NOVARTIS

Patient Safety & Pharmacovigilance

Tislelizumab

VDT482A

EU Safety Risk Management Plan

Active substance(s) (INN or common name):	Tislelizumab
Product(s) concerned (brand name(s)):	Tevimbra
Document status:	Final
Version number:	1.0
Data lock point for this RMP	PBRER reporting period: 26-Dec-2021 to 25-Dec-2022 Clinical data-lock point of the last study contributing to the SCS: 01-Dec-2020
Date of final sign off	11-Jul-2023

Rationale for submitting an updated RMP:

This European Union (EU) Risk Management Plan (RMP) is prepared in response to the Committee for Medicinal Products for Human Use (CHMP) Day 195 List of Outstanding Issues (Procedure #: EMEA/H/C/5919 dated 05-Jul-2023).

Summary of significant changes in this RMP:

The key changes for this RMP version 1.0 update compared to RMP v 0.22 are provided below:

- Change in trade name to "Tevimbra"
- Patient/Caregiver Guide was removed and the key messages in Patient Card were updated in Annex 6

Part	Major changes in v 1.0 compared to RMP v 0.22
Part I	No change
Part II	
Module SI	No change
Module SII	No change
Module SIII	No change
Module SIV	No change
Module SV	No change
Module SVI	No change
Module SVII	Patient/Caregiver Guide was removed
Module SVIII	No change
Part III	No change
Part IV	No change
Part V	Patient/caregiver Guide was removed
Part VI	• Tradename was updated • Patient/caregiver Guide was removed
Part VII	
Annex Number	
Annex 1	No change
Annex 2	No change
Annex 3	No change
Annex 4	No change
Annex 5	No change
Annex 6	• The key messages in the Patient Card were updated • Patient/Caregiver Guide was removed • New texts were added for clarification
Annex 7	Redundant text was removed
Annex 8	No change

Other RMP versions under evaluation

CCI

Details of the currently approved RMP:

There is no currently approved EU RMP; therefore, this section is not applicable.

QPPV name: Dr. David Lewis

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

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ADR	Adverse drug reaction
AE	Adverse event
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
ASR	Age-standardized rate
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical classification system
CI	Confidence interval
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CPS	Combined Positive Score
CrCl	Creatinine clearance
CSS	Cancer-specific survival
CTCAE	Common Terminology Criteria for Adverse Event
CTLA4	Cytotoxic T-lymphocyte-associated protein 4
dCRT	Definitive chemoradiation
DLP	Data-lock point
dMMR	Deficient DNA mismatch repair
EAC	Esophageal adenocarcinoma
EC	Esophageal carcinoma
EEA	European Economic Area
eGFR	Estimated glomerular filtration rate
EGFR	Epidermal growth factor receptor
EM	Erythema multiforme
EMA	European Medicines Agency
ESCC	Esophageal squamous cell carcinoma
FDA	Food and Drug Administration
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCP	Healthcare professional
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
i.v.	Intravenous
ICD	Immune complex disease
ICI	Immune checkpoint inhibitor
Ig	Immunoglobulin
imAE	Immune-mediated adverse event
imAR	Immune-mediated adverse reaction
INN	International Non-proprietary Names
IR	Incidence rate

IRR	Infusion-related reaction
LoOI	List of Outstanding Issues
mAb	Monoclonal antibody
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MSI-H	Microsatellite instability-high
NCI	National Cancer Institute
NHP	Non-human primates
NSCLC	Non-small cell lung cancer
OS	Overall survival
PBRER	Periodic Benefit-Risk Evaluation Report
PD	Programmed cell death protein
PD-L	Programmed cell death ligand
PFS	Progression free survival
PK	Pharmacokinetics
PL	Patient leaflet
PSUR	Periodic Safety Update Report
PT	Preferred term
QPPV	Qualified Person for Pharmacovigilance
RMP	Risk Management Plan
RS	Relative survival
RT	Radiation therapy
SAE	Serious adverse event
SCAR	Severe cutaneous adverse reaction
SEER	Surveillance, Epidemiology, and End Results
SJS	Stevens-Johnson syndrome
SmPC	Summary of Product Characteristics
TEAE	Treatment-emergent adverse event
TEN	Toxic epidermal necrolysis
UK	United Kingdom
ULN	Upper limit of normal
US	United States of America

1 Part I: Product(s) Overview

Table 1-1 Part I.1 – Product(s) Overview

Active substance(s) (INN or common name)	Tislelizumab
Pharmacotherapeutic group(s) (ATC Code)	L01FF09
Marketing Authorization Applicant	Novartis Europharm Limited
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Tevimbra
Marketing authorization procedure	Centralized Procedure
Brief description of the product	**Chemical class:** Tislelizumab is a humanized immunoglobulin (Ig) 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 programmed cell death ligand (PD-L) -1 and PD-L2, thus inhibiting PD-1 mediated negative signaling and enhancing the functional activity in T-cells at the site of the tumor.
	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	[Proposed SmPC]
Indication(s) in the EEA	**Current:** Tevimbra, as monotherapy, is indicated for the treatment of adult patients with unresectable locally advanced or metastatic esophageal squamous cell carcinoma (ESCC) after prior platinum-based chemotherapy.
	Proposed (if applicable): Not applicable
Dosage in the EEA	**Current:** 200 mg administered as an intravenous (i.v.) infusion every 3 weeks.
	Proposed (if applicable): Not applicable
Pharmaceutical form(s) and strengths	**Current (if applicable):** 100 mg/10 mL (10 mg/mL) concentrate for solution for infusion
	Proposed (if applicable): Not applicable
Is/will the product be subject to additional monitoring in the EU?	Yes

2 Part II Safety specification Module SI: Epidemiology of the indication(s) and target population

2.1 Indication: Esophageal squamous cell carcinoma

Esophageal carcinoma (EC) was the seventh most common cancer worldwide in 2020, with an estimated 604000 new cases (3.1% of all cancers), and the sixth leading cause of all cancer deaths, with 544000 deaths (5.5% of all cancer mortality), based on the GLOBOCAN 2020 database (Sung et al 2021). Esophageal squamous cell carcinoma is the predominant type of EC accounting for approximately 87% of all EC cases globally (Uhlenhopp et al 2020). The geographic distribution of ESCC 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 esophageal cancers, and these trends are region specific. In the US, Europe, Australia, and many other Western countries, the incidence of ESCC had been decreasing for several decades, whereas the incidence of esophageal adenocarcinoma has increased. In Eastern Europe, Japan, and South America, ESCC still predominates. In most of Asia and Sub-Saharan Africa, ECs occur almost exclusively as ESCCs (Abnet et al 2018).

Incidence

In Europe, the age-adjusted incidence rate (IR) of EC as estimated from the GLOBOCAN database, was 3.3 per 100000 in 2020 (Ferlay et al 2020). In a recent publication also using the GLOBOCAN database, the age-adjusted IRs of ESCC per 100000 in 2018 by European region, were as follows: Eastern Europe 2.5, Western Europe 2.3, Northern Europe 1.8, Southern Europe 1.3 (Arnold et al 2020). Additionally, Rumgay et al (2021a) used the Cancer Incidence in Five Continents Plus (CI5Plus) database of population-based cancer registry data and multiple subnational cancer registries, to examine EC subtype incidence patterns in 27 countries. In European countries, for years 2003-2012, the age-standardized IR of ESCC ranged from 0.9 to 3.0 per 100000, the highest being within Eastern and Central Europe in Slovakia (3.0 per 100000) and the lowest within Northern Europe in Norway (0.9 per 100000). The proportion of ESCC cases of total EC in that European country ranged from 30% to 77% with the highest in Slovakia (77%), followed by Slovenia (70%) and the lowest, within the EU27, in The Netherlands (31%), followed by Norway (37%). Table 21 shows the ESCC cases, the proportion of total EC cases, and the ESCC age-adjusted IR per 100000 persons by population from 2003 to 2012 (Rumgay et al 2021b). Additionally, based on the analysis of data from Czech National Cancer Registry, Kroupa et al (2020) reported an age-adjusted IR of ESCC as 1.67 per 100000 from 2013 to 2017.

Table 2-1 Esophageal squamous cell carcinoma cases, proportion of total Esophageal carcinoma cases, Esophageal squamous cell carcinoma age-standardized incidence rate per 100000 by population from 2003 to 2012

Esophageal Squamous Cell carcinoma			
Population	**Cases**	**Proportion of total EC cases (%)**	**ASR per 100000**
North America			
Canada*	418	33%	0.9

Esophageal Squamous Cell carcinoma			
Population	**Cases**	**Proportion of total EC cases (%)**	**ASR per 100000**
US black*	100	65%	2.6
US white*	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*	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*	142	60%	1.4
Slovenia	61	70%	1.7
Spain*	273	63%	2.1
Western Europe			
Austria	178	45%	1.3
France (Metropolitan)*	284	65%	3.0
Germany*	117	47%	2.2
Switzerland*	78	57%	2.5
The Netherlands	558	31%	1.9

* 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

US=United States of America; UK=United Kingdom; ASR=Age-standardized rate

In the US, a recent, retrospective analyses of Surveillance, Epidemiology, and End Results (SEER) database for the period 2004-2015, identified 13919 ESCC cases with an age-adjusted IR of 1.9 per 100000 (Then et al 2020). In Canada, a nationwide population-based study conducted in 1992-2010 identified 9115 ESCC cases with a reported annual age-adjusted IR of 1.04 per 100000 (Cattelan et al 2020). This is slightly higher than the

age-adjusted IR of 0.9 per 100000 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 (CI5X) database estimated the age-adjusted IR per 100000 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 1988-2010, followed by India as 3.6 for 1983-2012, China as 3.0 for 1998-2012, Republic of Korea as 2.5 for 1998-2012 and Turkey as 1.1 for 1998-2012 (Rumgay et al 2021b).

Prevalence

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

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

Table 2-2 Esophageal carcinoma 5-year prevalence count and proportion per 10000 persons, worldwide, in Europe and in 4 European Regions

Region	Prevalence count (5-year duration)	Prevalence proportion (5-year duration per 10000 persons)
Worldwide	666388	0.85
Europe	70575	0.76
Central and Eastern Europe	18106	0.62
Northern Europe	3509	0.92
+ United Kingdom	15650	1.48
Southern Europe	7451	0.50
Western Europe	22854	1.17
EU27	37360	0.84

The worldwide 5-year prevalence proportion of EC was 0.85 per 10000. The EU-27 prevalence proportion was 0.84 per 10000 (Ferlay et al 2020). Prevalence was lowest in Southern Europe (0.50 per 10000) and Central/Eastern Europe (0.62 per 10000) while the highest was in Western Europe (1.17 per 10000) followed by Northern Europe (0.92 per 10000). These differences partially reflect differences in the underlying incidence of EC, 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 authorized indication – age, gender, racial and/or ethnic origin and risk factors for the disease

The mean age of ESCC was 66.3 ± 10 years based on SEER data of 13919 ESCC patients between 2004-2015 (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 1992-2010. In that study, the age-adjusted IR of ESCC increased with age: for age <30 years the incidence was 0.0 per 100000, increasing gradually until ages 60-69 (4.2 per 100000) and peaking at ages 70-79 (7.1 per 100000) (Cattelan et al 2020).

Globally, the IRs of ESCC are higher in men as compared to women. In 2012, the IR of ESCC was 7.7 per 100000 in men and 2.8 per 100000 in women. The global male to female ratio was reported as 2.7 per 100000 with substantial geographical variations; it was highest in Eastern Europe (7.8 per 100000) and lowest in Northern Africa and Western Asia (1.2 per 100000). The estimates were based on a study by Arnold et al (2015) analyzing data from Cancer Incidence in Five Continents Vol. X (CI5X) and GLOBOCAN 2012.

It has been reported that the frequency of ESCC varies substantially depending on race/ethnicity and geographical region. About 80% of the global ESCC cases (corresponding to 315000 cases) occurred in the Central and South-East Asian region. China alone contributed more than half of the global cases (53% or 210000 cases). The reported age-adjusted IR per 100000 was the highest in Eastern/South-East Asia at 13.6 per 100000 in men and 4.3 per 100000 in women, followed by sub-Saharan Africa and Central Asia. Using the same data source, Malhotra et al (2017) reported the highest ESCC age-adjusted IR per 100000 in Asia (9.6 in men and 4.4 in women) and the lowest age-adjusted IR per 100000 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 100000).

Regarding risk factors, smoking and alcohol consumption and particularly their synergistic effect, are well-established risk factors for ESCC. The adjusted odds ratio (OR) for current smokers and ever drinkers was reported as 2.2 (95% CI: 1.6-2.92); p value of interaction=0.003 (Yang et al 2017). Other risk factors include age (ESCC 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 ESCC among 16189 participants, reported that use of biomass fuel for cooking and or heating increased the risk of ESCC (pooled OR 3.02; 95% CI: 2.2-4.1) (Okello et al 2019).

The main existing treatment options

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

Second-line ESCC systemic therapy is recommended for patients with good performance status (0–1). Barbetta et al (2019) observed significantly worse survival among ESCC patients with recurrence within 6 months of chemoradiation followed by surgery. Patients relapsing after

platinum-based chemotherapy, during adjuvant/neo-adjuvant treatment, or within 6 months of dCRT are treated with single agent docetaxel, paclitaxel, or irinotecan (NCCN 2020). The treatment benefit from these agents is typically less than 6 months, with median OS of 5 to 7 months.

Table 23 outlines some of the references to the studies conducted for the second-line chemotherapy for ESCC.

Table 2-3 Second-line chemotherapy for Esophageal 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	ESCC (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	ESCC (n=35) EAC (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)	Multicenter, collaborative trial in US patients	ESCC (n=32) EAC (n=63)	80 mg/m^2 weekly	9.0[a]	3.1[a]
Docetaxel (Shirakawa et al 2014)	Retrospective in Japanese patients	ESCC (n=132)	70 mg/m^2 Q3W	5.5	2.3
Docetaxel (Mizota et al 2011)	Retrospective study in Japanese patients	ESCC (n=84) EAC (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	ESCC (n=41)	Not specified	5.2	3.2
Docetaxel (Albertsson et al 2007)	Prospective study in Scandinavian patients	ESCC (n=39) EAC (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	ESCC (n=7) EAC (n=7)	100 mg/m^2 weekly x 3 every 4 weeks	5[a]	2[a]

Abbreviations: EAC=Esophageal adenocarcinoma; ESCC=Esophageal squamous cell carcinoma; mo=Month; OS=Overall survival; PFS=Progression-free survival.

[a] Combined ESCC and EAC histology (and first- and second-line combined, Ilson et al 2007)

[b] Study I: complete response (CR), 5%; partial response (PR), 26%

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

More recently immune checkpoint inhibitors (ICI) targeting the PD-1/PD-L1 axis have further shaped the treatment landscape for patients with ESCC. Programmed cell death protein-1 inhibitors have demonstrated survival improvement over chemotherapy in advanced or metastatic ESCC patients with disease progression after prior systemic therapies (Kojima et al 2019, Kato et al 2019). Pembrolizumab was approved by Food and Drug Administration (FDA) in Jul-2019 for the treatment of recurrent, locally advanced or metastatic ESCC but only in patients whose tumors express PD-L1 (Combined Positive Score [CPS] ≥10) as determined by an FDA-approved test with disease progression after 1 or more prior lines of systemic therapy. Nivolumab was approved by European Medicines Agency (EMA) and FDA, in Nov-2020 and Jun-2020, respectively, for the treatment of patients with unresectable advanced, recurrent, or metastatic ESCC after prior fluoropyrimidine- and platinum-based chemotherapy regardless of PD-L1 level. Nivolumab was approved by EMA and FDA in Jul-2021 and May-2021, respectively, for adjuvant treatment of completely resected esophageal or gastroesophageal junction cancer with residual pathologic disease in patients who have received neoadjuvant chemoradiotherapy.

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

Esophageal squamous cell carcinoma is characterized 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: 33.3-34.6) and the 5-year RS was reported at 10.1% (95% CI: 9.7-10.6), based on a study that utilized cancer survival data for patients diagnosed in 1995-1999 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 13919 patients with ESCC, 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 esophagus, tumor grade 3 and tumor Stage IV and lack of surgery treatment, based on SEER data during 2004-2015 (Then et al 2020). Another recent US study based on SEER data identified 6890 ESCC patients from 2007-2015. 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 ESCC patients ≥80 years, 5-year OS did not differ by sex (Li et al 2021).

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

Table 2-4 outlines details on OS and RS across calendar periods:

Table 2-4 Overall and relative 1-year and 5-year survivals

	Overall survival in % (95% CI)		Relative survival in % (95% CI)	
Calendar period	**1-year**	**5-year**	**1-year**	**5-year**
1990-1994	19 (16-22)	2 (1-3)	20 (17-23)	3 (1-4)
1995-1999	19 (17-22)	4 (2-5)	21 (18-24)	5 (3-6)
2000-2004	25 (22-28)	3 (2-5)	26 (23-29)	4 (2-5)
2005-2009	23 (20-26)	4 (3-6)	24 (21-27)	5 (3-7)
2010-2013	24 (20-27)	5 (3-7)	25 (21-29)	6 (4-8)

Source: Adapted from Kauppila et al (2018)

Important co-morbidities

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

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

3 Part II Safety specification Module SII: Non-clinical part of the safety specification

Table 3-1 Key safety findings from non-clinical studies and relevance to human usage:

Key Safety findings (from non-clinical studies)	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 following i.v. infusion at doses of 3, 10, or 30 mg/kg once every 2 weeks (7 dose administrations) for 13 weeks. At 60 mg/kg, there were treatment-related changes observed consistent with immunogenicity (anti-drug-antibodies) against tislelizumab and immune complex disease (ICD).	The risk of acute toxicities in patients is considered minimal. Immunogenicity-related changes in preclinical species are not predictive for humans.
Reproductive and developmental toxicity No apparent treatment-related histopathological changes in tissues or organs, including male and female reproductive system, 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 embryofetal toxicity demonstrated that the pharmacologically mediated blockade of PD-1/PD-L1 interaction in animal models can result in fetal loss (Guleria et al 2005). This is due to disrupting immune tolerance to a fetus as there is a role played by the PD-1/PD-L1 pathway in the maintenance of tolerance to the fetus (Tripathi and Guleria 2015). The PD-1 binding to the abundantly expressed PD-L1 in tumors is analogous to the PD-1 binding to a highly-expressed PD-L1 at the utero-placental 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 fetus. Women of child-bearing 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 (ICH guideline S6 (R1) - preclinical safety evaluation of biotechnology-derived pharmaceuticals, 2011).	Not applicable.

Key Safety findings (from non-clinical studies)	Relevance to human usage
Carcinogenicity Carcinogenicity studies have not been conducted with tislelizumab since they are not warranted to support marketing for therapeutics intended to treat patients with advanced cancer (ICH guideline S9 nonclinical evaluation for anticancer pharmaceuticals, 2010).	Not applicable.
Cardiovascular, nervous and respiratory systems No specific concerns were identified on vital functions, including cardiovascular system, central nervous system (CNS), or respiratory system.	Based on nonclinical data, a direct impact on the functions of the cardiovascular, respiratory, and CNS is not expected.
Mechanisms for drug interactions No studies were conducted in line with ICH guideline S6 (R1) - preclinical safety evaluation of biotechnology-derived pharmaceuticals, 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 metabolizing 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.

4 Part II Safety specification Module SIII: Clinical trial exposure

4.1 Part II Module SIII Clinical trial exposure

Tislelizumab was studied in 1 indication as mentioned below:

Tislelizumab, as monotherapy, is indicated for the treatment of adult patients (≥18 years of age) with unresectable recurrent locally advanced or metastatic ESCC after prior systemic therapy.

The safety analysis of patients receiving tislelizumab is based primarily on the pivotal study, BGB-A317-302 (Study 302), which compared tislelizumab with chemotherapy in patients with ESCC. Safety data from the use of tislelizumab in patients with ESCC in other clinical trials and safety data from clinical trials evaluating tislelizumab in multiple tumor types are provided as supportive information.

Pivotal Study 302 population

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

All Doses All Indications Population

The All Dose All Indication population included patients from clinical studies in which patients received tislelizumab monotherapy. 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, including ESCC.

This integrated safety population included 1972 patients with different tumor types who received ≥1 dose of tislelizumab monotherapy. The pivotal Study 302 and the 6 supportive studies included in this analysis are summarized in Table 4-1.

Table 4-1 Details of tislelizumab monotherapy studies

Study number (Disease type; region)	Data cut-off dates	Tislelizumab dose	Total number of patients who received tislelizumab as monotherapy (N=1972)
Pivotal study			
BGB-A317-302 (Advanced unresectable or metastatic ESCC, with disease progression during or after 1L systemic therapy; Global)	01-Dec-2020	200 mg Q3W	255

Study number (Disease type; region)	Data cut-off dates	Tislelizumab dose	Total number of patients who received tislelizumab as monotherapy (N=1972)
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).			
Supporting studies			
BGB-A317_Study_001 (Advanced tumors; 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 antiPD1 mAb, tislelizumab in patients with advanced tumors (hereafter referred to as Study 001)	26-Aug-2020	0.5, 2, 5 or 10 mg/kg Q2W; 2 or 5 mg/kg Q3W; 200 mg Q3W	451
BGB-A317-102 (Advanced solid tumors; China) A Phase I/II study investigating safety, tolerability, PK and preliminary anti-tumor 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, the Q3W	300
BGB-A317-203 (Relapsed or refractory classical Hodgkin lymphoma; China) A single arm, multicenter, Phase II study of tislelizumab as monotherapy in relapsed or refractory classical Hodgkin lymphoma (hereafter referred to as Study 203).	26-Nov-2018	200 mg Q3W	70
BGB-A317-204 (PD-L1+ locally advanced or metastatic urothelial cancer; China and South Korea) A single-arm, multicenter, Phase II study of tislelizumab in patients with previously treated PD-L1+ locally advanced or metastatic urothelial cancer (hereafter referred to as Study 204).	16-Sep-2019	200 mg Q3W	113
BGB-A317-208 (Previously treated hepatocellular unresectable carcinoma; Global) A Phase II, open-label, multicenter study to investigate the efficacy, safety, and PK of the anti-PD-1 mAb, tislelizumab in patients with previously treated hepatocellular unresectable carcinoma (hereafter referred to as Study 208).	27-Feb-2020	200 mg Q3W	249

Study number (Disease type; region)	Data cut-off dates	Tislelizumab dose	Total number of patients who received tislelizumab as monotherapy (N=1972)
BGB-A317-303 (Non−small cell lung cancer 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-PD1 antibody) compared with docetaxel in patients with NSCLC who have progressed on a prior platinum-containing regimen (hereafter referred to as Study 303).	10-Aug-2020	200 mg Q3W	534

Exposure to tislelizumab in clinical trials is summarized in Table 4-2 through Table 4-5 by duration of exposure, by age group and gender, by dose and by race including ethnic origin.

Table 4-2 Duration of Tislelizumab Exposure (for ESCC Indication) All Tislelizumab Treated Population

Indication Duration of Tislelizumab Exposure	Persons n (%)	Person Time
ESCC		
<1 month	38 (12.4)	24.18
1 - <3 months	138 (45.0)	286.78
3 - <6 months	56 (18.2)	245.36
6 - <12 months	42 (13.7)	358.31
12 - <18 months	14 (4.6)	203.10
18 - <24 months	14 (4.6)	290.50
>24 months	5 (1.6)	139.40
Total	307 (100.0)	1547.63

Source data: Annex 7-Table 1.1

Person Time is sum of treatment duration (months) for all patients in the row.

The statistical outputs for tislelizumab were generated to support 2 indications – Non-small cell lung cancer (NSCLC) and ESCC. Hence, the footnote of all exposure tables in Annex 7 refers to data from both monotherapy studies (302, 001, 102, 203, 204, 208, 303) and combination therapy studies (BGB-A317-206 [Study 206], BGB-A317-304 [Study 304], BGB-A317-307 [Study 307]). However, as detailed in Part II Module SII Clinical trial exposure, the data for ESCC population is derived from monotherapy studies (302, 001, 102, 203, 204, 208, 303) only.

Table 4-3 Exposure of Tislelizumab by Age Group and Gender (for ESCC Indication)
All Tislelizumab Treated Population

Indication Age Group	Persons n (%)		Person Time	
	Male	Female	Male	Female
ESCC				
>=18 and <55 years	58 (18.9)	13 (4.2)	213.42	59.04
>=55 and <65 years	110 (35.8)	12 (3.9)	616.48	27.76
>=65 and <75 years	76 (24.8)	22 (7.2)	450.27	118.28
>=75 years	12 (3.9)	4 (1.3)	47.28	15.11
Total	**256 (83.4)**	**51 (16.6)**	**1327.44**	**220.19**

Source data: Annex 7-Table 1.5

Person Time is sum of treatment duration (months) for all patients in the row.

Percentages are based on the number of patients who received at least a dose of Tislelizumab.

The statistical outputs for tislelizumab were generated to support 2 indications – NSCLC and ESCC. Hence, the footnote of all exposure tables in Annex 7 refers to data from both monotherapy and combination therapy studies. However, as detailed in Part II Module SII Clinical trial exposure, the data for ESCC population is derived from monotherapy studies (302, 001, 102, 203, 204, 208, 303) only.

Table 4-4 Exposure of Tislelizumab by Dose (for ESCC Indication)
All Tislelizumab Treated Population

Indication Dose Level of Exposure	Persons n (%)	Person Time
ESCC		
200 mg Q3W	281 (91.5)	1417.20
5.0 mg/kg Q3W	26 (8.5)	130.43
2.0 mg/kg Q3W	0 (0.0)	
10.0 mg/kg Q2W	0 (0.0)	
5.0 mg/kg Q2W	0 (0.0)	
2.0 mg/kg Q2W	0 (0.0)	
0.5 mg/kg Q2W	0 (0.0)	
Total	**307 (100.0)**	**1547.63**

Source data: Annex 7-Table 1.3

Person Time is sum of treatment duration (months) for all patients in the row.

Percentages are based on the number of patients who received at least a dose of Tislelizumab.

The statistical outputs for tislelizumab were generated to support 2 indications – NSCLC and ESCC. Hence, the footnote of all exposure tables in Annex 7 refers to data from both monotherapy and combination therapy studies. However, as detailed in Part II Module SII Clinical trial exposure, the data for ESCC population is derived from monotherapy studies (302, 001, 102, 203, 204, 208, 303) only.

Table 4-5 Exposure of Tislelizumab by Race (for ESCC Indication) All Tislelizumab Treated Population

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

Source data: Annex 7- Table 1.9

Person Time is sum of treatment duration (months) for all patients in the row.

Percentages are based on the number of patients who received at least a dose of Tislelizumab.

Annex 7-Table 1.8 provides the information regarding Ethnic origin (Hispanic or Latino [0.5%], Not Hispanic or Latino [93.5%], Not reported [6.0%], for any of the indications).

The statistical outputs for tislelizumab were generated to support 2 indications – NSCLC and ESCC. Hence, the footnote of all exposure tables in Annex 7 refers to data from both monotherapy and combination therapy studies. However, as detailed in Part II Module SII Clinical trial exposure, the data for ESCC population is derived from monotherapy studies (302, 001, 102, 203, 204, 208, 303) only.

5 Part II Safety specification Module SIV: Populations not studied in clinical trials

5.1 Part II Module SIV.1 Exclusion criteria in pivotal clinical studies within the development program

Table 5-1 Important exclusion criteria in pivotal studies in the development program

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale for not including as missing information
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.	By disrupting PD-1-mediated signaling, tislelizumab acts to restore anti-tumor immunity and halt progression of tumor growth. This restoration of immune function may result in immune-mediated adverse reactions (imARs) 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.	No	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 trials. Additionally, the treating physician would be expected to evaluate the benefit and risks in individual patients and follow patients closely for any evidence of 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 characterization.
Prior active malignancy within 2 to 3 years, or active leptomeningeal disease or uncontrolled and untreated brain metastases[a].	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.	No	These patients were excluded from the trials and there is no expectation that the safety profile would be different. However, the treating physician would be expected to evaluate the benefit 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.	Immunosuppressive medications may attenuate the effects of anti-PD-1 treatment. Such conditions may impact the	No	Prior to starting tislelizumab, corticosteroids and other immunosuppressants should be avoided because of their potential interference with the pharmacodynamic activity of

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale for not including as missing information
	interpretation of study results.		tislelizumab. For the same reason, these patients were excluded in the clinical trials. However, systemic corticosteroids and other immunosuppressants can be used after starting tislelizumab to treat imARs, in the post-marketing setting.
History of interstitial lung disease, noninfectious pneumonitis or uncontrolled systemic diseases, including diabetes, hypertension, pulmonary fibrosis, acute lung diseases.	Such conditions may impact the interpretation of study results.	No	These patients may benefit from treatment with tislelizumab; however, such conditions and associated therapies may confound efficacy and safety assessment of the trial and were therefore excluded. The treating physician would be expected to evaluate the benefit and risks in individual patients.
History of severe hypersensitivity reactions to monoclonal antibodies.	To reduce the risk of a patient experiencing hypersensitivity to tislelizumab.	No	Hypersensitivity to tislelizumab is listed as a contraindication in the EU Summary of Product Characteristics (SmPC).
Prior therapy targeting PD-1 or PD-L1.	Prior therapy targeting PD-1 or PD-L1 may impact the interpretation of study results.	No	The target population is intended to be naïve to treatment with anti-PD-1/PD-L1 therapy.
Use of live or attenuated vaccines within 4 weeks.	Use of live or attenuated vaccines within 4 weeks may impact the interpretation of study results.	No	Live vaccines are not recommended for patients who are receiving immune-oncology therapies (Cancer Research UK 2019). Accordingly, patients who received live vaccines within 4 weeks from the start of treatment were excluded from clinical studies for tislelizumab.
Prior chemotherapy, radiation therapy (RT), immunotherapy within ≤28 days (or ≤5 half-lives, whichever is shorter.	Carryover of the effect from prior chemotherapy, RT, immunotherapy within 2 weeks may impact the interpretation of study results.	No	These patients may benefit from treatment with tislelizumab; however, to avoid carryover effect, patients were required to wait 2 weeks after discontinuation of prior therapy before enrolling in the study. There is no expectation that the tislelizumab safety profile would be different. However, in the post-marketing setting the treating physician would be expected to evaluate the benefit and risks in individual patients.
Prior allogeneic or solid organ transplantation.	Prior allogeneic or solid organ transplantation may impact the interpretation of study results.	No	The treating physician would be expected to evaluate the benefit and risks in individual patients and follow patients closely for evidence

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale for not including as missing information
	Treatment with PD-1 blocking antibodies may increase the risk of rejection in solid organ transplant recipients and increase the risk of post-allogeneic haematopoietic stem cell transplantation complications.		of transplant-related complications and intervene promptly (SmPC).
Clinically important cardiovascular impairment[b].	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.	No	As discussed in Table 3-1, no apparent effects on cardiovascular function were identified in nonclinical studies.
Severe hepatic impairment[c].	Severe hepatic impairment may impact the interpretation of study results.	No	Tislelizumab is a mAb and unlikely to be metabolized by the liver. As such, formal pharmacokinetic interaction studies have not been conducted and are not warranted.
Severe renal impairment[d].	Severe renal impairment may impact the interpretation of study results.	No	Tislelizumab is a mAb and unlikely to be metabolized by the kidneys. As such, formal pharmacokinetic interaction studies have not been conducted and are not warranted.
Severe chronic or active infections requiring systemic therapy.	Infection may impact the interpretation of study results.	No	There is no evidence that tislelizumab worsens bacterial infections. These patients may benefit from treatment. The treating physician would be expected to evaluate the benefit and risks in individual patients.
Untreated chronic hepatitis B (HBV) or chronic HBV carriers with HBV DNA ≥200 to 500 IU/mL (1000 to 2500 copies/mL), or active hepatitis C[e] (HCV), or human immunodeficiency virus (HIV) infection.	Infection may impact the interpretation of study results.	No	Patients with HCV and HBV have been included in clinical trials 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 benefit and risks in individual patients.
Patients aged <18 years.	Pediatric patients were not included in the clinical development program.	No	Use in pediatric patients is not recommended and is also not expected considering the

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale for not including as missing information
			indications' incidence/prevalence in this age group.
Use during pregnancy or lactation.	The blockade of the PD-1/PD-L1 pathway in inducing fetal 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 child-bearing potential should be advised to avoid pregnancy and breastfeed while taking tislelizumab.	No	There is no available human data regarding the risk of embryofetal toxicity. Women of child-bearing 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.	Such conditions may impact the interpretation of study results.	No	General exclusion criterion to ensure patient safety in clinical studies and is not associated with specific safety concerns for tislelizumab. These patients may benefit from treatment with tislelizumab in the post-marketing setting. The treating physician would be expected to evaluate the benefit and risks in individual patients.
Major surgery within 28 days[e].	To ensure patient safety. Major surgery within 4 weeks of entering the study may impact the interpretation of study results.	No	These patients may benefit from treatment with tislelizumab; however, major surgery may confound efficacy and safety assessment of the trial. In the post-marketing setting, it is expected that the treating physician will evaluate when the individual patient has recovered enough from major surgery to receive new anti-cancer therapy.

[a] In studies 302, 303, 304, 307, 309, patients with a history of treated and, at the time of screening, asymptomatic CNS metastases were eligible, provided they met the specified criteria in the protocol.

[b] For example, heart failure of New York Heart Association cardiac disease Class III or greater, myocardial infarction, unstable arrhythmias or unstable angina.

[c] For example, serum total bilirubin ≥1.5 × 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 × ULN, or AST and ALT ≥5 × ULN for patients with liver metastases or HCC.

[d] For example, estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 by Chronic Kidney Disease Epidemiology Collaboration Equation (Levey et al 2009, Stevens and Levin 2013).

[e] Active Hepatitis C and major surgery within 28 days were exclusion criteria for non-HCC indications only.

5.2 Part II Module SIV.2. Limitations to detect adverse reactions in clinical trial development programs

The clinical development program 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.

5.3 Part II Module SIV.3. Limitations in respect to populations typically underrepresented in clinical trial development programs

Table 5-2 Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Pregnant women	Not included in the clinical development program.
Breast-feeding women	Not included in the clinical development program.
Patients with relevant comorbidities:	
Patients with renal impairment[b]	Renal impairment was reported in 1053/2469 (42.6%) patients (8709.16 person time[a]) who received tislelizumab as monotherapy in Study 001, Study 102, Study 203, Study 204, Study 208, Study 302 and Study 303 and as combination therapy from Study 206, Study 304 and Study 307. Normal renal function was reported in 1416 (57.4%) patients (10581.09 person time) (Annex 7-Table 2.1). Based on a population PK analysis, no dose adjustment of tislelizumab is recommended for patients with mild to moderate renal impairment (creatinine clearance [CrCl] ≥30 mL/min). Specific PK studies in patients with renal impairment are not warranted.
Patients with hepatic impairment[c]	Hepatic impairment was reported in 411 (16.6%) patients (2303.06 person time) who received tislelizumab as monotherapy in Study 001, Study 102, Study 203, Study 204, Study 208, Study 302 and Study 303 and as combination therapy from Study 206, Study 304 and Study 307. Normal hepatic function was reported in 2052 (83.1%) patients (16949.67 person time). In 6 (0.2%) patients, information on hepatic impairment were missing (Annex 7-Table 2.1). Based on a population PK analysis, no dose adjustment of tislelizumab is recommended for patients with mild to moderate hepatic impairment (total bilirubin ≤3 times ULN and any AST). Specific PK studies in patients with renal impairment are not warranted.
Patients with cardiovascular impairment[d]	Not included in the clinical development program.
Immunocompromised patients	Not included in the clinical development program.
Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program.
Population with relevant different ethnic origin	Clinical trial exposure data on race including ethnicity is presented in Table 4-5.

Type of special population	Exposure
Subpopulations carrying relevant genetic polymorphisms	Patients with known epidermal growth factor (EGFR) sensitizing 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.

[a] Person time is sum of treatment duration (months).

[b] Defined as eGFR 60 to 89 mL/min/1.73 m^2, mild; eGFR 30 to 59 mL/min/1.73 m^2, moderate; and eGFR 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).

[c] Defined as AST >ULN; serum total bilirubin >1 to 1.5×ULN, mild; serum total bilirubin >1.5 to 3×ULN, moderate; and serum total bilirubin >3×ULN, severe.

[d] For example, heart failure of New York Heart Association cardiac disease Class III or greater, myocardial infarction, unstable arrhythmias or unstable angina.

Table 5-3 Exposure of Tislelizumab by Special Population - All Tislelizumab Treated Population

	Persons n (%)	Person Time
Renal impairment status at baseline		
Normal	1416 (57.4)	10581.09
Impairment	1053 (42.6)	8709.16
Hepatic impairment status at baseline		
Normal	2052 (83.1)	16949.67
Impairment	411 (16.6)	2303.06
Missing	6 (0.2)	37.52

Source data: Annex 7-Table 2.1

Person Time is sum of treatment duration (months) for all patients in the row.

	Persons n (%)	Person Time
Percentages are based on the number of patients who received at least a dose of Tislelizumab.		
The hepatic impairment status at baseline was determined by the baseline total bilirubin and AST value according to the criterion below. Patients with missing baseline total bilirubin or AST (if any) would be considered and reported as “Missing” for hepatic impairment status.		
Total bilirubin: Normal ≤ULN; Mild (Scenario 1): ≤ULN, Mild (Scenario 2): >1 to 1.5xULN; Moderate: >1.5 to 3xULN; Severe: >3xULN.		
Aspartate aminotransferase: Normal ≤ULN; Mild Scenario 1: >ULN, Mild Scenario 2: Any; Moderate: Any; Severe: Any		
The renal impairment status at baseline was determined by the estimated GFR (ml/min) according to the criterion below. The estimated GFR was calculated using the CKD-EPI equation with serum creatinine at baseline, sex, race and age at baseline for patients in the Tislelizumab Monotherapy Safety Analysis Set and the Cockcroft-Gault equation with serum creatinine, age and weight at baseline for patients in the Tislelizumab Combination Therapy Safety Analysis Set. Patients with missing serum creatinine at baseline (if any) would be considered and reported as “Missing” for renal impairment status.		
Renal Impairment status (eGFR [mL/min or mL/min/1.73m^2]):		
Normal: ≥90; Mild impairment: 60 to <90; Moderate impairment: 30 to <60; Severe impairment: 15 to <30; End state: <15.		
The statistical outputs for tislelizumab were generated to support 2 indications – NSCLC and ESCC. Hence, the footnote of all exposure tables in Annex 7 refers to data from both monotherapy and combination therapy studies. However, as detailed in Part II Module SII Clinical trial exposure, the data for ESCC population is derived from only monotherapy studies (302, 001, 102, 203, 204, 208, 303).		

6 Part II Safety specification Module SV: Post-authorization experience

Tislelizumab was first authorized in China on 26-Dec-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-Apr-2020), first-line, unresectable, locally advanced or metastatic squamous NSCLC (12-Jan-2021), first-line unresectable, locally advanced or metastatic non-squamous NSCLC (22-Jun-2021), HCC that has been previously treated with at least one systemic therapy (22-Jun-2021), locally advanced or metastatic NSCLC that has progressed after or did not tolerate prior platinum-based chemotherapy (31-Dec-2021), advanced unresectable or metastatic MSI-H or dMMR solid tumors (08-Mar-2022), first-line locally advanced or metastatic ESCC (08-Apr-2022), and first-line recurrent or metastatic nasopharyngeal cancer (07-Jun-2022).

6.1 Part II Module SV.1. Post-authorization exposure

As of Periodic Benefit-Risk Evaluation Report (PBRER) DLP (25-Dec-2022), CCI

6.1.1 Part II Module SV.1.1 Method used to calculate exposure

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

The number of doses supplied is defined as mg CCI The Patient-years of exposure is defined as doses supplied/17.3.

6.1.2 Part II Module SV.1.2. Exposure

Table 6-1 Cumulative exposure from marketing experience

Channel		Sales and sample volume data (China)	Estimated number of infusions (China)
Ex-factory sales units (vials)	Total units sold to distributors	CCI	CCI
Samples (vials)	Total units delivered to charities in China	CCI	CCI
Total		CCI	CCI
PBRER DLP: 25-Dec-2022			

7 Part II Safety specification Module SVI: Additional EU requirements for the safety specification

7.1 Potential for misuse for illegal purposes

Commonly misused classes of prescription drugs include opioid pain relievers, stimulants, and CNS depressants (sedatives and tranquilizers). 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 recognized misuse potential and is not deemed to have misuse potential.

8 Part II Safety specification Module SVII: Identified and potential risks

8.1 Part II Module SVII.1. Identification of safety concerns in the initial RMP submission

8.1.1 Part II Module SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Table 8-1 Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Risks	Justification
Risks with minimal clinical impact on patients (in relation to the severity of the indication treated)	
None	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	None
Known risks that require no further characterization and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimization messages in the product information are adhered to by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorized)	
• Infusion-related reaction	Infusion-related reactions (IRR) 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. Infusion-related reaction 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. Adverse events related to IRR led to treatment discontinuation for 5 (0.3%) patients and dose interruption for 18 (0.9%) patients (Annex 7-Table 3.1.2.1, Table 3.2.2.1, Table 3.3.2.1).
Known risks that do not impact the risk-benefit profile	
None	None
Other reasons for considering the risks not important	
Hypersensitivity events (by immunogenicity) in anti-drug antibody (ADA) positive patients	There was no evidence of relevant hypersensitivity reactions known to be triggered by patients' ADA positivity.

8.1.2 Part II Module SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Table 8-2 Important identified risks

Important identified risk	Risk-benefit impact (Reasons for classification as 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. **Immune-mediated pneumonitis** Immune-mediated pneumonitis, including fatal cases, has been observed in patients receiving tislelizumab. ***Data from monotherapy studies*:*** 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 1 (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%) of patients and dose modification in 29 (1.5%) of patients. **Immune-mediated hepatitis** Immune-mediated hepatitis has been reported in patients receiving tislelizumab, including fatal cases. ***Data from monotherapy studies*:*** 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 dose modification in 21 patients (1.1%). **Immune-mediated skin adverse reaction** Immune-mediated skin adverse reactions have been observed in patients receiving tislelizumab. ***Data from monotherapy studies*:*** 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 (0.2%), recovering/resolving for 1 (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%) of patients.

Important identified risk	Risk-benefit impact (Reasons for classification as important identified risk)
	Immune-mediated colitis Immune-mediated colitis, which may present as diarrhea, has been observed in patients receiving tislelizumab. ***Data from monotherapy studies*:*** 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%) of patients and dose modification in 12 patients (0.6%). **Immune-mediated myositis/rhabdomyolysis** Immune-mediated myositis/rhabdomyolysis has been reported in patients receiving tislelizumab. ***Data from monotherapy studies*:*** 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%). **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*:*** 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. Adverse event of hypothyroidism led to dose modification in 6 (0.3%) of patients. ***Hyperthyroidism*** ***Data from monotherapy studies*:*** 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 the discontinuation and dose modification was reported in 1 patient (0.1%). ***Thyroiditis*** ***Data from monotherapy studies*:*** 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%). ***Adrenal insufficiency*** ***Data from monotherapy studies*:*** 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%) of patients. ***Pituitary dysfunction*** ***Data from monotherapy studies*:*** Pituitary dysfunction was reported for 1 (0.1%) of the 1972 patients who received tislelizumab as monotherapy. In these

Important identified risk	Risk-benefit impact (Reasons for classification as important identified risk)
	studies, there were no serious events of pituitary dysfunction. ***<u>Type 1 Diabetes mellitus</u>*** ***Data from monotherapy studies*:*** **I**mmune-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 (0.1%), recovering/resolving for 2 patients (0.1%) and not recovered/not resolved in 4 (0.2% of patients. Immune-mediated type 1 diabetes mellitus led to dose discontinuation in 3 (0.2%) and dose modification in 2 (0.1%) of patients. **Immune-mediated nephritis and renal dysfunction** Immune-mediated nephritis and renal dysfunction has been observed in patients receiving tislelizumab including fatal case. ***Data from monotherapy studies*:*** 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%) of patients. **Immune-mediated myocarditis** Immune-mediated myocarditis has been reported in patients receiving tislelizumab. ***Data from monotherapy studies*:*** 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%) and dose modification in 3 (0.2%) of patients. **Immune-mediated nervous system disorders** Immune-mediated nervous system disorders have been reported in patients receiving tislelizumab. ***Data from monotherapy studies*:*** No AEs related to immune-mediated nervous disorders were reported. **Immune-mediated pancreatitis** Immune-mediated pancreatitis has been reported in patients receiving tislelizumab ***Data from monotherapy studies*:*** 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%). **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.

Important identified risk	Risk-benefit impact (Reasons for classification as important identified risk)
	Data from monotherapy studies*: Other immune-mediated reactions (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 (0.1%) and dose modification in 2 patients (0.1%) were reported By disrupting PD1-mediated signaling, tislelizumab acts to restore anti-tumor immunity and halt progression of tumor growth. This restoration of immune system activity may result in imARs 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 Table 8-6.
* Monotherapy studies include Study 001, Study 102, Study 203, Study 204, Study 208, Study 302 and Study 303	

Table 8-3 Important potential risks

Important potential risk	Risk-benefit impact (Reasons for classification as important potential risks)
Reproductive and developmental toxicity	No events of reproductive and development toxicity were reported from the monotherapy studies*. Based on the mechanism of action, the administration of tislelizumab during pregnancy could cause harm to the fetus (SmPC). Pregnant women should be advised of the potential risk to the fetus. Women of child-bearing 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 Table 8-7.
* Monotherapy studies include Study 302, Study 001, Study 102, Study 203, Study 204, Study 208 and Study 303	

Table 8-4 Missing information

Missing information	Risk-benefit impact (Reasons for classification as missing information)
None	None

8.2 Part II Module SVII.2: New safety concerns and reclassification with a submission of an updated RMP

There is no currently approved EU RMP and therefore there are no new safety concerns and/or reclassification.

8.3 Part II Module SVII.3: Details of important identified risks, important potential risks, and missing information

8.3.1 Part II Module SVII.3.1. Presentation of important identified risks and important potential risks

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

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

8.3.1.1 Important Identified Risk: Immune-mediated adverse reactions

The clinical trial data including incidence, severity and nature of risk, SAEs, and outcome of SAEs are summarized in Table 8-5. Other important details including potential mechanisms, evidence sources, characterization of the risk, risk factors and risk groups, preventability, impact on the benefic-risk balance of the product and public health impact are summarized in Table 8-6.

Table 8-5 Clinical trial data of Immune-mediated adverse reactions

Immune-mediated pneumonitis

Immune-mediated pneumonitis	**Monotherapy Total (N = 1972) n (%) (95% CI)[a]**
Incidence	
Patients with at least one AE	77 (3.9) (3.1, 4.9)
Pneumonitis	44 (2.2)
Immune-mediated pneumonitis	13 (0.7)
Interstitial lung disease	12 (0.6)
Pneumonia	6 (0.3)
Organising pneumonia	2 (0.1)
Severity and Nature of risk	
Patients with worst grade 3 AE	29 (1.5)
Pneumonitis	17 (0.9)

Immune-mediated pneumonitis	Monotherapy Total (N = 1972) n (%) (95% CI)[a]
Interstitial lung disease	6 (0.3)
Immune-mediated pneumonitis	3 (0.2)
Organising pneumonia	2 (0.1)
Pneumonia	1 (0.1)
Patients with worst grade 4 AE	5 (0.3)
Immune-mediated pneumonitis	2 (0.1)
Interstitial lung disease	2 (0.1)
Pneumonitis	1 (0.1)
Patients with worst grade 5 AE	4 (0.2)
Pneumonitis	2 (0.1)
Pneumonia	2 (0.1)
Patients with at least one AE leading to discontinuation of Tislelizumab	36 (1.8)
Pneumonitis	21 (1.1)
Immune-mediated pneumonitis	7 (0.4)
Interstitial lung disease	6 (0.3)
Organising pneumonia	1 (0.1)
Pneumonia	1 (0.1)
Patients with at least one immune-mediated AE leading to dose modification of Tislelizumab	29 (1.5)
Pneumonitis	16 (0.8)
Pneumonia	2 (0.1)
Immune-mediated pneumonitis	5 (0.3)
Interstitial lung disease	5 (0.3)
Organising pneumonia	1 (0.1)
Patients with at least one SAE	55 (2.8) (2.1, 3.6)
Pneumonitis	28 (1.4)
Immune-mediated pneumonitis	11 (0.6)
Interstitial lung disease	9 (0.5)
Pneumonia	5 (0.3)
Organising pneumonia	2 (0.1)
Outcome (of SAEs)	
Death	4 (0.2)
Pneumonitis	2 (0.1)
Pneumonia	2 (0.1)
Recovered/resolved	25 (1.3)
Pneumonitis	12 (0.6)
Immune-mediated pneumonitis	6 (0.3)
Pneumonia	3 (0.2)
Interstitial lung disease	3 (0.2)
Organising pneumonia	1 (0.1)
Recovered/resolved with sequelae	1 (0.1)
Organising pneumonia	1 (0.1)

Immune-mediated pneumonitis	Monotherapy Total (N = 1972) n (%) (95% CI)[a]
Recovering/resolving	12 (0.6)
Pneumonitis	5 (0.3)
Interstitial lung disease	4 (0.2)
Immune-mediated pneumonitis	3 (0.2)
Not recovered/not resolved	14 (0.7)
Pneumonitis	9 (0.5)
Immune-mediated pneumonitis	2 (0.1)
Interstitial lung disease	2 (0.1)
Pneumonia	1 (0.1)

Source data: Annex 7-Table 3.1.1.1, Table 3.2.1.1, Table 3.3.1.1, Table 2.7.4.2.2.6.1.

Studies include monotherapy studies (001, 102, 203, 204, 208, 302, 303) only.

Immune-mediated adverse events were firstly sorted by descending frequency of category, and then sorted by PTs within the category by descending frequency.

Treatment-emergent adverse event leading to the dose modification is defined as a TEAE with action taken 'Dose delay', 'Dose delayed', 'Drug interrupted', 'Dose interrupted', 'Dose held/interrupted' or 'Infusion rate decrease' by investigator.

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

Adverse events were coded using the MedDRA Version 23.0.

Adverse event grades were evaluated based on NCI-CTCAE (version 4.03).

Immune-mediated hepatitis

Immune-mediated hepatitis	Monotherapy Total (N = 1972) n (%) (95% CI)[a]
Incidence	
Patients with at least one AE	36 (1.8) (1.3, 2.5)
Alanine aminotransferase increased	12 (0.6)
Aspartate aminotransferase increased	9 (0.5)
Hepatitis	8 (0.4)
Immune-mediated hepatitis	6 (0.3)
Blood bilirubin increased	2 (0.1)
Hepatic failure	2 (0.1)
Hepatocellular injury	2 (0.1)
Liver injury	2 (0.1)
Autoimmune hepatitis	1 (0.1)
Bilirubin conjugated increased	1 (0.1)
Drug-induced liver injury	1 (0.1)
Gamma-glutamyltransferase increased	1 (0.1)
Transaminases increased	1 (0.1)

Immune-mediated hepatitis	Monotherapy Total (N = 1972) n (%) (95% CI)[a]
Severity and Nature of risk	
Patients with worst grade 3 AE	20 (1.0)
Alanine aminotransferase increased	5 (0.3)
Aspartate aminotransferase increased	5 (0.3)
Hepatitis	5 (0.3)
Hepatocellular injury	2 (0.1)
Immune-mediated hepatitis	2 (0.1)
Liver injury	2 (0.1)
Drug-induced liver injury	1 (0.1)
Gamma-glutamyltransferase increased	1 (0.1)
Transaminases increased	1 (0.1)
Patients with worst grade 4 AE	1 (0.1)
Immune-mediated hepatitis	1 (0.1)
Patients with worst grade 5 AE	2 (0.1)
Hepatic failure	2 (0.1)
Patients with at least one AE leading to discontinuation of Tislelizumab	9 (0.5)
Alanine aminotransferase increased	2 (0.1)
Aspartate aminotransferase increased	2 (0.1)
Hepatitis	2 (0.1)
Drug-induced liver injury	1 (0.1)
Hepatic failure	1 (0.1)
Hepatocellular injury	1 (0.1)
Liver injury	1 (0.1)
Transaminases increased	1 (0.1)
Patients with at least one immune-mediated AE leading to dose modification of Tislelizumab	21 (1.1)
Alanine aminotransferase increased	9 (0.5)
Aspartate aminotransferase increased	6 (0.3)
Immune-mediated hepatitis	4 (0.2)
Autoimmune hepatitis	1 (0.1)
Blood bilirubin increased	1 (0.1)
Hepatitis	4 (0.2)
Hepatocellular injury	2 (0.1)
Transaminases increased	1 (0.1)
Patients with at least one SAE	12 (0.6) (0.3, 1.1)
Hepatitis	3 (0.2)
Alanine aminotransferase increased	2 (0.1)
Aspartate aminotransferase increased	2 (0.1)
Hepatic failure	2 (0.1)
Immune-mediated hepatitis	2 (0.1)
Drug-induced liver injury	1 (0.1)
Liver injury	1 (0.1)

Immune-mediated hepatitis	Monotherapy Total (N = 1972) n (%) (95% CI)[a]
Transaminases increased	1 (0.1)
Outcome (for SAEs)	
Death	2 (0.1)
Hepatic failure	2 (0.1)
Recovered/resolved	7 (0.4)
Hepatitis	3 (0.2)
Alanine aminotransferase increased	2 (0.1)
Aspartate aminotransferase increased	2 (0.1)
Drug-induced liver injury	1 (0.1)
Immune-mediated hepatitis	1 (0.1)
Recovering/resolving	2 (0.1)
Liver injury	1 (0.1)
Transaminases increased	1 (0.1)
Not recovered/not resolved	1 (0.1)
Immune-mediated hepatitis	1 (0.1)

Source data: Annex 7-Table 3.1.1.1, Table 3.2.1.1, Table 3.3.1.1, Table 2.7.4.2.2.6.1.

Studies include monotherapy studies (001, 102, 203, 204, 208, 302, 303) only.

Immune-mediated adverse events were firstly sorted by descending frequency of category, and then sorted by PTs within the category by descending frequency.

Treatment-emergent adverse event leading to the dose modification is defined as a TEAE with action taken 'Dose delay', 'Dose delayed', 'Drug interrupted', 'Dose interrupted', 'Dose held/interrupted' or 'Infusion rate decrease' by investigator.

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

Adverse events were coded using the MedDRA Version 23.0.

Adverse event grades were evaluated based on NCI-CTCAE (version 4.03).

Immune-mediated skin adverse reaction

Immune-mediated skin adverse reaction	Monotherapy Total (N = 1972) n (%) (95% CI)[a]
Incidence	
Patients with at least one AE	32 (1.6) (1.1, 2.3)
Rash	15 (0.8)
Drug eruption	5 (0.3)
Pruritus	4 (0.2)
Rash maculo-papular	2 (0.1)
Acute febrile neutrophilic dermatosis	1 (0.1)
Dermatitis	1 (0.1)
Dermatitis allergic	1 (0.1)
Erythema multiforme	1 (0.1)
Rash macular	1 (0.1)
Rash papular	1 (0.1)

Immune-mediated skin adverse reaction	Monotherapy Total (N = 1972) n (%) (95% CI)[a]
Rash pruritic	1 (0.1)
Vitiligo	1 (0.1)
Severity and Nature of risk	
Patients with worst grade 3 AE	8 (0.4)
Rash	3 (0.2)
Rash maculo-papular	2 (0.1)
Dermatitis	1 (0.1)
Drug eruption	1 (0.1)
Rash macular	1 (0.1)
Rash papular	1 (0.1)
Patients with worst grade 4 AE	4 (0.2)
Drug eruption	3 (0.2)
Rash	1 (0.1)
Patients with worst grade 5 AE	0 (0.0)
Patients with at least one AE leading to discontinuation of Tislelizumab	5 (0.3)
Drug eruption	4 (0.2)
Rash	1 (0.1)
Patients with at least one immune-mediated AE leading to dose modification of Tislelizumab	11 (0.6)
Acute febrile neutrophilic dermatosis	1 (0.1)
Dermatitis	1 (0.1)
Dermatitis allergic	1 (0.1)
Drug eruption	1 (0.1)
Pruritus	1 (0.1)
Rash	4 (0.2)
Rash macular	1 (0.1)
Rash maculo-papular	2 (0.1)
Patients with at least one SAE	6 (0.3) (0.1, 0.7)
Drug eruption	4 (0.2)
Dermatitis	1 (0.1)
Dermatitis allergic	1 (0.1)
Outcome (for SAEs)	
Death	0 (0.0)
Recovered/resolved	4 (0.2)
Drug eruption	2 (0.1)
Dermatitis	1 (0.1)
Dermatitis allergic	1 (0.1)
Recovering/resolving	1 (0.1)
Drug eruption	1 (0.1)
Not recovered/not resolved	1 (0.1)
Drug eruption	1 (0.1)

Immune-mediated skin adverse reaction	Monotherapy Total (N = 1972) n (%) (95% CI)[a]

Source data: Annex 7-Table 3.1.1.1, Table 3.2.1.1, Table 3.3.1.1, Table 2.7.4.2.2.6.1.

Studies include monotherapy studies (001, 102, 203, 204, 208, 302, 303) only.

Immune-mediated adverse events were firstly sorted by descending frequency of category, and then sorted by PTs within the category by descending frequency.

Treatment-emergent adverse event leading to the dose modification is defined as a TEAE with action taken 'Dose delay', 'Dose delayed', 'Drug interrupted', 'Dose interrupted', 'Dose held/interrupted' or 'Infusion rate decrease' by investigator.

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

Adverse events were coded using the MedDRA Version 23.0.

Adverse event grades were evaluated based on NCI-CTCAE (version 4.03).

Immune-mediated colitis

Immune-mediated colitis	Monotherapy Total (N = 1972) n (%) (95% CI)[a]
Incidence	
Patients with at least one AE	19 (1.0) (0.6, 1.5)
Diarrhoea	9 (0.5)
Colitis	8 (0.4)
Immune-mediated enterocolitis	2 (0.1)
Colitis ulcerative	1 (0.1)
Rectal haemorrhage	1 (0.1)
Severity and Nature of risk	
Patients with worst grade 3 AE	7 (0.4)
Diarrhoea	4 (0.2)
Colitis	3 (0.2)
Immune-mediated enterocolitis	1 (0.1)
Patients with worst grade 4 AE	0 (0.0)
Patients with worst grade 5 AE	0 (0.0)
Patients with at least one AE leading to discontinuation of Tislelizumab	3 (0.2)
Colitis	2 (0.1)
Immune-mediated enterocolitis	1 (0.1)
Patients with at least one immune-mediated AE leading to dose modification of Tislelizumab	12 (0.6)
Colitis	3 (0.2)
Diarrhoea	6 (0.3)
Colitis ulcerative	1 (0.1)
Immune-mediated enterocolitis	2 (0.1)
Patients with at least one SAE	11 (0.6) (0.3, 1.0)
Colitis	6 (0.3)
Diarrhoea	4 (0.2)
Immune-mediated enterocolitis	1 (0.1)

Immune-mediated colitis	Monotherapy Total (N = 1972) n (%) (95% CI)[a]
Outcome (for SAEs)	
Death	0 (0.0)
Recovered/resolved	8 (0.4)
Colitis	4 (0.2)
Diarrhoea	4 (0.2)
Recovered/resolved with sequelae	2 (0.1)
Colitis	2 (0.1)
Not recovered/not resolved	1 (0.1)
Immune-mediated enterocolitis	1 (0.1)

Source data: Annex 7-Table 3.1.1.1, Table 3.2.1.1, Table 3.3.1.1, Table 2.7.4.2.2.6.1.

Studies include monotherapy studies (001, 102, 203, 204, 208, 302, 303) only.

Immune-mediated adverse events were firstly sorted by descending frequency of category, and then sorted by PTs within the category by descending frequency.

Treatment-emergent adverse event leading to the dose modification is defined as a TEAE with action taken 'Dose delay', 'Dose delayed', 'Drug interrupted', 'Dose interrupted', 'Dose held/interrupted' or 'Infusion rate decrease' by investigator.

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

Adverse events were coded using the MedDRA Version 23.0.

Adverse event grades were evaluated based on NCI-CTCAE (version 4.03).

Immune-mediated myositis/rhabdomyolysis

Immune-mediated myositis/Rhabdomyolysis	Monotherapy Total (N = 1972) n (%) (95% CI)[a]
Incidence	
Patients with at least one AE	14 (0.7) (0.4, 1.2)
Blood creatine phosphokinase increased	7 (0.4)
Myositis	5 (0.3)
Immune-mediated myositis	3 (0.2)
Severity and Nature of risk	
Patients with worst grade 3 AE	5 (0.3)
Blood creatine phosphokinase increased	2 (0.1)
Immune-mediated myositis	2 (0.1)
Myositis	2 (0.1)
Patients with worst grade 4 AE	1 (0.1)
Blood creatine phosphokinase increased	1 (0.1)
Patients with worst grade 5 AE	0 (0.0)
Patients with at least one AE leading to discontinuation of Tislelizumab	3 (0.2)
Immune-mediated myositis	2 (0.1)
Myositis	1 (0.1)

Immune-mediated myositis/Rhabdomyolysis	Monotherapy Total (N = 1972) n (%) (95% CI)[a]
Patients with at least one immune-mediated AE leading to dose modification of Tislelizumab	10 (0.5)
Immune-mediated myositis	2 (0.1)
Blood creatine phosphokinase increased	5 (0.3)
Myositis	3 (0.2)
Patients with at least one SAE	7 (0.4) (0.1, 0.7)
Myositis	4 (0.2)
Immune-mediated myositis	2 (0.1)
Blood creatine phosphokinase increased	1 (0.1)
Outcome (for SAEs)	
Death	0 (0.0)
Recovered/resolved	3 (0.2)
Blood creatine phosphokinase increased	1 (0.1)
Immune-mediated myositis	1 (0.1)
Myositis	1 (0.1)
Not recovered/not resolved	4 (0.2)
Myositis	3 (0.2)
Immune-mediated myositis	1 (0.1)

Source data: Annex 7-Table 3.1.1.1, Table 3.2.1.1, Table 3.3.1.1, Table 2.7.4.2.2.6.1.

Studies include monotherapy studies (001, 102, 203, 204, 208, 302, 303) only.

Immune-mediated adverse events were firstly sorted by descending frequency of category, and then sorted by PTs within the category by descending frequency.

Treatment-emergent adverse event leading to the dose modification is defined as a TEAE with action taken 'Dose delay', 'Dose delayed', 'Drug interrupted', 'Dose interrupted', 'Dose held/interrupted' or 'Infusion rate decrease' by investigator.

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

Adverse events were coded using the MedDRA Version 23.0.

Adverse event grades were evaluated based on NCI-CTCAE (version 4.03).

Immune-mediated endocrinopathies (Hypothyroidism, Hyperthyroidism, Thyroiditis, Adrenal insufficiency, Pituitary dysfunction, Type 1 Diabetes mellitus)

Immune-mediated endocrinopathies (adrenal insufficiency, thyroiditis, hyperthyroidism, hypothyroidism, pituitary dysfunction, type 1 diabetes mellitus)	Monotherapy Total (N = 1972) n (%) (95% CI)[a]
Immune-mediated adrenal insufficiency	
Incidence	
Patients with at least one AE	6 (0.3) (0.1, 0.7)
Adrenal insufficiency	6 (0.3)
Severity and Nature of risk	
Patients with worst grade 3 AE	1 (0.1)
Adrenal insufficiency	1 (0.1)

Immune-mediated endocrinopathies (adrenal insufficiency, thyroiditis, hyperthyroidism, hypothyroidism, pituitary dysfunction, type 1 diabetes mellitus)	Monotherapy Total (N = 1972) n (%) (95% CI)[a]
Patients with worst grade 4 AE	1 (0.1)
Adrenal insufficiency	1 (0.1)
Patients with worst grade 5 AE	0 (0.0)
Patients with at least one AE leading to discontinuation of Tislelizumab	0 (0.0)
Patients with at least one immune-mediated AE leading to dose modification of Tislelizumab	5 (0.3)
Adrenal insufficiency	5 (0.3)
Patients with at least one SAE	2 (0.1) (0.0, 0.4)
Adrenal insufficiency	2 (0.1)
Outcome (for SAEs)	
Death	0 (0.0)
Recovered/resolved	1 (0.1)
Adrenal insufficiency	1 (0.1)
Recovering/resolving	1 (0.1)
Adrenal insufficiency	1 (0.1)
Immune-mediated thyroiditis	
Incidence	
Patients with at least one AE	13 (0.7) (0.4, 1.1)
Thyroiditis	6 (0.3)
Autoimmune thyroiditis	5 (0.3)
Thyroiditis subacute	1 (0.1)
Thyroid function test abnormal	1 (0.1)
Severity and Nature of risk	
Patients with worst grade 3 AE	0 (0.0)
Patients with worst grade 4 AE	0 (0.0)
Patients with worst grade 5 AE	0 (0.0)
Patients with at least one AE leading to discontinuation of Tislelizumab	0 (0.0)
Patients with at least one immune-mediated AE leading to dose modification of Tislelizumab	2 (0.1)
Thyroiditis	1 (0.1)
Thyroiditis subacute	1 (0.1)
Patients with at least one SAE	0 (0.0)
Outcome (for SAEs)	
Death	0 (0.0)
Recovered/resolved	0 (0.0)
Immune-mediated hyperthyroidism	
Incidence	
Patients with at least one AE	12 (0.6) (0.3, 1.1)
Hyperthyroidism	12 (0.6)
Severity and Nature of risk	
Patients with worst grade 3 AE	1 (0.1)
Hyperthyroidism	1 (0.1)

Immune-mediated endocrinopathies (adrenal insufficiency, thyroiditis, hyperthyroidism, hypothyroidism, pituitary dysfunction, type 1 diabetes mellitus)	Monotherapy Total (N = 1972) n (%) (95% CI)[a]
Patients with worst grade 4 AE	0 (0.0)
Patients with worst grade 5 AE	0 (0.0)
Patients with at least one AE leading to discontinuation of Tislelizumab	1 (0.1)
Hyperthyroidism	1 (0.1)
Patients with at least one immune-mediated AE leading to dose modification of Tislelizumab	1 (0.1)
Hyperthyroidism	1 (0.1)
Patients with at least one SAE	0 (0.0)
Outcome (for SAEs)	
Death	0 (0.0)
Recovered/resolved	0 (0.0)
Immune-mediated hypothyroidism	
Incidence	
Patients with at least one AE	133 (6.7) (5.7, 7.9)
Hypothyroidism	131 (6.6)
Tri-iodothyronine free decreased	2 (0.1)
Tri-iodothyronine decreased	1 (0.1)
Primary hypothyroidism	1 (0.1)
Thyroxine free decreased	1 (0.1)
Severity and Nature of risk	
Patients with worst grade 3 AE	0 (0.0)
Patients with worst grade 4 AE	1 (0.1)
Hypothyroidism	1 (0.1)
Patients with worst grade 5 AE	0 (0.0)
Patients with at least one AE leading to discontinuation of Tislelizumab	0 (0.0)
Patients with at least one immune-mediated AE leading to dose modification of Tislelizumab	6 (0.3)
Hypothyroidism	6 (0.3)
Patients with at least one SAE	1 (0.1) (0.0, 0.3)
Hypothyroidism	1 (0.1)
Outcome (for SAEs)	
Death	0 (0.0)
Recovered/resolved	1 (0.1)
Hypothyroidism	1 (0.1)
Immune-Mediated Type 1 Diabetes Mellitus	
Incidence	
Patients with at least one AE	8 (0.4) (0.2, 0.8)
Type 1 diabetes mellitus	5 (0.3)
Hyperglycaemia	3 (0.2)
Diabetic ketoacidosis	2 (0.1)
Latent autoimmune diabetes in adults	1 (0.1)

Immune-mediated endocrinopathies (adrenal insufficiency, thyroiditis, hyperthyroidism, hypothyroidism, pituitary dysfunction, type 1 diabetes mellitus)	Monotherapy Total (N = 1972) n (%) (95% CI)[a]
Severity and Nature of risk	
Patients with worst grade 3 AE	6 (0.3)
Type 1 diabetes mellitus	4 (0.2)
Hyperglycaemia	2 (0.1)
Diabetic ketoacidosis	1 (0.1)
Latent autoimmune diabetes in adults	1 (0.1)
Patients with worst grade 4 AE	1 (0.1)
Diabetic ketoacidosis	1 (0.1)
Type 1 diabetes mellitus	1 (0.1)
Patients with worst grade 5 AE	0 (0.0)
Patients with at least one AE leading to discontinuation of Tislelizumab	3 (0.2)
Diabetic ketoacidosis	1 (0.1)
Hyperglycaemia	1 (0.1)
Type 1 diabetes mellitus	1 (0.1)
Patients with at least one immune-mediated AE leading to dose modification of Tislelizumab	2 (0.1)
Type 1 diabetes mellitus	1 (0.1)
Hyperglycaemia	1 (0.1)
Latent autoimmune diabetes in adults	1 (0.1)
Patients with at least one SAE	6 (0.3) (0.1, 0.7)
Type 1 diabetes mellitus	4 (0.2)
Diabetic ketoacidosis	2 (0.1)
Hyperglycaemia	2 (0.1)
Latent autoimmune diabetes in adults	1 (0.1)
Outcome (for SAEs)	
Death	0 (0.0)
Recovered/resolved	2 (0.1)
Diabetic ketoacidosis	1 (0.1)
Hyperglycaemia	1 (0.1)
Recovered/resolved with sequelae	1 (0.1)
Diabetic ketoacidosis	1 (0.1)
Recovering/resolving	2 (0.1)
Hyperglycaemia	1 (0.1)
Type 1 diabetes mellitus	1 (0.1)
Not recovered/not resolved	4 (0.2)
Type 1 diabetes mellitus	3 (0.2)
Latent autoimmune diabetes in adults	1 (0.1)
Immune-Mediated Pituitary dysfunction	
Incidence	
Patients with at least one AE	1 (0.1) (0.0, 0.3)
Hypopituitarism	1 (0.1)

Immune-mediated endocrinopathies (adrenal insufficiency, thyroiditis, hyperthyroidism, hypothyroidism, pituitary dysfunction, type 1 diabetes mellitus)	Monotherapy Total (N = 1972) n (%) (95% CI)[a]
Severity and Nature of risk	0 (0.0)
Patients with worst grade 3 AE	0 (0.0)
Patients with worst grade 4 AE	0 (0.0)
Patients with worst grade 5 AE	0 (0.0)
Patients with at least one AE leading to discontinuation of Tislelizumab	0 (0.0)
Patients with at least one SAE	0 (0.0)
Outcome (for SAEs)	
Death	0 (0.0)
Recovered/resolved	0 (0.0)

Source data: Annex 7-Table 3.1.1.1, Table 3.2.1.1, Table 3.3.1.1, Table 2.7.4.2.2.6.1.

Studies include monotherapy studies (001, 102, 203, 204, 208, 302, 303) only.

Immune-mediated adverse events were firstly sorted by descending frequency of category, and then sorted by PTs within the category by descending frequency.

Treatment-emergent adverse event leading to the dose modification is defined as a TEAE with action taken 'Dose delay', 'Dose delayed', 'Drug interrupted', 'Dose interrupted', 'Dose held/interrupted' or 'Infusion rate decrease' by investigator.

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

Adverse events were coded using the MedDRA Version 23.0.

Adverse event grades were evaluated based on NCI-CTCAE (version 4.03).

Immune-mediated nephritis and renal dysfunction

Immune-mediated nephritis and renal dysfunction	Monotherapy Total (N = 1972) n (%) (95% CI)[a]
Incidence	
Patients with at least one AE	10 (0.5) (0.2, 0.9)
Renal failure	2 (0.1)
Blood creatinine increased	2 (0.1)
Renal impairment	2 (0.1)
Acute kidney injury	1 (0.1)
Focal segmental glomerulosclerosis	1 (0.1)
Immune-mediated nephritis	1 (0.1)
Nephritis	1 (0.1)
Severity and Nature of risk	
Patients with worst grade 3 AE	3 (0.2)
Acute kidney injury	1 (0.1)
Focal segmental glomerulosclerosis	1 (0.1)
Renal failure	1 (0.1)
Patients with worst grade 4 AE	2 (0.1)
Renal failure	1 (0.1)
Renal impairment	1 (0.1)

Immune-mediated nephritis and renal dysfunction	Monotherapy Total (N = 1972) n (%) (95% CI)[a]
Patients with worst grade 5 AE	1 (0.1)
Renal impairment	1 (0.1)
Patients with at least one AE leading to discontinuation of Tislelizumab	4 (0.2)
Renal failure	2 (0.1)
Focal segmental glomerulosclerosis	1 (0.1)
Renal impairment	1 (0.1)
Patients with at least one immune-mediated AE leading to dose modification of Tislelizumab	4 (0.2)
Blood creatinine increased	2 (0.1)
Immune-mediated nephritis	1 (0.1)
Nephritis	1 (0.1)
Patients with at least one SAE	5 (0.3) (0.1, 0.6)
Renal failure	2 (0.1)
Acute kidney injury	1 (0.1)
Focal segmental glomerulosclerosis	1 (0.1)
Renal impairment	1 (0.1)
Outcome (for SAEs)	
Death	1 (0.1)
Renal impairment	1 (0.1)
Recovered/resolved	1 (0.1)
Renal failure	1 (0.1)
Recovered/resolved with sequelae	2 (0.1)
Acute kidney injury	1 (0.1)
Renal failure	1 (0.1)
Recovering/resolving	1 (0.1)
Focal segmental glomerulosclerosis	1 (0.1)

Source data: Annex 7-Table 3.1.1.1, Table 3.2.1.1, Table 3.3.1.1, Table 2.7.4.2.2.6.1.

Studies include monotherapy studies (001, 102, 203, 204, 208, 302, 303) only.

Immune-mediated adverse events were firstly sorted by descending frequency of category, and then sorted by PTs within the category by descending frequency.

Treatment-emergent adverse event leading to the dose modification is defined as a TEAE with action taken 'Dose delay', 'Dose delayed', 'Drug interrupted', 'Dose interrupted', 'Dose held/interrupted' or 'Infusion rate decrease' by investigator.

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

Adverse events were coded using the MedDRA Version 23.0.

Adverse event grades were evaluated based on NCI-CTCAE (version 4.03).

Immune-mediated myocarditis

Immune-mediated myocarditis	Monotherapy Total (N = 1972) n (%) (95% CI)[a]
Incidence	
Patients with at least one AE	7 (0.4) (0.1, 0.7)
Immune-mediated myocarditis	3 (0.2)
Myocarditis	3 (0.2)
Autoimmune myocarditis	1 (0.1)
Severity and Nature of risk	
Patients with worst grade 3 AE	3 (0.2)
Immune-mediated myocarditis	3 (0.2)
Patients with worst grade 4 AE	1 (0.1)
Myocarditis	1 (0.1)
Patients with worst grade 5 AE	0 (0.0)
Patients with at least one AE leading to discontinuation of Tislelizumab	5 (0.3)
Immune-mediated myocarditis	2 (0.1)
Myocarditis	2 (0.1)
Autoimmune myocarditis	1 (0.1)
Patients with at least one immune-mediated AE leading to dose modification of Tislelizumab	3 (0.2)
Autoimmune myocarditis	1 (0.1)
Immune-mediated myocarditis	1 (0.1)
Myocarditis	1 (0.1)
Patients with at least one SAE	7 (0.4) (0.1, 0.7)
Immune-mediated myocarditis	3 (0.2)
Myocarditis	3 (0.2)
Autoimmune myocarditis	1 (0.1)
Outcome (for SAEs)	
Death	0 (0.0)
Recovered/resolved	4 (0.2)
Immune-mediated myocarditis	2 (0.1)
Autoimmune myocarditis	1 (0.1)
Myocarditis	1 (0.1)
Recovering/resolving	1 (0.1)
Myocarditis	1 (0.1)
Not recovered/not resolved	2 (0.1)
Immune-mediated myocarditis	1 (0.1)
Myocarditis	1 (0.1)

Immune-mediated myocarditis	Monotherapy Total (N = 1972) n (%) (95% CI)[a]

Source data: Annex 7-Table 3.1.1.1, Table 3.2.1.1, Table 3.3.1.1, Table 2.7.4.2.2.6.1.

Studies include monotherapy studies (001, 102, 203, 204, 208, 302, 303) only.

Immune-mediated adverse events were firstly sorted by descending frequency of category, and then sorted by PTs within the category by descending frequency.

Treatment-emergent adverse event leading to the dose modification is defined as a TEAE with action taken 'Dose delay', 'Dose delayed', 'Drug interrupted', 'Dose interrupted', 'Dose held/interrupted' or 'Infusion rate decrease' by investigator.

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

Adverse events were coded using the MedDRA Version 23.0.

Adverse event grades were evaluated based on NCI-CTCAE (version 4.03).

Immune-mediated nervous system disorder

Immune-mediated nervous system disorder	Monotherapy Total (N = 1972) n (%) (95% CI)[a]
Incidence	
Patients with at least one AE	0 (0.0)
Severity and Nature of risk	
Patients with worst grade 3 AE	0 (0.0)
Patients with worst grade 4 AE	0 (0.0)
Patients with worst grade 5 AE	0 (0.0)
Patients with at least one AE leading to discontinuation of Tislelizumab	0 (0.0)
Patients with at least one immune-mediated AE leading to dose modification of Tislelizumab	0 (0.0)
Patients with at least one SAE	0 (0.0)
Outcome (for SAEs)	
Death	0 (0.0)
Recovered/resolved	0 (0.0)

Source data: Annex 7-Table 3.1.1.1, Table 3.2.1.1, Table 3.3.1.1, Table 2.7.4.2.2.6.1.

Studies include monotherapy studies (001, 102, 203, 204, 208, 302, 303) only.

Immune-mediated adverse events were firstly sorted by descending frequency of category, and then sorted by PTs within the category by descending frequency.

Treatment-emergent adverse event leading to the dose modification is defined as a TEAE with action taken 'Dose delay', 'Dose delayed', 'Drug interrupted', 'Dose interrupted', 'Dose held/interrupted' or 'Infusion rate decrease' by investigator.

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

Adverse events were coded using the MedDRA Version 23.0.

Adverse event grades were evaluated based on NCI-CTCAE (version 4.03).

Immune-mediated pancreatitis

Immune-mediated pancreatitis	Monotherapy Total (N = 1972) n (%) (95% CI)[a]
Incidence	
Patients with at least one AE	1 (0.1) (0.0, 0.3)
Pancreatitis	1 (0.1)
Severity and Nature of risk	
Patients with worst grade 3 AE	1 (0.1)
Pancreatitis	1 (0.1)
Patients with worst grade 4 AE	0 (0.0)
Patients with worst grade 5 AE	0 (0.0)
Patients with at least one AE leading to discontinuation of Tislelizumab	0 (0.0)
Patients with at least one immune-mediated AE leading to dose modification of Tislelizumab	1 (0.1)
Pancreatitis	1 (0.1)
Patients with at least one SAE	1 (0.1) (0.0, 0.3)
Pancreatitis	1 (0.1)
Outcome (for SAEs)	
Death	0 (0.0)
Recovered/resolved	1 (0.1)
Pancreatitis	1 (0.1)

Source data: Annex 7-Table 3.1.1.1, Table 3.2.1.1, Table 3.3.1.1, Table 2.7.4.2.2.6.1.

Studies include monotherapy studies (001, 102, 203, 204, 208, 302, 303) only.

Immune-mediated adverse events were firstly sorted by descending frequency of category, and then sorted by PTs within the category by descending frequency.

Treatment-emergent adverse event leading to the dose modification is defined as a TEAE with action taken 'Dose delay', 'Dose delayed', 'Drug interrupted', 'Dose interrupted', 'Dose held/interrupted' or 'Infusion rate decrease' by investigator.

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

Adverse events were coded using the MedDRA Version 23.0.

Adverse event grades were evaluated based on NCI-CTCAE (version 4.03).

Other immune-mediated reactions

Other Immune-Mediated Reactions	Monotherapy Total (N = 1972) n (%) (95% CI)[a]
Incidence	
Patients with at least one AE	7 (0.4) (0.1, 0.7)
Arthritis	4 (0.2)
Immune-mediated arthritis	1 (0.1)
Pericarditis	1 (0.1)
Polymyalgia rheumatica	1 (0.1)
Severity and Nature of risk	

Other Immune-Mediated Reactions	Monotherapy Total (N = 1972) n (%) (95% CI)[a]
Patients with worst grade 3 AE	1 (0.1)
Arthritis	1 (0.1)
Patients with worst grade 4 AE	0 (0.0)
Patients with worst grade 5 AE	0 (0.0)
Patients with at least one AE leading to discontinuation of Tislelizumab	1 (0.1)
Arthritis	1 (0.1)
Patients with at least one immune-mediated AE leading to dose modification of Tislelizumab	2 (0.1)
Immune-mediated arthritis	1 (0.1)
Pericarditis	1 (0.1)
Patients with at least one SAE	2 (0.1) (0.0, 0.4)
Arthritis	2 (0.1)
Outcome (for SAEs)	
Death	0 (0.0)
Recovered/resolved	2 (0.1)
Arthritis	2 (0.1)

Source data: Annex 7-Table 3.1.1.1, Table 3.2.1.1, Table 3.3.1.1, Table 2.7.4.2.2.6.1.

Studies include monotherapy studies (001, 102, 203, 204, 208, 302, 303) only.

Immune-mediated adverse events were firstly sorted by descending frequency of category, and then sorted by PTs within the category by descending frequency.

Treatment-emergent adverse event leading to the dose modification is defined as a TEAE with action taken 'Dose delay', 'Dose delayed', 'Drug interrupted', 'Dose interrupted', 'Dose held/interrupted' or 'Infusion rate decrease' by investigator.

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

Adverse events were coded using the MedDRA Version 23.0.

Adverse event grades were evaluated based on NCI-CTCAE (version 4.03).

Table 8-6 Important identified risk Immune-mediated adverse reactions: Other details

Immune-mediated adverse reactions	Details
Potential mechanisms	The use of mAbs that block co-inhibitory immune checkpoint molecules, such as tislelizumab, may serve to increase a baseline T-cell-specific immune response that enhances the immune anti-tumor 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 trial data, post-marketing experience and literature regarding immune-mediated adverse reactions (including immune-mediated pneumonitis, immune-mediated hepatitis, immune-mediated skin adverse reaction, immune-mediated colitis, immune-mediated myositis/rhabdomyolysis, immune-mediated endocrinopathies, immune-mediated nephritis and renal dysfunction, immune-mediated myocarditis, immune-mediated nervous system disorder,

Immune-mediated adverse reactions	Details
	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 lungs was observed in cynomolgus monkeys following i.v. infusion at doses of 3, 10, 30, 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). **Immune-mediated hepatitis** *Nonclinical data:* No treatment-related hepatic inflammation was observed in cynomolgus monkeys following i.v. infusion at doses of 3, 10, 30, 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 due to 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 following i.v. infusion at doses of 3, 10, 30, 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 CTLA4 (ipilimumab in 43% to 45% of the patients) or PD-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 diarrhea or gastrointestinal tract inflammation was observed in cynomolgus monkeys following i.v. infusion at doses of 3, 10, 30, or 60 mg/kg (once every 2 weeks, 7 doses) for 13 weeks. *Clinical data:* Diarrhea and colitis are more frequent with anti-cytotoxic T lymphocyte-associated protein 4 (CTLA4) agents (e.g., ipilimumab) than with anti-PD-1 targeted agents including nivolumab or pembrolizumab, with grade 3 to 4 AEs occurring in 1% to 2% of cases (Haanen et al 2017). The presence of diarrhea 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 following i.v. infusion at doses of 3, 10, 30, 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 (AbdelRahman et al 2017). Recognizing musculoskeletal imAEs in the oncology setting is challenging due to the broad range

Immune-mediated adverse reactions	Details
	of potential presenting symptoms and the prevalence of musculoskeletal complaints in the general population. **Immune-mediated endocrinopathies (hypothyroidism, hyperthyroidism, thyroiditis, adrenal insufficiency, pituitary dysfunction, diabetes mellitus)** *Nonclinical data:* No treatment-related thyroid inflammation was observed in cynomolgus monkeys following i.v. infusion at doses of 3, 10, 30, 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 trials (Puzanov et al 2017). Pituitary dysfunction is a rare condition which occurs in 0.5-1% of patients treated with anti-PD-1/PD-L1 monotherapy and up to 10% with combination CTLA-4/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 following treatment with ICIs occurs in slightly less than 1% of patients; approximately 97% of all reported cases have arisen with anti-PD-1/PD-L1 monotherapy or combination treated patients (Wright et al 2021). **Immune-mediated nephritis and renal dysfunction** *Nonclinical data:* No treatment-related inflammation in kidneys was observed in cynomolgus monkeys following i.v. infusion at doses of 3, 10, 30, 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 (anti-drug antibodies). *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-1 monotherapy, and combination anti-CTLA-4/PD-1 treatment in melanoma (Puzanov et al 2017). **Immune-mediated myocarditis** *Nonclinical data:* No treatment-related inflammation of the heart was observed in cynomolgus monkeys following i.v. infusion at doses of 3, 10, 30, or 60 mg/kg (once every 2 weeks, 7 doses) for 13 weeks. *Clinical data:* Myocarditis and cardiac dysfunction due to ICIs are rare and the true incidence is unknown; current estimates suggest this incidence is less than 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 edema, palpitations, irregular heartbeat, rapid onset of heart failure symptoms or new heart block on electrocardiogram (ECG) 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 brain was observed in cynomolgus monkeys following i.v. infusion at doses of 3, 10, 30, or 60 mg/kg (once every 2 weeks, 7 doses) for 13 weeks. *Clinical data:* Neurologic immune-related adverse events are uncommon with an overall incidence up to 6% with anti-PD-1 antibodies and include auto-immune encephalitis, myasthenic syndrome, Guillain-Barre syndrome (Puzanov et al 2017). **Immune-mediated pancreatitis**

Immune-mediated adverse reactions	Details
	Nonclinical data: No treatment related inflammation in pancreas was observed in cynomolgus monkeys following i.v. infusion at doses of 3, 10, 30, 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 following i.v. infusion at doses of 3, 10, 30, or 60 mg/kg (once every 2 weeks, 7 doses) for 13 weeks. *Clinical data:* Immune-related adverse events can affect any organ system (Puzanov et al 2017), including hematological, ocular or rheumatological manifestations (Haanen et al 2017).
Characterization of the risk	Reference is made to the table above (Table 8-5).
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 program 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 (SCARs), including severe erythema multiforme (EM), Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN), HCPs should withhold tislelizumab and refer the patient

Immune-mediated adverse reactions	Details
	for specialized assessment and treatment. If SCARs, including SJS or TEN is confirmed, tislelizumab should be permanently discontinued. The HCPs should monitor patients for suspected severe skin reactions (including EM, SJS or TEN). If patients develop signs or symptoms of a possible severe skin reaction, which may include fever, flu-like symptoms, rash, itching, skin blistering or ulcers in the mouth or on other moist surfaces, they should notify their HCP. **Immune-mediated colitis** While on therapy with tislelizumab, patients should inform their HCP of any of the following symptoms that may indicate colitis: diarrhoea or more bowel movements than normal, black tarry, sticky stools or stools with blood or mucus, or severe abdominal pain or tenderness. Patients should be monitored for signs and symptoms of colitis. Infectious and disease related aetiologies should be ruled out. The HCPs should consider stopping treatment with tislelizumab temporarily or permanently and begin steroid therapy if indicated. The HCPs should monitor patients for signs and symptoms of colitis. Early detection and treatment may prevent and/or mitigate the risk. The SmPC includes details on how to manage immune-mediated colitis. **Immune-mediated myositis/rhabdomyolysis** Patients should inform their HCP if they are experiencing muscle pain, stiffness, weakness, chest pain or severe tiredness that may be related to myositis. If a diagnosis of myositis is confirmed, the HCP may decide to stop tislelizumab temporarily or permanently, and treatment with steroids may be needed. If a diagnosis of rhabdomyolysis is confirmed, the HCP may also decide to stop tislelizumab temporarily or permanently. Early detection and treatment may prevent and/or mitigate the risk. Treatment modification for immune-mediated myositis and rhabdomyolysis is included in the SmPC. **Immune-mediated endocrinopathies (hypothyroidism, hyperthyroidism, thyroiditis, adrenal insufficiency, pituitary dysfunction, type 1 diabetes mellitus)** The SmPC provide recommendations for treatment in the event of immune-mediated endocrinopathies. The HCPs should monitor for signs and symptoms of endocrinopathies and monitor thyroid function before and periodically during treatment with tislelizumab. While on therapy with tislelizumab, patients should inform the HCP of any of the following symptoms: fast heart rate, extreme tiredness, weight gain or weight loss, dizziness or fainting, hair loss, feeling cold, constipation, headaches that will not go away or unusual headaches. **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 color of their urine, pain while urinating or pain in kidney area. The HCP should monitor patients' renal function (serum creatinine). The SmPC provide recommendations for treatment in the event of immune-mediated nephritis and renal dysfunction, including withholding treatment, administering corticosteroids, and permanently discontinuing tislelizumab in patients with recurrent severe or life-threatening symptoms. **Immune-mediated myocarditis** While on therapy with tislelizumab, patients should inform their HCP about any of the following symptoms that may be related to myocarditis including chest pain, rapid or abnormal heartbeat, shortness of breath at rest or during activity, fluid build-up with swelling of the legs, ankles and feet and tiredness. If a diagnosis of myocarditis is

Immune-mediated adverse reactions	Details
	confirmed, the HCP may decide to stop tislelizumab temporarily or permanently. Healthcare professionals 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 which may cause difficulty breathing, 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, nausea and vomiting, 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 indicated) 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.

8.3.1.2 Important Potential Risk: Reproductive and developmental toxicity

Table 8-7 Important potential risk Reproductive and developmental toxicity: Other details

Reproductive and developmental toxicity	Details
Potential mechanisms	The PD-1/PD-L1 pathway is involved in the maintenance of tolerance to the fetus, PD-1 blockade can disrupt immune tolerance.
Evidence source(s) and strength of evidence	*Nonclinical data:* No treatment-related effects were observed in reproductive organs in cynomolgus monkeys following i.v. 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 embryofetal toxicity demonstrated that the pharmacologically mediated blockade of PD-1/PD-L1 interaction in animal models can result in fetal loss (Guleria et al 2005).

Reproductive and developmental toxicity	Details
	This is due to disruption of immune tolerance to the fetus 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 tumors is analogous to the PD-1 binding to a highly-expressed PD-L1 at the utero-placental interface (Guleria et al 2005, Habicht et al 2007, Petroff and Perchellet 2010). The blockade of the PD-1/PD-L1 pathway in inducing fetal 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 fetus.
Characterization of the risk	No TEAEs of reproductive and developmental toxicity have been reported in monotherapy studies (Study 302, Study 001, Study 102, Study 203, Study 204, Study 208 and Study 303).
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 child-bearing 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 child-bearing 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	The risk should be well managed by the guidance provided in the tislelizumab SmPC. There are no available human data regarding the risk of reproductive and developmental toxicity (SmPC).
Public health impact	The public health impact of this event attributable to tislelizumab treatment is expected to be low.

8.3.2 Part II Module SVII.3.2. Presentation of the missing information

None

9 Part II Safety specification Module SVIII: Summary of the safety concerns

Table 9-1 Table Part II SVIII.1: Summary of safety concerns

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

10 Part III: Pharmacovigilance plan (including post-authorization safety studies)

10.1 Part III.1. Routine pharmacovigilance activities

10.1.1 Routine pharmacovigilance activities beyond ADRs reporting and signal detection

Specific adverse reaction follow-up checklists:

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

Important identified risk

- Immune-mediated adverse reactions

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

Other forms of routine pharmacovigilance activities for risks

There are no other forms of routine pharmacovigilance activities.

10.2 Part III.2. Additional pharmacovigilance activities

None.

10.3 Part III.3 Summary Table of additional pharmacovigilance activities

None.

11 Part IV: Plans for post-authorization efficacy studies

There are no plans for post-authorization efficacy studies.

12 Part V: Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)

Risk Minimization Plan

12.1 Part V.1. Routine risk minimization measures

Table 12-1 Table Part V.1: Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization 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 minimization 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 where the adverse drug reactions (ADRs) 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 minimization 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 minimization activities recommending specific clinical measures to address the risk:** Advice that women of child-bearing 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 child-bearing 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 minimization measures beyond the Product Information:** Legal status: Restricted medical prescription
Missing information	
None	

12.2 Part V.2. Additional Risk minimization measures

Additional risk minimization measures

To increase understanding of the safe and effective use of Tevimbra (tislelizumab), physicians should provide patients or their caregiver 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 imARs 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 minimization activity:

Immune-mediated 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 hand over 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 PSURs including information collected via targeted follow-up checklist, when applicable.

12.3 Part V.3. Summary of risk minimization measures

Table 12-2 Summary of pharmacovigilance activities and risk minimization activities by safety concerns

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important identified risk		
Immune-mediated adverse reactions	**Routine risk minimization measures:** SmPC Section 4.2 where guidelines for withholding or permanent discontinuation of treatment are provided. SmPC Section 4.4 where advice is provided regarding monitoring and management of immune-mediated adverse reactions. SmPC Section 4.8 where the adverse drug reactions (ADRs) of immune-mediated adverse reactions are listed. PL Section 2 and PL Section 4 where guidance on how to early identify signs and symptoms and seek medical attention is included. Legal status: Restricted medical prescription	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Targeted follow-up checklist **Additional pharmacovigilance activities:** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Additional risk minimization measures: Patient Card	
Important potential risk		
Reproductive and developmental toxicity	**Routine risk minimization measures:** SmPC Section 4.6 where advice is provided regarding the need for women of child-bearing potential to avoid getting pregnant and for lactating women to avoid breastfeeding infants while taking tislelizumab and that, women of child-bearing potential should use effective contraception during treatment with tislelizumab and for 4 months after the last dose. SmPC Section 5.3 PL Section 2 where guidance on how to early identify signs and symptoms and seek medical attention is included. Legal status: Restricted medical prescription **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Missing Information		
None		

13 Part VI: Summary of the risk management plan for Tevimbra (Tislelizumab)

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

Tevimbra's SmPC and its package leaflet give essential information to HCPs 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 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.

13.1 Part VI: I. The medicine and what it is used for

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

It contains tislelizumab as the active substance and it is given by the i.v. 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 EMA website, under the medicine's webpage*:* https://www.ema.europa.eu/en/medicines/human/EPAR/tevimbra.

13.2 Part VI: II. Risks associated with the medicine and activities to minimize or further characterize the risks

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

Measures to minimize 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 HCPs;
- Important advice on the medicine's packaging;
- The authorized 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 (e.g., with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

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

13.2.1 Part VI: 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 minimize 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 (e.g., on the long-term use of the medicine).

Table 13-1 List of important risks and missing information

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

13.2.2 Part VI: II.B: Summary of important risks

Table 13-2 Important identified risk – Immune-mediated adverse reactions

Evidence for linking the risk to the medicine	Review of tislelizumab clinical trial data, post-marketing experience and literature regarding immune-mediated adverse reactions (including immune-mediated pneumonitis, immune-mediated hepatitis, immune-mediated skin adverse reaction, immune-mediated colitis, immune-mediated myositis/rhabdomyolysis, immune-mediated endocrinopathies, immune-mediated nephritis and renal dysfunction, immune-mediated myocarditis, immune-mediated nervous system disorder, immune-mediated pancreatitis, and other immune-mediated reactions) represent sufficient evidence of a causal association with tislelizumab exposure. **Immune-mediated pneumonitis** *Nonclinical data:* No treatment-related inflammation in lungs was observed in cynomolgus monkeys following i.v. infusion at doses of 3, 10, 30, 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. Patients with NSCLC were significantly more likely to experience any grade pneumonitis and grade 3 or higher pneumonitis compared with other tumor types. **Immune-mediated hepatitis** *Nonclinical data:* No treatment-related hepatic inflammation was observed in cynomolgus monkeys following i.v. infusion at doses of 3, 10, 30, 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 due to 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%.

Immune-mediated skin adverse reaction

Nonclinical data: No treatment-related skin rash was observed in cynomolgus monkeys following i.v. infusion at doses of 3, 10, 30, 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 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.

Immune-mediated colitis

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

Clinical data: Diarrhoea and colitis are more frequent with anti-cytotoxic T lymphocyte-associated protein 4 (CTLA4) agents (e.g., 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 diarrhea 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 following i.v. infusion at doses of 3, 10, 30, 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 imAEs in the oncology setting is challenging due to the broad range of potential presenting symptoms and the prevalence of musculoskeletal complaints in the general population.

Immune-mediated endocrinopathies (hypothyroidism, hyperthyroidism, thyroiditis, adrenal insufficiency, pituitary dysfunction, type 1 diabetes mellitus)

Nonclinical data: No treatment-related thyroid inflammation was observed in cynomolgus monkeys following i.v. infusion at doses of 3, 10, 30, 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 trials. Pituitary dysfunction is a rare condition which occurs in 0.5-1% of patients treated with anti-PD-1/PD-L1 monotherapy and up to 10% with combination CTLA-4/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 following treatment with ICIs occurs in slightly less than 1% of patients; approximately 97% of all reported cases have arisen with anti-PD-1/PD-L1 monotherapy or combination treated patients.

Immune-mediated nephritis and renal dysfunction

Nonclinical data: No treatment-related inflammation in kidneys was observed in cynomolgus monkeys following i.v. infusion at doses of 3, 10, 30, 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 (anti-drug-antibodies).

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 antiCTLA4/PD(L)1 treatment in melanoma.

Immune-mediated myocarditis

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

Clinical data: Myocarditis and cardiac dysfunction due to ICIs are rare and the true incidence is unknown; current estimates suggest this incidence is less than 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 edema, palpitations, irregular heartbeat, rapid onset of heart failure symptoms or new heart block on ECG 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 brain was observed in cynomolgus monkeys following i.v. infusion at doses of 3, 10, 30, or 60 mg/kg (once every 2 weeks, 7 doses) for 13 weeks.

Clinical data: Neurologic immune-related adverse events are uncommon with an overall incidence up to 6% with anti-PD-(L)1 antibodies and include auto-immune encephalitis, myasthenic syndrome, Guillain-Barre syndrome.

	Immune-mediated pancreatitis *Nonclinical data:* No treatment related inflammation in pancreas was observed in cynomolgus monkeys following i.v. infusion at doses of 3, 10, 30, 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 following i.v. infusion at doses of 3, 10, 30, or 60 mg/kg (once every 2 weeks, 7 doses) for 13 weeks. *Clinical data:* Immune-related adverse events can affect any organ system, including hematological, ocular or rheumatological manifestations.
Risk factors and risk groups	Patients with a history of or ongoing autoimmune disease may be at a higher risk of developing imAEs and are generally excluded from the clinical development program 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 minimization measures	**Routine risk minimization measures:** SmPC Section 4.2 where guidelines for withholding or permanent discontinuation of treatment are provided. SmPC Section 4.4 where advice is provided regarding monitoring and management of immune-mediated adverse reactions. SmPC Section 4.8 where the ADRs of immune-mediated adverse reactions are listed. PL Section 2 and PL Section 4 where guidance on how to early identify signs and symptoms and seek medical attention is included. Legal status: Restricted medical prescription **Additional risk minimization measures:** Patient Card

Table 13-3 Important potential risk – Reproductive and developmental toxicity

Evidence for linking the risk to the medicine	*Nonclinical data:* No treatment-related effects were observed in reproductive organs in cynomolgus monkeys following i.v. 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 embryofetal toxicity demonstrated that the pharmacologically mediated blockade of PD1/PDL1 interaction in animal models can result in fetal loss. This is due to disruption of immune tolerance to the fetus as the PD-1/PD-L1 pathway plays a role in the maintenance of tolerance. A clinical study further supported the animal model data and highlighted the potential importance of the PD1/PDL1 immune-checkpoint pathway in the induction of maternal tolerance during healthy pregnancy. The PD1 binding to the abundantly expressed PDL1 in tumors is analogous to the PD1 binding to a highly-expressed PDL1 at the uteroplacental interface. The blockade of the PD1/PDL1 pathway in inducing fetal 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 fetus.
Risk factors and risk groups	No relevant risk groups or risk factors have been identified.
Risk minimization measures	**Routine risk minimization measures:** SmPC Section 4.6 SmPC Section 5.3 PL Section 2 Advice that women of child-bearing potential should avoid becoming pregnant and lactating women should avoid breastfeeding infants while taking tislelizumab and that, women of child-bearing potential should use effective contraception during treatment with tislelizumab and for 4 months after the last dose is included in SmPC Section 4.6 and PL Section 2. SmPC Section 5.3 Legal status: Restricted medical prescription **Additional risk minimization measures:** None

13.2.3 Part VI: II.C: Post-authorization development plan

13.2.3.1 II.C.1. Studies which are conditions of the marketing authorization

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

13.2.3.2 II.C.2. Other studies in post-authorization development plan

There are no other studies required in post-authorization development plan for Tevimbra.

14 Part VII: Annexes

Annex 4 - Specific adverse drug reaction follow-up forms

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

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

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

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

Does the patient have a personal or family history of autoimmune disease? Yes No Unknown

If yes, please specify:

Were any autoantibodies detected? (if yes, please provide details below) Yes No Unknown

Autoantibody:

Value/ units:

Normal range:

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

Complete blood count including differential blood count

Relevant biochemistry test (including but not limited to glycemia, thyroid hormones, Adrenal, pituitary or other organ specific hormones)

Inflammatory markers (C-reactive protein, Erythrocyte Sedimentation Rate

Serology

Hepatitis B, (if yes, please specify) Anti-dsDNA (if yes, please specify)

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

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

Other organ specific antibodies (if yes, please specify) Anti-Scl 70

Biopsies (if yes, please specify)

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

Other (e.g. colonoscopy in the case of colitis)

Treatment received:

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

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

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

Treatment Name	Start	Stop	Route	Dose	Duration

Did the event improve or resolve with immunosuppressant treatment (e.g. Steroid therapy)? Yes No Unknown

Was suspect medication stopped due to event?

If yes, please provide the outcome of the event, de-challenge,

Was therapy with suspect medication restarted? Yes No

If yes, Please specify the dose and date:

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

Annex 6 - Details of proposed additional risk minimization activities (if applicable)

Key safety messages of additional risk minimization measures:

Prior to the launch of Tevimbra (tislelizumab) in each Member State, the MAH must agree about the content and format of the Patient Card, including communication media, distribution modalities, and any other aspects of the program, with the National Competent Authority.

The Patient Card is aimed at increasing the awareness of patients on the signs and symptoms relevant to the early recognition/identification of the potential immune-mediated adverse reactions (imARs) 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 for being always carried by the patient and to be presented to the healthcare professionals that may help them.

The MAH shall ensure that in each Member State where Tevimbra (tislelizumab) is marketed, all patients who are expected to use Tevimbra (tislelizumab) have access to/are provided with the Patient Card disseminated through healthcare professionals.

The Patient Card will contain the following key messages:

- Description of the main signs or symptoms of the immune-mediated adverse reactions (e.g.: pneumonitis, colitis, hepatitis, endocrinopathies, immune-mediated skin adverse reactions, nephritis and other imARs) and infusion-related reactions, and the importance of notifying their treating physician immediately if symptoms occur.
- The importance of not attempting to self-treat any symptoms without consulting their healthcare professional first.
- The importance of carrying the Patient Card at all times and to show it at all medical visits to healthcare professionals other than the prescriber (e.g. emergency healthcare professionals).
- A warning message for healthcare professionals treating the patient at any time, including in conditions of emergency, that the patient is treated with Tevimbra.
- A reminder that all known or suspected adverse drug reactions (ADRs) can also be reported to local regulatory authorities.
- The contact details of their Tevimbra prescriber.