0.2)
Tubulointerstitial nephritis	0 (0.0)	1 (0.2)
Severity and Nature of Risk		
Patients with worst Grade 3 AE	3 (0.2)	2 (0.4)
Acute kidney injury	1 (0.1)	1 (0.2)
Focal segmental glomerulosclerosis	1 (0.1)	0 (0.0)
Renal failure	1 (0.1)	0 (0.0)

Table Part II: Module SVII-2: Clinical Study Data of Immune-Mediated Adverse Reactions

	Monotherapy (N = 1972) n (%) (95% CI)[a]	Combination therapy (N = 497) n (%) (95% CI)[a]
Tubulointerstitial nephritis	0 (0.0)	1 (0.2)
Patients with worst Grade 4 AE	2 (0.1)	0 (0.0)
Renal failure	1 (0.1)	0 (0.0)
Renal impairment	1 (0.1)	0 (0.0)
Patients with worst Grade 5 AE	1 (0.1)	0 (0.0)
Renal impairment	1 (0.1)	0 (0.0)
Patients with at least one AE leading to discontinuation of tislelizumab	4 (0.2)	0 (0.0)
Renal failure	2 (0.1)	0 (0.0)
Focal segmental glomerulosclerosis	1 (0.1)	0 (0.0)
Renal impairment	1 (0.1)	0 (0.0)
Patients with at least one immune-mediated AE leading to dose modification of tislelizumab	4 (0.2)	5 (1.0)
Blood creatinine increased	2 (0.1)	2 (0.4)
Immune-mediated nephritis	1 (0.1)	0 (0.0)
Nephritis	1 (0.1)	2 (0.4)
Acute kidney injury	0 (0.0)	1 (0.2)
Renal injury	0 (0.0)	1 (0.2)
Tubulointerstitial nephritis	0 (0.0)	1 (0.2)

Table Part II: Module SVII-2: Clinical Study Data of Immune-Mediated Adverse Reactions

	Monotherapy (N = 1972) n (%) (95% CI)[a]	**Combination therapy (N = 497) n (%) (95% CI)[a]**
Patients with at least one SAE	5 (0.3) (0.1, 0.6)	2 (0.4) (0.0, 1.4)
Renal failure	2 (0.1)	0 (0.0)
Acute kidney injury	1 (0.1)	1 (0.2)
Focal segmental glomerulosclerosis	1 (0.1)	0 (0.0)
Renal impairment	1 (0.1)	0 (0.0)
Tubulointerstitial nephritis	0 (0.0)	1 (0.2)
Outcome (for SAEs)		
Death	1 (0.1)	0 (0.0)
Renal impairment	1 (0.1)	0 (0.0)
Recovered/resolved	1 (0.1)	1 (0.2)
Renal failure	1 (0.1)	0 (0.0)
Acute kidney injury	0 (0.0)	1 (0.2)
Recovered/resolved with sequelae	2 (0.1)	0 (0.0)
Acute kidney injury	1 (0.1)	0 (0.0)
Renal failure	1 (0.1)	0 (0.0)
Recovering/resolving	1 (0.1)	1 (0.2)
Focal segmental glomerulosclerosis	1 (0.1)	0 (0.0)
Tubulointerstitial nephritis	0 (0.0)	1 (0.2)

Table Part II: Module SVII-2: Clinical Study Data of Immune-Mediated Adverse Reactions

	Monotherapy (N = 1972) n (%) (95% CI)[a]	**Combination therapy (N = 497) n (%) (95% CI)[a]**
Immune-Mediated Myocarditis		
Incidence		
Patients with at least one AE	7 (0.4) (0.1, 0.7)	7 (1.4) (0.6, 2.9)
Immune-mediated myocarditis	3 (0.2)	2 (0.4)
Myocarditis	3 (0.2)	5 (1.0)
Autoimmune myocarditis	1 (0.1)	0 (0.0)
Severity and Nature of Risk		
Patients with worst Grade 3 AE	3 (0.2)	1 (0.2)
Immune-mediated myocarditis	3 (0.2)	0 (0.0)
Myocarditis	0 (0.0)	1 (0.2)
Patients with worst Grade 4 AE	1 (0.1)	1 (0.2)
Myocarditis	1 (0.1)	0 (0.0)
Immune-mediated myocarditis	0 (0.0)	1 (0.2)
Patients with worst Grade 5 AE	0 (0.0)	2 (0.4)
Myocarditis	0 (0.0)	2 (0.4)
Patients with at least one AE leading to discontinuation of tislelizumab	5 (0.3)	6 (1.2)
Immune-mediated myocarditis	2 (0.1)	2 (0.4)
Myocarditis	2 (0.1)	4 (0.8)

Table Part II: Module SVII-2: Clinical Study Data of Immune-Mediated Adverse Reactions

	Monotherapy (N = 1972) n (%) (95% CI)[a]	Combination therapy (N = 497) n (%) (95% CI)[a]
Autoimmune myocarditis	1 (0.1)	0 (0.0)
Patients with at least one immune-mediated AE leading to dose modification of tislelizumab	3 (0.2)	2 (0.4)
Autoimmune myocarditis	1 (0.1)	0 (0.0)
Immune-mediated myocarditis	1 (0.1)	0 (0.0)
Myocarditis	1 (0.1)	2 (0.4)
Patients with at least one SAE	7 (0.4) (0.1, 0.7)	5 (1.0) (0.3, 2.3)
Immune-mediated myocarditis	3 (0.2)	2 (0.4)
Myocarditis	3 (0.2)	3 (0.6)
Autoimmune myocarditis	1 (0.1)	0 (0.0)
Outcome (for SAEs)		
Death	0 (0.0)	2 (0.4)
Myocarditis	0 (0.0)	2 (0.4)
Recovered/resolved	4 (0.2)	2 (0.4)
Immune-mediated myocarditis	2 (0.1)	1 (0.2)
Autoimmune myocarditis	1 (0.1)	0 (0.0)
Myocarditis	1 (0.1)	1 (0.2)
Recovering/resolving	1 (0.1)	1 (0.2)
Myocarditis	1 (0.1)	0 (0.0)

Table Part II: Module SVII-2: Clinical Study Data of Immune-Mediated Adverse Reactions

	Monotherapy (N = 1972) n (%) (95% CI)[a]	Combination therapy (N = 497) n (%) (95% CI)[a]
Immune-mediated myocarditis	0 (0.0)	1 (0.2)
Not recovered/not resolved	2 (0.1)	0 (0.0)
Immune-mediated myocarditis	1 (0.1)	0 (0.0)
Myocarditis	1 (0.1)	0 (0.0)
Immune-Mediated Nervous System Disorder		
Incidence		
Patients with at least one AE	0 (0.0)	2 (0.4) (0.0, 1.4)
Guillain-Barre syndrome	0 (0.0)	1 (0.2)
Immune-mediated encephalitis	0 (0.0)	1 (0.2)
Severity and Nature of risk		
Patients with worst Grade 3 AE	0 (0.0)	2 (0.4)
Guillain-Barre syndrome	0 (0.0)	1 (0.2)
Immune-mediated encephalitis	0 (0.0)	1 (0.2)
Patients with worst Grade 4 AE	0 (0.0)	0 (0.0)
Patients with worst Grade 5 AE	0 (0.0)	0 (0.0)
Patients with at least one AE leading to discontinuation of tislelizumab	0 (0.0)	1 (0.2)
Immune-mediated encephalitis	0 (0.0)	1 (0.2)

Table Part II: Module SVII-2: Clinical Study Data of Immune-Mediated Adverse Reactions

	Monotherapy (N = 1972) n (%) (95% CI)[a]	**Combination therapy (N = 497) n (%) (95% CI)[a]**
Patients with at least one immune-mediated AE leading to dose modification of tislelizumab	0 (0.0)	1 (0.2)
Guillain-Barre syndrome	0 (0.0)	1 (0.2)
Patients with at least one SAE	0 (0.0)	2 (0.4) (0.0, 1.4)
Guillain-Barre syndrome	0 (0.0)	1 (0.2)
Immune-mediated encephalitis	0 (0.0)	1 (0.2)
Outcome (for SAEs)		
Death	0 (0.0)	0 (0.0)
Recovered/resolved	0 (0.0)	1 (0.2)
Immune-mediated encephalitis	0 (0.0)	1 (0.2)
Not recovered/not resolved	0 (0.0)	1 (0.2)
Guillain-Barre syndrome	0 (0.0)	1 (0.2)
Immune-Mediated Pancreatitis		
Incidence		
Patients with at least one AE	1 (0.1) (0.0, 0.3)	0 (0.0)
Pancreatitis	1 (0.1)	0 (0.0)
Severity and Nature of risk		
Patients with worst Grade 3 AE	1 (0.1)	0 (0.0)
Pancreatitis	1 (0.1)	0 (0.0)

Table Part II: Module SVII-2: Clinical Study Data of Immune-Mediated Adverse Reactions

	Monotherapy (N = 1972) n (%) (95% CI)[a]	**Combination therapy (N = 497) n (%) (95% CI)[a]**
Patients with worst Grade 4 AE	0 (0.0)	0 (0.0)
Patients with worst Grade 5 AE	0 (0.0)	0 (0.0)
Patients with at least one AE leading to discontinuation of tislelizumab	0 (0.0)	0 (0.0)
Patients with at least one immune-mediated AE leading to dose modification of tislelizumab	1 (0.1)	0 (0.0)
Pancreatitis	1 (0.1)	0 (0.0)
Patients with at least one SAE	1 (0.1) (0.0, 0.3)	0 (0.0)
Pancreatitis	1 (0.1)	0 (0.0)
Outcome (for SAEs)		
Death	0 (0.0)	0 (0.0)
Recovered/resolved	1 (0.1)	0 (0.0)
Pancreatitis	1 (0.1)	0 (0.0)
Other Immune-Mediated Reactions [b]		
Incidence		
Patients with at least one AE	7 (0.4) (0.1, 0.7)	0 (0.0)
Arthritis	4 (0.2)	0 (0.0)
Immune-mediated arthritis	1 (0.1)	0 (0.0)
Pericarditis	1 (0.1)	0 (0.0)
Polymyalgia rheumatica	1 (0.1)	0 (0.0)

Table Part II: Module SVII-2: Clinical Study Data of Immune-Mediated Adverse Reactions

	Monotherapy (N = 1972) n (%) (95% CI)[a]	**Combination therapy (N = 497) n (%) (95% CI)[a]**
Severity and Nature of Risk		
Patients with worst Grade 3 AE	1 (0.1)	0 (0.0)
Arthritis	1 (0.1)	0 (0.0)
Patients with worst Grade 4 AE	0 (0.0)	0 (0.0)
Patients with worst Grade 5 AE	0 (0.0)	0 (0.0)
Patients with at least one AE leading to discontinuation of tislelizumab	1 (0.1)	0 (0.0)
Arthritis	1 (0.1)	0 (0.0)
Patients with at least one immune-mediated AE leading to dose modification of tislelizumab	2 (0.1)	0 (0.0)
Immune-mediated arthritis	1 (0.1)	0 (0.0)
Pericarditis	1 (0.1)	0 (0.0)
Patients with at least one SAE	2 (0.1) (0.0, 0.4)	0 (0.0)
Arthritis	2 (0.1)	0 (0.0)
Outcome (for SAEs)		
Death	0 (0.0)	0 (0.0)
Recovered/resolved	2 (0.1)	0 (0.0)
Arthritis	2 (0.1)	0 (0.0)

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PT, Preferred Term; SAE, serious adverse events; SCLC, small cell lung cancer; TEAE, treatment-emergent adverse event.

[a] Two-sided 95% CI calculated using Clopper-Pearson method.

[b] The combination pool data are presented in the table above as per the PTs displayed for the monotherapy pool; hence, it may not be sorted by descending frequency of category or PTs.

AEs grades were evaluated based on NCI-CTCAE (Version 5.0) for Studies 304 and 307, and NCI-CTCAE (Version 4.03) for Study 206 and monotherapy studies.
AEs were coded using the MedDRA Version 23.0.
Monotherapy:
Source data: Annex 7 Table 3.1.1.1, Table 3.2.1.1, Table 3.3.1.1, Table 2.7.4.2.2.6.1.
Studies include monotherapy studies (Studies 001, 102, 203, 204, 208, 302, 303) only.
Immune-mediated AEs were firstly sorted by descending frequency of category, and then sorted PTs within the category by descending frequency.
TEAE leading to the dose modification is defined as a TEAE with action taken 'Dose delay', 'Dose delayed', 'Drug interrupted', 'Dose interrupted', 'Dose held/interrupted' or 'Infusion rate decrease' by investigator.
Combination therapy:
Source data: Annex 7 Table 3.1.1.2, Table 3.2.1.2, Table 3.3.1.2, Table 2.7.4.5.1.6.
Studies include combination studies (Studies 206, 304, 307) only.
Tislelizumab treated patients who switched from the chemotherapy control arms in Studies 304 and 307 were not included. Patients from SCLC cohort in Study 206 were not included.
The combination pool data are presented in the table above as per the PTs displayed for the monotherapy pool; hence, it may not be sorted by descending frequency of category or PTs.
Tislelizumab dose modification includes 'Dose delay', 'Infusion interrupted', 'Dose interrupted' or 'Infusion rate decrease' by investigator.

Risk Factors and Risk Groups:

Patients with a history of or ongoing autoimmune disease may be at a higher risk of developing imAEs and are generally excluded from the clinical development programme for tislelizumab. There are currently no identified risk groups or risk factors that may predispose patients to developing immune-mediated adverse reactions after treatment with tislelizumab.

Preventability:

Immune-Mediated Pneumonitis

While on therapy with tislelizumab, patients should inform their HCP about any of the following symptoms that may indicate inflammation of the lung: shortness of breath, chest pain, or cough.

Patients with suspected pneumonitis should be evaluated with radiographic imaging and infectious or disease related aetiologies should be ruled out.

The HCP should monitor for signs and symptoms of pneumonitis. Early detection and treatment may prevent and/or mitigate the risk. The SmPC includes details on how to manage immune-mediated pneumonitis.

Immune-Mediated Hepatitis

The SmPC provides recommendations for the treatment of immune-mediated hepatitis, including withholding tislelizumab, administering corticosteroids, and permanently discontinuing tislelizumab for severe or life-threatening symptoms. Tislelizumab may be reintroduced only after signs and symptoms of immune-mediated hepatitis resolve and upon careful consideration by the treating physician.

While on therapy with tislelizumab, patients should inform their HCP if they experience any of the following symptoms that may indicate inflammation of the liver: nausea, vomiting, loss of appetite, pain on the right side of the stomach, yellowing of the skin or whites of the eyes, drowsiness, dark coloured urine, bleeding or bruising more easily than normal. The HCPs should monitor patients' liver function tests (ALT/AST, direct and indirect bilirubin). If a patient develops hepatitis, the HCP may decide to stop tislelizumab temporarily or permanently. Treatment may be necessary, including steroids.

Immune-Mediated Skin Adverse Reaction

The SmPC contains recommendations for treatment in the event of immune-mediated skin reaction including administration and dosing of corticosteroids, and permanent discontinuation of tislelizumab in patients with Grade 4 rash. For signs or symptoms of suspected severe cutaneous adverse reactions, including severe erythema multiforme, Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN), HCPs should withhold tislelizumab and refer the patient for specialised assessment and treatment. If severe cutaneous adverse reactions, including SJS or TEN is confirmed, tislelizumab should be permanently discontinued.

The HCPs should monitor patients for suspected severe skin reactions (including erythema multiforme, SJS or TEN). If patients develop signs or symptoms of a possible severe skin reaction, which may include fever, flu-like symptoms, rash, itching, skin blistering, or ulcers in the mouth or on other moist surfaces, they should notify their HCP.

Immune-Mediated Colitis

While on therapy with tislelizumab, patients should inform their HCP of any of the following symptoms that may indicate colitis: diarrhoea or more bowel movements than normal, black tarry, sticky stools or stools with blood or mucus, or severe abdominal pain or tenderness. Patients should be monitored for signs and symptoms of colitis. Infectious and disease related aetiologies should be ruled out. The HCPs should consider stopping treatment with tislelizumab temporarily or permanently and begin steroid therapy if indicated.

The HCPs should monitor patients for signs and symptoms of colitis. Early detection and treatment may prevent and/or mitigate the risk. The SmPC includes details on how to manage immune-mediated colitis.

Immune-Mediated Myositis/Rhabdomyolysis

Patients should inform their HCP if they are experiencing muscle pain, stiffness, weakness, chest pain, or severe tiredness that may be related to myositis. If a diagnosis of myositis is confirmed, the HCP may decide to stop tislelizumab temporarily or permanently, and treatment with steroids may be needed. If a diagnosis of rhabdomyolysis is confirmed, the HCP may also decide to stop tislelizumab temporarily or permanently. Early detection and treatment may prevent and/or mitigate the risk. Treatment modification for immune-mediated myositis and rhabdomyolysis is included in the SmPC.

Immune-Mediated Endocrinopathies (Hypothyroidism, Hyperthyroidism, Thyroiditis, Adrenal Insufficiency, Pituitary Dysfunction, Type 1 Diabetes Mellitus)

The SmPC provide recommendations for treatment in the event of immune-mediated endocrinopathies.

The HCPs should monitor for signs and symptoms of endocrinopathies and monitor thyroid function before and periodically during treatment with tislelizumab. While on therapy with tislelizumab, patients should inform the HCP of any of the following symptoms: fast heartbeat, extreme tiredness or hyperactivity, weight gain or weight loss, dizziness or fainting, hair loss, feeling cold, constipation, headaches that will not go away or unusual headaches. For more signs and symptoms refer to SmPC.

Immune-Mediated Nephritis and Renal Dysfunction

While on therapy with tislelizumab, patients should notify their HCP if they notice a change in the amount or colour of their urine, pain while urinating, or pain in kidney area. The HCP should monitor patients' renal function (serum creatinine).

The SmPC provide recommendations for treatment in the event of immune-mediated nephritis and renal dysfunction, including withholding treatment, administering corticosteroids, and permanently discontinuing tislelizumab in patients with recurrent severe or life-threatening symptoms.

Immune-Mediated Myocarditis

While on therapy with tislelizumab, patients should inform their HCP about any of the following symptoms that may be related to myocarditis including chest pain, rapid or abnormal heartbeat, shortness of breath at rest or during activity, fluid build-up with swelling of the legs, ankles, and

feet, and tiredness. If a diagnosis of myocarditis is confirmed, the HCP may decide to stop tislelizumab temporarily or permanently. HCPs should consider administering specific treatment with steroids for myocarditis as soon as possible. Treatment modification for myocarditis is included in the SmPC.

Immune-Mediated Nervous System Disorders

On therapy with tislelizumab, patients should inform the HCP of any of the following symptoms: breathing difficulty, sensation of prickling or pins and needles in the fingers, toes, ankles, or wrists, weakness in the legs that spreads to the upper body, unsteady walking or inability to walk or climb stairs, difficulty with facial movements including speaking, chewing or swallowing, double vision or inability to move eyes, difficulty with bladder control or bowel function, rapid heart rate, and paralysis.

Early detection and treatment may prevent and/or mitigate the risk. If a patient develops immune-mediated encephalitis, the HCP may decide to stop tislelizumab treatment temporarily or permanently and treatment with steroids may be needed. The product label includes details on how to manage immune-mediated nervous system disorders.

Immune-Mediated Pancreatitis

The HCP should monitor patients for signs and symptoms of pancreatitis such as abdominal pain, severe upper stomach pain, nausea, vomiting, fever, tender abdomen, and onset of abdominal pain that may gradually or abruptly become severe. Blood amylase and lipase (at the start of treatment, at regular intervals during treatment, and as clinical assessment indicates) should also be monitored. Early detection and treatment may prevent and/or mitigate the risk.

Other Immune-Mediated Reactions

Recommendations for the treatment of other immune disorders are provided in the SmPC.

Impact on the Benefit-Risk Balance of the Product:

The risk should be managed by the guidance listed in the tislelizumab SmPC. A Patient Card will be given to patients to inform them about these risks, to improve communication with physicians and timely management of imAEs. Overall, the benefit-risk balance is positive given the clinical efficacy associated with the use of the product and the severity of the diseases.

Public Health Impact:

The public health impact of these events attributable to tislelizumab treatment is expected to be low.

Important Potential Risks:

Reproductive and Developmental Toxicity:

Potential Mechanisms:

The PD-1/PD-L1 pathway is involved in the maintenance of tolerance to the foetus, PD-1 blockade can disrupt immune tolerance.

Evidence Source(s) and Strength of Evidence:

Nonclinical data: No treatment-related effects were observed in the reproductive organs in cynomolgus monkeys after intravenous infusion at doses of 3, 10, 30 or 60 mg/kg (once every 2 weeks, 7 doses) for 13 weeks. However, not all animals in these studies were sexually mature. A literature-based assessment of effects on embryofoetal toxicity demonstrated that the pharmacologically mediated blockade of PD-1/PD-L1 interaction in animal models can result in foetal loss (Guleria et al 2005). This is due to disruption of immune tolerance to the foetus as the PD-1/PD-L1 pathway plays a role in the maintenance of tolerance (Tripathi and Guleria 2015).

Clinical data: A clinical study conducted by Meggyes et al (2019) further supports the animal model data and highlighted the potential importance of the PD-1/PD-L1 immune-checkpoint pathway in the induction of maternal tolerance during healthy pregnancy. The PD-1 binding to the abundantly expressed PD-L1 in tumours is analogous to the PD-1 binding to a highly expressed PD-L1 at the uteroplacental interface (Guleria et al 2005; Habicht et al 2007; Petroff and Perchellet 2010). The blockade of the PD-1/PD-L1 pathway in inducing foetal loss/abortion has been shown in murine models of allogeneic pregnancy. Therefore, the potential risks of administering a PD-1/PD-L1 inhibitor, including tislelizumab, during pregnancy include increased rates of abortion or stillbirth.

Based on the mechanism of action, the administration of tislelizumab during pregnancy could cause harm to the foetus.

Characterisation of the Risk:

No TEAEs of reproductive and developmental toxicity have been reported in monotherapy studies (Study 001, Study 102, Study 203, Study 204, Study 208, Study 302, and Study 303) and in combination therapy studies (Study 206, Study 304, and Study 307).

Risk Factors and Risk Groups:

No relevant risk groups or risk factors have been identified.

Preventability:

Tislelizumab should not be used during pregnancy and in women of childbearing potential not using effective contraception, unless the clinical benefit outweighs the potential risk. Women should be advised not to breast feed during treatment and for at least 4 months after the last dose of tislelizumab.

Women of childbearing potential should be advised to use effective contraception during treatment with tislelizumab and for 4 months after the last dose. The SmPC includes details on reproductive and developmental toxicity.

Impact on the Benefit-Risk Balance of the Product:

There are no available human data regarding the risk of reproductive and developmental toxicity.

The risk should be well managed by the guidance provided in the tislelizumab SmPC.

Public Health Impact:

The public health impact of this event attributable to tislelizumab treatment is expected to be low.

SVII.3.2 Presentation of the Missing Information

None.

PART II: MODULE SVIII SUMMARY OF SAFETY CONCERNS

Table Part II: Module SVIII-1: Summary of Safety Concerns

Summary of Safety Concerns	
Important Identified Risks	Immune-mediated adverse reactions
Important Potential Risks	Reproductive and developmental toxicity
Missing Information	None

PART III PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

Specific Adverse Reaction Follow-up Checklists:

Specific AE follow-up checklist will be used to collect data to help further characterise and/or closely monitor the safety concern as specified below:

Important Identified Risk

- Immune-mediated adverse reactions

The targeted follow-up checklist is provided in Annex 4.

Other Forms of Routine Pharmacovigilance Activities:

There are no other forms of routine pharmacovigilance activities.

III.2 Additional Pharmacovigilance Activities

None.

III.3 Summary Table of Additional Pharmacovigilance Activities

None.

PART IV PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

There are no plans for postauthorisation efficacy studies.

PART V RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

V.1 Routine Risk Minimisation Measures

Table Part V-1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
Important Identified Risk	
Immune-Mediated Adverse Reactions	Routine Risk Communication: SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 PL Section 2 PL Section 4 Routine Risk Minimisation Activities Recommending Specific Clinical Measures to Address the Risk: SmPC Section 4.2 includes guidelines for withholding or permanent discontinuation of treatment. Advice regarding monitoring and management of immune-mediated adverse reactions is included in SmPC Section 4.4. SmPC Section 4.8 is where the adverse drug reactions of immune-mediated adverse reactions are listed. Guidance on how to early identify signs and symptoms and seek medical attention is included in PL Section 2 and PL Section 4. Other Routine Risk Minimisation Measures Beyond the Product Information: Legal status: restricted medical prescription
Important Potential Risk	
Reproductive and Developmental Toxicity	Routine Risk Communication: SmPC Section 4.6 SmPC Section 5.3 PL Section 2 Routine Risk Minimisation Activities Recommending Specific Clinical Measures to Address the Risk: Advice that women of childbearing potential should avoid becoming pregnant and lactating women should avoid breastfeeding infants while taking tislelizumab and for 4 months after the last dose, and that women of childbearing potential should use effective contraception during treatment with tislelizumab and for 4 months after the last dose is included in SmPC Section 4.6 and PL Section 2. Other Routine Risk Minimisation Measures Beyond the Product Information: Legal status: restricted medical prescription
Missing Information	
None	

Abbreviations: PL, Product Label; SmPC, Summary of Product Characteristics.

V.2 Additional Risk Minimisation Measures

Additional Risk Minimisation Measures

To increase understanding of the safe and effective use of Tevimbra (tislelizumab), physicians should provide patients or their caregivers with the Patient Card.

Objectives:

The Patient Card is aimed to inform patients and increase their awareness on the signs and symptoms relevant to the early recognition/identification of the potential immune-mediated adverse reactions and prompt them about when to seek medical attention from their physician, ensuring rapid identification and treatment of these events.

The Patient Card is designed for being always carried by the patient and to be presented to the HCP that may assist them.

Rationale for the Additional Risk Minimisation Activity:

Immune-mediated adverse reactions may be serious and life-threatening and can be mitigated with early detection and treatment.

Target Audience and Planned Distribution Path:

Prescribers will receive Patient Cards to deliver to patients who are prescribed tislelizumab or to their caregivers.

Plans to Evaluate the Effectiveness of the Interventions and Criteria for Success:

Effectiveness will be considered through routine pharmacovigilance safety surveillance. Observations, findings, and outcomes of immune-mediated adverse reactions will be presented regularly in the Periodic Safety Update Reports including information collected via the targeted follow-up checklist, when applicable.

V.3 Summary of Risk Minimisation Measures

Table Part V-2: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risks		
Immune-Mediated Adverse Reactions	Routine Risk Minimisation Measures: SmPC Section 4.2 where guidelines for withholding or permanent discontinuation of treatment are provided. SmPC Section 4.4 where advice is provided regarding monitoring and management of immune-mediated adverse reactions. SmPC Section 4.8 where the adverse drug reactions of immune-mediated adverse reactions are listed.	Routine Pharmacovigilance Activities Beyond Adverse Reactions Reporting and Signal Detection: Targeted follow-up checklist Additional Pharmacovigilance Activities: None

Table Part V-2: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	PL Section 2 and PL Section 4 where guidance on how to early identify signs and symptoms and seek medical attention is included. Additional Risk Minimisation Measures: Patient card Legal Status: Restricted medical prescription	
Important Potential Risks		
Reproductive and Developmental Toxicity	Routine Risk Minimisation Measures: SmPC Section 4.6 where advice is provided regarding the need for women of childbearing potential to avoid getting pregnant for lactating women to avoid breastfeeding infants while taking tislelizumab, and that women of childbearing potential should use effective contraception during treatment with tislelizumab and for 4 months after the last dose. SmPC Section 5.3. PL Section 2 where guidance on how to early identify signs and symptoms and seek medical attention is included. Additional Risk Minimisation Measures: None Legal Status: Restricted medical prescription	Routine Pharmacovigilance Activities Beyond Adverse Reactions Reporting and Signal Detection: None Additional Pharmacovigilance Activities: None
Missing Information		
None		

Abbreviations: PL, Product Label; SmPC, Summary of Product Characteristics.

PART VI SUMMARY OF RISK MANAGEMENT PLAN FOR TEVIMBRA (TISLELIZUMAB)

This is a summary of the risk management plan (RMP) for Tevimbra. The RMP details important risks of Tevimbra, how these risks can be minimised, and how more information will be obtained about Tevimbra's risks and uncertainties (missing information).

Tevimbra's Summary of Product Characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Tevimbra should be used.

This summary of the RMP for Tevimbra should be read in the context of all this information, including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR). Important new concerns or changes to the current ones will be included in updates of Tevimbra's RMP.

I THE MEDICINE AND WHAT IT IS USED FOR

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

Tevimbra in combination with pemetrexed and platinum-containing chemotherapy is indicated for the first-line treatment of adult patients with nonsquamous non-small cell lung cancer (NSCLC) whose tumours have programmed cell death ligand 1 (PD-L1) expression on ≥ 50% of tumour cells with no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) positive mutations and who have:

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

Tevimbra in combination with carboplatin and either paclitaxel or nab-paclitaxel, is indicated for the first-line treatment of adult patients with squamous NSCLC who have:

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

Tevimbra as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic NSCLC after prior platinum-based therapy. Patients with epidermal growth factor receptor mutant or anaplastic lymphoma kinase positive NSCLC should also have received targeted therapies before receiving Tevimbra.

It contains tislelizumab as the active substance and it is given by the intravenous route of administration.

Further information about the evaluation of Tevimbra's benefits can be found in Tevimbra's EPAR, including in its plain-language summary, available on the European Medicines Agency website, under the medicine's webpage:
https://www.ema.europa.eu/en/medicines/human/EPAR/tevimbra.

II RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of Tevimbra, together with measures to minimise such risks and the proposed studies for learning more about Tevimbra's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so as to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A List of Important Risks and Missing Information

Important risks of Tevimbra are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Tevimbra. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

Summary of Safety Concerns	
Important Identified Risks	Immune-mediated adverse reactions
Important Potential Risks	Reproductive and developmental toxicity
Missing Information	None

II.B Summary of Important Risks

Important Identified Risk: Immune-Mediated Adverse Reactions	
Evidence for Linking the Risk to the Medicine	Review of tislelizumab clinical study data, postmarketing experience and literature regarding immune-mediated adverse reactions (including immune-mediated pneumonitis, immune-mediated hepatitis, immune-mediated skin adverse reaction, immune-mediated colitis, immune-mediated myositis/rhabdomyolysis, immune-mediated endocrinopathies, immune-mediated nephritis and renal dysfunction, immune-mediated myocarditis, immune-mediated nervous system disorder, immune-mediated pancreatitis, and other immune-mediated reactions) represent sufficient evidence of a causal association with tislelizumab exposure. *Immune-Mediated Pneumonitis* Nonclinical data: No treatment-related inflammation in the lungs was observed in cynomolgus monkeys after intravenous infusion at doses of 3, 10, 30 mg/kg or 60 mg/kg (once every 2 weeks, 7 doses) for 13 weeks. Clinical data: The most common lung toxicity observed in patients receiving immune checkpoint inhibitor (ICI) treatment is pneumonitis. Reports of pneumonitis were documented in 2% to 4% of patients, with 1% to 2% of patients having Grade $\geq$ 3 events, frequency of fatal pneumonitis in 0.2% of patients, and discontinuation due to pneumonitis in 0.2% to 4% of patients. Patients with NSCLC were significantly more likely to experience any grade pneumonitis and Grade 3 or higher pneumonitis compared with other tumour types. *Immune-Mediated Hepatitis* Nonclinical data: No treatment-related hepatic inflammation was observed in cynomolgus monkeys after intravenous infusion at doses of 3, 10, 30 mg/kg or 60 mg/kg (once every 2 weeks, 7 doses) for 13 weeks. Clinical data: Although infrequently observed, the occurrence of immune-mediated hepatitis is well established in patients treated with ICIs. These patients are typically asymptomatic, and diagnosis is made based on elevated liver enzymes such as alanine aminotransferase and/or aspartate aminotransferase, and occasionally hyperbilirubinemia. The median onset of transaminase elevation is approximately 6 to 14 weeks after starting ICI treatment, and the incidence of developing immune-mediated hepatitis in patients treated with ICIs is approximately 5%. *Immune-Mediated Skin Adverse Reaction* Nonclinical data: No treatment-related skin rash was observed in cynomolgus monkeys after intravenous infusion at doses of 3, 10, 30 mg/kg or 60 mg/kg (once every 2 weeks, 7 doses) for 13 weeks. Clinical data: Skin adverse events (AEs) are among the most frequent AEs observed in patients treated with mAbs inhibiting either immune checkpoints cytotoxic T lymphocyte-associated protein 4 (CTLA4; ipilimumab in 43% to 45% of the patients) or programmed cell death protein-1 (PD-[L]1; nivolumab and pembrolizumab in approximately 34% of the patients). However, serious skin AEs are rare and do not usually require dose reductions or treatment discontinuation. *Immune-Mediated Colitis* Nonclinical data: No treatment-related diarrhoea or gastrointestinal tract inflammation was observed in cynomolgus monkeys after intravenous infusion at doses of 3, 10, 30 mg/kg or 60 mg/kg (once every 2 weeks, 7 doses) for 13 weeks. Clinical data: Diarrhoea and colitis are more frequent with anti-CTLA4 agents (eg, ipilimumab) than with anti-PD-1 targeted agents including nivolumab or pembrolizumab, with Grade 3 to 4 AEs occurring in 1% to 2% of cases (Haanen et al 2017). The presence of diarrhoea in conjunction with abdominal pain, rectal bleeding, mucus in the stool, and fever should alert the clinician to the possibility of

Important Identified Risk: Immune-Mediated Adverse Reactions	
	colitis, a potentially serious or even life-threatening gastrointestinal complication of ICI therapy. *Immune-Mediated Myositis/Rhabdomyolysis* Nonclinical data: No treatment-related inflammation in muscle was observed in cynomolgus monkeys after intravenous infusion at doses of 3, 10, 30 mg/kg or 60 mg/kg (once every 2 weeks, 7 doses) for 13 weeks. Clinical data: Immune-mediated myositis/rhabdomyolysis occur uncommonly in cancer patients treated with ICIs. Recognizing musculoskeletal immune-mediated adverse events (imAEs) in the oncology setting is challenging due to the broad range of potential presenting symptoms and the prevalence of musculoskeletal complaints in the general population. *Immune-Mediated Endocrinopathies (hypothyroidism, hyperthyroidism, thyroiditis, adrenal insufficiency, pituitary dysfunction, type 1 diabetes mellitus)* Nonclinical data: No treatment-related thyroid inflammation was observed in cynomolgus monkeys after intravenous infusion at doses of 3, 10, 30 mg/kg or 60 mg/kg (once every 2 weeks, 7 doses) for 13 weeks. Clinical data: Thyroid disease or abnormalities in thyroid function tests (primary hypothyroidism and thyroiditis) is one of the most common endocrine imAEs. Thyroid dysfunction (hypothyroidism, hyperthyroidism, and thyroiditis) was reported in 6 to 20% of patients in large Phase III clinical studies. Pituitary dysfunction is a rare condition which occurs in 0.5 to 1% of patients treated with anti-PD-1/PD-L1 monotherapy and up to 10% with combination CTLA4/PD-1 blockade. In contrast to thyroid disorders, most patients with pituitary dysfunction present with clinical symptoms commonly related to neuro-compression or more often, to secondary adrenal insufficiency including fatigue and nausea. Primary adrenal insufficiency is a rare complication of ICI therapy. Diabetes Mellitus after treatment with ICIs occurs in slightly less than 1% of patients; approximately 97% of all reported cases have arisen with anti-PD-1/PD-L1 monotherapy or combination treated patients. *Immune-Mediated Nephritis and Renal Dysfunction* Nonclinical data: No treatment-related inflammation in the kidneys was observed in cynomolgus monkeys after intravenous infusion at doses of 3, 10, 30 mg/kg or 60 mg/kg (once every 2 weeks, 7 doses) for 13 weeks. Secondary renal changes were observed at 60 mg/kg due to immunogenicity against tislelizumab (ADAs). Clinical data: In the published literature, renal immune-mediated AEs are considered rare. Most reports document isolated cases of interstitial nephritis with specific agents and regimens, such as anti-PD-(L)1 monotherapy, and combination anti-CTLA4/PD-(L)1 treatment in melanoma. *Immune-Mediated Myocarditis* Nonclinical data: No treatment-related inflammation of the heart was observed in cynomolgus monkeys after intravenous infusion at doses of 3, 10, 30 mg/kg or 60 mg/kg (once every 2 weeks, 7 doses) for 13 weeks. Clinical data: Myocarditis and cardiac dysfunction due to ICIs are rare and the true incidence is unknown; current estimates suggest this incidence is < 1% of patients. Cardiac immune-mediated AEs due to ICIs may present with nonspecific symptoms such as fatigue and weakness. However, more typical cardiac symptoms of chest pain, shortness of breath, pulmonary or lower extremity oedema, palpitations, irregular heartbeat, rapid onset of heart failure symptoms, or new heart block on electrocardiogram can occur at any time, more frequently within the first few months of treatment, and may lead to death.

Important Identified Risk: Immune-Mediated Adverse Reactions	
	Immune-Mediated Nervous System Disorders Nonclinical data: No treatment-related inflammation in the brain was observed in cynomolgus monkeys after intravenous infusion at doses of 3, 10, 30 mg/kg or 60 mg/kg (once every 2 weeks, 7 doses) for 13 weeks. Clinical data: Neurologic immune-related AEs are uncommon with an overall incidence up to 6% with anti-PD-(L)1 antibodies and include autoimmune encephalitis, myasthenic syndrome, and Guillain-Barre syndrome. *Immune-Mediated Pancreatitis* Nonclinical data: No treatment-related inflammation in the pancreas was observed in cynomolgus monkeys after intravenous infusion at doses of 3, 10, 30 mg/kg or 60 mg/kg (once every 2 weeks, 7 doses) for 13 weeks. Clinical data: Acute pancreatitis has been reported but is rare in cancer patients treated with ICIs; asymptomatic elevation of lipase and amylase are more common. *Other Immune-Mediated Reactions* Nonclinical data: No other immune-mediated reactions were observed in cynomolgus monkeys after intravenous infusion at doses of 3, 10, 30 mg/kg or 60 mg/kg (once every 2 weeks, 7 doses) for 13 weeks. Clinical data: Immune-related AEs can affect any organ system, including haematological, ocular, or rheumatological manifestations.
Risk Factors and Risk Groups	Patients with a history of or ongoing autoimmune disease may be at a higher risk of developing imAEs and are generally excluded from the clinical development programme for tislelizumab. There are currently no identified risk groups or risk factors that may predispose patients to developing immune-mediated adverse reactions after treatment with tislelizumab.
Risk Minimisation Measures	Routine Risk Minimisation Measures: SmPC Section 4.2 where guidelines for withholding or permanent discontinuation of treatment are provided. SmPC Section 4.4 where advice is provided regarding monitoring and management of immune-mediated adverse reactions. SmPC Section 4.8 where the adverse drug reactions of immune-related adverse reactions are listed. Product Label (PL) Section 2 and PL Section 4 where guidance on how to early identify signs and symptoms and seek medical attention is included. Additional Risk Minimisation Measures: Patient Card Legal Status: Restricted medical prescription

Important Potential Risk: Reproductive and Developmental Toxicity	
Evidence for Linking the Risk to the Medicine	Nonclinical data: No treatment-related effects were observed in the reproductive organs in cynomolgus monkeys after intravenous infusion at doses of 3, 10, 30 or 60 mg/kg (once every 2 weeks, 7 doses) for 13 weeks. However, not all animals in these studies were sexually mature. A literature-based assessment of effects on embryofoetal toxicity demonstrated that the pharmacologically mediated blockade of PD-1/PD-L1 interaction in animal models can result in foetal loss. This is due to disruption of immune tolerance to the foetus as the PD-1/PD-L1 pathway plays a role in the maintenance of tolerance. Clinical data: A clinical study further supports the animal model data and highlighted the potential importance of the PD-1/PD-L1 immune checkpoint pathway in the induction of maternal tolerance during healthy pregnancy. The PD-1 binding to the abundantly expressed PD-L1 in tumours is analogous to the PD-1 binding to a highly expressed PD-L1 at the uteroplacental interface. The blockade of the PD-1/PD-L1 pathway in inducing foetal loss/abortion has been shown in murine models of allogeneic pregnancy. Therefore, the potential risks of administering tislelizumab during pregnancy include increased rates of abortion or stillbirth. Based on the mechanism of action, the administration of tislelizumab during pregnancy could cause harm to the foetus.
Risk Factors and Risk Groups	No relevant risk groups or risk factors have been identified.
Risk Minimisation Measures	Routine Risk Minimisation Measures: SmPC Section 4.6 SmPC Section 5.3 PL Section 2 Advice that women of childbearing potential should avoid becoming pregnant and lactating women should avoid breastfeeding infants while taking tislelizumab and that, women of childbearing potential should use effective contraception during treatment with tislelizumab and for 4 months after the last dose is included in SmPC Section 4.6 and PL Section 2. Additional Risk Minimisation Measures: None Legal Status: Restricted medical prescription

II.C Post-authorisation Development Plan

II.C.1 Studies Which Are Conditions of the Marketing Authorisation

There are no studies which are conditions of the Marketing Authorisation or specific obligation of Tevimbra.

II.C.2 Other Studies in Post-authorisation Development Plan

There are no other studies required in the postauthorisation development plan for Tevimbra.

PART VII ANNEXES

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ANNEX 1 EUDRAVIGILANCE INTERFACE

ANNEX 2 TABULATED SUMMARY OF PLANNED, ONGOING, AND COMPLETED PHARMACOVIGILANCE STUDY PROGRAMME

None.

ANNEX 3 PROTOCOLS FOR PROPOSED, ONGOING, AND COMPLETED STUDIES IN THE PHARMACOVIGILANCE PLAN

None.

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Targeted Follow-up Checklist-Immune-Mediated events (general); v01, dated 02 March 2022

In addition to collecting routine information for this adverse event, please ensure the following additional information provided and/or confirmed.

Please provide the immune mediated event final diagnosis and the following details:

Immune mediated event/condition	Signs / Symptoms/CTCAE grade	Onset date and time	End date

Does the patient have a personal or family history of autoimmune disease? Yes No Unknown
If yes, please specify:

Were any autoantibodies detected? (if yes, please provide details below) Yes No Unknown
Autoantibody:
Value/ units:
Normal range:

Please provide dates/results / normal ranges for any of the following, if relevant to the case:

Complete blood count including differential blood count
Relevant biochemistry test (including but not limited to glycemia, thyroid hormones, Adrenal, pituitary or other organ specific hormones)
Inflammatory markers (C-reactive protein, Erythrocyte Sedimentation Rate

Serology

Hepatitis B, (if yes, please specify)

Hepatitis C, (if yes, please specify)

ANA (if yes, please specify)

Other organ specific antibodies (if yes, please specify)

Anti-dsDNA (if yes, please specify)

Anti-SRP, anti-JO-1, anti-Mi2, (if yes, please specify)

Antiphospholipid autoantibodies (aPL), (if yes, please specify)

Anti-Scl 70

Biopsies *(if yes, please specify*)

Imaging tests (x-ray, ultrasound, CT, MRI; please specify findings or provide reports)

Other (eg, colonoscopy in the case of colitis)

Treatment received:

Corticosteroids: Yes No Unknown. If yes, please specify in the table below

Other immunosuppressant: Yes No Unknown. If yes, please specify in the table below
Did the patient receive any other therapy? Yes No Unknown. If yes, please specify in the table below

Treatment Name	Start	Stop	Route	Dose	Duration

Did the event improve or resolve with immunosuppressant treatment (eg, Steroid therapy)? Yes No Unknown

Was suspect medication stopped due to event?
If yes, please provide the outcome of the event, de-challenge,

Was therapy with suspect medication restarted? Yes No
If yes, Please specify the dose and date:

Did event re-occur after restarting the treatment? If yes, kindly mention the presentation of event, onset date, and re-challenge

ANNEX 5 PROTOCOLS FOR PROPOSED AND ONGOING STUDIES IN RMP PART IV

None.

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Key Safety Messages of Additional Risk Minimisation Measures:

Prior to the launch of Tevimbra in each Member State, the Marketing Authorisation Holder 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 about signs and symptoms relevant to the early recognition/identification of the potential immune-related adverse reactions adverse reactions and prompt them about when to seek medical attention. It also contains prompts to enter 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 HCPs who may help them.

The Marketing Authorisation Holder shall ensure that in each Member State where Tevimbra is marketed, all HCPs and patients/carers who are expected to prescribe and use Tevimbra have access to/are provided with the Patient Card disseminated through HCPs.

The Patient Card Will Contain the Following Key Elements:

- Description of the main signs or symptoms of immune-related adverse reactions (eg, pneumonitis, colitis, hepatitis, endocrinopathies, immune-mediated skin adverse reactions, nephritis and other immune-related adverse reactions) and IRRs, 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 HCP first.
- The importance of carrying the Patient Card at all times and to show it at all medical visits to HCPs other than the prescriber (eg, emergency HCPs).
- A warning message to inform HCPs 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 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.

ANNEX 7 OTHER SUPPORTING DATA (INCLUDING REFERENCED MATERIAL)

Brief Statistical Description and Supportive Outputs

The Brief Statistical Description portion and Supportive Outputs of Annex 7 is presented separately.

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ANNEX 8 SUMMARY OF CHANGES TO THE RISK MANAGEMENT PLAN OVER TIME

Version	Approval Date Procedure	Change
2.0		The following changes were made to tislelizumab RMP Version 2.0 for the addition of the NSCLC indication. <u>Safety Concerns</u> Addition of NSCLC-specific information and data, including: • NSCLC-specific epidemiology and target population information. • Inclusion of NSCLC combination therapy data from Studies BGB-A317-304, BGB-A317-307, and BGB-A317-206. No changes made to identified risks, potential risks, or missing information. <u>Pharmacovigilance Plan</u> No changes made. <u>Post-authorisation Efficacy Plan</u> No changes made. <u>Risk minimisation Measures</u> No changes made.

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Approval with eSignature	Olaf Schickling Drug Safety 12-Jul-2024 12:09:45 GMT+0000

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