EU RISK MANAGEMENT PLAN

TEVIMBRA (TISLELIZUMAB)

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

RMP Version number: 6.0

Data Lock Point for This RMP	25 June 2024	Version number	6.0
Date of Final Sign Off	09 July 2025		

Rationale for Submitting an Updated RMP:

This Tevimbra European Union (EU) RMP is prepared to add the perioperative treatment of non-small cell lung cancer (NSCLC) indication, and update the epidemiology section as per the latest information available.

Summary of Significant Changes in This RMP:

The key changes for this Tevimbra EU RMP (Version 6.0) compared with the Tevimbra EU RMP Version 5.0 are provided below:

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

Part	Module/Annex	Significant Changes in Each Module
Part I Product overview		Table Part I-1 was updated to include the additional proposed indication of the treatment of perioperative treatment of NSCLC.
Part II Safety specification	Module SI Epidemiology of the indication(s) and target population(s)	Revised with new supportive information/data to support the additional proposed indication of the treatment of perioperative treatment of NSCLC.

Part	Module/Annex	Significant Changes in Each Module
	Module SII Nonclinical part of the safety specification	No updates.
	Module SIII Clinical study exposure	No updates.
	Module SIV Populations not studied in clinical studies	No updates.
	Module SV Post-authorisation experience	No updates.
	Module SVI Additional EU requirements for the safety specification	No updates.
	Module SVII Identified and potential risks	New safety concerns and reclassification were revised based on the new information in Part II: Module SVII.2. Method for retrieval of immune-mediated adverse events was updated to align with the agreement with the Committee for Medicinal Products for Human Use in Part II: Module SVII.3.1.
	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)		The treatment of perioperative treatment of NSCLC wordings were added in Part VI: I. Part VI: IIB was updated to align with the changes of Table Part II: Module SVII-2.

Part	Module/Annex	Significant Changes in Each Module
Part VII Annexes	**ANNEX 4** Specific adverse drug reaction follow-up forms	No updates.
	ANNEX 6 Details of proposed additional risk minimisation activities (if applicable)	No updates.
	ANNEX 7 Other supporting data (including referenced material)	The list of references was updated to align with the changes within this document.

Other RMP Versions Under Evaluation:

[redacted]

Details of the Currently Approved RMP:

RMP Version Number	Approved With Procedure	Date of Approval (Opinion Date)
5.0	EMEA/H/C/5919/II/017	22 May 2025 (Opinion)

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

QPPV Oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder's QPPV. The electronic signature is available on file.

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LIST OF ABBREVIATIONS FOR ALL PARTS/MODULES

1L	First-line
ADA	antidrug antibody
AE	adverse event
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
CGC	cardia gastric cancer
CI	confidence interval
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CPI	checkpoint inhibitor
CPS	combined positive score
CSS	cancer-specific survival
CTLA4	cytotoxic T lymphocyte-associated protein 4
dCRT	definitive chemoradiation
ECOG	Eastern Cooperative Oncology Group
EEA	European Economic Area
EFS	event-free survival
EGFR	epidermal growth factor receptor
EPAR	European Public Assessment Report
ES-SCLC	extensive-stage small cell lung cancer
EU	European Union
FDA	Food And Drug Administration
G/GEJ	gastric/gastroesophageal junction
GAC	gastric adenocarcinoma
GC	gastric cancer
GEJA	gastroesophageal junction adenocarcinoma
HBV	hepatitis B virus
HCC	hepatocellular carcinoma

HCP	healthcare professional
HCV	hepatitis C virus
HER-2	human epidermal growth factor receptor-2
HR	hazard ratio
ICC	investigator-chosen chemotherapy
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
MAH	Marketing Authorisation Holder
nab-PC	nab-paclitaxel
NCGC	non-cardia gastric cancer
NHW	non-Hispanic White
NPC	nasopharyngeal carcinoma
NSCLC	non-small cell lung cancer
OC	oesophageal carcinoma
OS	overall survival
OSCC	oesophageal squamous cell carcinoma
pCR	pathological complete response
PD	programmed cell death protein
PD-L	programmed cell death ligand
PFS	progression-free survival
PK	pharmacokinetic(s)
PL	Product Label
PS	performance status
PT	Preferred Term

QPPV	Qualified Person Responsible for Pharmacovigilance
RMP	Risk Management Plan
RS	relative survival
SCLC	small cell lung cancer
SEER	Surveillance, Epidemiology, and End Results
SJS	Stevens-Johnson syndrome
SmPC	Summary of Product Characteristics
TAP	tumour area positivity
TC	tumour cell
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	BeOne Medicines 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 in combination with pemetrexed and platinum-containing chemotherapy is indicated for the first-line treatment of adult patients with non-squamous NSCLC whose tumours have PD-L1 expression on ≥ 50% of tumour cells with no EGFR or ALK positive mutations and who have: • locally advanced NSCLC and are not candidates for surgical resection or platinum-based chemoradiation, or

	• metastatic NSCLC. 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 EGFR mutant or ALK positive NSCLC should also have received targeted therapies before receiving tislelizumab. Tevimbra, in combination with etoposide and platinum chemotherapy is indicated for the first-line treatment of adult patients with extensive-stage small cell lung cancer. Tevimbra, in combination with platinum and fluoropyrimidine-based chemotherapy, is indicated for the first-line treatment of adult patients with human epidermal growth factor receptor-2 (HER-2) negative locally advanced unresectable or metastatic gastric or gastroesophageal junction (G/GEJ) adenocarcinoma whose tumours express PD-L1 with a TAP score ≥ 5%. Tevimbra, in combination with platinum-based chemotherapy, is indicated for the first-line treatment of adult patients with unresectable, locally advanced or metastatic OSCC whose tumours express PD-L1 with a TAP score ≥ 5%. Tevimbra, as monotherapy, is indicated for the treatment of adult patients with unresectable, locally advanced or metastatic OSCC after prior platinum-based chemotherapy. Tevimbra, in combination with gemcitabine and cisplatin, is indicated for the first-line treatment of adult patients with recurrent, not amenable to curative surgery or radiotherapy, or metastatic nasopharyngeal carcinoma.
	<u>Additional Indication Proposed:</u> Tevimbra, in combination with platinum-containing chemotherapy as neoadjuvant treatment and then continued as monotherapy as adjuvant treatment, is indicated for the treatment of adult patients with resectable NSCLC at high risk of recurrence (for selection criteria, see section 5.1).
Dosage in the EEA	<u>Current:</u> **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 change.
Pharmaceutical Form(s) and Strengths	Current: 100 mg/10 mL (10 mg/mL) concentrate for solution for infusion.
	Proposed: No change.
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 eleventh most common cancer worldwide in 2022, with an estimated 511,054 new cases, and the seventh leading cause of all cancer deaths, with 445,391 deaths (GLOBOCAN 2022). Oesophageal squamous cell carcinoma (OSCC) is the predominant type of OC 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 2022 (GLOBOCAN 2022a). The age-adjusted IRs of OSCC per 100,000 in 2022 by European region, were as follows: Eastern Europe 3.2, Western Europe 3.8, Northern Europe 5.0, Southern Europe 1.8 (GLOBOCAN 2022a). 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 ranged from 30% to 77% including countries such as Slovakia at the highest end of the spectrum (77%), followed by Slovenia (70%) and with countries within the EU27 reporting lower rates including The Netherlands (31%) and 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).

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

In 2022, there were 717,169 patients diagnosed with OSCC worldwide, with corresponding 5-year prevalence of 9.1 per 100,000 persons (GLOBOCAN 2022b). Table Part II: Module SI-2, shows the estimated prevalence of OSCC in Europe according to the GLOBOCAN database (GLOBOCAN 2022b).

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

Region	Prevalence Count (5-year duration)	Prevalence Proportion (5-year duration per 10,000 persons)
Europe	71,996	9.6
Eastern Europe	24,876	8.5
Western Europe	22,932	11.7
Northern Europe	15,611	14.6
Southern Europe	8,577	5.7

Prevalence was lowest in Southern Europe (5.7 per 100,000) and Eastern Europe (9.6 per 100,000) while the highest was in Northern Europe (14.6 per 100,000) followed by Western Europe (11.7 per 100,000). 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).

In Europe, the 2022 age-standardized IRs (per 100,000) of OSCC by age groups were as follows (GLOBOCAN 2022a): Age <34 (0.03), age 35-44 (0.86), age 45-54 (4.8), age 55-64 (8.6), age 65-74 (21.6) and age >=75 (23.4).

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. In Europe, the IR of OSCC (per 100,000) is higher in men compared to women (5.7 vs. 1.3) (GLOBOCAN 2022a).

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% confidence interval [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

First-line (1L) Treatment of OSCC

Prior to the era of immunotherapy, patients with advanced (metastatic, non resectable, or recurrent) OSCC were treated with palliative chemotherapy alone. Chemotherapy doublets

consisting of platinum agents (cisplatin or oxaliplatin) plus fluoropyrimidine (5-fluorouracil or capecitabine) or paclitaxel are commonly recommended as 1L treatments per international treatment guidelines (Lordick et al 2016; Kitagawa et al 2019; National Health Committee Guidelines 2018; NCCN Guidelines V4.2017). However, treatment benefit with chemotherapy alone for advanced or metastatic OSCC in the 1L setting is unsatisfying. The overall response rate of 1L chemotherapy ranges from 29% to 62% and the observed median overall survival (OS) ranges from 8.8 to 13.5 months (Lee et al 2015; Liu et al 2016; Luo et al 2021; Sun et al 2021).

Checkpoint inhibitors (CPIs) targeting the programmed cell death protein (PD)-1/programmed cell death ligand (PD-L1) pathway have brought promising advances in the treatment of OSCC. Recently CPIs such as pembrolizumab and nivolumab in combination with chemotherapy and nivolumab in combination with ipilimumab have demonstrated significant survival improvement over chemotherapy alone in the 1L treatment setting for patients with locally advanced unresectable or metastatic OSCC (Doki et al 2022, Sun et al 2021). Table Part II: Module SI-3 outlines efficacy results from global studies with CPIs conducted in 1L OSCC.

Table Part II: Module SI-3: Clinical Efficacy of 1L PD-1 Inhibitor Immunotherapies for Advanced or Metastatic OSCC From Global Studies

Product Key Study	Study Phase/ Population	Asian Patients in Overall Population (%)	Primary Endpoints	Results		
				OS HR Median (months)	PFS HR (95% CI) Median (months)	ORR (%)
Pembrolizumab KEYNOTE-590 (Sun et al 2021)	Phase III/ Untreated, locally advanced, unresectable or metastatic oesophageal cancer or Siewert type 1 gastro-oesophageal junction cancer	53.4	OS in OSCC and PD-L1 CPS ≥ 10	Pembro + chemo vs chemo 0.57 (95% CI: 0.43 to 0.75) p < 0.0001 13.9 vs 8.8	NA	NA
			OS and PFS in OSCC	Pembro + chemo vs chemo 0.72 (95% CI: 0.60 to 0.88) p = 0.0006 12.6 vs 9.8	Pembro + chemo vs chemo 0.65 (95% CI: 0.54 to 0.78) p < 0.0001 6.3 vs 5.8	
Nivolumab Checkmate-648 (Doki et al 2022)	Phase III/ Untreated, unresectable advanced, recurrent, or metastatic OSCC	70	OS and PFS in patients with tumour cell PD-L1 expression of ≥ 1%	Nivo + chemo vs chemo 0.54 (99.5% CI: 0.37 to 0.80) p < 0.001 15.4 vs 9.1	Nivo + chemo vs chemo 0.65 (98.5% CI: 0.46 to 0.92) p = 0.002 6.9 vs 4.4	53
				Nivo + ipi vs chemo 0.64 (98.6% CI: 0.46 to 0.90) p = 0.001 13.7 vs 9.1	Nivo + ipi vs chemob[a] 1.02 (98.5% CI: 0.73 to 1.43) p = 0.90 4.0 vs 4.4	

Abbreviations: 1L, first-line; chemo, chemotherapy with cisplatin and fluorouracil; CI, confidence interval; CPS, combined positive score; OSCC, oesophageal squamous cell carcinoma; HR, hazard ratio; ipi, ipilimumab; NA, not applicable; nivo, nivolumab; ORR, overall response rate; OS, overall survival; PD-1, programmed cell death protein-1; PD-L1, programmed cell death ligand-1; pembro, pembrolizumab; PFS, progression-free survival; vs, versus.

[a] Did not reach the prespecified boundaries for significance of 0.015.

Second-line Treatment of OSCC

Second-line OSCC systemic therapy is recommended for patients with good performance status (PS; 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 definitive chemoradiation (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. Study Rationale-302 joins other Phase 3 studies (KEYNOTE-181, and ATTRACTION-3) that evaluated immune CPIs as treatment for patients with advanced or metastatic OSCC to address the need for a treatment option with more favourable efficacy and safety profile compared with chemotherapy in second-line OSCC, which made tislelizumab, nivolumab and pembrolizumab to be the new treatment landscape in this disease setting (Kato et al 2019; Kojima et al 2020).

Table Part II: Module SI-4 outlines some of the references to the studies conducted for the second-line chemotherapy for OSCC.

Table Part II: Module SI-4: Second-line Systemic Therapy 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]
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

Agent	Study Design and Patient Population	Sample Size by Histology (N)	Regimen	Median OS (mo)	Median PFS (mo)
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]
Tislelizumab	Randomized global ph3 study	OSCC (n = 256)	200 mg, Q3W	8.6	1.6
Nivolumab (Kato et al 2019)	Randomized global ph3 study	OSCC (n = 210)	200 mg, Q3W	10.9	1.7
Pembrolizumab (Kojima et al 2020)	Randomized global ph3 study	OSCC and OAC OSCC (n = 198)	200 mg, Q3W	8.2	2.1

Abbreviations: CR, complete response; mo, month; NA, not applicable; OAC, oesophageal adenocarcinoma; OS, overall survival; OSCC, oesophageal squamous cell carcinoma; PFS, progression-free survival; ph3, phase 3; 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%.

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

Oesophageal squamous cell carcinoma 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).

Table Part II: Module SI-5 outlines details on OS and RS across calendar periods.

Table Part II: Module SI-5: 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)
2010-2013	24 (20-27)	5 (3-7)	25 (21-29)	6 (4-8)

Abbreviations: CI, confidence interval;
Source: Adapted from Kauppila et al (2018).

Important Comorbidities

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%), chronic obstructive pulmonary disease (COPD; 11%), ulcerative disease (9%), diabetes (6%), cerebrovascular disease (5%) and liver disease (3%) (Koppert et al 2004).

Gastric/Gastroesophageal Junction Adenocarcinoma

Indication

According to the latest available data from 2020, gastric cancer (GC) remains a significant public health burden globally. An estimated 1.1 million cases of GC were diagnosed worldwide in 2020, with 720,000 cases occurring in males and 370,000 cases in females, respectively (Iwu and Iwu-Jaja 2023). Gastric cancer is the fifth most commonly diagnosed cancer worldwide and accounted for 5.6% of all new cancers annually, with an estimated 768,793 deaths reported in 2020 (Kang et al 2022). Of these global numbers, an estimated 136,038 cases and 96,997 deaths occurred in Europe (Lordick et al 2022). GC incidence displays a substantial global variation, with a nearly 40-fold difference between the countries with the highest and lowest rates. The IRs are markedly elevated in Eastern Asian and Eastern European countries, while North American, North European, and African countries exhibit lower rates (Iwu and Iwu-Jaja 2023).

Incidence

According to the GLOBOCAN database, the worldwide age-adjusted IR of GC was 9.2 per 100,000 population in 2022 (GLOBOCAN 2022a). In Europe, the age-adjusted IR was 7.9 per 100,000 during the same year (GLOBOCAN 2022a).

The incidence was variable among European countries, and it ranged from 7.6 (Sweden) to 29.8 (Lithuania) per 100,000 and in the United Kingdom (UK) 10.0 according to ECIS 2020. In Europe, reported IR of adenocarcinoma form of GC per 100,000 population was between 8.0 (Bringeland et al 2017) and 12.4 (Abdulkarim et al 2022) among males and 2.9 (Abdulkarim et

al 2022) to 3.6 (Bringeland et al 2017) among females (Table Part II: Module SI-1). Incidence rate of gastroesophageal junction adenocarcinoma (GEJA) per 100,000 population was reported between 4.0 and 7.0 in Northern Europe, 5.4 in UK/Ireland (Manabe et al 2022), and between 0.6 among Black females to 3.8 (Buas and Vaughan 2013) among White males in US (Table Part II: Module SI-1).

Prevalence

According to 2022 estimates, the worldwide 5-year prevalence of all stages GC per 100,000 was 10.6 (GLOBOCAN 2022b). The 5-year reported counts and prevalence in Europe are shown in Table Part II: Module SI-6 based on 2022 GLOBOCAN database.

Table Part II: Module SI-6: Gastric Cancer 5-year Prevalence Count and Proportion per 100,000 Persons in Europe

Region	Prevalence Count (5-year duration)	Prevalence Proportion (5-year duration per 10,000 persons)
Europe	188,578	25.2
Eastern Europe	97,184	33.3
Western Europe	36,697	18.6
Northern Europe	14,578	13.6
Southern Europe	40,119	26.5

Stage distribution of gastroesophageal cancer

The proportion of patients with distant metastasis at diagnosis was 34% to 44% (Table Part II: Module SI-7).

Table Part II: Module SI-7: Stage Distribution of Gastric Adenocarcinoma Population

Country, period	Cancer	Stage distribution, %	References
US (1973-2014)	GAC	Localized: 24.6% Regional: 37.9% Distant: 34.4%	Milano et al 2019
Estonia (1995-2014)	GAC	Localized: 24% Local/regional spread: 24% Distant metastasis: 40% Unknown: 12%	Pärn et al 2019
Norway (2001-2011)	GAC	Stage 0: 1.8% Stage I: 10.3% Stage II: 12.7% Stage III: 17.1% Stage IV: 43.7% Stage X: 14.4%	Bringeland et al 2017

Abbreviations: GAC, gastric adenocarcinoma; US, United States.

Epidemiology of PD-L1 positive gastroesophageal cancer

As shown in Table Part II: Module SI-8, PD-L1 positivity of GEJA seems to be similar to that of gastric adenocarcinoma (GAC), despite different definitions of PD-L1 positivity by immunohistochemical staining across studies. Focusing on GEJA, PD-L1 positivity expression according to the Siewert classification was conflicting across studies.

Table Part II: Module SI-8: Summary of Studies Examining PD-L1 Expression of GEJ Adenocarcinoma Separated From That of Gastric Adenocarcinoma

Author (Country)	GEJ /oesophagus or gastric (No. of cases)	Method	Tumour PD-L1 positivity, %	Stromal PD-L1 positivity	Definition of PD-L1 positivity
Weinberg et al 2018 (US)	GEJ (N = 119) Gastric (N = 462)	IHC	GEJ, 9.7% Gastric, 7.6%	No data	Tumour, ≥ 5% tumour cell membranous expression
Xing et al 2017 (China)	GEJ (N = 8) Gastric (N = 4)	IHC	GEJ, 66.7% Gastric, 58.3%	GEJ, 75% Gastric, 50%	≥ 1% tumour cell expression; Stroma, any immune cell expression (≥ 1%)
Thompson et al 2017 (US)	GEJ (N = 5) Gastric (N = 29)	IHC	GEJ, 0% Gastric, 13.8%	GEJ, 20% Gastric, 48.3%	Tumour, ≥ 5% tumour cell expression; Stroma, any immune cell expression (≥ 1%)
Derks et al 2015 (US)	GEJ/oesophagus (N = 344)	IHC	GEJ/oesophagus, 18% (mid-proximal oesophagus, 0.6%; distal oesophagus, 4.7%; GEJ, 18.3%)	No data	Tumour, ≥ 5% tumour cell membranous expression (by tumour tissue microarray)
Kollmann et al 2018 (Austria, Czech, Switzerland, US)	GEJ/oesophagus (N = 168)	IHC	GEJ/oesophagus, 18% (Siewert type I, 26.8%; type II, 8.3%; type III, 8.3%)	No data	Tumour, any tumour cell expression (≥ 1%)
Knief et al 2019 (Germany)	GEJ/oesophagus (N = 135)	IHC	GEJ/oesophagus, 48.1%	No data	Combined positive score ≥ 1%
Wang et al 2020 (China)	GEJ/oesophagus (N = 96)	IHC	GEJ/oesophagus, 11.5% (Siewert type I, 0%; type II, 7.9%; type III, 15.7%)	No data	Tumour, ≥ 5 stained tumour cells in a 400x field

Abbreviations: GEJ, gastroesophageal junction; IHC, immunohistochemistry; N, number of cases; PD-L1, programmed death ligand one; US, United States.
Source: Imamura et al 2020

Demographics of the Population in the Authorized Indication – Age, Gender, Racial and/or Ethnic Origin, and Risk Factors for the Disease

IR of GC varies by age, and adenocarcinoma is rare (0.1% of cases) in the paediatric age range (Attard et al 2023). In a prospective cohort study by Schell et al (2022) in Australia, reported GC

IR per 100,000 person-years was only 0.6 for ages 18 to 50 years old while the rate was 13.4 for ages above 50 years. An increasing trend in IR by age was observed in a global GC cohort (Wang et al 2022), and in a GC cohort in US (Islami et al 2019).

Considerable sex differences in GC are well-described (Coleman et al 2018; Rutegård et al 2010; Wang et al 2022). Wang et al (2022) consistently observed a male predominance in GC across the world from 2003 to 2012, with male-to-female incidence ratios of 4.0:1 for cardia gastric cancer (CGC), and 2.1:1 for non-cardia gastric cancer (NCGC). By studying CGC and NCGC in US, Yao et al (2020) have shown that the male-to-female incidence ratio of CGC increased with age until peaking at ages 55 to 69 years and decreased thereafter, while the ratio for NCGC increased with age before ages < 60 years and remained stable onwards.

In Europe, the age-adjusted incidence (per 100,000) and 5-year prevalence (per 100,000) of GC is higher in men compared to women (1.3 and 30.9 vs. 0.64 and 19.9, respectively) (GLOBOCAN 2022b and GLOBOCAN 2022c). Both the incidence and prevalence of GC increase with age as shown in Table Part II: Module SI-9.

Table Part II: Module SI-9: Gastric Cancer age-adjusted incidence rate and 5-year Prevalence per 100,000 by Age Groups in Europe

Age Group (years)	Incidence per 100,000	5-year Prevalence per 100,000
<20	0.03	0.06
20-34	0.50	0.89
35-44	3.0	5.6
45-54	10.0	18.7
55-64	27.4	46.1
65-74	53.4	82.1
≥75	72.2	72.4

Regarding incidence patterns by race/ethnicity, a US-based study using SEER data from 2000 to 2014 (Gupta et al 2019), reported racial and ethnic minority groups had a significantly higher risk of developing NCGC but lower risk of developing CGC compared with non-Hispanic Whites (NHWs). Incidence rate ratios adjusted for NCGC increased 2.8-fold for Blacks and Hispanics, 3.9-fold for Asians or Pacific Islanders, and 1.7-fold for American Indians or Alaska Natives compared with NHWs. Mortality rates of NCGC were 2-3 times higher in Blacks, Hispanics, and Asians/Pacific Islanders compared to NHWs, and the rates were significant across all age groups and stages of disease (Laszkowska et al 2023). For CGC, mortality rates were higher in NHWs compared to Blacks and Asians/Pacific Islanders, particularly in individuals aged 50-64 years, and those with Stage IV disease (Laszkowska et al 2023).

Apart from age, sex, and race, other well-known lifestyle or environmental risk factors for GC include smoking, obesity, alcohol drinking, gastro-oesophageal reflux disease, and *Helicobacter pylori* (*H. pylori*) infection (Bonequi et al 2013; Coleman et al 2018; Poorolajal et al 2020). Consumption of salted and smoked foods are also known to increase the risk of GC and likely play an interactive role in the risk of this cancer. Both NCGC and CGC have overlapping risk factors, such as smoking, heavy alcohol consumption, and foods preserved by salting. However,

these two subsites have distinct aetiologies. Cardia gastric cancer is associated with gastroesophageal reflux and obesity, while NCGC is mostly attributable to *H. pylori* infection (Iwu and Iwu-Jaja 2023).

Main Existing Treatment Options

Treatment of advanced stage gastric/gastric oesophageal junction cancer is based on systemic therapy. The preferred regimen for human epidermal growth factor receptor-2 (HER-2) negative disease in the 1L setting was fluoropyrimidine (fluorouracil or capecitabine) combined with either oxaliplatin or cisplatin. Two-drug chemotherapy is the preferred regimen in the 1L setting, with 3-drug regimens (with the addition of a third cytotoxic drug, epirubicin or docetaxel) recommended only for patients with good PS, given the toxicity profile (Smyth et al 2016; Ajani et al 2022). Response rates with the 2-drug combination regimen of fluoropyrimidine and platinum agent were between 30% to 50%, with median PFS ranging from 5 to 7 months. Median OS ranged from 10 to 14 months, and after 5-years less than 10% of patients were still alive (Chau et al 2004; Van Cutsem et al 2006; Wagner et al 2006; Cunningham et al 2008; Kang et al 2009; Yamada et al 2015; Lee et al 2021; Kang et al 2022).

Based on the positive results of the Phase III CHECKMATE 649 study, the PD-1 inhibitor, nivolumab, was approved by the Food And Drug Administration (FDA) (advanced or metastatic gastric/gastric oesophageal junction cancer and oesophageal adenocarcinoma, April 2021) and in European Union (EU) (the 1L treatment of HER-2 negative advanced or metastatic gastric/gastric oesophageal junction cancer and oesophageal adenocarcinoma with tumours expressing PD-L1 combined positive score (CPS) ≥ 5, September 2021) for use in combination with fluoropyrimidine- and platinum-containing chemotherapy. In the Phase III ATTRACTION-4 study in previously untreated Asian patients (Japan; South Korea; and Taiwan, China) with advanced gastric/gastric oesophageal junction cancer, nivolumab plus chemotherapy significantly improved PFS but not OS in the all-randomised population (Kang et al 2022). Additionally, nivolumab was approved in Japan (November 2021) for the 1L treatment of unresectable advanced or recurrent GC in combination with chemotherapy. This approval was based on the results from both the ATTRACTION-4 and the CHECKMATE 649 studies.

Natural history of the indicated condition in the untreated population, including mortality and morbidity

No studies of untreated GC were found and therefore natural history is presented across various other treatments.

Generally, the overall prognosis in oesophageal adenocarcinoma and GAC is poor. Keshava et al (2017) studied untreated GC (n = 690) patients at clinical Stages I-III. The 5-year survival for operable GC patients was: 9.2%, 5.8%, 4.3% and for inoperable GC patients was 0.5%, 0.0%, 1.9% for Stages I-III, respectively (Keshava et al 2017). The 5-year survival rates of 101 untreated GC patients were 46.2% in Stage I and 0% in Stage II-IV in Korea (Oh et al 2019).

In Europe in 2020, there were 95,431 deaths related to GC with corresponding age-standardized mortality rate of 5.2 per 100,000 (GLOBOCAN 2022b), which accounted for 14.5% of all GC deaths in the world (GLOBOCAN 2022d).

In the EU, median survival of GAC was between 9.0 (Bringeland et al 2017) and 9.3 (van Der Kaaij et al 2020) months; metastatic: 3.6 (van Der Kaaij et al 2020); non-metastatic: 18 to

28 months (Huang et al 2022). 5-year RS was between 10% (Maharjan and Kauppila 2022) and 30% (Pärn et al 2019). 5-year RS for metastatic and non-metastatic GAC was reported 6.0% and 20.6%, respectively (Dikken et al 2012).

Qiu and Du (2021) performed a meta-analysis to investigate the prognostic significance of PD-L1 expression in GC. They included 15 studies (China n = 9, South Korea n = 3, Japan n = 2, and Germany n = 1) with total sample size of 3,218 cases, with individual sample sizes ranging from 56 to 478. Pooled analysis showed that positive expression of PD-L1 was related to a decrease in the 3-year survival rate (hazard ratio [HR] = 1.32, 95% CI: 1.02 to 1.49, p = 0.028) and 5-year survival rate (HR = 1.39, 95% CI: 1.14 to 1.69, p = 0.001). Patients with higher expressions of PD-L1 were more prone to lymph node metastasis (OR = 1.73, 95% CI: 1.18 to 2.54, p < 0.001). In a study by Zhang et al (2015) on 132 tumour specimens of Stage II and III GC, PD-L1 positive patients had significantly poorer survival than negative patients (5-year survival rates: PD-L1 negative 83.1%; PD-L1 positive 50.7%, p < 0.001).

Important Comorbidities

The prevalence of the main comorbidities in GC patients is presented in Table Part II: Module SI-10.

Table Part II: Module SI-10: Important Comorbidities in the Gastroesophageal Cancer Population

Country, period	Study population	Comorbidity prevalence, %	References
US (2010 to 2017)	Children age range (1-21y) with GC solid cancer	Hypertension: 8.1% Psychiatric comorbidity: 7.8% Hyperlipidaemia: 5.1% Type 2 DM: 4.5% Oesophageal reflux: 3.6% Constipation: 3.6% Diarrhoea: 3.0% Hyperlipidaemia: 2.7% Obesity: 2.4% Tobacco: 2.4% Obstructive sleep apnoea: 1.2%	Attard et al 2023
Sweden (2001 to 2005)	Patients who underwent surgery for OC or GEJC	Cardiac: 15% Hypertension: 22% Pulmonary: 13% DM: 11% Obesity: 17%	Backemar et al 2015
US (2000 to 2007)	Individuals, ≥ 66 years of age diagnosed with GC	Coronary artery disease: 30.3% Hypertension: 60.5% Diabetes: 23.6% Infectious disease: 18.9% Arrhythmia: 11.9% Anaemia: 17.3% Electrolyte disorder: 15.4% Atrial fibrillation: 14.1% Cerebral vascular disease: 12.2%	Lowe et al 2016

Country, period	Study population	Comorbidity prevalence, %	References
		Congestive heart failure: 16.4% COPD: 17.1% Osteoarthritis: 13.6%	

Abbreviations: COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; GC, gastric cancer; GEJC, gastroesophageal junction cancer; OC, oesophageal cancer; US, United States; y, year.

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 (12.4% of all cancers [Bray et al 2024]) and had, along with breast cancer, the highest incidence among all cancers in 2022. Further, LC accounts for the most cancer related deaths, causing 1.8 million deaths in 2022 based on GLOBOCAN data (International Agency for Research on International Agency for Research on Cancer Lung Cancer Fact Sheet 2022). Non-small cell lung cancer is the predominant histological subtype, accounting for approximately 76% to 85% of all LC (Lungevity 2021, Mangone et al 2023). 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 incidence of 28.8 per 100,000 in 2022, according to GLOBOCAN 2022a. Based on the assumption that 85% of LC is NSCLC, the estimated incidence of NSCLC is approximately 24.5 per 100,000 person-years. Table Part II: Module SI-11 shows the number of new cases and IRs of LC and the corresponding extrapolated estimates for NSCLC by European regions.

Table Part II: Module SI-11: Estimated Number of New LC and NSCLC Cases and Incidence Rates per 100,000 Person-Years by European Regions

European Region	Estimated Incidence of LC in 2022 (GLOBOCAN 2022a)		Estimated Incidence of NSCLC in 2022[a]	
	Number of New Cases	Rate per 100,000 person-years	Number of New Cases	Rate per 100,000 person-years
Eastern	158,147	27.6	134,425	23.5
Northern	73,608	28.0	62,567	23.8
Southern	106,610	27.7	90,619	23.5
Western	145,941	31.2	124,050	26.5

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).

In Europe, adenocarcinoma and squamous cell carcinoma account for 32% each among all subtypes of LC in male patients, while 47% and 15%, respectively, in female patients. Incidence and mortality rates are roughly 2 times higher in men than in women with similar male-to-female ratio based on age-standardised IR by world standard population (Sung et al 2021; WHO 2020a; WHO 2020b).

Prevalence

Worldwide, about 73% of patients with NSCLC have nonmetastatic stages I-III disease (15% stage II and 21% stage III) (Garcia-Pardo et al 2023). In Western Europe (France, Germany, Italy, Spain, and the UK), the prevalence counts of non-squamous and squamous NSCLC in 2026 are projected to be 174,177 and 46,286 respectively. These numbers represent a 7% increase of NSCLC from 2021 (Kanas et al 2022). In the same countries, stage IIIB/C prevalence is projected to be 10,417 for non-squamous NSCLC and 14,386 for squamous NSCLC (Kanas et al 2022).

Table Part II: Module SI-12 presents the estimated LC prevalence and extrapolated prevalence of NSCLC in all age groups for European regions based on GLOBOCAN 2022 data (GLOBOCAN 2022b). 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 35.8 per 100,000 people. The highest estimated NSCLC prevalence was reported in Northern America at 74.2 per 100,000 people, followed by Europe at 69.4 per 100,000 people, and the lowest prevalence was reported in Africa at 4.3 per 100,000 people. In Europe, the highest estimated NSCLC prevalence was in Western Europe at 79.4 per 100,000 people, followed by Southern Europe at 72.8 per 100,000 people and the lowest in Eastern Europe with a prevalence of 60.5 per 100,000 people.

Table Part II: Module SI-12: Estimated 5-year Number and Prevalence per 100,000 Persons of LC and NSCLC by European Region

European Region	Estimated 5-year Prevalence of LC (GLOBOCAN 2022b)		Estimated 5-year Prevalence of NSCLC[a]	
	Number	Proportion per 100,000 people	Number	Proportion per 100,000 people
Eastern	207,904	71.2	176,718	60.5
Northern	88,601	82.7	75,311	70.3
Southern	129,831	85.6	110,161	72.8
Western	183,833	93.4	156,258	79.4

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 (Carrato et al 2014; Morgan et al 2021).

In the UK, the mean age at NSCLC diagnosis was 44 years, with 75% of patients aged 41-50 years (Hughes et al 2022).

Risk factors for NSCLC include cigarette smoking, which attributes to 85%-90% of all LC cases (Mangone et al 2023). 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 , and the risk is proportionate with the quantity and duration of smoking (Mangone et al 2023). Other known risk factors are exposure to occupational and environmental carcinogens (such as asbestos, arsenic, radon, heavy metals, 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 mutations) (Molina et al 2008, ESMO 2019, Mangone et al 2023, Sheikh et al 2023).

Main Existing Treatment Options

1L Treatment of NSCLC Without Actionable Oncogenic Driver

Immune checkpoint inhibitor (ICI) therapy is the standard of care for the 1L treatment of metastatic NSCLC without actionable oncogenic driver. Immune checkpoint inhibitor monotherapy (Pembrolizumab, Atezolizumab and Cemiplimab) is approved for the patients with tumour cell (TC) PD-L1 high expression 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 1L 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 1L 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 epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), or ROS mutation. Of those administered chemotherapy alone as 1L 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 1L NSCLC, especially for PD-L1 low and PD-L1 negative patients.

ICI monotherapy as 1L treatment of NSCLC: Pembrolizumab is considered a standard 1L 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] 2024; Planchard et al 2018). The Phase III KEYNOTE024 study has established the role for pembrolizumab as 1L 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 2024). Additionally, atezolizumab represents another 1L 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 1L 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 2021) monotherapy has been approved for the 1L 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).

ICI in combination with other treatment as 1L treatment of NSCLC: 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 1L treatment of metastatic non-squamous NSCLC in adults whose tumours have no EGFR or ALK positive mutations; and in combination with carboplatin and either paclitaxel or nab-paclitaxel for the 1L treatment of metastatic squamous NSCLC in adults (Keytruda [pembrolizumab] EPAR 2024). Nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy is indicated for the 1L 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 1L treatment of adult patients with metastatic non-squamous NSCLC (Tecentriq [atezolizumab] EPAR 2021). LIBTAYO in combination with platinum-based chemotherapy is indicated for the first-line treatment of adult patients with locally advanced (not candidates for dCRT) or metastatic NSCLC expressing PD-L1 (in ≥ 1% of TCs), with no EGFR, ALK or c-ros oncogene 1 (ROS1) aberrations. (Libtayo [cemiplimab] EPAR 2021). IMFINZI in combination with tremelimumab and platinum-based chemotherapy is indicated for the 1L treatment of adults with metastatic NSCLC with no sensitising EGFR mutations or ALK positive mutations. (Imfinzi [Durvalumab] EPAR 2024). Sugemalimab in combination with platinum-based chemotherapy is indicated for the 1L treatment of adults with metastatic NSCLC with no sensitising EGFR mutations, or ALK, ROS1 or RET genomic tumour aberrations (Cejemly [sugemalimab] EPAR 2024). Tislelizumab in combination with pemetrexed and platinum-containing chemotherapy is indicated for the 1L treatment of adult patients with local advanced (not candidates for surgical resection or platinum-

based chemoradiation) or metastatic non-squamous NSCLC whose tumours have PD-L1 expression on ≥50% of TCs with no EGFR or ALK positive mutations. Tislelizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel is indicated for the 1L treatment of adult patients with local advanced (not candidates for surgical resection or platinum-based chemoradiation) or metastatic squamous NSCLC (Tislelizumab [Tevimbra] EPAR 2024). 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 Eastern Cooperative Oncology Group (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 non-squamous tumours. Pemetrexed use is restricted to non-squamous 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 non-squamous 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 in EU in the 2L setting. The 4 approved therapies in the immunotherapy-naive, second-line setting include nivolumab, pembrolizumab, atezolizumab, and tislelizumab (Opdivo [nivolumab] EPAR 2021; Keytruda [pembrolizumab] EPAR 2024; Tecentriq [atezolizumab] EPAR 2021, Tislelizumab [Tevimbra] EPAR 2024). 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 4 therapies to inform a single optimal choice, and no comparative studies have been conducted. Nivolumab, atezolizumab and tislelizumab 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 1L immunotherapy with pembrolizumab monotherapy, platinum-based chemotherapy is recommended as second-line treatment option.

With the increasing adoption of ICI as the 1L 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 non-squamous 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 1L 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 1L 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.

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; Hendriks et al 2023).

Perioperative Treatment of NSCLC Without Actionable Oncogenic Driver

Prior to the 2022 approval of ICIs as (neo)adjuvant therapy for resectable NSCLC in Europe, the primary treatment for resectable Stage II to IIIA NSCLC was surgery coupled with adjuvant platinum-based doublet chemotherapy; induction chemotherapy followed by surgery was an option for single-station N2 disease. Agents that have been partnered with either cisplatin or carboplatin for the treatment of NSCLC include taxanes (paclitaxel, *nab*-paclitaxel, docetaxel), vinorelbine, gemcitabine, and pemetrexed (feasible for adenocarcinoma) (Postmus et al 2017).

Several PD-1/PD-L1 inhibitors (eg, atezolizumab, nivolumab, durvalumab and pembrolizumab) have been approved in EU as neoadjuvant or adjuvant or perioperative treatment for adult patients with resectable NSCLC without *EGFR* or *ALK* genomic aberrations.

For NSCLC that can be removed by surgery but is at high risk of coming back, nivolumab was approved (whose tumours have PD-L1 expression ≥ 1% in EU) to be given before surgery (neoadjuvant treatment) based on phase III study CheckMate 816. A statistically significant improvement was demonstrated in pathological complete response (pCR) and event-free survival (EFS) for patients treated with nivolumab in combination with chemotherapy as compared to chemotherapy alone. The pCR response rate was 24% in the nivolumab in combination with chemotherapy arm and 2.2% in the chemotherapy arm (difference of pCR 21.6, 99% CI: 13.0, 30.3; stratified p-value < 0.0001). Median EFS was 31.6 months in the nivolumab in combination with chemotherapy arm and 20.8 months in the chemotherapy arm (HR = 0.63, 97.38% CI: 0.43, 0.91; stratified log-rank p-value 0.0052). The HR for OS was 0.57 (99.67% CI: 0.30, 1.07) for nivolumab in combination with chemotherapy vs. chemotherapy (Opdivo [nivolumab] EPAR 2021). Pembrolizumab was approved as monotherapy is indicated for the adjuvant treatment of adults with non-small cell lung carcinoma who are at high risk of recurrence following complete resection and platinum-based chemotherapy. The phase III study Keynote 091 demonstrated a statistically significant improvement in disease-free survival in the overall population (HR = 0.76 [95% CI: 0.63, 0.91; p = 0.0014]) at a pre-specified interim analysis for patients randomised to the pembrolizumab arm compared to patients randomised to the placebo arm (Keytruda [pembrolizumab] EPAR 2024). Atezolizumab was approved with similar indication but restricted in someone with PD-L1 expression on ≥ 5% of TC and do not have EGFR-mutant or ALK-positive NSCLC based on phase III study Impower 010. A clinically meaningful improvement in disease-free survival in the atezolizumab arm was observed compared to the best supportive care arm in this indicated population (HR = 0.49, [95% CI: 0.29, 0.81]) (Tecentriq [atezolizumab] EPAR 2021).

Pembrolizumab was also approved in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment, for the treatment of resectable NSCLC at high risk of recurrence in adults based on phase III study Keynote 671. At a pre-specified interim analysis (data cutoff 10 July 2023), the EFS HR was 0.59 (95% CI:0.48, 0.72) and the OS HR was 0.72 (95% CI:0.56, 0.93; p = 0.00517) (Keytruda [pembrolizumab] EPAR 2024)]. Tislelizumab was approved in October 2024 by the National Medical Products Administration in China based on study 315, with a clinically meaningful improvement in EFS (HR = 0.56, [95% CI: 0.40, 0.79, p = 0.0003]) for patients randomized to tislelizumab in combination with platinum-based chemotherapy as neoadjuvant treatment and tislelizumab monotherapy as adjuvant treatment following surgery in patients with perioperative stage II or IIIA NSCLC (BeiGene, 2024).

Durvalumab was approved in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment, for the treatment of resectable NSCLC at high risk of recurrence in adults based on phase III study AEGEAN. At a pre-specified interim analysis 2 (data cutoff 10 May 2024), the EFS HR was 0.69 (95% CI: 0.55-0.88) and the OS HR was 0.89 (95% CI: 0.70-1.14) (Imfinzi [durvalumab] EPAR 2024)].

Nivolumab was also approved in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment, for the treatment of resectable NSCLC at high risk of recurrence in adults (whose tumours have PD-L1 expression ≥ 1% in EU) based on phase III study CheckMate 77T. At updated interim analysis (data cutoff 11 Nov 2024), the EFS HR was 0.61 (0.46, 0.80) and the OS HR was 0.85 (0.61, 1.18) (Opdivo [nivolumab] EPAR 2021)].

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). Between 55% and 70% of patients with NSCLC are diagnosed with metastatic disease at time of presentation (de Jager et al 2024). Despite clinical and therapeutic advancements, LC remains the leading cause of death with 1.8 million deaths attributable to LC in 2022, and age-standardized mortality rate of 16.8 per 100,000 people (GLOBOCAN 2022c). In Europe, there were 375,569 deaths attributed to LC with corresponding mortality rate of 21.4 per 100,000 people (GLOBOCAN 2022c). Based on data from 21 cancer registries of 7 countries (as part of ICBP SURVMARK2 project), the 3-year age survival of NSCLC for the included European countries where as follows: survival was highest for Norway (28.0%), Denmark (26.2%, Ireland (25.7%) and slightly lower for the UK (22.2%). The 3-year survival rate of NSCLC for Canada, Australia and New Zealand were 31.8%, 29.0%, and23.1 (Morgan et al 2021). In the Netherlands, the 5-year NSCLC survival increased from 12% to 25% between 2004 and 2021 (Houda et al 2024).

In the US, the 5-year OS of NSCLC is 28% for all stages combined. The corresponding rates for localized and regional NSCLC are 65% and 37%, respectively (ACS 2024). In Central and Eastern Europe (Russia, Poland, Serbia, Czech Republic, and Romania), the 5-year survival rate of resectable stage I-IIIA is about 50% (Sheikh et al 2023).

Important Comorbidities

More than half of the patients with LC have 1-2 comorbidities, and 3.5% have at least 5 underlying medical conditions (Hernandez et al 2023). Approximately 66% of patients with nonmetastatic NSCLC have at least one comorbidity (Wong et al 2018), and 30% of patients have cardiometabolic and respiratory comorbidities, including COPD (19.6%); asthma (7.8%); coronary artery disease (13.5%); diabetes (10.1%); other cardiac diseases (8.7%); and vascular related diseases (5.7%) (Garcia-Pardo et al 2023). The distribution of common comorbidities in patients with LC in Germany include: COPD (37.9%); peripheral vascular disease (20.8%); diabetes (17.9%); heart failure (17.5%); renal disease (16.6%); cerebrovascular disease (10.3%); myocardial infarction (6.3%); liver disease (6.1%); rheumatoid arthritis (2.5%); and peptic ulcer (2.2%) (Hernandez et al 2023). Major comorbidities such as COPD and cardiovascular diseases are highly prevalent in patients with LC, due to the strong association with cigarette smoking and ageing.

Small-Cell Lung Cancer

Incidence

Lung cancer is the second most common cause of cancer morbidity and the most common cause of cancer-related death worldwide, with 2,480,675 new cases and 1,817,469 deaths observed in 2022 (GLOBOCAN 2022a). In the EU, LC is the foremost contributor to cancer mortality, accounting for 11.6% of newly diagnosed cancer cases and 19.5% of cancer-associated deaths in 2022 (ECIS 2023). Small cell lung cancer (SCLC) accounts for approximately 15% of all cases of LC, resulting in ~0.3 million new cases and ~0.2 million deaths worldwide in 2020 (American Cancer Society 2021; Rudin et al 2021).

Prevalence

In many regions, the pattern of LC prevalence rates (over 5 years) generally follows that of IRs, except for Northern Europe, North America, and the US, where prevalence rates for males and females are converging (Bray et al 2018; GLOBOCAN 2022b). Across Europe, the highest 5-year prevalence was reported for Western and Northern European countries; 93.4 and 82.7 per 100000, respectively (GLOBOCAN 2022b).

The estimated number of prevalent (re-staged, 5-year) cases of extensive-stage small cell lung cancer (ES-SCLC) was estimated at 92,340 in the US, Japan, UK and 4 EU countries (France, Germany, Italy and Spain) (Kantar Health 2018)

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

SCLC is strongly associated with smoking, with 98% of cases arising in current or former smokers (Varghese et al 2014). Several metrics measuring smoking exposure including duration, intensity, pack-years, time since quitting, and age at staring smoking have been studied in relation to LC risk. Non-smoking related risk factors include environmental and occupational

exposures and hormonal factors. Exposure to residential radon is associated with a higher risk of SCLC (Wang et al 2022).

Main Existing Treatment Options

For all patients with SCLC, treatment guidelines recommend certain combination chemotherapy plus immunotherapy regimens as preferred options for patients with ES-SCLC. Disease management is mainly dependent on the patient's ECOG PS, the existence of localized symptomatic sites or brain metastasis, and the time from initial therapy to relapse.

ICIs targeting the PD-1/PD-L1 pathway have revolutionized the therapeutic landscape of ES-SCLC over the last 5 years (see Table Part II: Module SI-13)

IMpower133 was the first frontline pivotal study demonstrating the benefit of adding a PD-L1 inhibitor (atezolizumab) to the chemotherapy backbone for the treatment of ES-SCLC. This study met its primary endpoints of OS and PFS and showed a statistically and clinically significant benefit of atezolizumab + carboplatin + etoposide over chemotherapy as 1L treatment in patients with ES-SCLC (FDA 2019; data in Table Part II: Module SI-13) leading to the first approval of an ICI in the EU in September 2019 (Roche 2019).

The CASPIAN study of durvalumab met its primary endpoint of OS and provided additional evidence of clinical benefit of adding an ICI into chemotherapy regimens as 1L treatment for ES-SCLC (Paz-Ares et al 2019; data in Table Part II: Module SI-13). Based on the reported survival benefit, durvalumab was approved in August 2020, as 1L treatment when used in combination with chemotherapy, in EU for the treatment of ES-SCLC (AstraZeneca 2020).

The ASTRUM-005 study of serplulimab met its primary endpoint of OS and provided additional evidence of clinical benefit of adding an ICI into chemotherapy regimens as 1L treatment for ES-SCLC (Cheng et al 2022; data in Table Part II: Module SI-13). Based on the reported survival benefit, serplulimab was approved in February 2025, as 1L treatment when used in combination with chemotherapy, in EU for the treatment of ES-SCLC (Henlius 2025).

Consolidative thoracic radiotherapy is beneficial for selected patients with extensive-stage disease and good response to systemic therapy before immunotherapy. The benefit of thoracic radiotherapy in the context of chemo-immunotherapy is under evaluation in the RAPTOR/NRG LU007 trial. Extensive-stage patients who also respond to systemic therapy may also receive PCI. If the patient has extensive disease with localised symptomatic sites, palliative radiotherapy should be administered directly to the symptomatic sites. Brain metastases could be treated with whole brain radiation therapy; but selected patients with a small number of metastases may be appropriately treated with stereotactic radiotherapy or radiosurgery (NCCN 2024).

Given the promising evidence, the addition of PD-L1 inhibitors to a standard platinum-etoposide backbone, with continuation of immunotherapy as maintenance, has become the primary clinical recommendation in many countries across the globe (CSCO 2020, Dingemans et al 2021, NCCN 2022).

Table Part II: Module SI-13: Summary of Phase 3 Studies With Publicly Available Data Evaluating Anti-PD-1/PD-L1 Antibodies in 1L ES-SCLC

Study	**IMpower133** (Liu et al 2021)	**CASPIAN** (Paz-Ares et al 2022)	**Astrum-005** (Cheng et al 2022)
Treatment	Atezolizumab + etoposide and carboplatin [a]	Durvalumab + etoposide and platinum [a]	Serplulimab + etoposide and platinum [a]
Primary endpoint	PFS by INV and OS	OS	OS
OS: Median (months)	12.3 vs 10.3	12.9 vs 10.5	15.4 vs 10.9
OS: HR	0.76 (95% CI: 0.60-0.95) p = 0.0154	0.75 (95% CI: 0.62-0.91) p = 0.0032	0.63 (95% CI: 0.49-0.82) P <0.001
PFS: Median (months)	5.2 vs 4.3	5.1 vs 5.4	5.7 vs 4.3
PFS: HR	0.77 (95% CI: 0.63-0.95)	0.80 (95% CI: 0.66-0.96)	0.48 (65% CI: 0.38-0.59)
ORR	60.2% vs 64.4%	68% vs 58%	80.2% vs 70.4%
Median Follow-up (months) [b]	22.9	25.1	12.3

Abbreviations: CI, confidence interval; HR, hazard ratio; INV, investigator; ORR, overall response rate; OS, overall survival; PFS, progression free survival;
[a] Platinum includes only carboplatin.
[b] Definition of follow-up time may differ among studies.

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

Patients with SCLC experience a short duration of symptoms prior to diagnosis, with lesions usually presenting with cough, wheezing, deep chest pain, and dyspnoea caused by airway obstruction (American Cancer Society 2024). At the time of diagnosis, most patients with SCLC have extensive-stage disease (Das et al 2021). SCLC is an aggressive type of LC with a 5-year survival rate of <7% (George et al 2024). According to an analysis of SEER data from 2000 to 2017, there was an overall increase in survival rates for SCLC (Cohen et al 2023). In 2000, 6.4% of patients with extensive-stage SCLC survived at least 2 years. This number increased to 8.4% by 2017. Stratification by sex showed that the 2-year survival rate among women with extensive-stage SCLC was greater than that of men. Survival rates among women increased from about 30% in 2000 to 37% in 2017. The 2-year survival rate among men increased from 23.4% in 2000 to 36.2% in 2017. In general, OS of LC has increased, with better survival rates observed in patients with NSCLC than those with SCLC (Lu et al 2019).

Important co-morbidities

Patients with SCLC often presented with multiple comorbidities that are associated with tobacco smoking, including COPD and cardiovascular disease (Das et al 2021). These comorbidities are associated with poor PS. Other common comorbidities include hypertension and diabetes (Aarts et al 2015). In addition to preexisting comorbidities, patients with SCLC who are treated with chemotherapy and radiation therapy are presented with treatment-related side-effects, including increased susceptibility for infections, nausea and vomiting, fatigue, anaemia, thrombocytopenia, radiation pneumonitis, pneumonopathy, and acute oesophagitis (Yavas and Yavas 2017; Crvenkova 2018).

Nasopharyngeal Carcinoma

Incidence

Nasopharyngeal carcinoma (NPC) is a rare cancer with a global incidence of approximately 1.5 per 100,000 people, and a geographical distribution extremely unbalanced, suggesting both genetic traits and environmental factors contribute to its development (GLOBOCAN 2022c). Worldwide, it is estimated that there were 120,434 cases of NPC (86,289 in men and 34,145 in women) in 2022 with an age-adjusted IR of 1.3 per 100,000 person-years (GLOBOCAN 2022c). This incidence estimate is projected to increase by nearly 35% in 2040 (Zhang et al 2023).

The standardized incidence of NPC for both males and females is < 1 case per 100,000 person-years in most regions, including Europe, but approaching 30 cases per 100,000 people in Southern China, Southeast Asia, and the Middle East/North Africa (Chang and Adami 2006; GLOBOCAN 2022c; Tang et al 2016). In Europe, the incidence of NPC is highest in Eastern regions and lowest in Northern areas. Table Part II: Module SI-14 shows the number of new cases and IRs of NPC in European Regions (GLOBOCAN 2022c).

Table Part II: Module SI-14: NPC Cases and Age-Standardized Incidence Rates (per 100,000 person-years) in Europe (2022)

European Region	Cases (n)	Incidence Rate
All Europe	4,513	0.39
Eastern Europe	1,697	0.39
Northern Europe	417	0.25
Southern Europe	1,389	0.55
Western Europe	1,010	0.34

Abbreviation: n, number of cases

According to the GLOBOCAN database (Table Part II: Module SI-15), Germany and Spain have the highest reported age-standardized incidence estimates of NPC (GLOBOCAN 2022c).

Table Part II: Module SI-15: NPC Cases and Age-Standardized Incidence Rates (per 100,000 person-years) in Select European Countries (2022)

Country	Cases (n)	Incidence Rate
Austria	48	0.31
Belgium	70	0.43
Denmark	21	0.22
France	337	0.37
Germany	426	0.31
Italy	532	0.54
The Netherlands	82	0.31
Poland	210	0.34
Spain	417	0.54
Sweden	28	0.19
Switzerland	45	0.32
UK	276	0.26

Abbreviation: n, number of cases

Prevalence

There is no direct literature reporting the prevalence of NPC (GLOBOCAN 2022c). The median survival time for NPC patients is reported to be 31.30 months (Siti-Azrin et al 2014). Using an indirect estimation method, where prevalence = incidence * disease duration, the estimated prevalence of NPC was 347,832 patients in 2020, globally.

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

The prognosis of NPC is closely related with the anatomic degree of metastatic lesions. Other negative prognostic determinants were age (older than 50 years), tumour volume > 30 cm^3, and synchronous nodal recurrence (Chua et al 2016). Most patients afflicted with NPC are

middle-aged. The average age of onset of NPC varies in Asian patients from 39.3 to 48.2 years (Zhang et al 2012) while the peak incidence occurs at approximately 55 years in the US (Argirion et al 2020) and a median age of 50 years in European patients with NPC was reported based on data from 13 EU publications (d'Espiney et al 2009; Eduardo et al 2010; Arnold et al 2013; Robinson et al 2013; Li et al 2014; Svajdler et al 2016; Ruuskanen et al 2018; Bossi et al 2019; Ruuskanen et al 2019; Economopoulou et al 2021; Grønlund et al 2021; Simon et al 2022; van Velsen et al 2024). Even though the average age of NPC may vary slightly across different regions or different genotypes, globally, the highest proportion of patients with NPC is in people older than 50 years of age (Yu et al 2022). The prognosis for the NPC patients is very poor, with median OS of only 20 to 29 months (McDowell et al 2020). Therefore, improvements in clinical outcomes are needed for patients with metastatic and for patients unsuitable for radiotherapy (Lee et al 2016; Zhang et al 2016).

The incidence and mortality rate of NPC have decreased in several areas with higher reported incidence, possibly due to lifestyle changes (Chang et al 2021; Lau et al 2013; Hsu et al 2006). Specifically, Epstein-Barr Virus, male sex, tobacco smoking, occupational exposure to wood dust, and salt-preserved food intake have been highlighted as major risk factors (Tang et al 2016, Zhang et al 2023).

The age-adjusted incidence of NPC (per 100,000 person-years) is higher in men compared to women, globally (1.9 vs. 0.73) and in Europe (0.59 vs. 0.20) (GLOBOCAN 2022c). Table Part II: Module SI-16 shows the number of new cases and IRs of NPC by age groups in Europe (GLOBOCAN 2022c).

Table Part II: Module SI-16: NPC Cases and Age-Standardized Incidence Rates (per 100,000 person-years) by Age Groups in Europe (2022)

Age group (years)	Cases (n)	Incidence Rate
20 – 44	722	0.27
45 – 54	1,009	0.97
55 – 64	1,214	1.20
65 – 74	951	1.20
75 – 84	420	0.91
≥ 85	115	0.56

Abbreviation: n, number of cases

Main Existing Treatment Options

More than 70% of NPC patients present with advanced disease stage while approximately one-third present with metastatic disease (Tang et al 2016, Sham and Choy 1990, Heng et al 1999, Tsai et al 1996). Despite the best available treatment, local recurrence ranges between 5% to 15%, and distant metastases from 15% to 30%, and represent the main reason for treatment failure (Chiesa and De Paoli 2001; Lee et al 2015b; Lee et al 1992; Liu et al 2003; Ng et al 2014; Sun et al 2014).

Cytotoxic chemotherapy has remained the mainstay treatment for recurrent or metastatic NPC, and it was for many years the primary front-line treatment option prior to the advent of ICIs. Prior to the introduction of anti-PD-1 ICIs, international treatment guidelines recommended the

combination of gemcitabine plus cisplatin as the preferred 1L therapy for NPC Bossi et al 2021 NCCN 2021). For patients with Stage IVB, the reported median PFS is 7 months, the median OS is 20 to 29 months while drug-related adverse events (AEs) such as leukopenia, neutropenia, thrombocytopenia, and mucositis were commonly reported (Zhang et al 2016; Au and Ang 1994; Boussen et al 1991; Chan 2010; Chua et al 2005; Li et al 2008; Ma et al 2009; Ngan et al 2002; Taamma et al 1999; Yeo et al 1998). Currently in the 1L setting, three Phase 3 studies that assessed effects of the anti-PD-1 antibodies tislelizumab (Study 309), toripalimab (JUPITER-02) and camrelizumab (CAPTAIN-1st), in combination with gemcitabine plus cisplatin, have reported positive outcomes and met their primary endpoints demonstrating longer median PFS for the experimental arms compared to the control arms:

- Study 309 (9.2 months versus 7.4 months, respectively; PFS HR = 0.52 [95% CI: 0.38, 0.73]; p < 0.0001; Yang et al 2023),
- JUPITER-02 (11.7 months versus 8.0 months, respectively; PFS HR = 0.52 [95% CI: 0.36, 0.74]; p = 0.0003; Mai et al 2021), and
- CAPTAIN-1st (9.7 months versus 6.9 months, respectively; PFS HR = 0.54 [95% CI: 0.39, 0.76]; p = 0.0002; Yang et al 2021)

In July 2024, toripalimab, in combination with gemcitabine and cisplatin, received CHMP positive opinion for the 1L treatment of adult patients with recurrent, not amenable to surgery or radiotherapy, or metastatic NPC based on the results from the JUPITER-02 Phase 3 study (Mai et al 2021). Such findings advocate for the integration of PD-1 inhibitors alongside chemotherapy in the 1L setting for recurrent or metastatic NPC, aligning with recommendations by National Comprehensive Cancer Network, European Society for Medical Oncology, and Asian treatment guidelines. Moreover, the Chinese Society of Clinical Oncology guidelines concur with the incorporation of advanced radiotherapy techniques such as intensity-modulated radiation therapy and the consideration of Epstein-Barr virus DNA levels in risk assessment, reinforcing a comprehensive approach to treatment that is reflected in the latest guidelines (Tang et al 2021).

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

NPC remains an important cause of death for patients diagnosed with the disease, with an estimated 73,482 deaths globally and 2,563 deaths in Europe in 2022 and corresponding to age-adjusted mortality rates of 0.77 and 0.18 per 100,000 people, respectively (GLOBOCAN 2022c). Mortality rates were relatively higher in Eastern and Southern Europe compared to Northern and Western European regions (Table Part II: Module SI-17) (GLOBOCAN 2022c).

Table Part II: Module SI-17: NPC Deaths and Age-Standardized Mortality Rates (per 100,000 person-years) in European Regions (2022)

European Region	Deaths (n)	Mortality Rate
Eastern Europe	1,059	0.22
Northern Europe	256	0.12
Southern Europe	703	0.22

Western Europe	545	0.13

Abbreviation: n, number of deaths

Most patients receive an NPC diagnosis in advanced stages, where the 5-year survival rate drops to 49% (Liu & Wang 2023; Peng et al 2023) and to a 3-year survival of 7% to 40% for patients with metastatic NPC (Li et al 2014; Toumi et al 2020; Xu et al 2020). In these patients, liver metastasis has the greatest negative impact on OS although bone is the most frequent metastatic lesion (Xu et al 2020). In early stages of nonmetastatic carcinoma, the 5-year survival rate is 70% to 90% with radiotherapy alone (The American Cancer Society Medical and Editorial Content Team 2020; Blanchard et al 2015; Cancer Research UK 2018; Guan et al 2020).

Important co-morbidities

According to a 2007 study, 44% of patients with NPC have comorbidities, with 27% of those patients having cardiovascular system issues. Other comorbidities include fever, leukemoid reaction, osteoarticular or rheumatic syndromes, sensory neuropathy, demyelinating motor polyneuropathy, and optic neuritis (Ramakrishnan et al 2007).

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 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.
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, 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.

Abbreviations: ADA, antidrug antibody; CNS, central nervous system; PD-1, programmed cell death protein-1; PD-L1, programmed cell death ligand-1.

PART II: MODULE SIII CLINICAL STUDY EXPOSURE

Overview of Clinical Development

Tislelizumab is being developed for the treatment of several indications as presented in Part I of the RMP.

Pivotal Phase III Study in OSCC

The safety analysis of patients receiving tislelizumab is based primarily on the pivotal studies, BGB-A317-306 (Study 306) and BGB-A317-302 (Study 302). 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 306 population includes treatment-naïve patients with unresectable, locally advanced or metastatic OSCC who received ≥ 1 dose of either tislelizumab 200 mg once every 3 weeks in combination with investigator-chosen chemotherapy (ICC; tislelizumab arm: 324 patients) or placebo with ICC (placebo arm: 321 patients). Chemotherapy consisted of platinum (cisplatin or oxaliplatin) and either a fluoropyrimidine (capecitabine or 5-fluorouracil) or paclitaxel and had to be determined prior to randomisation.

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 ICC (ICC arm: 240 patients). The safety analysis results of ICC 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 neoadjuvant/adjuvant chemotherapy or dCRT. This patient population was eligible for treatment with single-agent chemotherapy.

Pivotal Phase III Study in GC

The pivotal Study 305 population includes patients with locally advanced unresectable or metastatic GC/GEJA who received ≥ 1 dose of either tislelizumab 200 mg once every 3 weeks (tislelizumab plus PtF arm: 498 patients) or matched placebo in combination with fluoropyrimidine- and platinum-based chemotherapy (placebo + PtF arm: 494 patients).

Pivotal Phase III Studies in NSCLC

Three completed pivotal Phase III studies contributed to key safety data. In these studies, tislelizumab was 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 non-squamous NSCLC (Study BGB-A317-304) and squamous NSCLC (Study BGB-A317-307) (Table Part II: Module SIII-2).
- Neoadjuvant treatment in combination with chemotherapy and adjuvant monotherapy after surgery for patients with resectable stage II or IIIA NSCLC (Study BGB-A317-315) (Table Part II: Module SIII-2).

Pivotal Phase III Study in ES-SCLC

The pivotal Study 312 population includes patients with ES-SCLC who received ≥ 1 dose of either tislelizumab 200 mg once every 3 weeks (tislelizumab plus chemotherapy arm: 227 patients) or matched placebo in combination with (placebo plus chemotherapy arm: 230 patients).

Pivotal Phase III Study in NPC

The pivotal Study 309 population includes patients with recurrent or metastatic NPC who received ≥ 1 dose of either tislelizumab 200 mg once every 3 weeks (tislelizumab plus chemotherapy arm: 131 patients) or matched placebo in combination with gemcitabine and cisplatin (placebo plus chemotherapy arm: 132 patients).

Studies Providing Supportive Safety Data

Several studies with tislelizumab in OSCC, NSCLC, GC, NPC, ES-SCLC and other cancers provided safety data in this submission.

- Safety data from patients who received tislelizumab monotherapy at the registrational dose of 200 mg every 3 weeks from studies BGB-A317-Study-001, BGB-A317-102, BGB-A317-203, BGB-A317-204, BGB-A317-208, BGB-A317-209, BGB-A317-301, BGB-A317-302, and BGB-A317-303 form the tislelizumab monotherapy safety pool (Table Part II: Module SIII-1).
- Safety data from studies BGB-A317-205, BGB-A317-206, BGB-A317-304, BGB-A317-305, BGB-A317-306, BGB-A317-307, BGB-A317-309, BGB-A317-312 and BGB-A317-315 form the tislelizumab in combination therapy pool (Table Part II: Module SIII-2).

The goal of this pooled analysis was to provide a comprehensive safety profile for tislelizumab and to provide supportive data for the safety profile of tislelizumab in a larger population, as well as to identify possible rare safety signals. The analysis of this population reflects the full experience with tislelizumab in advanced cancers.

This integrated safety population included 1950 patients who received ≥ 1 dose of tislelizumab + chemotherapy and 1952 patients with different tumour types who received ≥ 1 dose of tislelizumab monotherapy. The pivotal Studies (Study 302, Study 303, Study 304, Study 305, Study 306, Study 307, Study 309, Study 312 and Study 315) and the 9 supportive studies included in this analysis are summarised in Table Part II: Module SIII-1 and Table Part II: Module SIII-2.

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).	28 December 2022	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).	18 January 2024	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).	12 August 2020	200 mg Q3W	13

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).	02 November 2020	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).	11 March 2021	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).	06 July 2022	200 mg Q3W	249

Study Numbers (Disease Type; Location)	Data Cutoff Dates	Tislelizumab Dose	Number of Patients who Received Tislelizumab
BGB-A317-209 (Previously treated locally advanced unresectable or metastatic microsatellite instability-high or mismatch repair deficient solid tumours; China) A single-arm, multi-center, open-label, Phase II study to evaluate efficacy and safety of tislelizumab (BGB-A317), an anti-PD-1 monoclonal antibody, as monotherapy in patients with previously treated locally advanced unresectable or metastatic microsatellite instability-high or mismatch repair deficient solid tumors (hereafter referred to as Study 209)	08 July 2021	200 mg Q3W	80
BGB-A317-301 (Unresectable hepatocellular carcinoma; Global) A randomized, open-label, multicenter Phase III study to compare the efficacy and safety of BGB-A317 versus sorafenib as 1L treatment in patients with unresectable hepatocellular carcinoma (hereafter referred to as Study 301)	14 December 2023	200 mg Q3W	338
Total Patients who Received Tislelizumab as Monotherapy			**1952**

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 (Stage IIIB or IV 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 April 2023	200 mg Q3W	222
BGB-A317-305 (Locally advanced, unresectable, or metastatic gastric or gastroesophageal junction adenocarcinoma, Global) A randomized, double-blind, placebo-controlled, phase 3 clinical study comparing the efficacy and safety of tislelizumab (BGB-A317) plus platinum and fluoropyrimidine versus placebo plus platinum and fluoropyrimidine as first-line treatment in patients with locally advanced unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma (hereafter referred to as Study 305).	28 February 2023	200 mg Q3W	498
BGB-A317-306 (Unresectable, locally advanced recurrent or metastatic OSCC, Global) A multi-regional, randomized, placebo-controlled, double-blind Phase III study evaluating the efficacy and safety of tislelizumab in combination with chemotherapy compared to placebo in combination with chemotherapy as first-line treatment in patients with unresectable or locally advanced recurrent or metastatic OSCC (hereafter referred to as Study 306).	28 February 2022	200 mg Q3W	324
BGB-A317-307 (Untreated, advanced 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).	28 April 2023	200 mg Q3W	238

Study Numbers (Disease Type; Location)	Data Cutoff Dates	Tislelizumab Dose	Number of Patients who Received Tislelizumab
BGB-A317-309 (Recurrent or metastatic nasopharyngeal carcinoma, China) A Phase III, multicenter, double-blind, randomized, placebo-controlled study to compare the efficacy and safety of tislelizumab (BGB-A317) combined with gemcitabine plus cisplatin versus placebo combined with gemcitabine plus cisplatin as first-line treatment for recurrent or metastatic nasopharyngeal cancer (hereafter referred to as Study 309).	08 December 2023	200 mg Q3W	131
BGB-A317-312 (Untreated ES-SCLC, China) A Phase III, randomized, double-blind, placebo-controlled study of platinum plus etoposide with or without tislelizumab (BGB-A317) in patients with untreated ES-SCLC (hereafter referred to as Study 312).	29 December 2023	200 mg Q3W	227
BGB-A317-315 (Resectable Stage II or IIIA Perioperative treatment of NSCLC, China) A randomized, double-blind, placebo-controlled, Phase III study to compare the efficacy and safety of neoadjuvant treatment with tislelizumab (BGB-A317, anti-PD-1 antibody) or placebo plus platinum-based doublet chemotherapy followed by adjuvant tislelizumab or placebo in resectable stage II or IIIA NSCLC (hereafter referred to as Study 315).	21 August 2023	200 mg Q3W (neoadjuvant phase) and 400 mg Q6W (adjuvant phase)	226
Supporting Study			
BGB-A317-205 (Inoperable, locally advanced or metastatic G/GEJ carcinoma, China) A Phase II, multi-cohort study to investigate the safety, pharmacokinetics and preliminary antitumor activity of the anti-PD-1 monoclonal antibody BGB-A317 in combination with chemotherapy as first-line treatment in adults with inoperable, locally advanced or metastatic esophageal, gastric, or gastroesophageal junction carcinoma (hereafter referred to as 205).	31 March 2019	200 mg Q3W	30
BGB-A317-206 (NSQ NSCLC, SQ NSCLC, SCLC; China)	31 December 2019	200 mg Q3W	54

Study Numbers (Disease Type; Location)	Data Cutoff Dates	Tislelizumab Dose	Number of Patients who Received Tislelizumab
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 tislelizumab in combination with platinum-containing doublet chemotherapy (hereafter referred to as Study 206).			
Total Patients who Received Tislelizumab as Combination Therapy			**1950**

Abbreviations: AUC, area under the curve; D, day; ES-SCLC, extensive-stage small cell lung cancer; G/GEJ, gastric/gastroesophageal junction; GC, gemcitabine + cisplatin/carboplatin; IV, intravenous; LC, lung cancer; nab-PC, nab-paclitaxel; NSCLC, non-small cell lung cancer; NSQ, non-squamous; OSCC, oesophageal squamous cell carcinoma; PC, paclitaxel + carboplatin/carboplatin; PD, programmed cell death protein; PP, pemetrexed + platinum; SCLC, small cell lung cancer; SQ, squamous; Q3W, every 3 weeks; T, tislelizumab.

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, indication, by age group and sex, and by race, including ethnic origin.

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

Duration of Exposure	Patients n (%)	Patient Time (months)
Total Population		
< 1 month	254 (6.5)	168.84
1 - < 3 months	937 (24.0)	1935.84
3 - < 6 months	815 (20.9)	3691.96
6 - < 12 months	790 (20.2)	6657.71
12 - < 18 months	417 (10.7)	6028.65
18 - < 24 months	177 (4.5)	3705.49
> 24 months	512 (13.1)	18,528.46
Total	**3902 (100.0)**	**40,716.94**

Abbreviations: n, number.
Source data: ADSL
Patient time is the sum of each patient's treatment exposure in months.
Percentages are based on the total number of patients who received at least a dose of tislelizumab.

Table Part II: Module SIII-4: Duration of Tislelizumab Exposure by Indication - All Tislelizumab Treated Population (Safety Analysis Set)

Indication Duration of Exposure	Patients n (%)	Patient Time (months)
1L OSCC		
<1 month	22 (6.8)	14.23
1 - <3 months	55 (17.0)	110.65
3 - <6 months	76 (23.5)	363.43
6 - <12 months	95 (29.3)	778.51
12 - <18 months	30 (9.3)	451.22
18 - <24 months	21 (6.5)	432.00
>=24 months	25 (7.7)	701.34
Total	324 (100.0)	2851.38
1L GC		
<1 month	27 (5.4)	17.22
1 - <3 months	87 (17.5)	180.80
3 - <6 months	139 (27.9)	656.33

Indication **Duration of Exposure**	**Patients** **n (%)**	**Patient Time** **(months)**
6 - <12 months	122 (24.5)	1027.71
12 - <18 months	42 (8.4)	602.74
18 - <24 months	21 (4.2)	440.74
>=24 months	60 (12.0)	1908.53
Total	498 (100.0)	4834.07
1L NPC		
<1 month	8 (6.1)	4.86
1 - <3 months	12 (9.2)	25.03
3 - <6 months	15 (11.5)	79.05
6 - <12 months	36 (27.5)	313.30
12 - <18 months	21 (16.0)	292.47
18 - <24 months	9 (6.9)	188.02
>=24 months	30 (22.9)	1150.13
Total	131 (100.0)	2052.86
1L NSCLC		
<1 month	26 (5.7)	17.94
1 - <3 months	51 (11.1)	106.09
3 - <6 months	79 (17.2)	388.30
6 - <12 months	132 (28.7)	1164.75
12 - <18 months	50 (10.9)	743.29
18 - <24 months	29 (6.3)	602.81
>=24 months	93 (20.2)	3676.62
Total	460 (100.0)	6699.79
1L SCLC		
<1 month	10 (4.4)	6.21
1 - <3 months	33 (14.5)	67.61
3 - <6 months	103 (45.4)	454.77
6 - <12 months	35 (15.4)	291.68
12 - <18 months	14 (6.2)	196.76
18 - <24 months	4 (1.8)	84.11
>=24 months	28 (12.3)	1056.59
Total	227 (100.0)	2157.73
2L OSCC		
<1 month	29 (11.4)	18.89

Indication **Duration of Exposure**	**Patients** **n (%)**	**Patient Time** **(months)**
1 - <3 months	118 (46.3)	245.59
3 - <6 months	43 (16.9)	188.52
6 - <12 months	35 (13.7)	301.77
12 - <18 months	11 (4.3)	159.61
18 - <24 months	5 (2.0)	105.59
>=24 months	14 (5.5)	471.56
Total	255 (100.0)	1491.52
2L NSCLC		
<1 month	37 (6.9)	23.95
1 - <3 months	144 (27.0)	291.25
3 - <6 months	98 (18.4)	423.49
6 - <12 months	113 (21.2)	915.61
12 - <18 months	39 (7.3)	566.11
18 - <24 months	27 (5.1)	569.79
>=24 months	76 (14.2)	3271.16
Total	534 (100.0)	6061.37
Neoadjuvant & adjuvant NSCLC		
<1 month	9 (4.0)	5.88
1 - <3 months	44 (19.5)	98.10
3 - <6 months	19 (8.4)	79.97
6 - <12 months	36 (15.9)	338.14
12 - <18 months	117 (51.8)	1663.74
18 - <24 months	1 (0.4)	18.73
Total	226 (100.0)	2204.55
Other		
<1 month	86 (6.9)	59.66
1 - <3 months	393 (31.5)	810.71
3 - <6 months	243 (19.5)	1058.10
6 - <12 months	186 (14.9)	1526.24
12 - <18 months	93 (7.5)	1352.71
18 - <24 months	60 (4.8)	1263.70
>=24 months	186 (14.9)	6292.53
Total	1247 (100.0)	12363.66

Abbreviations: 1L, first-line; 2L, second-line; GC, gastric cancer; n, number; NSCLC, non-small cell lung cancer; NPC, nasopharyngeal carcinoma; OSCC, oesophageal squamous cell carcinoma; SCLC, small cell lung cancer;
Source: ADSL,
Percentages are based on the total number of patients who received at least one dose of Tislelizumab.
Patient time is the sum of each patient's treatment exposure in months.

Table Part II: Module SIII-5: Duration of Tislelizumab Exposure by Age Group, Gender, and Indication - All Tislelizumab Treated Population (Safety Analysis Set)

	Patients n (%)			Patient Time (months)		
Indication Age Group	**Male**	**Female**	**All**	**Male**	**Female**	**All**
1L OSCC						
>=18 and <55 years	37 (11.4)	6 (1.9)	43 (13.3)	238.13	49.74	287.87
>=55 and <65 years	118 (36.4)	14 (4.3)	132 (40.7)	1033.26	196.27	1229.54
>=65 and <75 years	114 (35.2)	22 (6.8)	136 (42.0)	971.76	270.19	1241.95
>=75 years	11 (3.4)	2 (0.6)	13 (4.0)	62.75	29.27	92.02
Total	280 (86.4)	44 (13.6)	324 (100.0)	2305.91	545.48	2851.38
1L GC						
>=18 and <55 years	83 (16.7)	75 (15.1)	158 (31.7)	770.04	610.83	1380.86
>=55 and <65 years	143 (28.7)	36 (7.2)	179 (35.9)	1493.59	403.02	1896.61
>=65 and <75 years	96 (19.3)	37 (7.4)	133 (26.7)	1031.98	347.53	1379.52
>=75 years	21 (4.2)	7 (1.4)	28 (5.6)	146.69	30.39	177.08
Total	343 (68.9)	155 (31.1)	498 (100.0)	3442.30	1391.77	4834.07
1L NPC						
>=18 and <55 years	73 (55.7)	18 (13.7)	91 (69.5)	1257.10	262.37	1519.47
>=55 and <65 years	23 (17.6)	7 (5.3)	30 (22.9)	264.61	134.87	399.47
>=65 and <75 years	7 (5.3)	3 (2.3)	10 (7.6)	115.42	18.50	133.91
>=75 years	0 (0.0)	0 (0.0)	0 (0.0)	0	0	0
Total	103 (78.6)	28 (21.4)	131 (100.0)	1637.13	415.74	2052.86
1L NSCLC						
>=18 and <55 years	55 (12.0)	27 (5.9)	82 (17.8)	956.68	362.68	1319.36
>=55 and <65 years	187 (40.7)	32 (7.0)	219 (47.6)	2705.22	463.97	3169.18
>=65 and <75 years	139 (30.2)	16 (3.5)	155 (33.7)	1919.61	250.35	2169.95
>=75 years	4 (0.9)	0 (0.0)	4 (0.9)	41.30	0	41.30
Total	385 (83.7)	75 (16.3)	460 (100.0)	5622.80	1076.99	6699.79
1L SCLC						
>=18 and <55 years	30 (13.2)	9 (4.0)	39 (17.2)	262.54	93.21	355.75

	Patients n (%)			Patient Time (months)		
Indication Age Group	**Male**	**Female**	**All**	**Male**	**Female**	**All**
>=55 and <65 years	85 (37.4)	14 (6.2)	99 (43.6)	964.17	159.74	1123.91
>=65 and <75 years	65 (28.6)	16 (7.0)	81 (35.7)	479.93	133.88	613.82
>=75 years	6 (2.6)	2 (0.9)	8 (3.5)	55.26	9.00	64.26
Total	186 (81.9)	41 (18.1)	227 (100.0)	1761.91	395.83	2157.73
2L OSCC						
>=18 and <55 years	44 (17.3)	9 (3.5)	53 (20.8)	153.36	81.97	235.33
>=55 and <65 years	91 (35.7)	8 (3.1)	99 (38.8)	514.66	19.42	534.08
>=65 and <75 years	70 (27.5)	20 (7.8)	90 (35.3)	540.12	125.67	665.79
>=75 years	11 (4.3)	2 (0.8)	13 (5.1)	46.59	9.72	56.31
Total	216 (84.7)	39 (15.3)	255 (100.0)	1254.74	236.78	1491.52
2L NSCLC						
>=18 and <55 years	84 (15.7)	40 (7.5)	124 (23.2)	1190.14	322.86	1513.00
>=55 and <65 years	182 (34.1)	45 (8.4)	227 (42.5)	1908.76	520.97	2429.73
>=65 and <75 years	137 (25.7)	29 (5.4)	166 (31.1)	1622.93	374.90	1997.83
>=75 years	13 (2.4)	4 (0.7)	17 (3.2)	96.62	24.18	120.80
Total	416 (77.9)	118 (22.1)	534 (100.0)	4818.46	1242.91	6061.37
Neoadjuvant & adjuvant NSCLC						
>=18 and <55 Years	36 (15.9)	5 (2.2)	41 (18.1)	382.39	63.57	445.96
>=55 and <65 Years	92 (40.7)	10 (4.4)	102 (45.1)	882.99	83.84	966.83
>=65 and <75 Years	71 (31.4)	6 (2.7)	77 (34.1)	666.32	71.66	737.97
>=75 Years	6 (2.7)	0 (0.0)	6 (2.7)	53.78	0	53.78
Total	205 (90.7)	21 (9.3)	226 (100.0)	1985.48	219.07	2204.55
Other						
>=18 and <55 years	338 (27.1)	139 (11.1)	477 (38.3)	3403.83	1577.30	4981.13
>=55 and <65 years	294 (23.6)	71 (5.7)	365 (29.3)	2786.50	680.84	3467.33
>=65 and <75 years	253 (20.3)	67 (5.4)	320 (25.7)	2340.53	712.48	3053.01
>=75 years	64 (5.1)	21 (1.7)	85 (6.8)	523.63	338.56	862.19
Total	949 (76.1)	298 (23.9)	1247 (100.0)	9054.49	3309.17	12,363.66

Abbreviations: 1L, first-line; 2L, second-line; GC, gastric cancer; n, number; NSCLC, non-small cell lung cancer; NPC, nasopharyngeal carcinoma; OSCC, oesophageal squamous cell carcinoma; SCLC, small cell lung cancer;
Source: ADSL
Percentages are based on the total number of patients who received at least one dose of Tislelizumab.
Patient time is the sum of each patient's treatment exposure in months.

Table Part II: Module SIII-6: Duration of Tislelizumab Exposure by Race and Indication - All Tislelizumab Treated Population (Safety Analysis Set)

Indication Race	Patients n (%)	Patient Time (months)
1L OSCC		
Asian	241 (74.4)	2118.51
White	66 (20.4)	604.88
Not Reported	17 (5.2)	128.00
Total	324 (100.0)	2851.38
1L GC		
Asian	375 (75.3)	3955.38
White	114 (22.9)	846.42
Not Reported	8 (1.6)	20.53
Other	1 (0.2)	11.73
Total	498 (100.0)	4834.07
1L NPC		
Asian	131 (100.0)	2052.86
Total	131 (100.0)	2052.86
1L NSCLC		
Asian	460 (100.0)	6699.79
Total	460 (100.0)	6699.79
1L SCLC		
Asian	227 (100.0)	2157.73
Total	227 (100.0)	2157.73
2L OSCC		
Asian	201 (78.8)	1170.79
White	33 (12.9)	200.48
Not Reported	20 (7.8)	119.56
Unknown	1 (0.4)	0.69
Total	255 (100.0)	1491.52
2L NSCLC		
American Indian or Alaska Native	12 (2.2)	116.01
Asian	423 (79.2)	4507.99
Black or African American	1 (0.2)	6.14
Native Hawaiian or Other Pacific Islander	3 (0.6)	9.10
White	93 (17.4)	1373.80

Indication **Race**	**Patients** **n (%)**	**Patient Time** **(months)**
Other	2 (0.4)	48.33
Total	534 (100.0)	6061.37
Neoadjuvant & adjuvant NSCLC		
Asian	226 (100.0)	2204.55
Total	226 (100.0)	2204.55
Other		
Asian	1023 (82.0)	10320.10
Black or African American	3 (0.2)	9.66
White	116 (9.3)	1110.41
Not Reported	102 (8.2)	914.53
Unknown	1 (0.1)	2.30
Other	2 (0.2)	6.67
Total	1247 (100.0)	12363.66

Abbreviations: 1L, first-line; 2L, second-line; GC, gastric cancer: n, number; NSCLC, non-small cell lung cancer; NPC, nasopharyngeal carcinoma; OSCC, oesophageal squamous cell carcinoma; SCLC, small cell lung cancer;
Source: ADSL.
Percentages are based on the total number of patients who received at least one dose of Tislelizumab.
Patient time is the sum of each patient's treatment exposure in months.
For study 208, 301, 302, 305 and 306, the race of French patients was counted under ‘Not Reported’.

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, 305, 306, 307, 309, 312 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

	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.
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 2018). 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 4 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.
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.	
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)	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.
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.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CNS, central nervous system; DNA, deoxyribonucleic acid; EU, European Union; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; imAE, immune-mediated adverse event; IU, international unit; mAb, monoclonal antibody; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; PK, pharmacokinetics; SmPC, summary of product characteristics; ULN, upper limit of normal.

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 1018/3902 (26.1%) patients (10,436.99 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 209, Study 301, Study 302, and Study 303 and as combination therapy from Study 205, Study 206, Study 304, Study 305, Study 306, Study 307, Study 309, Study 312 and Study 315. Normal renal function was reported in 2884 (73.9%) patients (30,279.95 person time). 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 682/3902 (17.5%) patients (5282.69 person time) who received tislelizumab as monotherapy in Study 001, Study 102, Study 203, Study 204, Study 208, Study 209, Study 301, Study 302, and Study 303 and as combination therapy from Study 205, Study 206, Study 304, Study 305, Study 306, Study 307, Study 309, Study 312 and Study 315. Normal hepatic function was reported in 3219 (82.5%) patients (35,432.84 person time). In 1 (0.02%) patient, information on hepatic impairment at baseline was missing. 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.

Type of Special Population	Exposure
Population With Relevant Different Ethnic Origin	Clinical study exposure data on race including ethnicity is presented in Table Part II: Module SIII-6.
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 non-squamous histology in Study 303. Additionally, although patients with known ALK-fusion oncogene were excluded, patients (non-squamous or squamous histology in 3 studies) with unknown ALK-fusion oncogene status were not required to be tested at screening.

Abbreviations: AST, aspartate aminotransferase; ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; PK, pharmacokinetics; ULN, upper limit of normal.

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

	Patients n (%)	Patient Time (months)
Renal Impairment Status at Baseline		
Normal	2884 (73.9)	30,279.95
Impairment	1018 (26.1)	10,436.99
Total	3902 (100.0)	40,716.94
Hepatic Impairment Status at Baseline		
Normal	3219 (82.5)	35,432.84
Impairment	682 (17.5)	5282.69
Missing	1 (0.0)	1.41
Total	3902 (100.0)	40,716.94

Abbreviations: n, number.
Source data: ADSL
Studies include monotherapy studies (Studies 001, 102, 203, 204, 208, 209, 301, 302, 303) and combination studies (Studies 205, 206, 304, 305, 306, 307, 309, 312, 315).
Percentages are based on the total number of patients who received at least one dose of Tislelizumab.
Patient time is the sum of each patient's treatment exposure in months.
Impairment includes mild, moderate and severe impairments.
Baseline is defined as the last non-missing value collected on or prior to the randomization (for studies 301, 302, 303, 304, 305, 306, 307, 309, 312 and 315), or the first dose of study drug (for studies 001, 102, 203, 204, 205, 206, 208 and 209).

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), 1L, unresectable, locally advanced or metastatic squamous NSCLC (12 January 2021), 1L unresectable, locally advanced or metastatic non-squamous NSCLC (22 June 2021), second-/third-line hepatocellular carcinoma 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), 1L locally advanced or metastatic OSCC (08 April 2022), 1L recurrent or metastatic NPC (07 June 2022), 1L treatment with locally advanced unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma with high PD-L1 expression (21 February 2023), 1L treatment with unresectable, locally advanced recurrent or metastatic OSCC (19 May 2023), locally advance unresectable or metastatic gastric/gastroesophageal junction (G/GEJ) adenocarcinoma (24 April 2024) and 1L treatment of patients with extensive stage SCLC (25 June 2024).

Tislelizumab, as monotherapy, was approved in EU for the indications of treatment of unresectable, locally advanced recurrent or metastatic OSCC after prior platinum-based chemotherapy (15 September 2023).

Subsequently, the indications including treatment of adult patients with locally advanced or metastatic NSCLC after prior platinum-based therapy (08 July 2024), and as combination therapy for 1L treatment of adult patients with non-squamous NSCLC whose tumours have PD-L1 expression on ≥50% of TCs with no EGFR or ALK positive mutations and 1L treatment of adult patients with squamous NSCLC were approved in EU on 08 July 2024.

On 25 November 2024, the indications of 1L treatment of adult patients with unresectable, locally advanced or metastatic OSCC whose tumours express PD-L1 with a tumour area positivity (TAP) score ≥ 5% and 1L treatment of adult patients with HER-2 negative locally advanced unresectable or metastatic G/GEJ adenocarcinoma whose tumours express PD-L1 with a TAP score ≥ 5% were approved in EU.

On 02 May 2025, the indication of 1L treatment of adult patients with ES-SCLC was approved in EU.

On 22 May 2025, the indication of 1L treatment of adult patients with NPC received a positive CHMP opinion.

SV.1 Post-authorisation Exposure

As of Periodic Benefit-Risk Evaluation Report data lock point (25 June 2024), 9,206,133 vials of tislelizumab have been supplied to the market in China and Macao, China (equivalent to 4,603,067 infusions based on the recommended dose of 200 mg per infusion). This represents an exposure of approximately 266,073 patient-treatment-years (3,192,876 patient-treatment months) based on the treatment cycle of 3 weeks (17.3 doses per annum).

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 supplied/200 (fixed dose of tislelizumab). Tislelizumab is given every 3 weeks (17.3 doses-per-year). 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

Territory	Sales and Sample Volume Data	Estimated Number of Infusions	Person-months	Person-years
China	[redacted]			
Macao, China				
Total	9,206,133	4,603,067	3,192,876	266,073

Periodic Benefit-Risk Evaluation Report data lock point: 25 June 2024.

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.

  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.

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. The following modification of existing list of safety concerns was made: Minor changes in the naming and categorisation of terms/risks/elements included in the important identified risk of “Immune-mediated adverse reactions” such as:

- Renamed “Immune-mediated endocrinopathies (pituitary dysfunction)” to “Immune-mediated endocrinopathies (hypophysitis)”,
- Moved “Pericarditis” from “Other immune-mediated reactions” to “Immune-mediated myocarditis/pericarditis”,
- Added “Ocular”, “Musculoskeletal”, and “Blood dyscrasias” to “Other immune-mediated reactions”. Immune-mediated pancreatitis and Immune-mediated nervous system disorder were also reclassified under “Other immune-mediated reactions”,
- “Other immune-mediated reactions” category includes the following subcategories:
    1. Newly added “Other immune-mediated reactions (ocular)”
    2. Renamed “Other immune-mediated reactions (musculoskeletal)”
    3. Reclassified “Other immune-mediated reactions (pancreatitis)”
    4. Reclassified “Other immune-mediated reactions (nervous system)
    5. Newly added “Other immune-mediated reactions (blood dyscrasias)”

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 1952 patients treated with tislelizumab monotherapy in Study 001, Study 102, Study 203, Study 204, Study 208, Study 209, Study 301, Study 302, and Study 303, and 1950 patients from Study 304, Study 307, Study 205, Study 206, Study 305, Study 306, Study 309, Study 312 and Study 315 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 1L-OSCC indication who have received tislelizumab is 2851.38 patient-months, for 1L-GC indication who have received tislelizumab is 4834.07 patient-months, for 1L NPC indication who have received tislelizumab is 2052.86 patient-months, for 1L-SCLC indication who have received tislelizumab is 2157.73 patient-months, for neoadjuvant and adjuvant NSCLC who have received tislelizumab is 2204.55 patient-months, and the total person time of exposure to date for all patients who have received tislelizumab is 40,716.94 patient-months.

As agreed with the Committee for Medicinal Products for Human Use as part of the scientific advice (EMA/SA/0000121172) dated 23 February 2023, a programmatic algorithmic method for retrieval of immune-mediated adverse events (imAEs) was utilized (a description of the broad and narrow list terms is provided in the ADAM datasets).

The proposed methodology is based on a list of terms with the following two components:

- A narrow list of terms for which the immune-mediated aetiology is specified in the PT and that are always considered imAEs (eg, immune-mediated hypothyroidism).
- A broad list of terms that are known or possible imAEs, and that are considered imAEs when any of the following additional criteria are met:
    a. Treatment of the AE with steroids, other immunosuppressants or hormonal replacement therapy.
    b. Investigator assessment as imAE in the Case Report Form.
    c. Investigator causality assessment as related to the study drug.
    d. Action taken with any study drug as drug interruption/discontinuation.

An AE was defined as an imAE as long as it satisfied one of the two components above.

An imADR was defined as any PT flagged as adverse reaction and reported as an imAE in at least one patient of the monotherapy pool or the combination therapy pool.

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/pericarditis, 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, Type 1 Diabetes Mellitus, Hypophysitis)

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).

Hypophysitis is most commonly seen with anti-CTLA4 antibody monotherapy (ipilimumab, with an incidence of ≤ 10% at a dose of 3 mg/kg and up to 17% at 10 mg/kg), and with combination ipilimumab/nivolumab (incidence ≤ 13%) (Puzanov et al 2017).

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/Pericarditis

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, pericarditis 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). 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). 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.

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

	Tislelizumab Monotherapy (N=1952) n (%)	**Tislelizumab Combination Therapy (N=1950) n (%)**
Immune-mediated endocrinopathies (hypothyroidism)		
Patients in the Category, n (%) (95% CI)	269 (13.8) (12.3, 15.4)	296 (15.2) (13.6, 16.8)
Hypothyroidism	247 (12.7)	266 (13.6)
Thyroxine free decreased	10 (0.5)	20 (1.0)
Tri-iodothyronine free decreased	13 (0.7)	15 (0.8)
Tri-iodothyronine decreased	3 (0.2)	7 (0.4)
Thyroxine decreased	2 (0.1)	1 (0.1)
Primary hypothyroidism	1 (0.1)	0 (0.0)
Thyroid hormones decreased	1 (0.1)	0 (0.0)
Immune-mediated hypothyroidism	0 (0.0)	1 (0.1)
Worst Grade		
Grade 3	1 (0.1)	4 (0.2)
Hypothyroidism	1 (0.1)	4 (0.2)
Grade 4	1 (0.1)	1 (0.1)
Hypothyroidism	1 (0.1)	1 (0.1)
Patients with At Least One Serious Immune-Mediated Adverse Reaction, n (%) (95% CI)	2 (0.1) (0.0, 0.4)	7 (0.4) (0.1, 0.7)
Hypothyroidism	2 (0.1)	7 (0.4)
Serious Immune-Mediated ADR Event Outcome		
Recovered/resolved	1 (0.1)	3 (0.2)
Hypothyroidism	1 (0.1)	3 (0.2)
Recovering/Resolving	0 (0.0)	2 (0.1)
Hypothyroidism	1 (0.1)	2 (0.1)
Not Recovered/Not Resolved	1 (0.1)	2 (0.1)
Hypothyroidism	1 (0.1)	2 (0.1)
Patients With At Least One Immune-Mediated ADR Leading to Tislelizumab Discontinuation	2 (0.1)	7 (0.4)
Hypothyroidism	2 (0.1)	7 (0.4)
Patients With At Least One Immune-Mediated ADR Leading to Treatment Modification of Tislelizumab	12 (0.6)	38 (1.9)

	Tislelizumab Monotherapy (N=1952) n (%)	Tislelizumab Combination Therapy (N=1950) n (%)
Hypothyroidism	12 (0.6)	37 (1.9)
Thyroxine free decreased	0 (0.0)	1 (0.1)
Tri-iodothyronine free decreased	0 (0.0)	1 (0.1)
Immune-mediated skin adverse reaction		
Patients in the Category, n (%) (95% CI)	246 (12.6) (11.2, 14.2)	327 (16.8) (15.1, 18.5)
Rash	168 (8.6)	259 (13.3)
Rash maculo-papular	21 (1.1)	27 (1.4)
Eczema	12 (0.6)	12 (0.6)
Dermatitis allergic	8 (0.4)	11 (0.6)
Dermatitis	10 (0.5)	8 (0.4)
Rash erythematous	5 (0.3)	4 (0.2)
Psoriasis	8 (0.4)	7 (0.4)
Rash papular	7 (0.4)	3 (0.2)
Rash pruritic	7 (0.4)	4 (0.2)
Erythema multiforme	3 (0.2)	0 (0.0)
Vitiligo	3 (0.2)	2 (0.1)
Immune-mediated dermatitis	4 (0.2)	4 (0.2)
Leukoderma	1 (0.1)	2 (0.1)
Acute febrile neutrophilic dermatosis	1 (0.1)	0 (0.0)
Rash macular	4 (0.2)	0 (0.0)
Sjogren's syndrome	0 (0.0)	2 (0.1)
Autoimmune dermatitis	1 (0.1)	2 (0.1)
Dermatitis exfoliative	0 (0.0)	1 (0.1)
Stevens-Johnson syndrome	1 (0.1)	0 (0.0)
Worst Grade		
Grade 3	20 (1.0)	43 (2.2)
Rash	10 (0.5)	30 (1.5)
Immune-mediated dermatitis	3 (0.2)	3 (0.2)
Rash maculo-papular	3 (0.2)	3 (0.2)
Psoriasis	2 (0.1)	3 (0.2)
Erythema multiforme	1 (0.1)	0 (0.0)
Rash papular	1 (0.1)	0 (0.0)

	Tislelizumab Monotherapy (N=1952) n (%)	**Tislelizumab Combination Therapy (N=1950) n (%)**
Autoimmune dermatitis	0 (0.0)	1 (0.1)
Dermatitis	0 (0.0)	1 (0.1)
Eczema	0 (0.0)	1 (0.1)
Rash erythematous	0 (0.0)	1 (0.1)
Grade 4	2 (0.1)	1 (0.1)
Rash	1 (0.1)	1 (0.1)
Stevens-Johnson syndrome	1 (0.1)	0 (0.0)
Patients with At Least One Serious Immune-Mediated Adverse Reaction, n (%) (95% CI)	8 (0.4) (0.2, 0.8)	12 (0.6) (0.3, 1.1)
Rash	4 (0.2)	6 (0.3)
Dermatitis allergic	1 (0.1)	0 (0.0)
Immune-mediated dermatitis	1 (0.1)	1 (0.1)
Rash maculo-papular	1 (0.1)	0 (0.0)
Stevens-Johnson syndrome	1 (0.1)	0 (0.0)
Eczema	0 (0.0)	2 (0.1)
Psoriasis	0 (0.0)	2 (0.1)
Rash erythematous	0 (0.0)	1 (0.1)
Serious Immune-Mediated ADR Event Outcome		
Recovered/resolved	7 (0.4)	9 (0.5)
Rash	3 (0.2)	5 (0.3)
Rash maculo-papular	2 (0.1)	0 (0.0)
Dermatitis allergic	1 (0.1)	0 (0.0)
Stevens-Johnson syndrome	1 (0.1)	0 (0.0)
Eczema	0 (0.0)	1 (0.1)
Immune-mediated dermatitis	0 (0.0)	1 (0.1)
Psoriasis	0 (0.0)	1 (0.1)
Rash erythematous	0 (0.0)	1 (0.1)
Recovering/resolving	0 (0.0)	1 (0.1)
Psoriasis	0 (0.0)	1 (0.1)
Not recovered/not resolved	1 (0.1)	1 (0.1)
Immune-mediated dermatitis	1 (0.1)	0 (0.0)
Eczema	0 (0.0)	1 (0.1)
Unknown	1 (0.1)	1 (0.1)

	Tislelizumab Monotherapy (N=1952) n (%)	Tislelizumab Combination Therapy (N=1950) n (%)
Rash	1 (0.1)	1 (0.1)
Patients With At Least One Immune-Mediated ADR Leading to Tislelizumab Discontinuation	2 (0.1)	11 (0.6)
Immune-mediated dermatitis	1 (0.1)	2 (0.1)
Rash	1 (0.1)	4 (0.2)
Autoimmune dermatitis	0 (0.0)	1 (0.1)
Dermatitis	0 (0.0)	1 (0.1)
Dermatitis exfoliative	0 (0.0)	1 (0.1)
Psoriasis	0 (0.0)	2 (0.1)
Patients With At Least One Immune-Mediated ADR Leading to Treatment Modification of Tislelizumab	25 (1.3)	46 (2.4)
Rash	13 (0.7)	29 (1.5)
Immune-mediated dermatitis	3 (0.2)	3 (0.2)
Dermatitis allergic	2 (0.1)	0 (0.0)
Erythema multiforme	2 (0.1)	0 (0.0)
Rash maculo-papular	2 (0.1)	3 (0.2)
Acute febrile neutrophilic dermatosis	1 (0.1)	0 (0.0)
Eczema	1 (0.1)	3 (0.2)
Psoriasis	1 (0.1)	4 (0.2)
Dermatitis	0 (0.0)	1 (0.1)
Rash erythematous	0 (0.0)	1 (0.1)
Sjogren's syndrome	0 (0.0)	2 (0.1)
Immune-mediated pneumonitis		
Patients in the Category, n (%) (95% CI)	100 (5.1) (4.2, 6.2)	151 (7.7) (6.6, 9.0)
Pneumonitis	61 (3.1)	113 (5.8)
Immune-mediated lung disease	21 (1.1)	25 (1.3)
Interstitial lung disease	19 (1.0)	15 (0.8)
Worst Grade		
Grade 3	26 (1.3)	34 (1.7)
Pneumonitis	15 (0.8)	26 (1.3)
Interstitial lung disease	8 (0.4)	1 (0.1)
Immune-mediated lung disease	3 (0.2)	7 (0.4)

	Tislelizumab Monotherapy (N=1952) n (%)	**Tislelizumab Combination Therapy (N=1950) n (%)**
Grade 4	6 (0.3)	3 (0.2)
Interstitial lung disease	3 (0.2)	1 (0.1)
Immune-mediated lung disease	2 (0.1)	0 (0.0)
Pneumonitis	1 (0.1)	2 (0.1)
Grade 5	2 (0.1)	6 (0.3)
Immune-mediated lung disease	1 (0.1)	1 (0.1)
Pneumonitis	1 (0.1)	4 (0.2)
Interstitial lung disease	0 (0.0)	1 (0.1)
Patients with At Least One Serious Immune-Mediated ADR , n (%) (95% CI)	51 (2.6) (2.0, 3.4)	79 (4.1) (3.2, 5.0)
Pneumonitis	25 (1.3)	58 (3.0)
Immune-mediated lung disease	15 (0.8)	11 (0.6)
Interstitial lung disease	11 (0.6)	10 (0.5)
Serious Immune-Mediated ADR Event Outcome		
Fatal	2 (0.1)	6 (0.3)
Immune-mediated lung disease	1 (0.1)	1 (0.1)
Pneumonitis	1 (0.1)	4 (0.2)
Interstitial lung disease	0 (0.0)	1 (0.1)
Recovered/resolved	26 (1.3)	30 (1.5)
Pneumonitis	11 (0.6)	25 (1.3)
Immune-mediated lung disease	10 (0.5)	4 (0.2)
Interstitial lung disease	5 (0.3)	1 (0.1)
Recovered/resolved with sequelae	1 (0.1)	1 (0.1)
Pneumonitis	1 (0.1)	1 (0.1)
Recovering/resolving	8 (0.4)	18 (0.9)
Pneumonitis	5 (0.3)	11 (0.6)
Interstitial lung disease	2 (0.1)	4 (0.2)
Immune-mediated lung disease	1 (0.1)	3 (0.2)
Not recovered/not resolved	13 (0.7)	21 (1.1)
Pneumonitis	7 (0.4)	16 (0.8)
Immune-mediated lung disease	3 (0.2)	2 (0.1)
Interstitial lung disease	3 (0.2)	3 (0.2)
Unknown	1 (0.1)	3 (0.2)

	Tislelizumab Monotherapy (N=1952) n (%)	**Tislelizumab Combination Therapy (N=1950) n (%)**
Interstitial lung disease	1 (0.1)	1 (0.1)
Immune-mediated lung disease	0 (0.0)	1 (0.1)
Pneumonitis	0 (0.0)	1 (0.1)
Patients With At Least One Immune-Mediated ADR Leading to Tislelizumab Discontinuation	36 (1.8)	50 (2.6)
Pneumonitis	16 (0.8)	38 (1.9)
Immune-mediated lung disease	11 (0.6)	6 (0.3)
Interstitial lung disease	9 (0.5)	6 (0.3)
Patients With At Least One Immune-Mediated ADR Leading to Treatment Modification of Tislelizumab	37 (1.9)	67 (3.4)
Pneumonitis	22 (1.1)	42 (2.2)
Immune-mediated lung disease	9 (0.5)	15 (0.8)
Interstitial lung disease	6 (0.3)	10 (0.5)
Immune-mediated endocrinopathies (hyperthyroidism)		
Patients in the Category, n (%) (95% CI)	100 (5.1) (4.2, 6.2)	107 (5.5) (4.5, 6.6)
Hyperthyroidism	85 (4.4)	80 (4.1)
Thyroxine free increased	13 (0.7)	15 (0.8)
Thyroxine increased	2 (0.1)	15 (0.8)
Tri-iodothyronine increased	1 (0.1)	4 (0.2)
Immune-mediated hyperthyroidism	0 (0.0)	1 (0.1)
Worst Grade		
Grade 3	0 (0.0)	1 (0.1)
Hyperthyroidism	0 (0.0)	1 (0.1)
Patients with At Least One Serious Immune-Mediated ADR , n (%) (95% CI)	0 (0.0)	1 (0.1) (0.0, 0.3)
Hyperthyroidism	0 (0.0)	1 (0.1)
Serious Immune-Mediated ADR Event Outcome		
Recovered/Resolved	0 (0.0)	1 (0.1)
Hyperthyroidism	0 (0.0)	1 (0.1)
Patients With At Least One Immune-Mediated ADR Leading to Tislelizumab Discontinuation	1 (0.1)	2 (0.1)
Hyperthyroidism	1 (0.1)	2 (0.1)

	Tislelizumab Monotherapy (N=1952) n (%)	**Tislelizumab Combination Therapy (N=1950) n (%)**
Patients With At Least One Immune-Mediated ADR Leading to Treatment Modification of Tislelizumab	5 (0.3)	8 (0.4)
Hyperthyroidism	5 (0.3)	8 (0.4)
Immune-mediated endocrinopathies (thyroiditis)		
Patients in the Category, n (%) (95% CI)	21 (1.1) (0.7, 1.6)	14 (0.7) (0.4, 1.2)
Thyroiditis	11 (0.6)	6 (0.3)
Autoimmune thyroiditis	6 (0.3)	4 (0.2)
Thyroiditis subacute	4 (0.2)	2 (0.1)
Silent thyroiditis	1 (0.1)	1 (0.1)
Immune-mediated thyroiditis	0 (0.0)	1 (0.1)
Worst Grade		
Grade 3	0 (0.0)	1 (0.1)
Autoimmune thyroiditis	0 (0.0)	1 (0.1)
Patients with At Least One Serious Immune-Mediated ADR , n (%) (95% CI)	0 (0.0)	2 (0.1) (0.0, 0.4)
Autoimmune thyroiditis	0 (0.0)	1 (0.1)
Immune-mediated thyroiditis	0 (0.0)	1 (0.1)
Serious Immune-Mediated ADR Event Outcome		
Recovered/resolved	0 (0.0)	2 (0.1)
Autoimmune thyroiditis	0 (0.0)	1 (0.1)
Immune-mediated thyroiditis	0 (0.0)	1 (0.1)
Patients With At Least One Immune-Mediated ADR Leading to Tislelizumab Discontinuation	0 (0.0)	1 (0.1)
Immune-mediated thyroiditis	0 (0.0)	1 (0.1)
Patients With At Least One Immune-Mediated ADR Leading to Treatment Modification of Tislelizumab	4 (0.2)	4 (0.2)
Thyroiditis subacute	2 (0.1)	1 (0.1)
Autoimmune thyroiditis	1 (0.1)	1 (0.1)
Thyroiditis	1 (0.1)	2 (0.1)
Immune-mediated hepatitis		
Patients in the Category, n (%) (95% CI)	23 (1.2) (0.7, 1.8)	29 (1.5) (1.0, 2.1)
Immune-mediated hepatitis	11 (0.6)	16 (0.8)

	Tislelizumab Monotherapy (N=1952) n (%)	**Tislelizumab Combination Therapy (N=1950) n (%)**
Hepatitis	9 (0.5)	5 (0.3)
Autoimmune hepatitis	2 (0.1)	1 (0.1)
Drug-induced liver injury	1 (0.1)	6 (0.3)
Hepatotoxicity	1 (0.1)	1 (0.1)
Worst Grade		
Grade 3	12 (0.6)	21 (1.1)
Immune-mediated hepatitis	6 (0.3)	12 (0.6)
Hepatitis	5 (0.3)	4 (0.2)
Autoimmune hepatitis	1 (0.1)	1 (0.1)
Drug-induced liver injury	1 (0.1)	3 (0.2)
Hepatotoxicity	0 (0.0)	1 (0.1)
Grade 4	6 (0.3)	3 (0.2)
Immune-mediated hepatitis	3 (0.2)	3 (0.2)
Hepatitis	2 (0.1)	0 (0.0)
Autoimmune hepatitis	1 (0.1)	0 (0.0)
Patients with At Least One Serious Immune-Mediated ADR , n (%) (95% CI)	14 (0.7) (0.4, 1.2)	18 (0.9) (0.5, 1.5)
Immune-mediated hepatitis	7 (0.4)	13 (0.7)
Hepatitis	5 (0.3)	3 (0.2)
Autoimmune hepatitis	1 (0.1)	0 (0.0)
Drug-induced liver injury	1 (0.1)	2 (0.1)
Serious Immune-Mediated ADR Event Outcome		
Recovered/resolved	8 (0.4)	16 (0.8)
Immune-mediated hepatitis	4 (0.2)	11 (0.6)
Hepatitis	2 (0.1)	3 (0.2)
Autoimmune hepatitis	1 (0.1)	0 (0.0)
Drug-induced liver injury	1 (0.1)	2 (0.1)
Recovering/resolving	1 (0.1)	2 (0.1)
Immune-mediated hepatitis	1 (0.1)	2 (0.1)
Not recovered/not resolved	5 (0.3)	0 (0.0)
Hepatitis	3 (0.2)	0 (0.0)
Immune-mediated hepatitis	2 (0.1)	0 (0.0)

	Tislelizumab Monotherapy (N=1952) n (%)	Tislelizumab Combination Therapy (N=1950) n (%)
Patients With At Least One Immune-Mediated ADR Leading to Tislelizumab Discontinuation	5 (0.3)	9 (0.5)
Drug-induced liver injury	1 (0.1)	0 (0.0)
Hepatitis	2 (0.1)	1 (0.1)
Immune-mediated hepatitis	2 (0.1)	8 (0.4)
Patients With At Least One Immune-Mediated ADR Leading to Treatment Modification of Tislelizumab	15 (0.8)	16 (0.8)
Immune-mediated hepatitis	8 (0.4)	8 (0.4)
Hepatitis	7 (0.4)	4 (0.2)
Autoimmune hepatitis	1 (0.1)	0 (0.0)
Drug-induced liver injury	0 (0.0)	3 (0.2)
Hepatotoxicity	0 (0.0)	1 (0.1)
Immune-mediated endocrinopathies (type 1 diabetes mellitus)		
Patients in the Category, n (%) (95% CI)	12 (0.6) (0.3, 1.1)	28 (1.4) (1.0, 2.1)
Diabetes mellitus	7 (0.4)	15 (0.8)
Type 1 diabetes mellitus	4 (0.2)	8 (0.4)
Ketoacidosis	1 (0.1)	1 (0.1)
Latent autoimmune diabetes in adults	1 (0.1)	1 (0.1)
Diabetic ketoacidosis	0 (0.0)	3 (0.2)
Diabetic ketosis	0 (0.0)	1 (0.1)
Worst Grade		
Grade 3	4 (0.2)	14 (0.7)
Type 1 diabetes mellitus	3 (0.2)	6 (0.3)
Diabetes mellitus	1 (0.1)	6 (0.3)
Latent autoimmune diabetes in adults	1 (0.1)	0 (0.0)
Diabetic ketoacidosis	0 (0.0)	1 (0.1)
Diabetic ketosis	0 (0.0)	1 (0.1)
Grade 4	2 (0.1)	5 (0.3)
Ketoacidosis	1 (0.1)	0 (0.0)
Type 1 diabetes mellitus	0 (0.0)	2 (0.1)
Diabetes mellitus	0 (0.0)	1 (0.1)
Diabetic ketoacidosis	0 (0.0)	2 (0.1)

	Tislelizumab Monotherapy (N=1952) n (%)	**Tislelizumab Combination Therapy (N=1950) n (%)**
Latent autoimmune diabetes in adults	0 (0.0)	1 (0.1)
Patients with At Least One Serious Immune-Mediated ADR , n (%) (95% CI)	5 (0.3) (0.1, 0.6)	16 (0.8) (0.5, 1.3)
Type 1 diabetes mellitus	3 (0.2)	6 (0.3)
Ketoacidosis	1 (0.1)	0 (0.0)
Latent autoimmune diabetes in adults	1 (0.1)	1 (0.1)
Diabetes mellitus	0 (0.0)	5 (0.3)
Diabetic ketoacidosis	0 (0.0)	3 (0.2)
Diabetic ketosis	0 (0.0)	1 (0.1)
Serious Immune-Mediated ADR Event Outcome		
Recovered/resolved	1 (0.1)	4 (0.2)
Ketoacidosis	1 (0.1)	0 (0.0)
Diabetic ketoacidosis	0 (0.0)	2 (0.1)
Diabetic ketosis	0 (0.0)	2 (0.1)
Recovered/resolved with sequelae	0 (0.0)	2 (0.1)
Diabetes mellitus	0 (0.0)	1 (0.1)
Diabetic ketoacidosis	0 (0.0)	1 (0.1)
Recovering/resolving	1 (0.1)	5 (0.3)
Type 1 diabetes mellitus	1 (0.1)	3 (0.2)
Diabetes mellitus	0 (0.0)	2 (0.1)
Not recovered/not resolved	3 (0.2)	6 (0.3)
Type 1 diabetes mellitus	2 (0.1)	3 (0.2)
Latent autoimmune diabetes in adults	1 (0.1)	1 (0.1)
Diabetes mellitus	0 (0.0)	2 (0.1)
Patients With At Least One Immune-Mediated ADR Leading to Tislelizumab Discontinuation	3 (0.2)	1 (0.1)
Type 1 diabetes mellitus	2 (0.1)	1 (0.1)
Diabetes mellitus	1 (0.1)	0 (0.0)
Patients With At Least One Immune-Mediated ADR Leading to Treatment Modification of Tislelizumab	3 (0.2)	13 (0.7)
Ketoacidosis	1 (0.1)	0 (0.0)
Latent autoimmune diabetes in adults	1 (0.1)	0 (0.0)
Type 1 diabetes mellitus	1 (0.1)	6 (0.3)

	Tislelizumab Monotherapy (N=1952) n (%)	Tislelizumab Combination Therapy (N=1950) n (%)
Diabetes mellitus	0 (0.0)	4 (0.2)
Diabetic ketoacidosis	0 (0.0)	2 (0.1)
Diabetic ketosis	0 (0.0)	1 (0.1)
Immune-mediated myositis/rhabdomyolysis		
Patients in the Category, n (%) (95% CI)	16 (0.8) (0.5, 1.3)	13 (0.7) (0.4, 1.1)
Myositis	13 (0.7)	10 (0.5)
Immune-mediated myositis	3 (0.2)	1 (0.1)
Rhabdomyolysis	0 (0.0)	2 (0.1)
Worst Grade		
Grade 3	4 (0.2)	4 (0.2)
Immune-mediated myositis	2 (0.1)	1 (0.1)
Myositis	2 (0.1)	3 (0.2)
Grade 4	1 (0.1)	0 (0.0)
Myositis	1 (0.1)	0 (0.0)
Grade 5	0 (0.0)	1 (0.1)
Rhabdomyolysis	0 (0.0)	1 (0.1)
Patients with At Least One Serious Immune-Mediated ADR , n (%) (95% CI)	6 (0.3) (0.1, 0.7)	8 (0.4) (0.2, 0.8)
Myositis	4 (0.2)	5 (0.3)
Immune-mediated myositis	2 (0.1)	1 (0.1)
Rhabdomyolysis	0 (0.0)	2 (0.1)
Serious Immune-Mediated ADR Event Outcome		
Fatal	0 (0.0)	1 (0.1)
Rhabdomyolysis	0 (0.0)	1 (0.1)
Recovered/resolved	2 (0.1)	5 (0.3)
Immune-mediated myositis	1 (0.1)	1 (0.1)
Myositis	1 (0.1)	3 (0.2)
Rhabdomyolysis	0 (0.0)	1 (0.1)
Recovered/resolved with sequelae	0 (0.0)	1 (0.1)
Myositis	0 (0.0)	1 (0.1)
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)

	Tislelizumab Monotherapy (N=1952) n (%)	Tislelizumab Combination Therapy (N=1950) n (%)
Patients With At Least One Immune-Mediated ADR Leading to Tislelizumab Discontinuation	4 (0.2)	4 (0.2)
Immune-mediated myositis	2 (0.1)	0 (0.0)
Myositis	2 (0.1)	3 (0.2)
Rhabdomyolysis	0 (0.0)	1 (0.1)
Patients With At Least One Immune-Mediated ADR Leading to Treatment Modification of Tislelizumab	9 (0.5)	4 (0.2)
Myositis	7 (0.4)	4 (0.2)
Immune-mediated myositis	2 (0.1)	0 (0.0)
Immune-mediated myocarditis/pericarditis		
Patients in the Category, n (%) (95% CI)	15 (0.8) (0.4, 1.3)	23 (1.2) (0.7, 1.8)
Myocarditis	7 (0.4)	14 (0.7)
Immune-mediated myocarditis	4 (0.2)	7 (0.4)
Autoimmune myocarditis	2 (0.1)	1 (0.1)
Pericarditis	2 (0.1)	1 (0.1)
Worst Grade		
Grade 3	3 (0.2)	2 (0.1)
Immune-mediated myocarditis	3 (0.2)	0 (0.0)
Myocarditis	0 (0.0)	2 (0.1)
Grade 4	1 (0.1)	3 (0.2)
Myocarditis	1 (0.1)	0 (0.0)
Immune-mediated myocarditis	0 (0.0)	2 (0.1)
Pericarditis	0 (0.0)	1 (0.1)
Grade 5	0 (0.0)	4 (0.2)
Autoimmune myocarditis	0 (0.0)	1 (0.1)
Myocarditis	0 (0.0)	3 (0.2)
Patients with At Least One Serious Immune-Mediated ADR , n (%) (95% CI)	9 (0.5) (0.2, 0.9)	15 (0.8) (0.4, 1.3)
Myocarditis	4 (0.2)	7 (0.4)
Immune-mediated myocarditis	3 (0.2)	6 (0.3)
Autoimmune myocarditis	1 (0.1)	1 (0.1)
Pericarditis	1 (0.1)	1 (0.1)
Serious Immune-Mediated ADR Event Outcome		

	Tislelizumab Monotherapy (N=1952) n (%)	Tislelizumab Combination Therapy (N=1950) n (%)
Fatal	0 (0.0)	4 (0.2)
Autoimmune myocarditis	0 (0.0)	1 (0.1)
Myocarditis	0 (0.0)	3 (0.2)
Recovered/resolved	6 (0.3)	8 (0.4)
Immune-mediated myocarditis	2 (0.1)	4 (0.2)
Myocarditis	2 (0.1)	3 (0.2)
Autoimmune myocarditis	1 (0.1)	0 (0.0)
Pericarditis	1 (0.1)	1 (0.1)
Recovering/resolving	1 (0.1)	2 (0.1)
Myocarditis	1 (0.1)	1 (0.1)
Immune-mediated myocarditis	0 (0.0)	1 (0.1)
Not recovered/not resolved	2 (0.1)	1 (0.1)
Immune-mediated myocarditis	1 (0.1)	1 (0.1)
Myocarditis	1 (0.1)	0 (0.0)
Patients With At Least One Immune-Mediated ADR Leading to Tislelizumab Discontinuation	7 (0.4)	15 (0.8)
Myocarditis	4 (0.2)	8 (0.4)
Immune-mediated myocarditis	2 (0.1)	6 (0.3)
Autoimmune myocarditis	1 (0.1)	1 (0.1)
Patients With At Least One Immune-Mediated ADR Leading to Treatment Modification of Tislelizumab	8 (0.4)	5 (0.3)
Myocarditis	3 (0.2)	4 (0.2)
Autoimmune myocarditis	2 (0.1)	0 (0.0)
Pericarditis	2 (0.1)	0 (0.0)
Immune-mediated myocarditis	1 (0.1)	1 (0.1)
Other immune-mediated reactions (musculoskeletal)		
Patients in the Category, n (%) (95% CI)	15 (0.8) (0.4, 1.3)	13 (0.7) (0.4, 1.1)
Arthritis	12 (0.6)	10 (0.5)
Immune-mediated arthritis	3 (0.2)	3 (0.2)
Worst Grade		
Grade 3	2 (0.1)	4 (0.2)
Arthritis	2 (0.1)	2 (0.1)

	Tislelizumab Monotherapy (N=1952) n (%)	**Tislelizumab Combination Therapy (N=1950) n (%)**
Immune-mediated arthritis	0 (0.0)	2 (0.1)
Patients with At Least One Serious Immune-Mediated Adverse Reaction, n (%) (95% CI)	4 (0.2) (0.1, 0.5)	2 (0.1) (0.0, 0.4)
Arthritis	4 (0.2)	0 (0.0)
Immune-mediated arthritis	0 (0.0)	2 (0.1)
Serious Immune-Mediated ADR Event Outcome		
Recovered/resolved	1 (0.1)	2 (0.1)
Arthritis	1 (0.1)	0 (0.0)
Immune-mediated arthritis	0 (0.0)	2 (0.1)
Recovering/resolving	1 (0.1)	0 (0.0)
Arthritis	1 (0.1)	0 (0.0)
Not recovered/not resolved	2 (0.1)	1 (0.1)
Arthritis	2 (0.1)	0 (0.0)
Immune-mediated arthritis	0 (0.0)	1 (0.1)
Patients With At Least One Immune-Mediated ADR Leading to Tislelizumab Discontinuation	2 (0.1)	3 (0.2)
Arthritis	1 (0.1)	3 (0.2)
Immune-mediated arthritis	1 (0.1)	0 (0.0)
Patients With At Least One Immune-Mediated ADR Leading to Treatment Modification of Tislelizumab	2 (0.1)	8 (0.4)
Arthritis	1 (0.1)	5 (0.3)
Immune-mediated arthritis	1 (0.1)	3 (0.2)
Immune-mediated colitis		
Patients in the Category, n (%) (95% CI)	11 (0.6) (0.3, 1.0)	18 (0.9) (0.5, 1.5)
Colitis	5 (0.3)	10 (0.5)
Immune-mediated enterocolitis	3 (0.2)	7 (0.4)
Colitis ulcerative	2 (0.1)	1 (0.1)
Autoimmune colitis	1 (0.1)	0 (0.0)
Worst Grade		
Grade 3	4 (0.2)	8 (0.4)
Colitis	2 (0.1)	4 (0.2)
Colitis ulcerative	1 (0.1)	0 (0.0)
Immune-mediated enterocolitis	1 (0.1)	4 (0.2)

	Tislelizumab Monotherapy (N=1952) n (%)	**Tislelizumab Combination Therapy (N=1950) n (%)**
Grade 5	0 (0.0)	1 (0.1)
Colitis	0 (0.0)	1 (0.1)
Patients with At Least One Serious Immune-Mediated ADR , n (%) (95% CI)	6 (0.3) (0.1, 0.7)	13 (0.7) (0.4, 1.1)
Colitis	3 (0.2)	8 (0.4)
Immune-mediated enterocolitis	3 (0.2)	5 (0.3)
Serious Immune-Mediated ADR Event Outcome		
Fatal	0 (0.0)	1 (0.1)
Colitis	0 (0.0)	1 (0.1)
Recovered/resolved	2 (0.1)	10 (0.5)
Immune-mediated enterocolitis	2 (0.1)	3 (0.2)
Colitis	0 (0.0)	7 (0.4)
Recovered/resolved with sequelae	2 (0.1)	0 (0.0)
Colitis	2 (0.1)	0 (0.0)
Recovering/resolving	0 (0.0)	1 (0.1)
Immune-mediated enterocolitis	0 (0.0)	1 (0.1)
Not recovered/not resolved	2 (0.1)	1 (0.1)
Colitis	1 (0.1)	0 (0.0)
Immune-mediated enterocolitis	1 (0.1)	1 (0.1)
Patients With At Least One Immune-Mediated ADR Leading to Tislelizumab Discontinuation	2 (0.1)	7 (0.4)
Colitis ulcerative	1 (0.1)	0 (0.0)
Immune-mediated enterocolitis	1 (0.1)	4 (0.2)
Colitis	0 (0.0)	3 (0.2)
Patients With At Least One Immune-Mediated ADR Leading to Treatment Modification of Tislelizumab	8 (0.4)	8 (0.4)
Colitis	4 (0.2)	6 (0.3)
Colitis ulcerative	2 (0.1)	1 (0.1)
Autoimmune colitis	1 (0.1)	0 (0.0)
Immune-mediated enterocolitis	1 (0.1)	1 (0.1)
Immune-mediated endocrinopathies (adrenal insufficiency)		
Patients in the Category, n (%) (95% CI)	10 (0.5) (0.2, 0.9)	15 (0.8) (0.4, 1.3)

	Tislelizumab Monotherapy (N=1952) n (%)	Tislelizumab Combination Therapy (N=1950) n (%)
Adrenal insufficiency	5 (0.3)	15 (0.8)
Primary adrenal insufficiency	2 (0.1)	0 (0.0)
Addison's disease	1 (0.1)	0 (0.0)
Glucocorticoid deficiency	1 (0.1)	0 (0.0)
Immune-mediated adrenal insufficiency	1 (0.1)	0 (0.0)
Worst Grade		
Grade 3	4 (0.2)	8 (0.4)
Addison's disease	1 (0.1)	0 (0.0)
Adrenal insufficiency	1 (0.1)	8 (0.4)
Immune-mediated adrenal insufficiency	1 (0.1)	0 (0.0)
Primary adrenal insufficiency	1 (0.1)	0 (0.0)
Grade 4	1 (0.1)	0 (0.0)
Glucocorticoid deficiency	1 (0.1)	0 (0.0)
Patients with At Least One Serious Immune-Mediated ADR , n (%) (95% CI)	5 (0.3) (0.1, 0.6)	9 (0.5) (0.2, 0.9)
Addison's disease	1 (0.1)	0 (0.0)
Adrenal insufficiency	1 (0.1)	9 (0.5)
Glucocorticoid deficiency	1 (0.1)	0 (0.0)
Immune-mediated adrenal insufficiency	1 (0.1)	0 (0.0)
Primary adrenal insufficiency	1 (0.1)	0 (0.0)
Serious Immune-Mediated ADR Event Outcome		
Recovered/resolved	1 (0.1)	1 (0.1)
Glucocorticoid deficiency	1 (0.1)	0 (0.0)
Adrenal insufficiency	0 (0.0)	1 (0.1)
Recovered/resolved with sequelae	1 (0.1)	0 (0.0)
Immune-mediated adrenal insufficiency	1 (0.1)	0 (0.0)
Recovering/resolving	2 (0.1)	4 (0.2)
Adrenal insufficiency	1 (0.1)	4 (0.2)
Primary adrenal insufficiency	1 (0.1)	0 (0.0)
Not recovered/not resolved	1 (0.1)	4 (0.2)
Addison's disease	1 (0.1)	0 (0.0)
Adrenal insufficiency	0 (0.0)	4 (0.2)

	Tislelizumab Monotherapy (N=1952) n (%)	**Tislelizumab Combination Therapy (N=1950) n (%)**
Patients With At Least One Immune-Mediated ADR Leading to Tislelizumab Discontinuation	0 (0.0)	1 (0.1)
Adrenal insufficiency	0 (0.0)	1 (0.1)
Patients With At Least One Immune-Mediated ADR Leading to Treatment Modification of Tislelizumab	8 (0.4)	7 (0.4)
Adrenal insufficiency	4 (0.2)	7 (0.4)
Addison's disease	1 (0.1)	0 (0.0)
Glucocorticoid deficiency	1 (0.1)	0 (0.0)
Immune-mediated adrenal insufficiency	1 (0.1)	0 (0.0)
Primary adrenal insufficiency	1 (0.1)	0 (0.0)
Immune-mediated nephritis and renal dysfunction		
Patients in the Category, n (%) (95% CI)	4 (0.2) (0.1, 0.5)	8 (0.4) (0.2, 0.8)
Nephritis	2 (0.1)	3 (0.2)
Focal segmental glomerulosclerosis	1 (0.1)	0 (0.0)
Immune-mediated nephritis	1 (0.1)	1 (0.1)
Glomerulonephritis membranous	0 (0.0)	1 (0.1)
Immune-mediated renal disorder	0 (0.0)	1 (0.1)
Tubulointerstitial nephritis	0 (0.0)	2 (0.1)
Worst Grade		
Grade 3	1 (0.1)	4 (0.2)
Focal segmental glomerulosclerosis	1 (0.1)	0 (0.0)
Glomerulonephritis membranous	0 (0.0)	1 (0.1)
Immune-mediated renal disorder	0 (0.0)	1 (0.1)
Tubulointerstitial nephritis	0 (0.0)	2 (0.1)
Patients with At Least One Serious Immune-Mediated ADR, n (%) (95% CI)	1 (0.1) (0.0, 0.3)	5 (0.3) (0.1, 0.6)
Focal segmental glomerulosclerosis	1 (0.1)	0 (0.0)
Glomerulonephritis membranous	0 (0.0)	1 (0.1)
Immune-mediated renal disorder	0 (0.0)	1 (0.1)
Nephritis	0 (0.0)	1 (0.1)
Tubulointerstitial nephritis	0 (0.0)	2 (0.1)
Serious Immune-Mediated ADR Event Outcome		

	Tislelizumab Monotherapy (N=1952) n (%)	Tislelizumab Combination Therapy (N=1950) n (%)
Recovered/resolved	0 (0.0)	2 (0.1)
Nephritis	0 (0.0)	1 (0.1)
Tubulointerstitial nephritis	0 (0.0)	1 (0.1)
Recovering/resolving	1 (0.1)	1 (0.1)
Focal segmental glomerulosclerosis	1 (0.1)	0 (0.0)
Tubulointerstitial nephritis	0 (0.0)	1 (0.1)
Not recovered/not resolved	0 (0.0)	2 (0.1)
Glomerulonephritis membranous	0 (0.0)	1 (0.1)
Immune-mediated renal disorder	0 (0.0)	1 (0.1)
Patients With At Least One Immune-Mediated ADR Leading to Tislelizumab Discontinuation	1 (0.1)	2 (0.1)
Focal segmental glomerulosclerosis	1 (0.1)	0 (0.0)
Immune-mediated renal disorder	0 (0.0)	1 (0.1)
Tubulointerstitial nephritis	0 (0.0)	1 (0.1)
Patients With At Least One Immune-Mediated ADR Leading to Treatment Modification of Tislelizumab	2 (0.1)	4 (0.2)
Immune-mediated nephritis	1 (0.1)	0 (0.0)
Nephritis	1 (0.1)	2 (0.1)
Glomerulonephritis membranous	0 (0.0)	1 (0.1)
Tubulointerstitial nephritis	0 (0.0)	1 (0.1)
Other immune-mediated reactions (ocular)		
Patients in the Category, n (%) (95% CI)	2 (0.1) (0.0, 0.4)	2 (0.1) (0.0, 0.4)
Iritis	1 (0.1)	0 (0.0)
Uveitis	1 (0.1)	0 (0.0)
Chorioretinitis	0 (0.0)	1 (0.1)
Iridocyclitis	0 (0.0)	1 (0.1)
Worst Grade		
Grade 3	0 (0.0)	1 (0.1)
Chorioretinitis	0 (0.0)	1 (0.1)
Patients with At Least One Serious Immune-Mediated ADR, n (%) (95% CI)	0 (0.0)	0 (0.0)
Patients With At Least One Immune-Mediated ADR Leading to Tislelizumab Discontinuation	0 (0.0)	0 (0.0)

	Tislelizumab Monotherapy (N=1952) n (%)	**Tislelizumab Combination Therapy (N=1950) n (%)**
Patients With At Least One Immune-Mediated ADR Leading to Treatment Modification of Tislelizumab	1 (0.1)	1 (0.1)
Uveitis	1 (0.1)	0 (0.0)
Chorioretinitis	0 (0.0)	1 (0.1)
Immune-mediated endocrinopathies (hypophysitis)		
Patients in the Category, n (%) (95% CI)	5 (0.3) (0.1, 0.6)	11 (0.6) (0.3, 1.0)
Hypophysitis	2 (0.1)	2 (0.1)
Central hypothyroidism	1 (0.1)	1 (0.1)
Hypopituitarism	1 (0.1)	7 (0.4)
Secondary adrenocortical insufficiency	1 (0.1)	1 (0.1)
Worst Grade		
Grade 3	0 (0.0)	2 (0.1)
Hypopituitarism	0 (0.0)	1 (0.1)
Secondary adrenocortical insufficiency	0 (0.0)	1 (0.1)
Patients with At Least One Serious Immune-Mediated ADR , n (%) (95% CI)	0 (0.0)	2 (0.1) (0.0, 0.4)
Hypopituitarism	0 (0.0)	1 (0.1)
Secondary adrenocortical insufficiency	0 (0.0)	1 (0.1)
Serious Immune-Mediated ADR Event Outcome		
Recovered/resolved	0 (0.0)	2 (0.1)
Hypopituitarism	0 (0.0)	1 (0.1)
Secondary adrenocortical insufficiency	0 (0.0)	1 (0.1)
Patients With At Least One Immune-Mediated ADR Leading to Tislelizumab Discontinuation	0 (0.0)	1 (0.1)
Secondary adrenocortical insufficiency	0 (0.0)	1 (0.1)
Patients With At Least One Immune-Mediated ADR Leading to Treatment Modification of Tislelizumab	0 (0.0)	3 (0.2)
Hypopituitarism	0 (0.0)	2 (0.1)
Secondary adrenocortical insufficiency	0 (0.0)	1 (0.1)
Other immune-mediated reactions (pancreatitis)		
Patients in the Category, n (%) (95% CI)	5 (0.3) (0.1, 0.6)	8 (0.4) (0.2, 0.8)
Pancreatitis	3 (0.2)	6 (0.3)

	Tislelizumab Monotherapy (N=1952) n (%)	Tislelizumab Combination Therapy (N=1950) n (%)
Pancreatitis acute	2 (0.1)	2 (0.1)
Worst Grade		
Grade 3	5 (0.3)	2 (0.1)
Pancreatitis	3 (0.2)	1 (0.1)
Pancreatitis acute	2 (0.1)	1 (0.1)
Patients with At Least One Serious Immune-Mediated ADR, n (%) (95% CI)	4 (0.2) (0.1, 0.5)	2 (0.1) (0.0, 0.4)
Pancreatitis	2 (0.1)	1 (0.1)
Pancreatitis acute	2 (0.1)	1 (0.1)
Serious Immune-Mediated ADR Event Outcome		
Recovered/resolved	5 (0.3)	2 (0.1)
Pancreatitis acute	3 (0.2)	1 (0.1)
Pancreatitis	2 (0.1)	1 (0.1)
Patients With At Least One Immune-Mediated ADR Leading to Tislelizumab Discontinuation	0 (0.0)	0 (0.0)
Patients With At Least One Immune-Mediated ADR Leading to Treatment Modification of Tislelizumab	5 (0.3)	3 (0.2)
Pancreatitis	3 (0.2)	1 (0.1)
Pancreatitis acute	2 (0.1)	2 (0.1)
Other immune-mediated reactions (nervous system)		
Patients in the Category, n (%) (95% CI)	1 (0.1) (0.0, 0.3)	3 (0.2) (0.0, 0.4)
Guillain-Barre syndrome	1 (0.1)	1 (0.1)
Immune-mediated encephalitis	0 (0.0)	1 (0.1)
Myasthenia gravis	0 (0.0)	1 (0.1)
Worst Grade		
Grade 3	1 (0.1)	3 (0.2)
Guillain-Barre syndrome	1 (0.1)	1 (0.1)
Immune-mediated encephalitis	0 (0.0)	1 (0.1)
Myasthenia gravis	0 (0.0)	1 (0.1)
Patients with At Least One Serious Immune-Mediated ADR, n (%) (95% CI)	1 (0.1) (0.0, 0.3)	3 (0.2) (0.0, 0.4)
Guillain-Barre syndrome	1 (0.1)	1 (0.1)

	Tislelizumab Monotherapy (N=1952) n (%)	Tislelizumab Combination Therapy (N=1950) n (%)
Immune-mediated encephalitis	0 (0.0)	1 (0.1)
Myasthenia gravis	0 (0.0)	1 (0.1)
Serious Immune-Mediated ADR Event Outcome		
Recovered/resolved	1 (0.1)	2 (0.1)
Guillain-Barre syndrome	1 (0.1)	0 (0.0)
Immune-mediated encephalitis	0 (0.0)	1 (0.1)
Myasthenia gravis	0 (0.0)	1 (0.1)
Not recovered/not resolved	0 (0.0)	1 (0.1)
Guillain-Barre syndrome	0 (0.0)	1 (0.1)
Patients With At Least One Immune-Mediated ADR Leading to Tislelizumab Discontinuation	0 (0.0)	1 (0.1)
Immune-mediated encephalitis	0 (0.0)	1 (0.1)
Patients With At Least One Immune-Mediated ADR Leading to Treatment Modification of Tislelizumab	0 (0.0)	2 (0.1)
Guillain-Barre syndrome	0 (0.0)	1 (0.1)
Myasthenia gravis	0 (0.0)	1 (0.1)
Other immune-mediated reactions (blood dyscrasias)		
Patients in the Category, n (%) (95% CI)	0 (0.0)	1 (0.1) (0.0, 0.3)
Immune thrombocytopenia	0 (0.0)	1 (0.1)
Worst Grade		
Grade 3	0 (0.0)	1 (0.1)
Immune thrombocytopenia	0 (0.0)	1 (0.1)
Patients with At Least One Serious Immune-Mediated ADR , n (%) (95% CI)	0 (0.0)	1 (0.1) (0.0, 0.3)
Immune thrombocytopenia	0 (0.0)	1 (0.1)
Serious Immune-Mediated ADR Event Outcome		
Not recovered/not resolved	0 (0.0)	1 (0.1)
Immune thrombocytopenia	0 (0.0)	1 (0.1)
Patients With At Least One Immune-Mediated ADR Leading to Tislelizumab Discontinuation	0 (0.0)	1 (0.1)
Immune thrombocytopenia	0 (0.0)	1 (0.1)

	Tislelizumab Monotherapy (N=1952) n (%)	Tislelizumab Combination Therapy (N=1950) n (%)
Patients With At Least One Immune-Mediated ADR Leading to Treatment Modification of Tislelizumab	0 (0.0)	0 (0.0)

Abbreviations: ADR, adverse drug reaction; CI, confidence interval, n/N, number.
Patients with multiple events for a given Preferred Term and multiple Preferred Terms within a Category were counted once (at the worst grade if applicable) at the Preferred Term and Category levels, respectively.
Adverse events were classified based on MedDRA 26.1. Adverse events were graded for severity using CTCAE (v5.0 for studies 315, 209, 304, 305, 307, 309, and 312, v4.03 for studies 001, 102, 203, 204, 205, 206, 208, 301, 302, 303, and 306).
Two-sided 95% CI calculated using Clopper-Pearson method.
Immune-Mediated ADRs correspond to events qualified as ADR and reported as Immune-Mediated AE in at least one patient.
Dose modification for Tislelizumab includes dose interruption, dose delay, infusion rate decrease, and dose temporary discontinuation.

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, Type 1 Diabetes Mellitus, Hypophysitis)

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/Pericarditis

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 treatment-emergent adverse events of reproductive and developmental toxicity have been reported in monotherapy studies (Study 001, Study 102, Study 203, Study 204, Study 208, Study 209, Study 301, Study 302, and Study 303) and in combination therapy studies (Study 205, Study 206, Study 304, Study 305, Study 306, Study 307, Study 309, Study 312 and Study 315).

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:

There is no plan to use specific adverse reaction follow-up checklist for tislelizumab.

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 post-authorisation 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

Safety Concern	Routine Risk Minimisation Activities
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.

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. PL Section 2 and PL Section 4 where guidance on how to early identify signs and symptoms and seek medical attention is included. Additional Risk Minimisation Measures: Patient card Legal Status: Restricted medical prescription	Routine Pharmacovigilance Activities Beyond Adverse Reactions Reporting and Signal Detection: None Additional Pharmacovigilance Activities: None
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, in combination with platinum-containing chemotherapy as neoadjuvant treatment and then continued as monotherapy as adjuvant treatment, is indicated for the treatment of adult patients with resectable non-small cell lung cancer (NSCLC) at high risk of recurrence (for selection criteria, see section 5.1).

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 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 EGFR mutant or ALK positive NSCLC should also have received targeted therapies before receiving Tevimbra.

Tevimbra, in combination with etoposide and platinum chemotherapy is indicated for the first-line treatment of adult patients with extensive-stage small cell lung cancer.

Tevimbra, in combination with platinum and fluoropyrimidine-based chemotherapy, is indicated for the first-line treatment of adult patients with human epidermal growth factor receptor-2 (HER-2) negative locally advanced unresectable or metastatic gastric or gastroesophageal junction (G/GEJ) adenocarcinoma whose tumours express PD-L1 with a tumour area positivity (TAP) score ≥ 5%.

Tevimbra, in combination with platinum-based chemotherapy, is indicated for the first-line treatment of adult patients with unresectable, locally advanced or metastatic oesophageal squamous cell carcinoma (OSCC) whose tumours express PD-L1 with a TAP score ≥ 5%.

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

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

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/pericarditis, 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 ≥ 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

Important Identified Risk: Immune-Mediated Adverse Reactions	
	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. *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, Type 1 diabetes mellitus, hypophysitis)* 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. Hypophysitis is most commonly seen with anti-CTLA4 antibody monotherapy (ipilimumab, with an incidence of ≤ 10% at a dose of 3 mg/kg and up to 17% at 10 mg/kg), and with combination ipilimumab/nivolumab (incidence ≤ 13%). *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/Pericarditis* 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, pericarditis, 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

Important Identified Risk: Immune-Mediated Adverse Reactions	
	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. *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. Acute pancreatitis has been reported but is rare in cancer patients treated with ICIs; asymptomatic elevation of lipase and amylase are more common.
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 post-authorisation development plan for Tevimbra.

PART VII ANNEXES

LIST OF ANNEXES

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Not applicable.

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 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 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)

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