EU RISK MANAGEMENT PLAN

TIZVENI (TISLELIZUMAB)

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

RMP Version number: 1.0

Data Lock Point for This RMP	Clinical data: 01 December 2020 Global Safety Database: 25 December 2022 Postmarketing exposure data: 25 December 2022	Version number	1.0
Date of Final Sign Off	21 February 2024		

Rationale for Submitting an Updated RMP:

Prepared in response to the Committee for Medicinal Products for Human Use Day 195 List of Outstanding Issues for procedure EMA/H/C/005542 (dated 07 February 2024).

Summary of Significant Changes in This RMP:

"Patient/Caregiver Guide" was removed. "Patient Alert Card" was renamed to "Patient Card" and key messages in Patient Card were updated in Annex 6.

Change in "Tradename" to "Tizveni".

Updated to align with the approved European Union (EU) RMP (Version 1.0, dated 11 July 2023) and proposed Summary of Product Characteristics (SmPC) for Tizveni (Procedure number: EMA/H/C/005542).

Aligned with latest Periodic Benefit Risk Evaluation Report (PBRER) reporting period 26 December 2021 to 25 December 2022.

Part	Module/Annex	Significant Changes in Each Module
Part I Product overview		Tradename was updated. Indication in the European Economic Area updated to align with the proposed SmPC.
Part II Safety specification	Module SI Epidemiology of the indication(s) and target population(s)	No updates.
	Module SII Nonclinical part of the safety specification	Updated nonclinical data with respect to immunogenicity and reproductive toxicity.

Part	Module/Annex	Significant Changes in Each Module
	Module SIII Clinical study exposure	No updates.
	Module SIV Populations not studied in clinical studies	No updates.
	Module SV Postauthorisation experience	Update in alignment with latest PBRER, data lock point (DLP): 25 December 2022.
	Module SV1 Additional EU requirements for the safety specification	No updates.
	Module SVII Identified and potential risks	Patient/Caregiver Guide was removed. Updated nonclinical data with respect to 60 mg/kg infusion dose. Updated nonclinical data with respect to immunogenicity and reproductive toxicity.
	Module SVIII Summary of the safety concerns	No updates
Part III Pharmacovigilance plan (including postauthorization safety studies)		No updates.
Part IV Plan for postauthorization efficacy studies		No updates.
Part V Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)		Patient/Caregiver Guide was removed.
Part VI Summary of Risk Management Plan for TIZVENI (tislelizumab)		Patient/Caregiver Guide was removed. Tradename was updated. Updated nonclinical data with respect to 60 mg/kg infusion dose. Indication in the European Economic Area updated to align with the proposed SmPC.
Part VII Annexes	**ANNEX 1** Eudravigilance interface	No updates.
	ANNEX 2 Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme	No updates.

Part	Module/Annex	Significant Changes in Each Module
	ANNEX 3 Protocols for proposed, ongoing and completed studies in the pharmacovigilance plan	No updates.
	ANNEX 4 Specific adverse drug reaction follow-up forms	No updates.
	ANNEX 5 Protocols for proposed and ongoing studies in RMP Part IV	No updates.
	ANNEX 6 Details of proposed additional risk minimization activities (if applicable)	Patient/Caregiver Guide was removed. The key messages in the Patient Card were updated. New texts were added for clarification.
	ANNEX 7 Other supporting data (including referenced material)	No updates.
	ANNEX 8 Summary of changes to the RMP over time	No updates.

Other RMP Versions Under Evaluation:

None

Details of the Currently Approved RMP:

None

QPPV Name: Dr Olaf Schickling

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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LIST OF ABBREVIATIONS FOR ALL PARTS/MODULES

ADA	Antidrug antibody
AE	Adverse event
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CNS	Central nervous system
CSS	Cancer-specific survival
CTLA4	Cytotoxic T lymphocyte-associated protein 4
DLP	Data lock point
eGFR	Estimated glomerular filtration rate
EGFR	Epidermal growth factor receptor
EPAR	European Public Assessment Report
EU	European Union
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCP	Healthcare professional
HCV	Hepatitis C virus
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICI	Immune checkpoint inhibitor
imAE	Immune-mediated adverse event
IR	Incidence rate
IRR	Infusion-related reaction
LC	Lung cancer
mAb	Monoclonal antibody
nab-PC	Nab-paclitaxel
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	Pharmacokinetic(s)

PT	Preferred Term
RMP	Risk Management Plan
RSR	Relative survival rate
SJS	Stevens-Johnson syndrome
SmPC	Summary of Product Characteristics
TC	Tumor cells
TEAE	Treatment-emergent adverse event
TEN	Toxic epidermal necrolysis
UK	United Kingdom
ULN	Upper limit of normal
US	United States (of America)

PART I PRODUCT(S) OVERVIEW

Table Part I-1: Product Overview

Active Substance(s) (INN or Common Name)	Tislelizumab
Pharmacotherapeutic Group(s) (ATC Code)	L01FF09
Marketing Authorization Applicant	BeiGene Ireland, Ltd. 10 Earlsfort Terrace Dublin 2 D02 T380 Ireland
Medicinal Products to Which This RMP Refers	1
Invented Name(s)	Tizveni
Marketing Authorization Procedure	Centralized procedure
Brief Description of the Product	Chemical class: Tislelizumab is a humanized immunoglobulin G4 variant monoclonal antibody (mAb).
	Summary of mode of action: Tislelizumab binds to the extracellular domain of human programmed cell death protein (PD)-1 with high specificity and affinity. Tislelizumab competitively blocks the binding of both 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	Tislelizumab SmPC

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

PART II SAFETY SPECIFICATION

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

Non-small Cell Lung Cancer

Indication

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

Incidence

Published population-based studies on NSCLC are sparse.

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

Table Part II: Module SI-1: Estimated Number of New LC and NSCLC Cases and IR per 100,000 by EU27 Region and Country in 2020 Based on the European Cancer Information System

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

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

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

Table Part II: Module SI-2 presents the results of this study by number of new cases and the IR per 100,000 of NSCLC in the included countries from highest to lowest IR.

Table Part II: Module SI-2: Annual Incidence of NSCLC in Central and Southeastern Europe

Country	New Cases in 2017	Annual IR per 100,000
Hungary	11,000	110.0
Serbia	5,500	76.4
Croatia	2,800	65.1
Slovenia	1,100	55.0
Austria	4,000	47.1
Poland	18,000	46.8
Slovakia	2,500	46.3
Romania	8,500	44.7
Czech Republic	4,500	42.9
Bulgaria	2,300	31.1
Total	**60,200**	**53.4**

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

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

Prevalence

No publications were identified that reported the prevalence of NSCLC.

Table Part II: Module SI-3 presents the estimated prevalence of NSCLC in all age groups for all world regions based on GLOBOCAN 2020 data (highest to lowest proportions per 100,000). The estimates for NSCLC were calculated based on the assumption that NSCLC constitutes approximately 85% of all LC cases (Lungevity 2021). Worldwide, the estimated NSCLC prevalence was 28.4 per 100,000. The highest estimated NSCLC prevalence was reported in Northern America at 75.7 per 100,000, followed by Europe at 66.1 per 100,000, and the lowest prevalence was reported in Africa at 3.1 per 100,000. Among 5 European countries, the highest estimated NSCLC prevalence was in Germany at 85.9 per 100,000, followed by United Kingdom (UK) at 82.4 per 100,000 and the lowest in Spain with 65.0 per 100,000.

Table Part II: Module SI-3: Estimated 5-year Prevalence of LC and NSCLC and Proportion per 100,000 by Country or Region in GLOBOCAN 2020

Country/Region	Estimated 5-year Prevalence of LC		Estimated 5-year Prevalence of NSCLC[a]	
	Number	Proportion per 100,000	Number	Proportion per 100,000
Worldwide	2,604,791	33.4	2,214,072	28.4
Northern America	328,224	89.0	278,990	75.7
Europe	582,924	77.8	495,485	66.1
France	59,708	91.5	50,752	77.8
Germany	84,586	101.0	71,898	85.9
Italy	49,423	81.7	42,010	69.4
Spain	35,729	76.4	30,370	65.0
United Kingdom	65,836	97.0	55,960	82.5
Oceania	21,677	50.8	18,425	43.2
Asia	1,515,321	32.7	1,288,022	27.8
Latin America and the Caribbean	106,459	16.3	90,490	13.9
Africa	50,186	3.7	42,658	3.1

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

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

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

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

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

abstained from alcohol), and genetic factors (an increased risk of LC was found in the carriers of TP53 gene) (Molina et al 2008).

Main Existing Treatment Options

First-line Treatment of NSCLC Without Actionable Oncogenic Driver

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

Pembrolizumab is considered a standard first-line option for patients with advanced NSCLC with PD-L1 expression either ≥ 1% or ≥ 50% (depending on the country approval label) who do not otherwise have contraindications to use of immunotherapy (Keytruda [pembrolizumab] European Public Assessment Report [EPAR] 2020; Planchard et al 2018). The Phase III KEYNOTE024 study has established the role for pembrolizumab as first-line treatment in patients with untreated, advanced NSCLC and tumor characterized by PD-L1 expression ≥ 50% in absence of EGFR mutation or ALK translocations (Reck et al 2016). In this study, the median overall survival (OS) doubled in patients who received pembrolizumab compared with chemotherapy (30 versus 14 months) (Planchard et al 2018). In the subsequent KEYNOTE042 study, pembrolizumab monotherapy also demonstrated efficacy expanding the patients to PD-L1 ≥ 1% (Mok et al 2019), although this expansion was only approved in the US but not in the EU (Keytruda [pembrolizumab] USPI 2021, Keytruda [pembrolizumab] EPAR 2020). Additionally, atezolizumab represents another first-line treatment option in patients with PD-L1 selected NSCLC. In the Phase III IMpower110 study, patients were randomized 1:1 to receive atezolizumab, 1200 mg or platinum-based chemotherapy (for 4 or 6 cycles) once every 3 weeks (Spigel et al 2019). In an interim analysis, atezolizumab monotherapy improved OS compared with platinum-based chemotherapy as a first-line treatment of patients with wildtype NSCLC who had ≥ 50% expression of PD-L1 on TC3 or ≥ 10% expression on tumor infiltrating immune cells (IC3).

Atezolizumab monotherapy improved OS by 7.1 months compared with chemotherapy alone. More recently, cemiplimab (Libtayo [cemiplimab] EPAR 2019) monotherapy has been approved for the first-line treatment of adult patients with locally advanced (not candidate for definitive chemoradiation) or metastatic NSCLC expressing PD-L1 (in ≥ 50% TC), with no EGFR, ALK, or receptor tyrosine kinase 1 aberration, based on EMPOWER Lung 1 study that showed statistically significant improvement in OS for patients randomized to cemiplimab as compared with chemotherapy (Sezer et al 2021).

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

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

Second-line Treatment of NSCLC Without Actionable Oncogenic Driver

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

progression after first-line immunotherapy with pembrolizumab monotherapy, platinum-based chemotherapy is recommended as second-line treatment option.

With the increasing adoption of ICI as the first-line therapy for advanced NSCLC, the number of patients who are not eligible for immunotherapy as the second-line option is also increasing given ICI is only approved in the immunotherapy-naive population. For those patients who are not immunotherapy-naive along with patients who are not suitable for immunotherapy due to underlying medical conditions, chemotherapy remains the recommended treatment option. Docetaxel and pemetrexed (for nonsquamous cell only) are standard treatment options in second-line chemotherapy, with comparable efficacy. Moreover, docetaxel in combination either with ramucirumab or nintedanib is a treatment option in patients with NSCLC progressing after first-line chemotherapy or immunotherapy. In the REVEL study, ramucirumab, an antivascular endothelial growth factor receptor-2 antibody, in combination with docetaxel, showed a superior OS (median OS 10.5 versus 9.1 months, hazard ratio 0.86, 95% CI 0.75, 0.98, p = 0.032) and progression-free survival (PFS; modified PFS 4.5 versus 3 months, p< 0.0001) compared with docetaxel and placebo regardless of histology and represents a treatment option in patients with NSCLC progressing after first-line chemotherapy with ECOG PS 0 to 2. Nintedanib, an oral angiokinase inhibitor, improved PFS in combination with docetaxel compared with chemotherapy alone in the LUME1 study (modified PFS 3.4 versus 2.7 months, hazard ratio 0.79, 95% CI 0.68, 0.92, p = 0.0019) and represents a treatment option for patients with adenocarcinoma progressing after previous chemotherapy.

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

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

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

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

NSCLC is associated with a relatively poor prognosis. Approximately 79.90% of NSCLC patients who die within the first 6 years of diagnoses, do so from the disease itself rather than comorbidities (Janssen-Heijnen et al 2015). In Europe, a multinational prospective cohort study including 3,508 NSCLC patients enrolled consecutively from 01 January 2009 to 31 July 2009 were followed up for 12 months or until death, reported 1-year OS by disease stage at diagnosis and by histological subtype. The 1-year OS was the lowest for advanced stages, from 45% with a median OS time of 10.8 months for Stage IV, to 61% with a median OS time of 14.3 month for Stage IIIb, and the highest for first disease stages: 90% for Stage IIa , to 95% for Stage Ia. Among the histologic NSCLC subtypes, large cell carcinoma had a lower 1year OS (48%) and a shorter OS time (median 11.9 months) compared with adenocarcinoma (58%, median OS time 14.4 months), squamous cell carcinoma (65%, median OS time > 15 months) and other histologies (64%, median OS time > 15 months) (Carrato et al 2014). Based on data from 21 cancer registries of 7 countries (as part of ICBP SURVMARK2 project), the 1 year and 3-year age-standardized net survival (alternative terms: disease-specific survival/cancer-specific survival [CSS]) were estimated for a total of

262,040 NSCLC patients, diagnosed during 2010 to 2014 and followed until 2015. For the included European countries, the 1-year CSS was highest for Norway (50.3%; 95% CI: 49.0, 51.6), Denmark (49.4%; 95% CI: 48.3, 50.4), Ireland (47.4%; 95% CI: 45.9, 48.9) and slightly lower for the UK (44.3%; 95% CI: 43.9, 44.7). The 3-year CSS showed a similar pattern: highest for Norway (28.0%; 95% CI: 26.8, 29.2), Denmark (26.2%; 95% CI: 25.2, 27.1), Ireland (25.7%; 95% CI: 24.4, 26.9) and slightly lower for UK (22.2%; 95% CI: 21.8, 22.5). In Canada the 1-year CSS was reported as 53.0% (95% CI: 52.4, 53.5) and 3-year CSS was 31.8% (95% CI: 31.2, 32.3). For Australia, the 1-year CSS was 52.4% (95% CI: 51.6, 53.2) and the 3-year CSS was 29.0% (95% CI: 28.3, 29.8). For New Zealand, the 1-year CSS was 45.2% (95% CI: 43.6, 46.7) and the 3-year CSS was 23.1 (95% CI: 21.7, 24.4) (Morgan et al 2021).

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

Important Comorbidities

In a retrospective medical record review of 9,640 adults diagnosed with Stage I to III NSCLC treated with definitive resection in 2006 to 2007 and randomly selected from hospital based cancer registries participating in the US National Cancer Database, approximately two-thirds of the patients had at least 1 comorbidity (Wong et al 2018). The medical records from 30 days before surgery and up to 90 days after surgery indicated that the following comorbidities were present in at least 5% of patients: Chronic obstructive pulmonary disease (40.4%), coronary artery disease (20.8%), diabetes (15.4%), peripheral vascular disease (8.4%), and congestive heart failure (5.7%). Major comorbidities such as chronic obstructive pulmonary disease and cardiovascular diseases are highly prevalent in patients with LC, due to the strong association with cigarette smoking and aging.

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

PART II: MODULE SII NONCLINICAL PART OF THE SAFETY SPECIFICATION

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

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

Key Safety Findings	Relevance to Human Usage
Toxicity	
Single- and Repeated-dose Toxicity No mortality or apparent toxicity was noted at single doses up to 100 mg/kg in mice or cynomolgus monkeys. No apparent toxicity and/or treatment-related changes were observed in cynomolgus monkeys after intravenous infusion at doses of 3, 10, 30 or 60 mg/kg once every 2 weeks for 13 weeks (7 dose administrations). At 60 mg/kg, there were treatment-related changes observed consistent with immunogenicity (antidrug antibodies; ADAs) against tislelizumab and immune complex disease.	The risk of acute toxicities in patients is considered minimal. Immunogenicity-related changes in nonclinical species are not predictive for humans.
Reproductive/Developmental Toxicity	
No apparent treatment-related histopathological changes in tissues or organs, including male and female reproductive 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 uteroplacental interface (Guleria et al 2005; Habicht et al 2007; Petroff and Perchellet 2010).	Based on the mechanism of action and published literature, tislelizumab may cause harm to the fetus. Women of childbearing potential should be advised to use effective methods of contraception and avoid pregnancy while taking tislelizumab and for at least 4 months after the last dose.
Genotoxicity	
Genotoxicity studies have not been conducted with tislelizumab since the range and type of genotoxicity studies routinely conducted for pharmaceuticals are not applicable to biotechnology-derived pharmaceuticals (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [ICH] S6[R1] 2011).	Not applicable.

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

Key Safety Findings	Relevance to Human Usage
Carcinogenicity	
Carcinogenicity studies have not been conducted with tislelizumab since they are not warranted to support marketing for therapeutics intended to treat patients with advanced cancer (ICH S9 2010).	Not applicable.
Cardiovascular, Nervous, and Respiratory System	
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 S6(R1) 2011.	The potential for drug-drug interaction between tislelizumab and small molecule drug products is very low, given that tislelizumab is a therapeutic mAb and is expected to be degraded into amino acids via catabolism; therefore, it is unlikely to influence drug 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.

PART II: MODULE SIII CLINICAL STUDY EXPOSURE

Overview of Clinical Development

Tislelizumab was studied in 3 indications as mentioned below:

- Tislelizumab, in combination with pemetrexed and platinum-containing chemotherapy, is indicated for the first-line treatment of locally advanced or metastatic non-squamous NSCLC in adults expressing (≥ 18 years of age) whose tumors have no EGFR or ALK.
- Tislelizumab, in combination with carboplatin and either paclitaxel or nab-PC, is indicated for the first-line treatment of locally advanced or metastatic squamous NSCLC in adults expressing (≥ 18 years of age).
- Tislelizumab, as monotherapy is indicated for the treatment of locally advanced or metastatic NSCLC after prior chemotherapy regimen in adults (≥ 18 years of age).

Pivotal Phase III Studies

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

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

Studies Providing Supportive Safety Data

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

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

Safety Analysis Set

All analyses were performed in the Tislelizumab Safety Analysis Set. The Tislelizumab Safety Analysis Set includes all patients who received at least 1 dose of tislelizumab, either as monotherapy or in combination with other study drug.

- The Tislelizumab Monotherapy Safety Analysis Set includes all patients who received at least 1 dose of tislelizumab monotherapy from the 7 tislelizumab monotherapy studies (Studies BGB-A317-303, BGB-A317-001, BGB-A317-102, BGB-A317-203, BGB-A317-204, BGB-A317-208, BGB-A317-302).
- The Tislelizumab Combination Therapy Safety Analysis Set includes all NSCLC patients who received tislelizumab in combination with any chemotherapy from the 3 tislelizumab combination therapy studies (Studies BGB-A317-304, BGB-A317-307, BGB-A317-206). Patients in the Tislelizumab + Chemotherapy arms in Studies BGB-A317-304, BGB-A317-307 who crossed over to receive Tislelizumab were excluded from the analysis sets. Seventeen small cell LC patients from Study BGB-A317-206 were excluded from the analysis sets.

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

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

Study Numbers (Disease Type; Location)	Data Cutoff Dates	Tislelizumab Dose	Number of Patients who Received Tislelizumab
Pivotal Study			
BGB-A317-303 (NSCLC in the second- or third-line Setting; Global) A Phase III, open-label, multicenter, randomized study to investigate the efficacy and safety of tislelizumab (anti-PD-1 antibody) compared with docetaxel in patients with NSCLC who have progressed on a prior platinum-containing regimen (hereafter referred to as Study 303).	10 August 2020	200 mg Q3W	534
Supporting Studies			
BGB-A317_Study_001 (Advanced 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 anti-PD-1 mAb, tislelizumab in patients with advanced tumors (hereafter referred to as Study 001).	26 August 2020	0.5, 2, 5 or 10 mg/kg Q2W 2 or 5 mg/kg Q3W 200 mg Q3W	451
BGB-A317-102 (Advanced solid tumors; China) A Phase I/II study investigating safety, tolerability, PK and preliminary antitumor activities of anti-PD-1 mAb, tislelizumab in patients with advanced solid tumors (hereafter referred to as Study 102).	31 May 2020	200 mg Q3W; 200 mg W1D1, W5D1, then Q3W	300
BGB-A317-203 (Relapsed or refractory classical Hodgkin lymphoma; China) A single arm, multicenter, Phase II study of tislelizumab as monotherapy in relapsed or refractory classical Hodgkin lymphoma (hereafter referred to as Study 203).	26 November 2018	200 mg Q3W	70
BGB-A317-204 (PD-L1+ locally advanced or metastatic urothelial cancer; China and South Korea) A single-arm, multicenter, Phase II study of tislelizumab in patients with previously treated PD-L1+ locally advanced or metastatic urothelial cancer (hereafter referred to as Study 204).	16 September 2019	200 mg Q3W	113

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

Study Numbers (Disease Type; Location)	Data Cutoff Dates	Tislelizumab Dose	Number of Patients who Received Tislelizumab
BGB-A317-208 (Previously treated hepatocellular unresectable carcinoma; Global) A Phase II, open-label, multicenter study to investigate the efficacy, safety, and PK of the anti-PD-1 mAb, tislelizumab in patients with previously treated hepatocellular unresectable carcinoma (hereafter referred to as Study 208).	27 February 2020	200 mg Q3W	249
BGB-A317-302 (Advanced unresectable or metastatic ESCC, with disease progression during or after 1L systemic therapy; Global) A randomized, controlled, open-label, global Phase III study comparing the efficacy of the anti-PD-1 antibody tislelizumab versus chemotherapy as second-line treatment in patients with advanced unresectable/metastatic esophageal squamous cell carcinoma (hereafter referred to as Study 302).	01 December 2020	200 mg Q3W	255
Total Patients who Received Tislelizumab as Monotherapy			**1,972**

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

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

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

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

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

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

Study Numbers (Disease Type; Location)	Data Cutoff Dates	Tislelizumab Dose	Number of Patients who Received Tislelizumab
		SQ-B: *Arm T + GC* Tislelizumab + gemcitabine + cisplatin (or carboplatin) Q3W 4-6 cycles, followed by Tislelizumab Q3W SCLC: Tislelizumab + etoposide + cisplatin (or carboplatin) Q3W 4-6 cycles, followed by Tislelizumab Q3W	
Total Patients who Received Tislelizumab as Monotherapy			**497**

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

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

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

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

Extent of Exposure

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

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

Duration of Exposure	Patients n (%)	Person Time
Total Population		
< 1 month	189 (7.7)	126.53
1 - < 3 months	758 (30.7)	1,536.42
3 - < 6 months	460 (18.6)	2,049.65
6 - < 12 months	472 (19.1)	4,003.25
12 - < 18 months	301 (12.2)	4,483.57
18 - < 24 months	176 (7.1)	3,589.13
> 24 months	113 (4.6)	3,501.70
Total	**2,469 (100.0)**	**19,290.25**
1L SQ NSCLC		
< 1 month	14 (5.4)	9.63
1 - < 3 months	28 (10.8)	53.94
3 - < 6 months	44 (16.9)	223.54
6 - < 12 months	72 (27.7)	664.03
12 - < 18 months	49 (18.8)	758.64
18 - < 24 months	45 (17.3)	923.45
> 24 months	8 (3.1)	202.12
Total	**260 (100.0)**	**2,835.35**
1L NSQ NSCLC		
< 1 month	14 (5.8)	9.66
1 - < 3 months	27 (11.3)	63.54
3 - < 6 months	45 (18.8)	210.04
6 - < 12 months	67 (27.9)	561.07
12 - < 18 months	52 (21.7)	818.94
18 - < 24 months	31 (12.9)	637.59
> 24 months	4 (1.7)	105.53
Total	**240 (100.0)**	**2,406.37**
2L+ NSCLC		
< 1 month	44 (6.9)	28.06
1 - < 3 months	177 (27.8)	359.52
3 - < 6 months	136 (21.4)	595.61

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

Duration of Exposure	Patients n (%)	Person Time
6 - < 12 months	140 (22.0)	1,173.75
12 - < 18 months	69 (10.8)	1,004.91
18 - < 24 months	35 (5.5)	719.54
> 24 months	35 (5.5)	1,059.06
Total	**636 (100.0)**	**4,940.45**

Abbreviations: 1L, first-line; 2L+, second-line onwards; NSQ, non-squamous; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; SQ, squamous.
Source data: Annex 7 Table 1.1 and Annex 7 Table 1.2.
Studies include monotherapy studies (Studies 001, 102, 203, 204, 208, 302, 303) and combination studies (Studies 206, 304, 307).
Tislelizumab-treated patients who switched from the chemotherapy control arms in Studies 304 and 307 were not included. Patients from SCLC cohort in Study 206 were not included.
Person time is sum of treatment duration (months) for all patients in the row.
Percentages are based on the number of patients who received at least a dose of tislelizumab.

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

Age Group	Sex			
	Male		Female	
	Persons n (%)	Person Time	Persons n (%)	Person Time
1L SQ NSCLC				
≥ 18 and < 55 years	37 (14.2)	430.53	10 (3.8)	116.87
≥ 55 and < 65 years	109 (41.9)	1132.74	7 (2.7)	78.29
≥ 65 and < 75 years	91 (35.0)	1003.48	6 (2.3)	73.44
≥ 75 years	0 (0.0)	0	0 (0.0)	0
Total	**237 (91.2)**	**2,566.75**	**23 (8.8)**	**268.60**
1L NSQ NSCLC				
≥ 18 and < 55 years	35 (14.6)	362.07	22 (9.2)	217.46
≥ 55 and < 65 years	89 (37.1)	892.50	27 (11.3)	298.86
≥ 65 and < 75 years	49 (20.4)	480.28	13 (5.4)	111.31
≥ 75 years	5 (2.1)	43.90	0 (0.0)	0
Total	**178 (74.2)**	**1,778.74**	**62 (25.8)**	**627.63**
2L+ NSCLC				
≥ 18 and < 55 years	108 (17.0)	942.09	59 (9.3)	373.06
≥ 55 and < 65 years	208 (32.7)	1551.74	58 (9.1)	394.45
≥ 65 and < 75 years	151 (23.7)	1275.79	35 (5.5)	296.38

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

Age Group	Sex			
	Male		Female	
	Persons n (%)	Person Time	Persons n (%)	Person Time
≥ 75 years	13 (2.0)	83.94	4 (0.6)	23.00
Total	**480 (75.5)**	**3,853.57**	**156 (24.5)**	**1,086.88**

Abbreviations: 1L, first-line; 2L+, second-line onwards; NSQ, non-squamous; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; SQ, squamous.
Source data: Annex 7 Table 1.5.
Studies include monotherapy studies (Studies 001, 102, 203, 204, 208, 302, 303) and combination studies (Studies 206, 304, 307).
Tislelizumab-treated patients who switched from the chemotherapy control arms in Studies 304 and 307 were not included. Patients from SCLC cohort in Study 206 were not included.
Person time is sum of treatment duration (months) for all patients in the row.
Percentages are based on the number of patients who received at least a dose of tislelizumab.

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

Dose Level of Exposure	Persons n (%)	Person Time
1L SQ NSCLC		
200 mg Q3W	260 (100.0)	2,835.35
5.0 mg/kg Q3W	0 (0.0)	0
2.0 mg/kg Q3W	0 (0.0)	0
10.0 mg/kg Q2W	0 (0.0)	0
5.0 mg/kg Q2W	0 (0.0)	0
2.0 mg/kg Q2W	0 (0.0)	0
0.5 mg/kg Q2W	0 (0.0)	0
Total	**260 (100.0)**	**2,835.35**
1L NSQ NSCLC		
200 mg Q3W	238 (99.2)	2397.34
5.0 mg/kg Q3W	2 (0.8)	9.03
2.0 mg/kg Q3W	0 (0.0)	0
10.0 mg/kg Q2W	0 (0.0)	0
5.0 mg/kg Q2W	0 (0.0)	0
2.0 mg/kg Q2W	0 (0.0)	0
0.5 mg/kg Q2W	0 (0.0)	0
Total	**240 (100.0)**	**2,406.37**

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

Dose Level of Exposure	Persons n (%)	Person Time
2L+ NSCLC		
200 mg Q3W	589 (92.6)	4,531.45
5.0 mg/kg Q3W	47 (7.4)	409.00
2.0 mg/kg Q3W	0 (0.0)	0
10.0 mg/kg Q2W	0 (0.0)	0
5.0 mg/kg Q2W	0 (0.0)	0
2.0 mg/kg Q2W	0 (0.0)	0
0.5 mg/kg Q2W	0 (0.0)	0
Total	**636 (100.0)**	**4,940.45**

Abbreviations: 1L, first-line; 2L+, second-line onwards; NSQ, non-squamous; NSCLC, non-small cell lung cancer; QxW, every x weeks; SCLC, small cell lung cancer; SQ, squamous.
Source data: Annex 7 Table 1.3.
Studies include monotherapy studies (Studies 001, 102, 203, 204, 208, 302, 303) and combination studies (Studies 206, 304, 307).
Tislelizumab-treated patients who switched from the chemotherapy control arms in Studies 304 and 307 were not included. Patients from SCLC cohort in Study 206 were not included.
Person time is sum of treatment duration (months) for all patients in the row.
Percentages are based on the number of patients who received at least a dose of tislelizumab.

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

Race	Persons n (%)	Person Time
1L SQ NSCLC		
American Indian or Alaska Native	0 (0.0)	0
Asian	260 (100.0)	2,835.35
Black or African American	0 (0.0)	0
Native Hawaiian or Other Pacific Islander	0 (0.0)	0
White	0 (0.0)	0
Other	0 (0.0)	0
Not Reported	0 (0.0)	0
Total	**260 (100.0)**	**2,835.35**
1L NSQ NSCLC		
American Indian or Alaska Native	0 (0.0)	0
Asian	238 (99.2)	2,397.34
Black or African American	0 (0.0)	0
Native Hawaiian or Other Pacific Islander	0 (0.0)	0

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

Race	Persons n (%)	Person Time
White	2 (0.8)	9.03
Other	0 (0.0)	0
Not Reported	0 (0.0)	0
Total	**240 (100.0)**	**2,406.37**
2L+ NSCLC		
American Indian or Alaska Native	12 (1.9)	70.11
Asian	499 (78.5)	3,956.57
Black or African American	2 (0.3)	8.31
Native Hawaiian or Other Pacific Islander	4 (0.6)	47.74
White	115 (18.1)	844.75
Other	4 (0.6)	12.98
Not Reported	0 (0.0)	0
Total	**636 (100.0)**	**4,940.45**

Abbreviations: 1L, first-line; 2L+, second-line onwards; NSQ, non-squamous; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; SQ, squamous.
Source data: Annex 7 Table 1.9.
Studies include monotherapy studies (Studies 001, 102, 203, 204, 208, 302, 303) and combination studies (Studies 206, 304, 307).
Tislelizumab-treated patients who switched from the chemotherapy control arms in Studies 304 and 307 were not included. Patients from SCLC cohort in Study 206 were not included.
Person time is sum of treatment duration (months) for all patients in the row.
Percentages are based on the number of patients who received at least a dose of tislelizumab.
Annex 7 Table 1.8 provides the information regarding ethnic origin (Hispanic or Latino [0.5%], Not Hispanic or Latino [93.5%], Not reported [6.0%], for any of the indications).

PART II: MODULE SIV POPULATIONS NOT STUDIED IN CLINICAL STUDIES

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

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

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

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

Conditions requiring systemic treatment with corticosteroids or other immunosuppressive medications.	
Reason for Being an Exclusion Criterion	Immunosuppressive medications may attenuate the effects of anti-PD-1 treatment. Such conditions may impact the interpretation of study results.
Considered to be Included as Missing Information	No
Rationale (if not included as missing information)	Prior to starting tislelizumab, corticosteroids and other immunosuppressants should be avoided because of their potential interference with the pharmacodynamic activity of tislelizumab. For the same reason, these patients were excluded in the clinical studies. However, systemic corticosteroids and other immunosuppressants can be used after starting tislelizumab to treat immune-mediated adverse reactions, in the postmarketing setting.
History of Interstitial Lung Disease, Noninfectious Pneumonitis or Uncontrolled Systemic Diseases, Including Diabetes, Hypertension, Pulmonary Fibrosis, Acute Lung Diseases.	
Reason for Being an Exclusion Criterion	Such conditions may impact the interpretation of study results.
Considered to be Included as Missing Information	No
Rationale (if not included as missing information)	These patients may benefit from treatment with tislelizumab; however, such conditions and associated therapies may confound efficacy and safety assessment of the study and were therefore excluded. The treating physician would be expected to evaluate the benefit and risks in individual patients.
History of Severe Hypersensitivity Reactions to mAbs.	
Reason for Being an Exclusion Criterion	To reduce the risk of a patient experiencing hypersensitivity to tislelizumab.
Considered to be Included as Missing Information	No
Rationale (if not included as missing information)	Hypersensitivity to tislelizumab is listed as a contraindication in the EU SmPC.
Prior Therapy Targeting PD-1 or PD-L1.	
Reason for Being an Exclusion Criterion	Prior therapy targeting PD-1 or PD-L1 may impact the interpretation of study results.
Considered to be Included as Missing Information	No
Rationale (if not included as missing information)	The target population is intended to be naïve to treatment with anti-PD-1/PD-L1 therapy.
Use of Live or Attenuated Vaccines Within 4 weeks.	
Reason for Being an Exclusion Criterion	Use of live or attenuated vaccines within 4 weeks may impact the interpretation of study results.
Considered to be Included as Missing Information	No

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

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

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

Severe Hepatic Impairment. (eg, serum total bilirubin ≥ 1.5 x upper limit of normal [ULN], or serum total bilirubin ≥ 34.2 µmol/L [2 mg/dL] for patients with hepatocellular carcinoma [HCC]; aspartate aminotransferase [AST] and alanine aminotransferase [ALT] ≥ 2.5 x ULN, or AST and ALT ≥ 5 x ULN for patients with liver metastases or HCC.)	
Reason for Being an Exclusion Criterion	Severe hepatic impairment may impact the interpretation of study results.
Considered to be Included as Missing Information	No
Rationale (if not included as missing information)	Tislelizumab is a mAb and unlikely to be metabolized by the liver. As such, formal pharmacokinetic (PK) interaction studies have not been conducted and are not warranted.
Severe Renal Impairment. (eg, estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m^2 by Chronic Kidney Disease Epidemiology Collaboration Equation [Levey et al 2009; Stevens and Levin 2013].)	
Reason for Being an Exclusion Criterion	Severe renal impairment may impact the interpretation of study results.
Considered to be Included as Missing Information	No
Rationale (if not included as missing information)	Tislelizumab is a mAb and unlikely to be metabolized by the kidneys. As such, formal PK interaction studies have not been conducted and are not warranted.
Severe Chronic or Active Infections Requiring Systemic Therapy.	
Reason for Being an Exclusion Criterion	Infection may impact the interpretation of study results.
Considered to be Included as Missing Information	No
Rationale (if not included as missing information)	There is no evidence that tislelizumab worsens bacterial infections. These patients may benefit from treatment. The treating physician would be expected to evaluate the benefit and risks in individual patients.
Untreated Chronic Hepatitis B Virus (HBV) or Chronic HBV Carriers with HBV DNA ≥ 200 to 500 IU/mL (1000 to 2500 copies/mL), or Active Hepatitis C Virus (HCV), or Human Immunodeficiency Virus Infection. (Active HCV and major surgery within 28 days were exclusion criteria for non-HCC indications only.)	
Reason for Being an Exclusion Criterion	Infection may impact the interpretation of study results.
Considered to be Included as Missing Information	No
Rationale (if not included as missing information)	Patients with HCV and HBV have been included in clinical studies investigating the use of tislelizumab. There is no evidence that tislelizumab worsens viral infections. These patients may benefit from treatment. The treating physician would be expected to evaluate the benefit and risks in individual patients.
Patients Aged < 18 Years.	
Reason for Being an Exclusion Criterion	Pediatric patients were not included in the clinical development program.

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

Considered to be Included as Missing Information	No
Rationale (if not included as missing information)	Use in pediatric patients is not recommended and is also not expected considering the indications' incidence/prevalence in this age group.
Use During Pregnancy or Lactation.	
Reason for Being an Exclusion Criterion	The blockade of the PD-1/PD-L1 pathway in inducing 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 childbearing potential should be advised to avoid pregnancy and breastfeed while taking tislelizumab.
Considered to be Included as Missing Information	No
Rationale (if not included as missing information)	There is no available human data regarding the risk of embryofetal toxicity. Women of childbearing potential should be advised to use effective contraception during treatment with tislelizumab and for 4 months after the last dose (SmPC). This topic is covered within the important potential risk of reproductive and developmental toxicity.
Uncontrollable Pleural Effusion, Pericardial Effusion, or Ascites Requiring Repeated Drainage.	
Reason for Being an Exclusion Criterion	Such conditions may impact the interpretation of study results.
Considered to be Included as Missing Information	No
Rationale (if not included as missing information)	General exclusion criterion to ensure patient safety in clinical studies not associated with specific safety concerns for tislelizumab. These patients may benefit from treatment with tislelizumab. In the postmarketing setting the treating physician would be expected to evaluate the benefit and risks in individual patients.
Major Surgery Within 28 Days. (Active HCV and major surgery within 28 days were exclusion criteria for non-HCC indications only.)	
Reason for Being an Exclusion Criterion	To ensure patient safety. Major surgery within 4 weeks of entering the study may impact the interpretation of study results.
Considered to be Included as Missing Information	No
Rationale (if not included as missing information)	These patients may benefit from treatment with tislelizumab; however, major surgery may confound efficacy and safety assessment of the study. In the postmarketing setting it is expected that the treating physician will evaluate when the individual patient has recovered enough from major surgery to receive new anticancer therapy.

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

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.

SIV.3 Limitations in Respect to Populations Typically Underrepresented in Clinical Study Development Programs

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

Type of Special Population	Exposure
Pregnant Women	Not included in the clinical development program.
Breastfeeding Women	Not included in the clinical development program.
Patients with Relevant Comorbidities:	
Patients with Renal Impairment (Defined as eGFR 60 to 89 mL/min/1.73 m^2, mild; 30 to 59 mL/min/1.73 m^2, moderate; and 15 to 29 mL/min/1.73 m^2, severe; using the Chronic Kidney Disease Epidemiology Collaboration Equation [Levey et al 2009; Stevens and Levin 2013].)	Renal impairment was reported in 1,053/2,469 (42.6%) patients (8,709.16 person-time; person time is sum of treatment duration [months]) who received tislelizumab as monotherapy in Study 001, Study 102, Study 203, Study 204, Study 208, Study 302 and Study 303 and as combination therapy from Study 206, Study 304, and Study 307. Normal renal function was reported in 1,416 (57.4%) patients (10,581.09 person-time) (Annex 7 Table 2.1). Based on a population PK analysis, no dose adjustment of tislelizumab is recommended for patients with mild to moderate renal impairment (creatinine clearance ≥ 30 mL/min). Specific PK studies in patients with renal impairment are not warranted.
Patients with Hepatic Impairment (Defined as AST > ULN; serum total bilirubin > 1 to 1.5 x ULN, mild; > 1.5 to 3 x ULN, moderate; and > 3 x ULN, severe.)	Hepatic impairment was reported in 411/2,469 (16.6%) patients (2,303.06 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 2,052 (83.1%) patients (16,949.67 person-time). In 6 (0.2%) patients, information on hepatic impairment at baseline 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 hepatic impairment (total bilirubin ≤ 3 times ULN and any AST). Specific PK studies in patients with hepatic impairment are not warranted.
Patients with Cardiovascular Impairment (For example, heart failure of New York Heart Association cardiac disease Class III or greater, myocardial infarction, unstable arrhythmias, or unstable angina.)	Not included in the clinical development 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 study exposure data on race including ethnicity is presented in Table Part II: Module SIII-6.

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

Type of Special Population	Exposure
Subpopulations Carrying Relevant Genetic Polymorphisms.	Patients with known 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 nonsquamous histology in Study 303. Additionally, although patients with known ALK-fusion oncogene were excluded, patients (nonsquamous or squamous histology in 3 studies) with unknown ALK-fusion oncogene status were not required to be tested at screening.

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

	Persons n (%)	Person Time
Renal Impairment Status at Baseline		
Normal	1,416 (57.4)	10,581.09
Impairment	1,053 (42.6)	8,709.16
Hepatic Impairment Status at Baseline		
Normal	2,052 (83.1)	16,949.67
Impairment	411 (16.6)	2,303.06
Missing	6 (0.2)	37.52

Abbreviations: AST, aspartate aminotransferase; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; SCLC, small cell lung cancer; ULN, upper limit of normal.
Source data: Annex 7 Table 2.1.
Studies include monotherapy studies (Studies 001, 102, 203, 204, 208, 302, 303) and combination studies (Studies 206, 304, 307).
Tislelizumab-treated patients who switched from the chemotherapy control arms in Studies 304 and 307 were not included. Patients from SCLC cohort in Study 206 were not included.
Person time is sum of treatment duration (months) for all patients in the row.
Percentages are based on the number of patients who received at least a dose of tislelizumab.
The hepatic impairment status at baseline was determined by the baseline total bilirubin and AST value according to the criterion below. Patients with missing baseline total bilirubin or AST (if any) would be considered and reported as "Missing" for hepatic impairment status.
Total bilirubin: Normal ≤ ULN; Mild (Scenario 1): ≤ ULN, Mild (Scenario 2): > 1 to 1.5 x ULN; Moderate: > 1.5 to 3 x ULN; Severe: > 3 x ULN.
Aspartate aminotransferase: Normal ≤ ULN; Mild Scenario 1: > ULN, Mild Scenario 2: Any; Moderate: Any; Severe: Any.
The renal impairment status at baseline was determined by the eGFR (ml/min) according to the criterion below. The eGFR was calculated using the CKD-EPI equation with serum creatinine at baseline, sex, race, and age at baseline for patients in the Tislelizumab Monotherapy Safety Analysis Set and the Cockcroft-Gault equation with serum creatinine, age and weight at baseline for patients in the Tislelizumab Combination Therapy Safety Analysis Set. Patients with missing serum creatinine at baseline (if any) would be considered and reported as "Missing" for renal impairment status.
Renal Impairment status (eGFR [mL/min or mL/min/1.73 m^2]):
Normal: ≥ 90; Mild impairment: 60 to < 90; Moderate impairment: 30 to < 60; Severe impairment: 15 to < 30; End state: < 15.

PART II: MODULE SV POST-AUTHORIZATION EXPERIENCE

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

SV.1 Post-authorization Exposure

As of PBRER DLP (25 December 2022), CCI [redacted]

SV.1.1 Method Used to Calculate Exposure

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

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

SV.1.2 Exposure

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

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

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

PART II: MODULE SVI ADDITIONAL REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for Misuse for Illegal Purposes

Commonly misused classes of prescription drugs include opioid pain relievers, stimulants, and CNS depressants (sedatives and 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.

PART II: MODULE SVII IDENTIFIED AND POTENTIAL RISKS

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

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

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

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

- None

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

- None

Known risks that require no further 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 (eg, actions being part of standard clinical practice in each EU Member state where the product is authorized):

- **Infusion-related Reaction**

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

  IRR was reported in 83 (4.2%) of the 1,972 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 adverse event (AE), of which the outcome was recovered/resolved in all 7 (0.4%) patients. AEs related to IRR led to treatment discontinuation for 5 (0.3%) patients and dose interruption for 18 (0.9%) patients (Annex 7 Table 3.1.2.1, Annex 7 Table 3.2.2.1, Annex 7 Table 3.3.2.1).

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

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

- None

Other reasons for considering the risks not important:

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

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

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

Reason for Classification as an Important Identified Risk:

- **Immune-mediated Adverse Reactions**

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

  Immune-mediated adverse reactions were reported in 335 (17%) of the 1,972 patients who received tislelizumab as monotherapy.

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

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

  Data from monotherapy studies (including Study 001, Study 102, Study 203, Study 204, Study 208, Study 302, and Study 303): Immune-mediated pneumonitis was reported for 77 (3.9%) of the 1,972 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.

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

  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 1,972 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 dose modification in 21 patients (1.1%).

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

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

Data from monotherapy studies: Immune-mediated skin adverse reaction was reported for 32 (1.6%) of the 1,972 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.

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

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 1,972 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%).

Data from combination therapy studies: In combination therapy, immune-mediated colitis was reported in 7 (1.4%) of the 497 patients. In these studies, 4 patients (0.8%) experienced a serious event of immune-mediated colitis, of which the outcomes were recovered/resolved for 2 patients (0.4%), recovering/resolving for 1 patient (0.2%) and not recovered/not resolved for 1 patient (0.2%). Immune-mediated colitis led to treatment discontinuation for 3 (0.6%) and dose modification in 3 (0.6%) of patients.

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 1,972 patients who received tislelizumab as monotherapy. In these studies, 7 patients (0.4%) experienced a serious event of immune-mediated myositis/rhabdomyolysis of which the outcomes were

recovered/resolved in 3 patients (0.2%) and not recovered/not resolved for 4 patients (0.2%). Immune-mediated myositis/rhabdomyolysis led to treatment discontinuation for 3 patients (0.2%) and dose modification in 10 patients (0.5%).

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

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

Hypothyroidism

Data from monotherapy studies: Immune-mediated hypothyroidism was reported for 133 (6.7%) of the 1,972 patients who received tislelizumab as monotherapy. In these studies, 1 patient (0.1%) experienced a serious event of immune-mediated hypothyroidism, of which the outcome was recovered/resolved. AE of hypothyroidism led to dose modification in 6 (0.3%) of patients.

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

Hyperthyroidism

Data from monotherapy studies: Immune-mediated hyperthyroidism was reported for 12 (0.6%) of the 1,972 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%).

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

Thyroiditis

Data from monotherapy studies: Immune-mediated thyroiditis was reported for 13 (0.7%) of the 1,972 patients who received tislelizumab as monotherapy. In these studies, there were no serious events of immune-mediated thyroiditis. Dose modification was reported in 2 patients (0.1%).

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

Adrenal Insufficiency

Data from monotherapy studies: Immune-mediated adrenal insufficiency was reported for 6 (0.3%) of the 1,972 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.

Data from combination therapy studies: No events of immune-mediated adrenal insufficiency were reported in the combination therapy.

Pituitary Dysfunction

Data from monotherapy studies: Pituitary dysfunction was reported for 1 (0.1%) of the 1,972 patients who received tislelizumab as monotherapy. In these studies, there were no serious events of pituitary dysfunction.

Data from combination therapy studies: No events of pituitary dysfunction were reported in the combination therapy.

Type 1 Diabetes Mellitus

Data from monotherapy studies: Immune-mediated type 1 diabetes mellitus was reported for 8 (0.4%) of the 1,972 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.

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

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

Data from monotherapy studies: Immune-mediated nephritis and renal dysfunction was reported in 10 (0.5%) of the 1,972 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.

Data from combination therapy studies: In combination therapy, immune-mediated nephritis and renal dysfunction was reported in 5 (1.0%) of the 497 patients. In these studies, 2 patients (0.4%) experienced a serious event of

immune-mediated nephritis and renal dysfunction, of which the outcomes were recovered/resolved and recovering/resolving in 1 patient (0.2%), each. No treatment discontinuation was reported; however, dose modification was reported in 5 (1.0%) of patients.

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

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 1,972 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.

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

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

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

Data from monotherapy studies: Immune-mediated pancreatitis was reported in 1 patient (0.1%) who received tislelizumab as monotherapy. In these studies, 1 (0.1%) of the 1,972 patients experienced a serious event of immune-mediated pancreatitis, the outcome of which was recovered/resolved. Immune-mediated pancreatitis led to dose modification in 1 patient (0.1%).

Data from combination therapy studies: In combination therapy studies, no AEs related to immune-mediated pancreatitis were reported.

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

Data from monotherapy studies: Other immune-mediated reactions (Preferred Terms [PTs]: Arthritis, [n = 4], Immune-mediated arthritis [n = 1], Pericarditis [n = 1 and Polymyalgia rheumatica [n = 1]) were reported in 7 (0.4%) of the 1,972 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.

Data from combination therapy studies: No events of other immune-mediated reactions were reported in the combination therapy.

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

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

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

Reason for Classification as an Important Potential Risk:

- **Reproductive and Developmental Toxicity**

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

  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 childbearing potential should use effective contraception during treatment with tislelizumab and for at least 4 months after the last dose of tislelizumab.

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

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

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

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

There are no new safety concerns and/or reclassification.

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

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

The data presented in this EU RMP are based on a population of 1,972 patients treated with tislelizumab monotherapy in Study 001, Study 102, Study 203, Study 204, Study 208, Study 302, and Study 303, and 497 patients from Study 304, Study 307, and Study 206 in chemotherapy combination therapy. As discussed in Part II: Module SIII, the total person time of exposure to date for all patients who have received tislelizumab is 19,290.25 patient-months.

For the immune-mediated identified and potential risks, the Medical Dictionary for Regulatory Activities PTs listed in Annex 7 Listing 1.1 were used to identify potential immune-mediated events. The methodology for diagnostic evaluation and management of imAEs was based on American Society of Clinical Oncology and European Society for Medical Oncology guidelines (Brahmer et al 2018; Haanen et al 2017). Potential imAEs included treatment-emergent AEs (TEAEs) that started on or after the first dose of tislelizumab and required treatment with systemic corticosteroids or other 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 etiologies of potential imAE cases.

Important Identified Risk:

Immune-mediated Adverse Reactions:

Potential Mechanisms:

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

Evidence Source(s) and Strength of Evidence:

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

Immune-mediated Pneumonitis

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

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

Immune-mediated Hepatitis

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

Clinical data: Although infrequently observed, the occurrence of immune-mediated hepatitis is well established in patients treated with ICIs. These patients are typically asymptomatic, and diagnosis is made 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 after intravenous infusion at doses of 3, 10, 30 mg/kg or 60 mg/kg (once every 2 weeks, 7 doses) for 13 weeks.

Clinical data: Skin AEs are among the most frequent AEs observed in patients treated with mAbs inhibiting either immune checkpoints cytotoxic T lymphocyte-associated protein 4 (CTLA4; ipilimumab in 43% to 45% of the patients) or PD-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 after intravenous infusion at doses of 3, 10, 30 mg/kg or 60 mg/kg (once every 2 weeks, 7 doses) for 13 weeks.

Clinical data: Diarrhea and colitis are more frequent with anti-CTLA4 agents (eg, ipilimumab) than with anti-PD-1 targeted agents including nivolumab or pembrolizumab, with Grade 3 to 4 AEs occurring in 1% to 2% of cases (Haanen et al 2017). The presence of 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 after intravenous infusion at doses of 3, 10, 30 mg/kg or 60 mg/kg (once every 2 weeks, 7 doses) for 13 weeks.

Clinical data: Immune-mediated myositis/rhabdomyolysis occur uncommonly in cancer patients treated with ICIs (Abdel-Rahman et al 2017). 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 after intravenous infusion at doses of 3, 10, 30 mg/kg or 60 mg/kg (once every 2 weeks, 7 doses) for 13 weeks.

Clinical data: Thyroid disease or abnormalities in thyroid function tests (primary hypothyroidism and thyroiditis) is one of the most common endocrine imAEs. Thyroid dysfunction (hypothyroidism, hyperthyroidism, and thyroiditis) was reported in 6 to 20% of patients in large Phase III clinical studies (Puzanov et al 2017). Pituitary dysfunction is a rare condition which occurs in 0.5-1% of patients treated with anti-PD-1/PD-L1 monotherapy and up to 10% with combination CTLA4/PD-1 blockade. In contrast to thyroid disorders, most patients with pituitary dysfunction present with clinical symptoms commonly related to neuro-compression or more often, to secondary adrenal insufficiency including fatigue and nausea. Primary adrenal insufficiency is a rare complication of ICI therapy. Diabetes Mellitus after treatment with ICIs occurs in slightly < 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 after intravenous infusion at doses of 3, 10, 30 mg/kg or 60 mg/kg (once every 2 weeks, 7 doses) for 13 weeks. Secondary renal changes were observed at 60 mg/kg due to immunogenicity against tislelizumab (ADAs).

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

Immune-mediated Myocarditis

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

Clinical data: Myocarditis and cardiac dysfunction due to ICIs are rare and the true incidence is unknown; current estimates suggest this incidence is < 1% of patients. Cardiac immune-mediated AEs due to ICIs may present with nonspecific symptoms such as fatigue and weakness. However, more typical cardiac symptoms of chest pain, shortness of breath, pulmonary or lower extremity edema, palpitations, irregular heartbeat, rapid onset of heart failure symptoms or new heart block on electrocardiogram can occur at any time, more frequently within the first few months of treatment and may lead to death (Puzanov et al 2017).

Immune-mediated Nervous System Disorders

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

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

Immune-mediated Pancreatitis

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

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

Other Immune-mediated Reactions

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

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

Characterization of the Risk - Data:

See Table Part II: Module SVII-2.

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

	Monotherapy (N = 1,972) n (%) (95% CI)[a]	**Combination therapy (N = 497) n (%) (95% CI)[a]**
Immune-mediated Pneumonitis		
Incidence		
Patients with at least one AE	77 (3.9) (3.1, 4.9)	45 (9.1) (6.7, 11.9)
Pneumonitis	44 (2.2)	33 (6.6)
Immune-mediated pneumonitis	13 (0.7)	8 (1.6)
Interstitial lung disease	12 (0.6)	4 (0.8)
Pneumonia	6 (0.3)	2 (0.4)
Organising pneumonia	2 (0.1)	0 (0.0)
Severity and Nature of Risk		
Patients with worst Grade 3 AE	29 (1.5)	15 (3.0)
Pneumonitis	17 (0.9)	11 (2.2)
Interstitial lung disease	6 (0.3)	0 (0.0)
Immune-mediated pneumonitis	3 (0.2)	4 (0.8)
Organising pneumonia	2 (0.1)	0 (0.0)
Pneumonia	1 (0.1)	0 (0.0)
Patients with worst Grade 4 AE	5 (0.3)	2 (0.4)
Immune-mediated pneumonitis	2 (0.1)	0 (0.0)
Interstitial lung disease	2 (0.1)	1 (0.2)
Pneumonitis	1 (0.1)	1 (0.2)
Patients with worst Grade 5 AE	4 (0.2)	3 (0.6)
Pneumonitis	2 (0.1)	3 (0.6)

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

	Monotherapy (N = 1,972) n (%) (95% CI)[a]	**Combination therapy (N = 497) n (%) (95% CI)[a]**
Pneumonia	2 (0.1)	0 (0.0)
Patients with at least one AE leading to discontinuation of Tislelizumab	36 (1.8)	20 (4.0)
Pneumonitis	21 (1.1)	15 (3.0)
Immune-mediated pneumonitis	7 (0.4)	3 (0.6)
Interstitial lung disease	6 (0.3)	2 (0.4)
Organising pneumonia	1 (0.1)	0 (0.0)
Pneumonia	1 (0.1)	0 (0.0)
Patients with at least one immune-mediated AE leading to dose modification of Tislelizumab	29 (1.5)	21 (4.2)
Pneumonitis	16 (0.8)	15 (3.0)
Pneumonia	2 (0.1)	1 (0.2)
Immune-mediated pneumonitis	5 (0.3)	3 (0.6)
Interstitial lung disease	5 (0.3)	2 (0.4)
Organising pneumonia	1 (0.1)	0 (0.0)
Patients with at Least One SAE	55 (2.8) (2.1, 3.6)	33 (6.6) (4.6, 9.2)
Pneumonitis	28 (1.4)	26 (5.2)
Immune-mediated pneumonitis	11 (0.6)	4 (0.8)
Interstitial lung disease	9 (0.5)	3 (0.6)
Pneumonia	5 (0.3)	0 (0.0)
Organising pneumonia	2 (0.1)	0 (0.0)
Outcome (of SAEs)		
Death	4 (0.2)	3 (0.6)

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

	Monotherapy (N = 1,972) n (%) (95% CI)[a]	**Combination therapy (N = 497) n (%) (95% CI)[a]**
Pneumonitis	2 (0.1)	3 (0.6)
Pneumonia	2 (0.1)	0 (0.0)
Recovered/resolved	25 (1.3)	13 (2.6)
Pneumonitis	12 (0.6)	10 (2.0)
Immune-mediated pneumonitis	6 (0.3)	3 (0.6)
Pneumonia	3 (0.2)	0 (0.0)
Interstitial lung disease	3 (0.2)	0 (0.0)
Organising pneumonia	1 (0.1)	0 (0.0)
Recovered/resolved with sequelae	1 (0.1)	0 (0.0)
Organising pneumonia	1 (0.1)	0 (0.0)
Recovering/resolving	12 (0.6)	10 (2.0)
Pneumonitis	5 (0.3)	7 (1.4)
Interstitial lung disease	4 (0.2)	2 (0.4)
Immune-mediated pneumonitis	3 (0.2)	1 (0.2)
Not recovered/not resolved	14 (0.7)	6 (1.2)
Pneumonitis	9 (0.5)	6 (1.2)
Immune-mediated pneumonitis	2 (0.1)	0 (0.0)
Interstitial lung disease	2 (0.1)	0 (0.0)
Pneumonia	1 (0.1)	0 (0.0)
Unknown	0 (0.0)	1 (0.2)
Interstitial lung disease	0 (0.0)	1 (0.2)

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

	Monotherapy (N = 1,972) n (%) (95% CI)[a]	**Combination therapy (N = 497) n (%) (95% CI)[a]**
Immune-mediated Hepatitis		
Incidence		
Patients with at least one AE	36 (1.8) (1.3, 2.5)	8 (1.6) (0.7, 3.1)
Alanine aminotransferase increased	12 (0.6)	1 (0.2)
Aspartate aminotransferase increased	9 (0.5)	1 (0.2)
Hepatitis	8 (0.4)	0 (0.0)
Immune-mediated hepatitis	6 (0.3)	3 (0.6)
Blood bilirubin increased	2 (0.1)	2 (0.4)
Hepatic failure	2 (0.1)	1 (0.2)
Hepatocellular injury	2 (0.1)	0 (0.0)
Liver injury	2 (0.1)	1 (0.2)
Autoimmune hepatitis	1 (0.1)	0 (0.0)
Bilirubin conjugated increased	1 (0.1)	1 (0.2)
Drug-induced liver injury	1 (0.1)	0 (0.0)
Gamma-glutamyltransferase increased	1 (0.1)	1 (0.2)
Transaminases increased	1 (0.1)	0 (0.0)
Severity and Nature of Risk		
Patients with worst Grade 3 AE	20 (1.0)	6 (1.2)
Alanine aminotransferase increased	5 (0.3)	1 (0.2)
Aspartate aminotransferase increased	5 (0.3)	0 (0.0)
Hepatitis	5 (0.3)	0 (0.0)

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

	Monotherapy (N = 1,972) n (%) (95% CI)[a]	**Combination therapy (N = 497) n (%) (95% CI)[a]**
Hepatocellular injury	2 (0.1)	0 (0.0)
Immune-mediated hepatitis	2 (0.1)	3 (0.6)
Liver injury	2 (0.1)	0 (0.0)
Drug-induced liver injury	1 (0.1)	0 (0.0)
Gamma-glutamyltransferase increased	1 (0.1)	1 (0.2)
Transaminases increased	1 (0.1)	0 (0.0)
Bilirubin conjugated increased	0 (0.0)	1 (0.2)
Patients with worst Grade 4 AE	1 (0.1)	0 (0.0)
Immune-mediated hepatitis	1 (0.1)	0 (0.0)
Patients with worst Grade 5 AE	2 (0.1)	1 (0.2)
Hepatic failure	2 (0.1)	1 (0.2)
Patients with at least one AE leading to discontinuation of Tislelizumab	9 (0.5)	3 (0.6)
Alanine aminotransferase increased	2 (0.1)	0 (0.0)
Aspartate aminotransferase increased	2 (0.1)	0 (0.0)
Hepatitis	2 (0.1)	0 (0.0)
Drug-induced liver injury	1 (0.1)	0 (0.0)
Hepatic failure	1 (0.1)	1 (0.2)
Hepatocellular injury	1 (0.1)	0 (0.0)
Liver injury	1 (0.1)	0 (0.0)
Transaminases increased	1 (0.1)	0 (0.0)
Bilirubin conjugated increased	0 (0.0)	1 (0.2)

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

	Monotherapy (N = 1,972) n (%) (95% CI)[a]	**Combination therapy (N = 497) n (%) (95% CI)[a]**
Immune-mediated hepatitis	0 (0.0)	1 (0.2)
Patients with at least one immune-mediated AE leading to dose modification of Tislelizumab	21 (1.1)	4 (0.8)
Alanine aminotransferase increased	9 (0.5)	1 (0.2)
Aspartate aminotransferase increased	6 (0.3)	1 (0.2)
Immune-mediated hepatitis	4 (0.2)	2 (0.4)
Autoimmune hepatitis	1 (0.1)	0 (0.0)
Blood bilirubin increased	1 (0.1)	1 (0.2)
Hepatitis	4 (0.2)	0 (0.0)
Hepatocellular injury	2 (0.1)	0 (0.0)
Transaminases increased	1 (0.1)	0 (0.0)
Liver injury	0 (0.0)	1 (0.2)
Patients With at Least One SAE	12 (0.6) (0.3, 1.1)	3 (0.6) (0.1, 1.8)
Hepatitis	3 (0.2)	0 (0.0)
Alanine aminotransferase increased	2 (0.1)	0 (0.0)
Aspartate aminotransferase increased	2 (0.1)	0 (0.0)
Hepatic failure	2 (0.1)	1 (0.2)
Immune-mediated hepatitis	2 (0.1)	2 (0.4)
Drug-induced liver injury	1 (0.1)	0 (0.0)
Liver injury	1 (0.1)	0 (0.0)
Transaminases increased	1 (0.1)	0 (0.0)

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

	Monotherapy (N = 1,972) n (%) (95% CI)[a]	**Combination therapy (N = 497) n (%) (95% CI)[a]**
Outcome (of SAEs)		
Death	2 (0.1)	1 (0.2)
Hepatic failure	2 (0.1)	1 (0.2)
Recovered/resolved	7 (0.4)	2 (0.4)
Hepatitis	3 (0.2)	0 (0.0)
Alanine aminotransferase increased	2 (0.1)	0 (0.0)
Aspartate aminotransferase increased	2 (0.1)	0 (0.0)
Drug-induced liver injury	1 (0.1)	0 (0.0)
Immune-mediated hepatitis	1 (0.1)	2 (0.4)
Recovering/resolving	2 (0.1)	0 (0.0)
Liver injury	1 (0.1)	0 (0.0)
Transaminases increased	1 (0.1)	0 (0.0)
Not recovered/not resolved	1 (0.1)	0 (0.0)
Immune-mediated hepatitis	1 (0.1)	0 (0.0)
Immune-mediated Skin Adverse Reaction		
Incidence		
Patients with at least one AE	32 (1.6) (1.1, 2.3)	19 (3.8) (2.3, 5.9)
Rash	15 (0.8)	13 (2.6)
Drug eruption	5 (0.3)	3 (0.6)
Pruritus	4 (0.2)	0 (0.0)
Rash maculo-papular	2 (0.1)	0 (0.0)

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

	Monotherapy (N = 1,972) n (%) (95% CI)[a]	**Combination therapy (N = 497) n (%) (95% CI)[a]**
Acute febrile neutrophilic dermatosis	1 (0.1)	0 (0.0)
Dermatitis	1 (0.1)	0 (0.0)
Dermatitis allergic	1 (0.1)	0 (0.0)
Erythema multiforme	1 (0.1)	0 (0.0)
Rash macular	1 (0.1)	0 (0.0)
Rash papular	1 (0.1)	0 (0.0)
Rash pruritic	1 (0.1)	0 (0.0)
Vitiligo	1 (0.1)	0 (0.0)
Rash erythematous	0 (0.0)	1 (0.2)
Rash pustular	0 (0.0)	2 (0.4)
Severity and Nature of Risk		
Patients with worst Grade 3 AE	8 (0.4)	11 (2.2)
Rash	3 (0.2)	7 (1.4)
Rash maculo-papular	2 (0.1)	0 (0.0)
Dermatitis	1 (0.1)	0 (0.0)
Drug eruption	1 (0.1)	2 (0.4)
Rash macular	1 (0.1)	0 (0.0)
Rash papular	1 (0.1)	1 (0.2)
Rash erythematous	0 (0.0)	1 (0.2)
Patients with worst Grade 4 AE	4 (0.2)	0 (0.0)
Drug eruption	3 (0.2)	0 (0.0)

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

	Monotherapy (N = 1,972) n (%) (95% CI)[a]	**Combination therapy (N = 497) n (%) (95% CI)[a]**
Rash	1 (0.1)	0 (0.0)
Patients with worst Grade 5 AE	0 (0.0)	0 (0.0)
Patients with at least one AE leading to discontinuation of Tislelizumab		
Drug eruption	4 (0.2)	0 (0.0)
Rash	1 (0.1)	1 (0.2)
Rash pustular	0 (0.0)	1 (0.2)
Patients with at least one immune-mediated AE leading to dose modification of Tislelizumab		
Acute febrile neutrophilic dermatosis	1 (0.1)	0 (0.0)
Dermatitis	1 (0.1)	0 (0.0)
Dermatitis allergic	1 (0.1)	0 (0.0)
Drug eruption	1 (0.1)	1 (0.2)
Pruritus	1 (0.1)	0 (0.0)
Rash	4 (0.2)	7 (1.4)
Rash macular	1 (0.1)	0 (0.0)
Rash maculo-papular	2 (0.1)	0 (0.0)
Rash erythematous	0 (0.0)	1 (0.2)
Patients With at Least One SAE	6 (0.3) (0.1, 0.7)	5 (1.0) (0.3, 2.3)
Drug eruption	4 (0.2)	1 (0.2)
Dermatitis	1 (0.1)	0 (0.0)
Dermatitis allergic	1 (0.1)	0 (0.0)
Rash	0 (0.0)	2 (0.4)

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

	Monotherapy (N = 1,972) n (%) (95% CI)[a]	**Combination therapy (N = 497) n (%) (95% CI)[a]**
Rash erythematous	0 (0.0)	1 (0.2)
Rash pustular	0 (0.0)	1 (0.2)
Outcome (of SAEs)		
Death	0 (0.0)	0 (0.0)
Recovered/resolved	4 (0.2)	4 (0.8)
Drug eruption	2 (0.1)	1 (0.2)
Dermatitis	1 (0.1)	0 (0.0)
Dermatitis allergic	1 (0.1)	0 (0.0)
Rash	0 (0.0)	2 (0.4)
Rash erythematous	0 (0.0)	1 (0.2)
Recovering/resolving	1 (0.1)	1 (0.2)
Drug eruption	1 (0.1)	0 (0.0)
Rash pustular	0 (0.0)	1 (0.2)
Not recovered/not resolved	1 (0.1)	0 (0.0)
Drug eruption	1 (0.1)	0 (0.0)
Immune-mediated Colitis		
Incidence		
Patients with at least one AE	19 (1.0) (0.6, 1.5)	7 (1.4) (0.6, 2.9)
Diarrhoea	9 (0.5)	2 (0.4)
Colitis	8 (0.4)	1 (0.2)
Immune-mediated enterocolitis	2 (0.1)	4 (0.8)

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

	Monotherapy (N = 1,972) n (%) (95% CI)[a]	**Combination therapy (N = 497) n (%) (95% CI)[a]**
Colitis ulcerative	1 (0.1)	0 (0.0)
Rectal haemorrhage	1 (0.1)	0 (0.0)
Severity and Nature of Risk		
Patients with worst Grade 3 AE	7 (0.4)	3 (0.6)
Diarrhoea	4 (0.2)	0 (0.0)
Colitis	3 (0.2)	1 (0.2)
Immune-mediated enterocolitis	1 (0.1)	2 (0.4)
Patients with worst Grade 4 AE	0 (0.0)	0 (0.0)
Patients with worst Grade 5 AE	0 (0.0)	0 (0.0)
Patients with at least one AE leading to discontinuation of Tislelizumab		
Colitis	2 (0.1)	0 (0.0)
Immune-mediated enterocolitis	1 (0.1)	3 (0.6)
Patients with at least one immune-mediated AE leading to dose modification of Tislelizumab		
Colitis	3 (0.2)	1 (0.2)
Diarrhoea	6 (0.3)	1 (0.2)
Colitis ulcerative	1 (0.1)	0 (0.0)
Immune-mediated enterocolitis	2 (0.1)	1 (0.2)
Patients With at Least One SAE	11 (0.6) (0.3, 1.0)	4 (0.8) (0.2, 2.0)
Colitis	6 (0.3)	1 (0.2)
Diarrhoea	4 (0.2)	0 (0.0)
Immune-mediated enterocolitis	1 (0.1)	3 (0.6)

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

	Monotherapy (N = 1,972) n (%) (95% CI)[a]	**Combination therapy (N = 497) n (%) (95% CI)[a]**
Outcome (of SAEs)		
Death	0 (0.0)	0 (0.0)
Recovered/resolved	8 (0.4)	2 (0.4)
Colitis	4 (0.2)	1 (0.2)
Diarrhoea	4 (0.2)	0 (0.0)
Immune-mediated enterocolitis	0 (0.0)	1 (0.2)
Recovered/resolved with sequelae	2 (0.1)	0 (0.0)
Colitis	2 (0.1)	0 (0.0)
Recovering/resolving	0 (0.0)	1 (0.2)
Immune-mediated enterocolitis	0 (0.0)	1 (0.2)
Not recovered/not resolved	1 (0.1)	1 (0.2)
Immune-mediated enterocolitis	1 (0.1)	1 (0.2)
Immune-mediated Myositis/Rhabdomyolysis		
Incidence		
Patients with at least one AE	14 (0.7) (0.4, 1.2)	6 (1.2) (0.4, 2.6)
Blood creatine phosphokinase increased	7 (0.4)	4 (0.8)
Myositis	5 (0.3)	1 (0.2)
Immune-mediated myositis	3 (0.2)	0 (0.0)
Rhabdomyolysis	0 (0.0)	1 (0.2)
Severity and Nature of Risk		
Patients with worst Grade 3 AE	5 (0.3)	3 (0.6)

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

	Monotherapy (N = 1,972) n (%) (95% CI)[a]	**Combination therapy (N = 497) n (%) (95% CI)[a]**
Blood creatine phosphokinase increased	2 (0.1)	2 (0.4)
Immune-mediated myositis	2 (0.1)	0 (0.0)
Myositis	2 (0.1)	1 (0.2)
Patients with worst Grade 4 AE	1 (0.1)	1 (0.2)
Blood creatine phosphokinase increased	1 (0.1)	1 (0.2)
Patients with worst Grade 5 AE	0 (0.0)	1 (0.2)
Rhabdomyolysis	0 (0.0)	1 (0.2)
Patients with at least one AE leading to discontinuation of Tislelizumab	3 (0.2)	5 (1.0)
Immune-mediated myositis	2 (0.1)	0 (0.0)
Myositis	1 (0.1)	1 (0.2)
Blood creatine phosphokinase increased	0 (0.0)	3 (0.6)
Rhabdomyolysis	0 (0.0)	1 (0.2)
Patients with at least one immune-mediated AE leading to dose modification of Tislelizumab	10 (0.5)	3 (0.6)
Immune-mediated myositis	2 (0.1)	0 (0.0)
Blood creatine phosphokinase increased	5 (0.3)	3 (0.6)
Myositis	3 (0.2)	0 (0.0)
Patients With at Least One SAE	7 (0.4) (0.1, 0.7)	4 (0.8) (0.2, 2.0)
Myositis	4 (0.2)	1 (0.2)
Immune-mediated myositis	2 (0.1)	0 (0.0)
Blood creatine phosphokinase increased	1 (0.1)	2 (0.4)
Rhabdomyolysis	0 (0.0)	1 (0.2)

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

	Monotherapy (N = 1,972) n (%) (95% CI)[a]	**Combination therapy (N = 497) n (%) (95% CI)[a]**
Outcome (for SAEs)		
Death	0 (0.0)	1 (0.2)
Rhabdomyolysis	0 (0.0)	1 (0.2)
Recovered/resolved	3 (0.2)	3 (0.6)
Blood creatine phosphokinase increased	1 (0.1)	2 (0.4)
Immune-mediated myositis	1 (0.1)	0 (0.0)
Myositis	1 (0.1)	1 (0.2)
Not recovered/not resolved	4 (0.2)	0 (0.0)
Myositis	3 (0.2)	0 (0.0)
Immune-mediated myositis	1 (0.1)	0 (0.0)
Immune-mediated Endocrinopathies (Hypothyroidism, Hyperthyroidism, Thyroiditis, Adrenal Insufficiency, Pituitary Dysfunction, Type 1 Diabetes Mellitus)		
Immune-mediated Adrenal Insufficiency		
Incidence		
Patients with at least one AE	6 (0.3) (0.1, 0.7)	0 (0.0)
Adrenal insufficiency	6 (0.3)	0 (0.0)
Severity and Nature of Risk		
Patients with worst Grade 3 AE	1 (0.1)	0 (0.0)
Adrenal insufficiency	1 (0.1)	0 (0.0)
Patients with worst Grade 4 AE	1 (0.1)	0 (0.0)
Adrenal insufficiency	1 (0.1)	0 (0.0)
Patients with worst Grade 5 AE	0 (0.0)	0 (0.0)

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

	Monotherapy (N = 1,972) n (%) (95% CI)[a]	**Combination therapy (N = 497) n (%) (95% CI)[a]**
Patients with at least one AE leading to discontinuation of Tislelizumab	0 (0.0)	0 (0.0)
Patients with at least one immune-mediated AE leading to dose modification of Tislelizumab	5 (0.3)	0 (0.0)
Adrenal insufficiency	5 (0.3)	0 (0.0)
Patients With at Least One SAE	2 (0.1) (0.0, 0.4)	0 (0.0)
Adrenal insufficiency	2 (0.1)	0 (0.0)
Outcome (for SAEs)		
Death	0 (0.0)	0 (0.0)
Recovered/resolved	1 (0.1)	0 (0.0)
Adrenal insufficiency	1 (0.1)	0 (0.0)
Recovering/resolving	1 (0.1)	0 (0.0)
Adrenal insufficiency	1 (0.1)	0 (0.0)
Immune-mediated Thyroiditis		
Incidence		
Patients with at least one AE	13 (0.7) (0.4, 1.1)	2 (0.4) (0.0, 1.4)
Thyroiditis	6 (0.3)	0 (0.0)
Autoimmune thyroiditis	5 (0.3)	1 (0.2)
Thyroiditis subacute	1 (0.1)	0 (0.0)
Thyroid function test abnormal	1 (0.1)	1 (0.2)
Severity and Nature of Risk		
Patients with worst Grade 3 AE	0 (0.0)	1 (0.2)
Autoimmune thyroiditis	0 (0.0)	1 (0.2)

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

	Monotherapy (N = 1,972) n (%) (95% CI)[a]	**Combination therapy (N = 497) n (%) (95% CI)[a]**
Patients with worst Grade 4 AE	0 (0.0)	0 (0.0)
Patients with worst Grade 5 AE	0 (0.0)	0 (0.0)
Patients with at least one AE leading to discontinuation of Tislelizumab	0 (0.0)	0 (0.0)
Patients with at least one immune-mediated AE leading to dose modification of Tislelizumab	2 (0.1)	0 (0.0)
Thyroiditis	1 (0.1)	0 (0.0)
Thyroiditis subacute	1 (0.1)	0 (0.0)
Patients With at Least One SAE	0 (0.0)	1 (0.2) (0.0, 1.1)
Autoimmune thyroiditis	0 (0.0)	1 (0.2)
Outcome (for SAEs)		
Death	0 (0.0)	0 (0.0)
Recovered/resolved	0 (0.0)	1 (0.2)
Autoimmune thyroiditis	0 (0.0)	1 (0.2)
Immune-mediated Hyperthyroidism		
Incidence		
Patients with at least one AE	12 (0.6) (0.3, 1.1)	3 (0.6) (0.1, 1.8)
Hyperthyroidism	12 (0.6)	2 (0.4)
Thyroxine free increased	0 (0.0)	1 (0.2)
Severity and Nature of Risk		
Patients with worst Grade 3 AE	1 (0.1)	0 (0.0)
Hyperthyroidism	1 (0.1)	0 (0.0)
Patients with worst Grade 4 AE	0 (0.0)	0 (0.0)

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

	Monotherapy (N = 1,972) n (%) (95% CI)[a]	**Combination therapy (N = 497) n (%) (95% CI)[a]**
Patients with worst Grade 5 AE	0 (0.0)	0 (0.0)
Patients with at least one AE leading to discontinuation of Tislelizumab	1 (0.1)	0 (0.0)
Hyperthyroidism	1 (0.1)	0 (0.0)
Patients with at least one immune-mediated AE leading to dose modification of Tislelizumab	1 (0.1)	1 (0.2)
Hyperthyroidism	1 (0.1)	1 (0.2)
Patients With at Least One SAE	0 (0.0)	0 (0.0)
Outcome (for SAEs)		
Death	0 (0.0)	0 (0.0)
Recovered/resolved	0 (0.0)	0 (0.0)
Immune-mediated Hypothyroidism		
Incidence		
Patients with at least one AE	133 (6.7) (5.7, 7.9)	45 (9.1) (6.7, 11.9)
Hypothyroidism	131 (6.6)	45 (9.1)
Tri-iodothyronine free decreased	2 (0.1)	1 (0.2)
Triiodothyronine decreased	1 (0.1)	1 (0.2)
Primary hypothyroidism	1 (0.1)	0 (0.0)
Thyroxine free decreased	1 (0.1)	0 (0.0)
Severity and Nature of Risk		
Patients with worst Grade 3 AE	0 (0.0)	0 (0.0)
Patients with worst Grade 4 AE	1 (0.1)	0 (0.0)
Hypothyroidism	1 (0.1)	0 (0.0)

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

	Monotherapy (N = 1,972) n (%) (95% CI)[a]	**Combination therapy (N = 497) n (%) (95% CI)[a]**
Patients with worst Grade 5 AE	0 (0.0)	0 (0.0)
Patients with at least one AE leading to discontinuation of Tislelizumab	0 (0.0)	4 (0.8)
Hypothyroidism	0 (0.0)	4 (0.8)
Patients with at least one immune-mediated AE leading to dose modification of Tislelizumab	6 (0.3)	19 (3.8)
Hypothyroidism	6 (0.3)	19 (3.8)
Patients With at Least One SAE	1 (0.1) (0.0, 0.3)	0 (0.0)
Hypothyroidism	1 (0.1)	0 (0.0)
Outcome (for SAEs)		
Death	0 (0.0)	0 (0.0)
Recovered/resolved	1 (0.1)	0 (0.0)
Hypothyroidism	1 (0.1)	0 (0.0)
Immune-mediated Type 1 Diabetes Mellitus		
Incidence		
Patients with at least one AE	8 (0.4) (0.2, 0.8)	5 (1.0) (0.3, 2.3)
Type 1 diabetes mellitus	5 (0.3)	1 (0.1)
Hyperglycaemia	3 (0.2)	2 (0.4)
Diabetic ketoacidosis	2 (0.1)	0 (0.0)
Latent autoimmune diabetes in adults	1 (0.1)	0 (0.0)
Diabetes mellitus	0 (0.0)	2 (0.4)

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

	Monotherapy (N = 1,972) n (%) (95% CI)[a]	**Combination therapy (N = 497) n (%) (95% CI)[a]**
Severity and Nature of risk		
Patients with worst Grade 3 AE	6 (0.3)	3 (0.6)
Type 1 diabetes mellitus	4 (0.2)	0 (0.0)
Hyperglycaemia	2 (0.1)	2 (0.4)
Diabetic ketoacidosis	1 (0.1)	0 (0.0)
Latent autoimmune diabetes in adults	1 (0.1)	0 (0.0)
Diabetes mellitus	0 (0.0)	1 (0.2)
Patients with worst Grade 4 AE	1 (0.1)	2 (0.4)
Diabetic ketoacidosis	1 (0.1)	0 (0.0)
Type 1 diabetes mellitus	1 (0.1)	1 (0.2)
Diabetes mellitus	0 (0.0)	1 (0.2)
Patients with worst Grade 5 AE	0 (0.0)	0 (0.0)
Patients with at least one AE leading to discontinuation of Tislelizumab	3 (0.2)	0 (0.0)
Diabetic ketoacidosis	1 (0.1)	0 (0.0)
Hyperglycaemia	1 (0.1)	0 (0.0)
Type 1 diabetes mellitus	1 (0.1)	0 (0.0)
Patients with at least one immune-mediated AE leading to dose modification of Tislelizumab	2 (0.1)	3 (0.6)
Type 1 diabetes mellitus	1 (0.1)	1 (0.2)
Hyperglycaemia	1 (0.1)	1 (0.2)
Latent autoimmune diabetes in adults	1 (0.1)	0 (0.0)
Diabetes mellitus	0 (0.0)	1 (0.2)

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

	Monotherapy (N = 1,972) n (%) (95% CI)[a]	**Combination therapy (N = 497) n (%) (95% CI)[a]**
Patients With at Least One SAE	6 (0.3) (0.1, 0.7)	2 (0.4) (0.0, 1.4)
Type 1 diabetes mellitus	4 (0.2)	1 (0.2)
Diabetic ketoacidosis	2 (0.1)	0 (0.0)
Hyperglycaemia	2 (0.1)	0 (0.0)
Latent autoimmune diabetes in adults	1 (0.1)	0 (0.0)
Diabetes mellitus	0 (0.0)	1 (0.2)
Outcome (for SAEs)		
Death	0 (0.0)	0 (0.0)
Recovered/resolved	2 (0.1)	0 (0.0)
Diabetic ketoacidosis	1 (0.1)	0 (0.0)
Hyperglycaemia	1 (0.1)	0 (0.0)
Recovered/resolved with sequelae	1 (0.1)	0 (0.0)
Diabetic ketoacidosis	1 (0.1)	0 (0.0)
Recovering/resolving	2 (0.1)	1 (0.2)
Hyperglycaemia	1 (0.1)	0 (0.0)
Type 1 diabetes mellitus	1 (0.1)	1 (0.2)
Not recovered/not resolved	4 (0.2)	1 (0.2)
Type 1 diabetes mellitus	3 (0.2)	0 (0.0)
Latent autoimmune diabetes in adults	1 (0.1)	0 (0.0)
Diabetes mellitus	0 (0.0)	1 (0.2)

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

	Monotherapy (N = 1,972) n (%) (95% CI)[a]	**Combination therapy (N = 497) n (%) (95% CI)[a]**
Immune-mediated Pituitary Dysfunction		
Incidence		
Patients with at least one AE	1 (0.1) (0.0, 0.3)	0 (0.0)
Hypopituitarism	1 (0.1)	0 (0.0)
Severity and Nature of Risk	0 (0.0)	0 (0.0)
Patients with worst Grade 3 AE	0 (0.0)	0 (0.0)
Patients with worst Grade 4 AE	0 (0.0)	0 (0.0)
Patients with worst Grade 5 AE	0 (0.0)	0 (0.0)
Patients with at least one AE leading to discontinuation of Tislelizumab	0 (0.0)	0 (0.0)
Patients with at least one AE leading to dose modification of Tislelizumab	0 (0.0)	0 (0.0)
Patients With at Least One SAE	0 (0.0)	0 (0.0)
Outcome (for SAEs)		
Death	0 (0.0)	0 (0.0)
Recovered/resolved	0 (0.0)	0 (0.0)
Immune-mediated Nephritis and Renal Dysfunction		
Incidence		
Patients with at least one AE	10 (0.5) (0.2, 0.9)	5 (1.0) (0.3, 2.3)
Renal failure	2 (0.1)	0 (0.0)
Blood creatinine increased	2 (0.1)	2 (0.4)
Renal impairment	2 (0.1)	0 (0.0)
Acute kidney injury	1 (0.1)	1 (0.2)

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

	Monotherapy (N = 1,972) n (%) (95% CI)[a]	**Combination therapy (N = 497) n (%) (95% CI)[a]**
Focal segmental glomerulosclerosis	1 (0.1)	0 (0.0)
Immune-mediated nephritis	1 (0.1)	0 (0.0)
Nephritis	1 (0.1)	2 (0.4)
Renal injury	0 (0.0)	1 (0.2)
Tubulointerstitial nephritis	0 (0.0)	1 (0.2)
Severity and Nature of Risk		
Patients with worst Grade 3 AE	3 (0.2)	2 (0.4)
Acute kidney injury	1 (0.1)	1 (0.2)
Focal segmental glomerulosclerosis	1 (0.1)	0 (0.0)
Renal failure	1 (0.1)	0 (0.0)
Tubulointerstitial nephritis	0 (0.0)	1 (0.2)
Patients with worst Grade 4 AE	2 (0.1)	0 (0.0)
Renal failure	1 (0.1)	0 (0.0)
Renal impairment	1 (0.1)	0 (0.0)
Patients with worst Grade 5 AE	1 (0.1)	0 (0.0)
Renal impairment	1 (0.1)	0 (0.0)
Patients with at least one AE leading to discontinuation of Tislelizumab	4 (0.2)	0 (0.0)
Renal failure	2 (0.1)	0 (0.0)
Focal segmental glomerulosclerosis	1 (0.1)	0 (0.0)
Renal impairment	1 (0.1)	0 (0.0)

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

	Monotherapy (N = 1,972) n (%) (95% CI)[a]	**Combination therapy (N = 497) n (%) (95% CI)[a]**
Patients with at least one immune-mediated AE leading to dose modification of Tislelizumab	4 (0.2)	5 (1.0)
Blood creatinine increased	2 (0.1)	2 (0.4)
Immune-mediated nephritis	1 (0.1)	0 (0.0)
Nephritis	1 (0.1)	2 (0.4)
Acute kidney injury	0 (0.0)	1 (0.2)
Renal injury	0 (0.0)	1 (0.2)
Tubulointerstitial nephritis	0 (0.0)	1 (0.2)
Patients With at Least One SAE	5 (0.3) (0.1, 0.6)	2 (0.4) (0.0, 1.4)
Renal failure	2 (0.1)	0 (0.0)
Acute kidney injury	1 (0.1)	1 (0.2)
Focal segmental glomerulosclerosis	1 (0.1)	0 (0.0)
Renal impairment	1 (0.1)	0 (0.0)
Tubulointerstitial nephritis	0 (0.0)	1 (0.2)
Outcome (for SAEs)		
Death	1 (0.1)	0 (0.0)
Renal impairment	1 (0.1)	0 (0.0)
Recovered/resolved	1 (0.1)	1 (0.2)
Renal failure	1 (0.1)	0 (0.0)
Acute kidney injury	0 (0.0)	1 (0.2)
Recovered/resolved with sequelae	2 (0.1)	0 (0.0)
Acute kidney injury	1 (0.1)	0 (0.0)

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

	Monotherapy (N = 1,972) n (%) (95% CI)[a]	**Combination therapy (N = 497) n (%) (95% CI)[a]**
Renal failure	1 (0.1)	0 (0.0)
Recovering/resolving	1 (0.1)	1 (0.2)
Focal segmental glomerulosclerosis	1 (0.1)	0 (0.0)
Tubulointerstitial nephritis	0 (0.0)	1 (0.2)
Immune-mediated Myocarditis		
Incidence		
Patients with at least one AE	7 (0.4) (0.1, 0.7)	7 (1.4) (0.6, 2.9)
Immune-mediated myocarditis	3 (0.2)	2 (0.4)
Myocarditis	3 (0.2)	5 (1.0)
Autoimmune myocarditis	1 (0.1)	0 (0.0)
Severity and Nature of Risk		
Patients with worst Grade 3 AE	3 (0.2)	1 (0.2)
Immune-mediated myocarditis	3 (0.2)	0 (0.0)
Myocarditis	0 (0.0)	1 (0.2)
Patients with worst Grade 4 AE	1 (0.1)	1 (0.2)
Myocarditis	1 (0.1)	0 (0.0)
Immune-mediated myocarditis	0 (0.0)	1 (0.2)
Patients with worst Grade 5 AE	0 (0.0)	2 (0.4)
Myocarditis	0 (0.0)	2 (0.4)
Patients with at least one AE leading to discontinuation of Tislelizumab	5 (0.3)	6 (1.2)
Immune-mediated myocarditis	2 (0.1)	2 (0.4)

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

	Monotherapy (N = 1,972) n (%) (95% CI)[a]	**Combination therapy (N = 497) n (%) (95% CI)[a]**
Myocarditis	2 (0.1)	4 (0.8)
Autoimmune myocarditis	1 (0.1)	0 (0.0)
Patients with at least one immune-mediated AE leading to dose modification of Tislelizumab	3 (0.2)	2 (0.4)
Autoimmune myocarditis	1 (0.1)	0 (0.0)
Immune-mediated myocarditis	1 (0.1)	0 (0.0)
Myocarditis	1 (0.1)	2 (0.4)
Patients With at Least One SAE	7 (0.4) (0.1, 0.7)	5 (1.0) (0.3, 2.3)
Immune-mediated myocarditis	3 (0.2)	2 (0.4)
Myocarditis	3 (0.2)	3 (0.6)
Autoimmune myocarditis	1 (0.1)	0 (0.0)
Outcome (for SAEs)		
Death	0 (0.0)	2 (0.4)
Myocarditis	0 (0.0)	2 (0.4)
Recovered/resolved	4 (0.2)	2 (0.4)
Immune-mediated myocarditis	2 (0.1)	1 (0.2)
Autoimmune myocarditis	1 (0.1)	0 (0.0)
Myocarditis	1 (0.1)	1 (0.2)
Recovering/resolving	1 (0.1)	1 (0.2)
Myocarditis	1 (0.1)	0 (0.0)
Immune-mediated myocarditis	0 (0.0)	1 (0.2)

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

	Monotherapy (N = 1,972) n (%) (95% CI)[a]	**Combination therapy (N = 497) n (%) (95% CI)[a]**
Not recovered/not resolved	2 (0.1)	0 (0.0)
Immune-mediated myocarditis	1 (0.1)	0 (0.0)
Myocarditis	1 (0.1)	0 (0.0)
Immune-mediated Nervous System Disorder		
Incidence		
Patients with at least one AE	0 (0.0)	2 (0.4) (0.0, 1.4)
Guillain-Barre syndrome	0 (0.0)	1 (0.2)
Immune-mediated encephalitis	0 (0.0)	1 (0.2)
Severity and Nature of risk		
Patients with worst Grade 3 AE	0 (0.0)	2 (0.4)
Guillain-Barre syndrome	0 (0.0)	1 (0.2)
Immune-mediated encephalitis	0 (0.0)	1 (0.2)
Patients with worst Grade 4 AE	0 (0.0)	0 (0.0)
Patients with worst Grade 5 AE	0 (0.0)	0 (0.0)
Patients with at least one AE leading to discontinuation of Tislelizumab	0 (0.0)	1 (0.2)
Immune-mediated encephalitis	0 (0.0)	1 (0.2)
Patients with at least one immune-mediated AE leading to dose modification of Tislelizumab	0 (0.0)	1 (0.2)
Guillain-Barre syndrome	0 (0.0)	1 (0.2)
Patients With at Least One SAE	0 (0.0)	2 (0.4) (0.0, 1.4)
Guillain-Barre syndrome	0 (0.0)	1 (0.2)
Immune-mediated encephalitis	0 (0.0)	1 (0.2)

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

	Monotherapy (N = 1,972) n (%) (95% CI)[a]	**Combination therapy (N = 497) n (%) (95% CI)[a]**
Outcome (for SAEs)		
Death	0 (0.0)	0 (0.0)
Recovered/resolved	0 (0.0)	1 (0.2)
Immune-mediated encephalitis	0 (0.0)	1 (0.2)
Not recovered/not resolved	0 (0.0)	1 (0.2)
Guillain-Barre syndrome	0 (0.0)	1 (0.2)
Immune-mediated Pancreatitis		
Incidence		
Patients with at least one AE	1 (0.1) (0.0, 0.3)	0 (0.0)
Pancreatitis	1 (0.1)	0 (0.0)
Severity and Nature of risk		
Patients with worst Grade 3 AE	1 (0.1)	0 (0.0)
Pancreatitis	1 (0.1)	0 (0.0)
Patients with worst Grade 4 AE	0 (0.0)	0 (0.0)
Patients with worst Grade 5 AE	0 (0.0)	0 (0.0)
Patients with at least one AE leading to discontinuation of Tislelizumab	0 (0.0)	0 (0.0)
Patients with at least one immune-mediated AE leading to dose modification of Tislelizumab	1 (0.1)	0 (0.0)
Pancreatitis	1 (0.1)	0 (0.0)
Patients With at Least One SAE	1 (0.1) (0.0, 0.3)	0 (0.0)
Pancreatitis	1 (0.1)	0 (0.0)

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

	Monotherapy (N = 1,972) n (%) (95% CI)[a]	**Combination therapy (N = 497) n (%) (95% CI)[a]**
Outcome (for SAEs)		
Death	0 (0.0)	0 (0.0)
Recovered/resolved	1 (0.1)	0 (0.0)
Pancreatitis	1 (0.1)	0 (0.0)
Other Immune-mediated Reactions [b]		
Incidence		
Patients with at least one AE	7 (0.4) (0.1, 0.7)	0 (0.0)
Arthritis	4 (0.2)	0 (0.0)
Immune-mediated arthritis	1 (0.1)	0 (0.0)
Pericarditis	1 (0.1)	0 (0.0)
Polymyalgia rheumatica	1 (0.1)	0 (0.0)
Severity and Nature of Risk		
Patients with worst Grade 3 AE	1 (0.1)	0 (0.0)
Arthritis	1 (0.1)	0 (0.0)
Patients with worst Grade 4 AE	0 (0.0)	0 (0.0)
Patients with worst Grade 5 AE	0 (0.0)	0 (0.0)
Patients with at least one AE leading to discontinuation of Tislelizumab	1 (0.1)	0 (0.0)
Arthritis	1 (0.1)	0 (0.0)
Patients with at least one immune-mediated AE leading to dose modification of Tislelizumab	2 (0.1)	0 (0.0)
Immune-mediated arthritis	1 (0.1)	0 (0.0)
Pericarditis	1 (0.1)	0 (0.0)

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

	Monotherapy (N = 1,972) n (%) (95% CI)[a]	**Combination therapy (N = 497) n (%) (95% CI)[a]**
Patients With at Least One SAE	2 (0.1) (0.0, 0.4)	0 (0.0)
Arthritis	2 (0.1)	0 (0.0)
Outcome (for SAEs)		
Death	0 (0.0)	0 (0.0)
Recovered/resolved	2 (0.1)	0 (0.0)
Arthritis	2 (0.1)	0 (0.0)

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

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

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

AEs grades were evaluated based on NCI-CTCAE (Version 5.0) for Studies 304 and 307, and NCI-CTCAE (Version 4.03) for Study 206 and monotherapy studies.
AEs were coded using the MedDRA Version 23.0.

Monotherapy:

Source data: Annex 7 Table 3.1.1.1, Table 3.2.1.1, Table 3.3.1.1, Table 2.7.4.2.2.6.1.
Studies include monotherapy studies (Studies 001, 102, 203, 204, 208, 302, 303) only.
Immune-mediated AEs were firstly sorted by descending frequency of category, and then sorted PTs within the category by descending frequency.
TEAE leading to the dose modification is defined as a TEAE with action taken 'Dose delay', 'Dose delayed', 'Drug interrupted', 'Dose interrupted', 'Dose held/interrupted' or 'Infusion rate decrease' by investigator.

Combination therapy:

Source data: Annex 7 Table 3.1.1.2, Table 3.2.1.2, Table 3.3.1.2, Table 2.7.4.5.1.6.
Studies include combination studies (Studies 206, 304, 307) only.
Tislelizumab-treated patients who switched from the chemotherapy control arms in Studies 304 and 307 were not included. Patients from SCLC cohort in Study 206 were not included.
The combination pool data are presented in the table above as per the PTs displayed for the monotherapy pool; hence, it may not be sorted by descending frequency of category or PTs.
Tislelizumab dose modification includes 'Dose delay', ‘Infusion interrupted', 'Dose interrupted' or 'Infusion rate decrease' by investigator.

Risk Factors and Risk Groups:

Patients with a history of or ongoing autoimmune disease may be at a higher risk of developing imAEs and are generally excluded from the clinical development 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 etiologies 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 colored urine, bleeding or bruising more easily than normal. The HCPs should monitor patients' liver function tests (ALT/AST, direct and indirect bilirubin). If a patient develops hepatitis, the HCP may decide to stop tislelizumab temporarily or permanently. Treatment may be necessary, including steroids.

Immune-mediated Skin Adverse Reaction

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

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

Immune-mediated Colitis

While on therapy with tislelizumab, patients should inform their HCP of any of the following symptoms that may indicate colitis: diarrhea 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 etiologies should be ruled out. The HCPs should consider stopping treatment with tislelizumab temporarily or permanently and begin steroid therapy if indicated.

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

Immune-mediated Myositis/Rhabdomyolysis

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

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

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

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

Immune-mediated Nephritis and Renal Dysfunction

While on therapy with tislelizumab, patients should notify their HCP if they notice a change in the amount or 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 confirmed, the HCP may decide to stop tislelizumab permanently. HCPs should consider administering specific treatment with steroids for myocarditis as soon as possible. Treatment modification for myocarditis is included in the SmPC.

Immune-mediated Nervous System Disorders

On therapy with tislelizumab, patients should inform the HCP of any of the following symptoms 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 severe upper stomach pain, nausea, vomiting, fever, or tender abdomen. Early detection and treatment may prevent and/or mitigate the risk.

Other Immune-mediated Reactions

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

Impact on the Benefit-Risk Balance of the Product:

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

Public Health Impact:

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

Important Potential Risks:

Reproductive and Developmental Toxicity:

Potential Mechanisms:

The PD-1/PD-L1 pathway is involved in the maintenance of tolerance to the 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 after intravenous infusion at doses of 3, 10, 30 mg/kg 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). 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 uteroplacental interface (Guleria et al 2005; Habicht et al 2007; Petroff and Perchellet 2010). The blockade of the PD-1/PD-L1 pathway in inducing 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 001, Study 102, Study 203, Study 204, Study 208, Study 302, and Study 303) and in combination therapy studies (Study 206, Study 304, and Study 307).

Risk Factors and Risk Groups:

No relevant risk groups or risk factors have been identified.

Preventability:

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

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

Impact on the Benefit-Risk Balance of the Product:

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

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

Public Health Impact:

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

SVII.3.2 Presentation of the Missing Information

None.

PART II: MODULE SVIII SUMMARY OF SAFETY CONCERNS

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

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

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

III.1 Routine Pharmacovigilance Activities

Specific Adverse Reaction Follow-up Checklists:

Specific AE follow-up checklist will be used to collect data to help further 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:

There are no other forms of routine pharmacovigilance activities.

III.2 Additional Pharmacovigilance Activities

None.

III.3 Summary Table of Additional Pharmacovigilance Activities

None.

PART IV PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

There are no plans for postauthorization efficacy studies.

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

V.1 Routine Risk Minimization Measures

Table Part V-2: 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 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 childbearing potential should avoid becoming pregnant and lactating women should avoid breastfeeding infants while taking tislelizumab and for 4 months after the last dose and that, women of childbearing potential should use effective contraception during treatment with tislelizumab and for 4 months after the last dose is included in SmPC Section 4.6 and PL Section 2. Other Routine Risk Minimization Measures Beyond the Product Information: Legal status: restricted medical prescription
Missing Information	
None	

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

V.2 Additional Risk Minimization Measures

Additional Risk Minimization Measures

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

Objectives:

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

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

Rationale for the Additional Risk Minimization Activity:

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

Target Audience and Planned Distribution Path:

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

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

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

V.3 Summary of Risk Minimization Measures

Table Part V-3: Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Identified Risks		
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 of immune-mediated adverse reactions are listed. PL Section 2 and PL Section 4 where guidance on how to early identify signs and symptoms and seek medical attention is included. Additional Risk Minimization Measures: Patient card Legal Status: Restricted medical prescription	Routine Pharmacovigilance Activities Beyond Adverse Reactions Reporting and Signal Detection:Targeted follow-up checklistAdditional Pharmacovigilance Activities: None

Table Part V-3: Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

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

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

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

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

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

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

I THE MEDICINE AND WHAT IT IS USED FOR

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

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

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

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

Tizveni as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic NSCLC after prior platinum-based therapy.

Patients with epidermal growth factor receptor mutant or anaplastic lymphoma kinase positive NSCLC should also have received targeted therapies before receiving tislelizumab.

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

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

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

Important risks of Tizveni, together with measures to minimize such risks and the proposed studies for learning more about Tizveni'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 healthcare professionals;
- 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 (eg, 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 analyzed, including Periodic Safety Update Report assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A List of Important Risks and Missing Information

Important risks of Tizveni 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 Tizveni. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

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

II.B Summary of Important Risks

Important Identified Risk: Immune-mediated Adverse Reactions	
Evidence for Linking the Risk to the Medicine	Review of tislelizumab clinical study data, postmarketing experience and literature regarding immune-mediated adverse reactions (including immune-mediated pneumonitis, immune-mediated hepatitis, immune-mediated skin adverse reaction, immune-mediated colitis, immune-mediated myositis/rhabdomyolysis, immune-mediated endocrinopathies, immune-mediated nephritis and renal dysfunction, immune-mediated myocarditis, immune-mediated nervous system disorder, immune-mediated pancreatitis, and other immune-mediated reactions) represent sufficient evidence of a causal association with tislelizumab exposure. *Immune-mediated Pneumonitis* Nonclinical data: No treatment-related inflammation in lungs was observed in cynomolgus monkeys after intravenous infusion at doses of 3, 10, 30 mg/kg or 60 mg/kg (once every 2 weeks, 7 doses) for 13 weeks. Clinical data: The most common lung toxicity observed in patients receiving immune checkpoint inhibitor (ICI) treatment is pneumonitis. Reports of pneumonitis were documented in 2% to 4% of patients, with 1% to 2% of patients having Grade ≥ 3 events, frequency of fatal pneumonitis in 0.2% of patients and discontinuation due to pneumonitis in 0.2% to 4% of patients. Patients with NSCLC were significantly more likely to experience any grade pneumonitis and Grade 3 or higher pneumonitis compared with other tumor types. *Immune-mediated Hepatitis* Nonclinical data: No treatment-related hepatic inflammation was observed in cynomolgus monkeys after intravenous infusion at doses of 3, 10, 30 mg/kg or 60 mg/kg (once every 2 weeks, 7 doses) for 13 weeks. Clinical data: Although infrequently observed, the occurrence of immune-mediated hepatitis is well established in patients treated with ICIs. These patients are typically asymptomatic, and diagnosis is made due to elevated liver enzymes such as alanine aminotransferase and/or aspartate aminotransferase, and occasionally hyperbilirubinemia. The median onset of transaminase elevation is approximately 6 to 14 weeks after starting ICI treatment, and the incidence of developing immune-mediated hepatitis in patients treated with ICIs is approximately 5% *Immune-mediated Skin Adverse Reaction* Nonclinical data: No treatment-related skin rash was observed in cynomolgus monkeys after intravenous infusion at doses of 3, 10, 30 mg/kg or 60 mg/kg (once every 2 weeks, 7 doses) for 13 weeks. Clinical data: Skin adverse events (AEs) are among the most frequent AEs observed in patients treated with monoclonal antibodies inhibiting either immune checkpoints cytotoxic T lymphocyte-associated protein 4 (CTLA4; ipilimumab in 43% to 45% of the patients) or programmed cell death protein-1 (PD-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 after intravenous infusion at doses of 3, 10, 30 mg/kg or 60 mg/kg (once every 2 weeks, 7 doses) for 13 weeks. Clinical data: Diarrhea and colitis are more frequent with anti-CTLA4 agents (eg, ipilimumab) than with anti-PD-1 targeted agents including nivolumab or pembrolizumab, with Grade 3 to 4 AEs occurring in 1% to 2% of cases (Haanen et al 2017). The presence of diarrhea in conjunction with abdominal pain, rectal

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

Important Identified Risk: Immune-mediated Adverse Reactions	
	Clinical data: Neurologic immune-related adverse events are uncommon with an overall incidence up to 6% with anti-PD-1 antibodies and include autoimmune encephalitis, myasthenic syndrome, Guillain-Barre syndrome. *Immune-mediated Pancreatitis* Nonclinical data: No treatment related inflammation in pancreas was observed in cynomolgus monkeys after intravenous infusion at doses of 3, 10, 30 mg/kg or 60 mg/kg (once every 2 weeks, 7 doses) for 13 weeks. Clinical data: Acute pancreatitis has been reported but is rare in cancer patients treated with ICIs; asymptomatic elevation of lipase and amylase are more common. *Other Immune-mediated Reactions* Nonclinical data: No other immune mediated reactions were observed in cynomolgus monkeys after intravenous infusion at doses of 3, 10, 30 mg/kg or 60 mg/kg (once every 2 weeks, 7 doses) for 13 weeks. Clinical data: Immune-related 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 adverse drug reactions of immune-related adverse reactions are listed. Product Label (PL) Section 2 and PL Section 4 where guidance on how to early identify signs and symptoms and seek medical attention is included. Additional Risk Minimization Measures: Patient Card Legal Status: Restricted medical prescription

Important Potential Risk: Reproductive and Developmental Toxicity	
Evidence for Linking the Risk to the Medicine	Nonclinical data: No treatment-related effects were observed in reproductive organs in cynomolgus monkeys after intravenous infusion at doses of 3, 10, 30 mg/kg or 60 mg/kg (once every 2 weeks, 7 doses) for 13 weeks. 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. 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 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 uteroplacental interface. 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. 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 childbearing potential should avoid becoming pregnant and lactating women should avoid breastfeeding infants while taking tislelizumab and that, women of childbearing potential should use effective contraception during treatment with tislelizumab and for 4 months after the last dose is included in SmPC Section 4.6 and PL Section 2. Additional Risk Minimization Measures: None Legal Status: Restricted medical prescription

II.C Post-authorization Development Plan

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 Tizveni.

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

There are no other studies required in postauthorization development plan for Tizveni.

PART VII ANNEXES

LIST OF ANNEXES

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ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

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

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

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

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

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

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

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

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

Serology

Hepatitis B, (if yes, please specify) *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 MINIMISATION ACTIVITIES (IF APPLICABLE)

Key Safety Messages of Additional Risk Minimization Measures:

Prior to the launch of Tizveni in each Member State, the Marketing Authorization Holder 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-related adverse reactions adverse reactions and prompt them about when to seek medical attention. It also contains prompts to enter contact details of the physician and to alert other physicians that the patient is being treated with Tizveni. The Patient Card is designed to be carried by the patient at all times and presented to any HCPs who may help them.

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

The Patient Card Will Contain the Following Key Elements:

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

The Patient Card reminds patients about key symptoms that need to be reported immediately to the physician.