ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Tizveni 100 mg concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of concentrate for solution for infusion contains 10 mg tislelizumab.

Each vial of 10 ml contains 100 mg tislelizumab.

Tislelizumab is an Fc-engineered humanised immunoglobulin G4 (IgG4) variant monoclonal antibody produced in recombinant Chinese hamster ovary cells.

Excipient with known effect

Each ml of concentrate for solution for infusion contains 0.069 mmol (or 1.6 mg) sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate)

Clear to slightly opalescent, colourless to slightly yellowish solution.

The solution has a pH of approximately 6.5 and an osmolality of approximately 270 to 330 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Non-small cell lung cancer (NSCLC)

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 tumour cells with no EGFR or ALK positive mutations and who have:

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

Tizveni in combination with carboplatin and either paclitaxel or nab-paclitaxel is indicated for the first-line treatment of adult patients with squamous non-small cell lung cancer who have:

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

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

4.2 Posology and method of administration

Tizveni treatment must be initiated and supervised by physicians experienced in the treatment of cancer.

Patients with first-line non-squamous non-small cell lung cancer should be evaluated for treatment based on the tumour cell expression of PD-L1 confirmed by a certified *in vitro* diagnostic medical device test (see section 5.1).

Posology

Tizveni monotherapy
The recommended dose of Tizveni is 200 mg administered by intravenous infusion once every 3 weeks.

Tizveni combination therapy
The recommended dose of Tizveni is 200 mg administered by intravenous infusion once every 3 weeks, in combination with chemotherapy.

When Tizveni and chemotherapy are administered on the same day, Tizveni should be administered before chemotherapy. The Summary of Product Characteristics (SmPC) for the chemotherapy product should be referred to for dosing as well as for recommendations on corticosteroid use as pre-medication for the prevention of chemotherapy-related adverse reactions.

Duration of treatment
Patients should be treated with Tizveni until disease progression or unacceptable toxicity.

Dose delay or discontinuation (see also section 4.4)
No dose reductions of Tizveni as monotherapy or in combination therapy are recommended. Tizveni should be withheld or discontinued as described in Table 1.

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

Table 1 Recommended treatment modifications for Tizveni

Immune-related adverse reaction	**Severity[1]**	**Tizveni treatment modification**
Pneumonitis	Grade 2	Withhold[2,3]
	Recurrent grade 2; grade 3 or 4	Permanently discontinue[3]
Hepatitis	ALT or AST >3 to 8 x ULN or total bilirubin >1.5 to 3 x ULN	Withhold[2,3]
	ALT or AST >8 x ULN or total bilirubin >3 x ULN	Permanently discontinue[3]
Rash	Grade 3	Withhold[2,3]
	Grade 4	Permanently discontinue[3]
Severe cutaneous adverse reactions (SCARs)	Suspected SCARs, including SJS or TEN	Withhold[2,3] For suspected SJS or TEN, do not resume unless SJS/TEN has been ruled out in consultation with appropriate specialist(s).
	Confirmed SCARs, including SJS or TEN	Permanently discontinue

Colitis	Grade 2 or 3	Withold[2,3]
	Recurrent grade 3; grade 4	Permanently discontinue[3]
Myositis/rhabdomyolysis	Grade 2 or 3	Withhold[2,3]
	Recurrent grade 3; grade 4	Permanently discontinue[3]
Hypothyroidism	Grade 2, 3 or 4	Hypothyroidism may be managed with replacement therapy without treatment interruption.
Hyperthyroidism	Grade 3 or 4	Withhold[2] For grade 3 or 4 that has improved to grade ≤2 and is controlled with anti-thyroid therapy, if indicated continuation of Tizveni may be considered after corticosteroid taper. Otherwise, treatment should be discontinued.
Adrenal insufficiency	Grade 2	Consider withholding treatment until controlled by HRT.
	Grade 3 or 4	Withhold[3] For grade 3 or 4 that has improved to grade ≤2 and is controlled with HRT, if indicated continuation of Tizveni may be considered after corticosteroid taper. Otherwise, treatment should be discontinued.[3]
Hypophysitis	Grade 2	Consider withholding treatment until controlled by HRT.
	Grade 3 or 4	Withhold[2,3] For grade 3 or 4 that has improved to grade ≤2 and is controlled with HRT, if indicated continuation of Tizveni may be considered after corticosteroid taper. Otherwise, treatment should be discontinued.[3]
Type 1 diabetes mellitus	Type 1 diabetes mellitus associated with grade ≥3 hyperglycaemia (glucose >250 mg/dl or >13.9 mmol/l) or associated with ketoacidosis	Withhold For grade 3 or 4 that has improved to grade ≤2 with insulin therapy, if indicated continuation of Tizveni may be considered once metabolic control is achieved. Otherwise, treatment should be discontinued.
Nephritis with renal dysfunction	Grade 2 (creatinine >1.5 to 3 x baseline or >1.5 to 3 x ULN)	Withhold[2,3]
	Grade 3 (creatinine >3 x baseline or >3 to 6 x ULN) or grade 4 (creatinine >6 x ULN)	Permanently discontinue[3]
Myocarditis	Grade 2, 3 or 4	Permanently discontinue[3]
Neurological toxicities	Grade 2	Withhold[2,3]
	Grade 3 or 4	Permanently discontinue[3]
Pancreatitis	Grade 3 pancreatitis or grade 3 or 4 serum amylase or lipase levels increased (>2 x ULN)	Withhold[2,3]
	Grade 4	Permanently discontinue[3]
Other immune-related adverse reactions	Grade 3	Withhold[2,3]
	Recurrent grade 3; grade 4	Permanently discontinue[3]

Other adverse drug reactions		
Infusion-related reactions	Grade 1	Consider pre-medication for prophylaxis of subsequent infusion reactions. Slow the rate of infusion by 50%.
	Grade 2	Interrupt infusion. Resume infusion if resolved or decreased to grade 1, and slow rate of infusion by 50%.
	Grade 3 or 4	Permanently discontinue

ALT = alanine aminotransferase, AST = aspartate aminotransferase, HRT= hormone replacement therapy, SJS = Stevens-Johnson syndrome, TEN = toxic epidermal necrolysis, ULN = upper limit normal

[1] Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI-CTCAE v4.0). Hypophysitis grade is in accordance with NCI-CTCAE v5.0.

[2] Resume in patients with complete or partial resolution (grade 0 to 1) after corticosteroid taper over at least 1 month. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating corticosteroids or inability to reduce prednisone to ≤10 mg/day (or equivalent) within 12 weeks of initiating corticosteroids.

[3] Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper to ≤10 mg/day (or equivalent) over at least 1 month is recommended, except for pneumonitis, where initial dose of 2 to 4 mg/kg/day is recommended.

Special populations

Paediatric population

The safety and efficacy of Tizveni in patients aged below 18 years have not been established. No data are available.

Elderly

No dose adjustment is needed for patients aged ≥65 years (see section 4.8).

Renal impairment

No dose adjustment is needed for patients with mild or moderate renal impairment. Data from patients with severe renal impairment are too limited to make dosing recommendations for this population (see section 5.2).

Hepatic impairment

No dose adjustment is needed for patients with mild or moderate hepatic impairment. Data from patients with severe hepatic impairment are too limited to make dosing recommendations for this population (see section 5.2).

Method of administration

Tizveni is for intravenous use only. It is to be administered as an infusion and must not be administered as an intravenous push or single bolus injection. For instructions on dilution of the medicinal product before administration, see section 6.6.

The first infusion should be administered over a period of 60 minutes. If this is well tolerated, the subsequent infusions may be administered over a period of 30 minutes. The infusion should be given via an intravenous line containing a sterile, non-pyrogenic, low-protein-binding 0.2 or 0.22 micron in-line or add-on filter.

Other medicinal products must not be mixed or co-administered through the same infusion line.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Patient Card

Patients treated with Tizveni must be given the Patient Card to be informed about the risks of immune-related adverse reactions during Tizveni therapy (see also Package Leaflet).

The prescriber must discuss the risks of immune-related adverse reactions during Tizveni therapy with the patient.

Immune-related adverse reactions

Immune-related adverse reactions have been reported, including fatal cases, during treatment with tislelizumab (see section 4.8). The majority of these events improved with interruption of tislelizumab, administration of corticosteroids and/or supportive care. Immune-related adverse reactions have also been reported after the last dose of tislelizumab. Immune-related adverse reactions affecting more than one body system can occur simultaneously.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Solid organ transplant rejection
Solid organ transplant rejection has been reported in the post-marketing setting in patients treated with PD-1 inhibitors. Treatment with tislelizumab may increase the risk of rejection in solid organ transplant recipients. The benefit of treatment with tislelizumab versus the risk of possible organ rejection should be considered in these patients.

Infusion-related reactions

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

Infusion-related reactions should be managed as recommended in Table 1 (see section 4.2).

Patients excluded from clinical studies

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

Patients on controlled sodium diet

Each ml of this medicinal product contains 0.069 mmol (or 1.6 mg) sodium. This medicinal product contains 16 mg sodium per 10 ml vial, equivalent to 0.8% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Tislelizumab is a humanised monoclonal antibody, cleared from the circulation through catabolism. As such, formal pharmacokinetic interaction studies have not been conducted. As monoclonal antibodies are not metabolised by cytochrome P450 (CYP) enzymes or other drug-metabolising enzymes, inhibition or induction of these enzymes by co-administered medicinal products is not anticipated to affect the pharmacokinetics of tislelizumab.

The use of systemic corticosteroids and other immunosuppressants at baseline, before starting tislelizumab, except for physiological doses of systemic corticosteroid (10 mg/day prednisone or equivalent), should be avoided because of their potential interference with the pharmacodynamic activity and efficacy. However, systemic corticosteroids and other immunosuppressants can be used after starting tislelizumab to treat immune-related adverse reactions (see section 4.4). Corticosteroids can also be used as pre-medication when tislelizumab is used in combination with chemotherapy, as antiemetic prophylaxis and/or to alleviate chemotherapy-related adverse reactions.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception

Tislelizumab should not be used in women of childbearing potential not using effective contraception unless the clinical condition of the woman requires treatment with tislelizumab. Women of childbearing potential should use effective contraception (methods that result in less than 1% pregnancy rates) during treatment and for at least 4 months following the last dose of tislelizumab.

Pregnancy

There are no available data on the use of tislelizumab in pregnant women. Based on its mechanism of action, tislelizumab can cause foetal harm when administered to a pregnant woman.

Animal reproduction studies have not been conducted with tislelizumab. However, in murine models of pregnancy, blockade of PD-1/PD-L1 signalling has been shown to disrupt tolerance to the foetus and to result in increased foetal loss.

Human IgG4 (immunoglobulins) are known to cross the placental barrier. Therefore, tislelizumab, being an IgG4 variant, has the potential to be transmitted from the mother to the developing foetus. Women should be advised of the potential risk to a foetus.

Tislelizumab should not be used during pregnancy unless the clinical condition of the woman requires treatment with tislelizumab.

Breast-feeding

It is unknown whether tislelizumab is excreted in human milk. Its effects on breast-fed newborns/infants and on milk production are also unknown.

Because of the potential for serious adverse drug reactions in breast-fed newborns/infants from Tizveni, women should be advised not to breast-feed during treatment and for at least 4 months after the last dose of Tizveni.

Fertility

No clinical data are available on the possible effects of tislelizumab on fertility. No reproductive and development toxicity studies have been conducted with tislelizumab. Based on a 3-month repeat-dose toxicity study, there were no notable effects in the male and female reproductive organs in cynomolgus monkeys when tislelizumab was given at doses of 3, 10, or 30 mg/kg every 2 weeks for 13 weeks (7 dose administrations) (see section 5.3).

4.7 Effects on ability to drive and use machines

Tizveni has minor influence on the ability to drive and use machines. In some patients, fatigue has been reported following administration of tislelizumab (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The safety of tislelizumab as monotherapy is based on pooled data in 1 534 patients across multiple tumour types who received 200 mg tislelizumab every 3 weeks. The most common adverse reactions were anaemia (29.2%), fatigue (22.9%) and aspartate aminotransferase increased (20.9%). The most common grade 3/4 adverse reactions were anaemia (5.0%), pneumonia (4.2%), hyponatraemia (2.7%), aspartate aminotransferase increased (2.6%), blood bilirubin increased (2.0%), pneumonitis (2.0%) and fatigue (2.0%). 1.2% of patients experienced adverse reactions leading to death. The adverse reactions leading to death were pneumonia (0.78%), hepatitis (0.13%), pneumonitis (0.07%), dyspnoea (0.07%), decreased appetite (0.07%) and thrombocytopenia (0.07%). Among the 1 534 patients, 40.1% were exposed to tislelizumab for longer than 6 months, and 22.2% were exposed for longer than 12 months.

The safety of tislelizumab given in combination with chemotherapy is based on data in 497 patients with NSCLC. The most common adverse reactions were anaemia (88.3%), neutropenia (86.5%), thrombocytopenia (67.0%), alanine aminotransferase increased (46.1%), fatigue (43.1%), aspartate aminotransferase increased (42.3%), nausea (41.4%), decreased appetite (40.6%) and rash (26.4%). The most common grade 3/4 adverse reactions were neutropenia (58.6%), thrombocytopenia (18.3%), anaemia (15.7%), pneumonia (5.0%), pneumonitis (3.4%), alanine aminotransferase increased (3.2%), lymphopenia (2.8%), rash (2.6%) and fatigue (2.2%). 1.6% of patients experienced adverse reactions leading to death. The adverse reactions leading to death were pneumonitis (0.60%), dyspnoea (0.40%), myocarditis (0.40%), pneumonia (0.20%) and hypokalaemia (0.20%). Among the 497 patients, 65.8% were exposed to tislelizumab for longer than 6 months, and 37.8% were exposed for longer than 12 months.

Tabulated list of adverse reactions

Adverse reactions reported in the pooled dataset for patients treated with Tizveni monotherapy (n = 1 534) and in combination with chemotherapy (n = 497) are presented in Table 2. Adverse reactions are listed according to system organ class in MedDRA. Within each system organ class, the adverse reactions are presented in decreasing frequency. The corresponding frequency category for each adverse reaction is defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1 000 to <1/100); rare (≥1/10 000 to <1/1 000); very rare (<1/10 000); not known (cannot be estimated from available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2 Adverse reactions with Tizveni as monotherapy (n = 1 534) and in combination with chemotherapy (n = 497)

	Tislelizumab monotherapy n = 1 534	**Tislelizumab plus chemotherapy n = 497**
Adverse reactions	**Frequency category (All grades)**	**Frequency category (All grades)**
Infections and infestations		
Pneumonia[1]	Common*	Very common*
Blood and lymphatic system disorders		
Anaemia[2]	Very common	Very common
Thrombocytopenia[3]	Common*	Very common
Neutropenia[4]	Common	Very common
Lymphopenia[5]	Common	Very common

Endocrine disorders		
Hypothyroidism[6]	Very common	Very common
Hyperthyroidism[7]	Common	Very common
Thyroiditis[8]	Common	Uncommon
Adrenal insufficiency[9]	Uncommon	-
Hypophysitis[10]	Rare	-
Metabolism and nutrition disorders		
Hyperglycaemia[11]	Common	Very common
Hyponatraemia[12]	Common	Very common
Hypokalaemia[13]	Common	Very common*
Diabetes mellitus[14]	Uncommon	Common
Nervous system disorders		
Guillain-Barré syndrome	-	Uncommon
Eye disorders		
Uveitis[15]	Uncommon	-
Cardiac disorders		
Myocarditis[16]	Uncommon	Common*
Pericarditis	Rare	-
Vascular disorders		
Hypertension[17]	Common	Common
Respiratory, thoracic and mediastinal disorders		
Cough	Very common	Very common
Dyspnoea	Common*	Very common*
Pneumonitis[18]	Common*	Very common*
Gastrointestinal disorders		
Nausea	Common	Very common
Diarrhoea[19]	Common	Very common
Stomatitis[20]	Common	Common
Pancreatitis[21]	Uncommon	Uncommon
Colitis[22]	Uncommon	Common
Hepatobiliary disorders		
Hepatitis[23]	Common*	Common
Skin and subcutaneous tissue disorders		
Rash[24]	Very common	Very common
Pruritus	Very common	Common
Severe skin reactions[25]	Rare	-
Musculoskeletal and connective tissue disorders		
Arthralgia	Common	Very common
Myalgia	Common	Common
Myositis[26]	Uncommon	Uncommon
Arthritis[27]	Uncommon	Common
Renal and urinary disorders		
Nephritis[28]	Uncommon	Uncommon
General disorders and administration site conditions		
Fatigue[29]	Very common	Very common
Decreased appetite	Very common*	Very common
Investigations		
Aspartate aminotransferase increased	Very common	Very common
Alanine aminotransferase increased	Very common	Very common
Blood bilirubin increased[30]	Very common	Very common
Blood alkaline phosphatase increased	Common	Very common
Blood creatinine increased	Common	Very common

Injury, poisoning and procedural complications		
Infusion-related reaction[31]	Uncommon	Common

[1] Pneumonia includes preferred terms (PTs) of pneumonia, lower respiratory tract infection, lower respiratory tract infection bacterial, pneumonia bacterial, pneumonia fungal and pneumocystis jirovecii pneumonia.
[2] Anaemia includes PTs of anaemia and haemoglobin decreased.
[3] Thrombocytopenia includes PTs of thrombocytopenia and platelet count decreased.
[4] Neutropenia includes PTs of neutropenia and neutrophil count decreased.
[5] Lymphopenia includes PTs of lymphopenia, lymphocyte count decreased and lymphocyte percentage decreased.
[6] Hypothyroidism includes preferred terms (PTs) of hypothyroidism, thyroxine free decreased, tri-iodothyronine free decreased, tri-iodothyronine decreased, primary hypothyroidism and thyroxine decreased.
[7] Hyperthyroidism includes PTs of hyperthyroidism, blood thyroid stimulating hormone decreased, tri-iodothyronine free increased, thyroxine free increased, thyroxine increased and tri-iodothyronine increased.
[8] Thyroiditis includes PTs of thyroiditis, autoimmune thyroiditis and thyroiditis subacute.
[9] Adrenal insufficiency includes PTs of adrenal insufficiency and secondary adrenocortical insufficiency.
[10] Hypophysitis includes PTs of hypophysitis and hypopituitarism.
[11] Hyperglycaemia includes PTs of hyperglycaemia and blood glucose increased.
[12] Hyponatraemia includes PTs of hyponatraemia and blood sodium decreased.
[13] Hypokalaemia includes PTs of hypokalaemia and blood potassium decreased.
[14] Diabetes mellitus includes PTs of diabetes mellitus, type 1 diabetes mellitus and latent autoimmune diabetes in adults.
[15] Uveitis includes PTs of uveitis and iritis.
[16] Myocarditis includes PTs of myocarditis, immune-mediated myocarditis and autoimmune myocarditis.
[17] Hypertension includes PTs of hypertension, blood pressure increased and essential hypertension.
[18] Pneumonitis includes PTs of pneumonitis, immune-mediated lung disease, interstitial lung disease and organising pneumonia.
[19] Diarrhoea includes PTs of diarrhoea and frequent bowel movements.
[20] Stomatitis includes PTs of stomatitis, mouth ulceration and aphthous ulcer.
[21] Pancreatitis includes PTs of amylase increased, lipase increased, and pancreatitis acute.
[22] Colitis includes PTs of colitis and immune-mediated enterocolitis.
[23] Hepatitis includes PTs of hepatitis, hepatic function abnormal, immune-mediated hepatitis and liver injury and autoimmune hepatitis.
[24] Rash includes PTs of rash, rash maculo-papular, eczema, rash erythematous, dermatitis, dermatitis allergic, rash papular, urticaria, erythema, skin exfoliation, drug eruption, rash macular, psoriasis, rash pustular, dermatitis acneiform, rash pruritic, lichenoid keratosis, hand dermatitis, immune-mediated dermatitis, rash follicular, acute febrile neutrophilic dermatosis, erythema nodosum and pemphigoid.
[25] Severe skin reaction includes erythema multiforme.
[26] Myositis includes PTs of myositis and immune-mediated myositis.
[27] Arthritis includes PTs of arthritis and immune-mediated arthritis.
[28] Nephritis includes PTs of nephritis, focal segmental glomerulosclerosis and immune-mediated nephritis.
[29] Fatigue includes PTs of fatigue, asthenia, malaise and lethargy.
[30] Blood bilirubin increased includes PTs of blood bilirubin increased, bilirubin conjugated increased, blood bilirubin unconjugated increased and hyperbilirubinaemia.
[31] Infusion-related reaction includes PTs of infusion-related reaction and infusion-related hypersensitivity reaction.
*including fatal outcomes

Description of selected adverse reactions

The data below reflect information for significant adverse drug reactions for tislelizumab as monotherapy in clinical studies. Details for the significant adverse reactions for tislelizumab when given in combination with chemotherapy are presented if clinically relevant differences were noted in comparison to tislelizumab monotherapy.

Immune-related pneumonitis
In patients treated with tislelizumab as monotherapy, immune-related pneumonitis occurred in 4.3% of patients, including grade 1 (0.3%), grade 2 (2.0%), grade 3 (1.5%), grade 4 (0.3%) and grade 5 (0.2%) events.

The median time from first dose to onset of the event was 3.2 months (range: 1.0 day to 16.5 months), and the median duration from onset to resolution was 6.1 months (range: 1.0+ day to 22.8+ months). + denotes a censored observation, with ongoing events at the time of the analysis. Tislelizumab was permanently discontinued in 1.8% of patients and tislelizumab treatment was interrupted in 1.8% of patients. Pneumonitis resolved in 45.5% of patients.

In patients treated with tislelizumab as monotherapy, pneumonitis occurred more frequently in patients with a history of prior thoracic radiation (6.3%) than in patients who did not receive prior thoracic radiation (2.8%).

Pneumonitis occurred in 9.1% of patients with NSCLC treated with tislelizumab in combination with chemotherapy. In patients with NSCLC treated with tislelizumab as monotherapy, pneumonitis occurred in 6.0% of patients.

Immune-related hepatitis
In patients treated with tislelizumab as monotherapy, immune-related hepatitis occurred in 1.7% of patients, including grade 1 (0.1%), grade 2 (0.5%), grade 3 (0.9%), grade 4 (0.1%) and grade 5 (0.1%) events.

The median time from first dose to onset of the event was 31.0 days (range: 8.0 days to 13.1 months), and the median duration from onset to resolution was 2.0 months (range: 1.0 day to 37.9+ months). + denotes a censored observation, with ongoing events at the time of the analysis. Tislelizumab was permanently discontinued in 0.4% of patients and tislelizumab treatment was interrupted in 1.0% of patients for immune-related hepatitis. Hepatitis resolved in 50.0% of patients.

Immune-related skin adverse reactions
In patients treated with tislelizumab as monotherapy, immune-related skin adverse reactions occurred in 1.8% of patients, including grade 1 (0.4%), grade 2 (0.8%), grade 3 (0.3%) and grade 4 (0.3%) events.

The median time from first dose to onset of the event was 2.5 months (range: 7.0 days to 11.6 months). The median duration from onset to resolution was 11.2 months (range: 4.0 days to 34.0+ months). + denotes a censored observation, with ongoing events at the time of the analysis. Tislelizumab was permanently discontinued in 0.3% of patients, and tislelizumab treatment was interrupted in 0.5% of patients. Skin adverse reactions resolved in 51.9% of patients.

Immune-related colitis
In patients treated with tislelizumab as monotherapy, immune-related colitis occurred in 0.7% of patients, including grade 2 (0.6%) and grade 3 (0.1%) events.

The median time from first dose to onset of the event was 6.0 months (range: 12.0 days to 14.4 months), and the median duration from onset to resolution was 28.0 days (range: 9.0 days to 3.6 months). Tislelizumab was not permanently discontinued in any patient and tislelizumab treatment was interrupted in 0.6% of patients. Colitis resolved in 81.8% of patients.

Immune-related myositis/rhabdomyolysis
In patients treated with tislelizumab as monotherapy, immune-related myositis/rhabdomyolysis occurred in 0.9% of patients, including grade 1 (0.2%), grade 2 (0.3%), grade 3 (0.3%) and grade 4 (0.1%) events.

The median time from first dose to onset of the event was 1.8 months (range: 15.0 days to 17.6 months), and the median duration from onset to resolution was 2.1 months (range: 5.0 days to 11.2+ months). + denotes a censored observation, with ongoing events at the time of the analysis. Tislelizumab was permanently discontinued in 0.2% of patients and tislelizumab treatment was interrupted in 0.7% of patients. Myositis/rhabdomyolysis resolved in 57.1% of patients.

Immune-related endocrinopathies
Thyroid disorders
Hypothyroidism:
In patients treated with tislelizumab as monotherapy, hypothyroidism occurred in 7.6% of patients, including grade 1 (1.4%), grade 2 (6.1%) and grade 4 (0.1%) events.

The median time from first dose to onset of the event was 3.7 months (range: 0 days to 16.6 months). The median duration from onset to resolution was 15.2 months (range: 12.0 days to 28.6+ months). + denotes a censored observation, with ongoing events at the time of the analysis. Tislelizumab was not permanently discontinued in any patient and tislelizumab treatment was interrupted in 0.4% of patients. Hypothyroidism resolved in 31.9% of patients.

Hyperthyroidism:
In patients treated with tislelizumab as monotherapy, hyperthyroidism occurred in 0.3% of patients, including grade 1 (0.1%) and grade 2 (0.3%) events.

The median time from first dose to onset of the event was 31.0 days (range: 19.0 days to 14.5 months). The median duration from onset to resolution was 1.4 months (range: 22.0 days to 4.0+ months). + denotes a censored observation, with ongoing events at the time of the analysis. Tislelizumab was permanently discontinued in 0.1% of patients and tislelizumab treatment was not interrupted in any patient. Hyperthyroidism resolved in 80.0% of patients.

Thyroiditis:
In patients treated with tislelizumab as monotherapy, thyroiditis occurred in 0.8% of patients, including grade 1 (0.2%) and grade 2 (0.6%) events.

The median time from first dose to onset of the event was 2.0 months (range: 20.0 days to 20.6 months). The median duration from onset to resolution was not evaluable based on currently available data (range: 22.0 days to 23.1+ months). + denotes a censored observation, with ongoing events at the time of the analysis. Tislelizumab was not permanently discontinued in any patient and tislelizumab treatment was interrupted in 0.1% of patients. Thyroiditis resolved in 16.7% of patients.

Adrenal insufficiency
In patients treated with tislelizumab as monotherapy, adrenal insufficiency occurred in 0.3% of patients, including grade 2 (0.1%), grade 3 (0.1%) and grade 4 (0.1%) events.

The median time from first dose to onset of the event was 3.1 months (range: 1.3 months to 11.6 months). The median duration from onset to resolution was not evaluable based on currently available data (range: 1 month to 6.5+ months). + denotes a censored observation, with ongoing events at the time of the analysis. Tislelizumab was not permanently discontinued in any patient and tislelizumab treatment was interrupted in 0.2% of patients. Adrenal insufficiency resolved in 25.0% of patients.

Hypophysitis
In patients treated with tislelizumab as monotherapy, hypopituitarism (grade 2) occurred in 0.1% of patients.

Type 1 diabetes mellitus
In patients treated with tislelizumab as monotherapy, type 1 diabetes mellitus occurred in 0.4% of patients, including grade 1 (0.1%) and grade 3 (0.3%) events.

The median time from first dose to onset of the event was 2.5 months (range: 33.0 days to 13.8 months). The median duration from onset to resolution was not evaluable based on currently available data (range: 4.0 days to 19.9+ months). + denotes a censored observation, with ongoing events at the time of the analysis. Tislelizumab was permanently discontinued in 0.1% of patients and tislelizumab treatment was interrupted in 0.1% of patients. Type 1 diabetes mellitus resolved in 16.7% of patients.

Immune-related nephritis and renal dysfunction
In patients treated with tislelizumab as monotherapy, immune-related nephritis and renal dysfunction occurred in 0.7% of patients, including grade 2 (0.3%), grade 3 (0.2%) grade 4 (0.1%) and grade 5 (0.1%) events.

The median time from first dose to onset of the event was 1.2 months (range: 3.0 days to 5.7 months). The median duration from onset to resolution was 1.9 months (range: 3.0+ days to 16.2+ months). + denotes a censored observation, with ongoing events at the time of the analysis. Tislelizumab was permanently discontinued in 0.3% of patients and tislelizumab treatment was interrupted in 0.3% of patients. Immune-related nephritis and renal dysfunction resolved in 50.0% of patients.

Immune-related myocarditis
In patients treated with tislelizumab as monotherapy, immune-related myocarditis occurred in 0.5% of patients, including grade 1 (0.1%), grade 2 (0.1%), grade 3 (0.2%) and grade 4 (0.1%) events.

The median time from first dose to onset of the event was 1.6 months (range: 14.0 days to 6.1 months), and the median duration from onset to resolution was 5.1 months (range: 4.0 days to 7.6 months). Tislelizumab was permanently discontinued in 0.3% of patients and tislelizumab treatment was interrupted in 0.2% of patients. Myocarditis resolved in 57.1% of patients.

Myocarditis occurred in 1.4% of patients treated with tislelizumab in combination with chemotherapy, including grade 5 (0.4%).

Infusion-related reactions
In patients treated with tislelizumab as monotherapy, infusion-related reactions occurred in 3.5% of patients, including grade 3 (0.3%) events. Tislelizumab was permanently discontinued in 0.1% of patients and tislelizumab treatment was interrupted in 0.5% of patients.

Laboratory abnormalities
In patients treated with tislelizumab monotherapy, the proportion of patients who experienced a shift from baseline to a grade 3 or 4 laboratory abnormality was as follows: 0.1% for increased haemoglobin, 4.4% for decreased haemoglobin, 0.9% for decreased leukocytes, 8.5% for decreased lymphocytes, 0.07% for increased lymphocytes, 1.7% for decreased neutrophils, 1.1% for decreased platelets, 2.0% for increased alanine aminotransferase, 0.4% for decreased albumin, 2.3% for increased alkaline phosphatase, 3.2% for increased aspartate aminotransferase, 2.2% for increased bilirubin, 2.0% for increased creatine kinase, 0.9% for increased creatinine, 0.9% for increased potassium, 2.2% for decreased potassium, 0.1% for increased sodium, 5.7% for decreased sodium.

In patients treated with tislelizumab in combination with chemotherapy, the proportion of patients who experienced a shift from baseline to a grade 3 or 4 laboratory abnormality was as follows: 14.2% for decreased haemoglobin, 17.3% for decreased leukocytes, 41.2% for decreased neutrophils, 4.6% for decreased platelets, 3.1% for increased alanine aminotransferase, 0.9% for increased alkaline phosphatase, 3.4% for increased aspartate aminotransferase, 0.6% for increased bilirubin, 1.6% for increased creatine kinase, 2.5% for increased creatinine, 2.8% for increased potassium, 10.2% for decreased potassium, 0.6% for increased sodium, 18.9% for decreased sodium.

Immunogenicity
Of 1 916 antidrug antibodies (ADA)-evaluable patients treated at the recommended dose of 200 mg once every 3 weeks, 18.3% of patients tested positive for treatment-emergent ADA, and neutralising antibodies (NAbs) were detected in 0.9% of patients. Population pharmacokinetic analysis showed that ADA status was a statistically significant covariate on clearance; however, the presence of treatment-emergent ADA against tislelizumab appears to have no clinically relevant impact on pharmacokinetics or efficacy.

Among ADA-evaluable patients, the following rates of adverse events (AEs) have been observed for the ADA-positive population compared to the ADA-negative population, respectively: grade ≥3 AEs 50.9% vs. 39.3%, serious adverse events (SAEs) 37.1% vs. 29.7%, AEs leading to treatment discontinuation 10.8% vs. 10.2%: (for monotherapy); grade ≥ 3 AEs 85.6% vs. 78.2%, SAEs 45.9% vs. 38.2%, AEs leading to treatment withdrawal 13.5% vs. 13.3% (for combination therapy). Patients who developed treatment-emergent ADAs tended to have overall poorer health and disease characteristics at baseline which can confound the interpretation of the safety analysis. Available data do not allow firm conclusions to be drawn on possible patterns of adverse drug reactions.

Elderly
No overall differences in safety were observed with tislelizumab monotherapy between patients aged <65 years and patients aged between 65 and 74 years. Data for patients aged 75 years and above are too limited to draw conclusions on this population.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is no information on overdose with tislelizumab. In case of overdose, patients should be closely monitored for signs or symptoms of adverse drug reactions, and appropriate symptomatic treatment instituted immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Monoclonal antibodies and antibody drug conjugates, ATC code: L01FF09

Mechanism of action

Tislelizumab is a humanised immunoglobulin G4 (IgG4) variant monoclonal antibody against PD-1, binding to the extracellular domain of human PD-1. It competitively blocks the binding of both PD-L1 and PD-L2, inhibiting PD-1-mediated negative signalling and enhancing the functional activity in T cells in *in vitro* cell-based assays.

Clinical efficacy and safety

Non-small cell lung cancer
First-line treatment of non-squamous NSCLC: BGB-A317-304
BGB-A317-304 was a randomised, open-label, multicentre phase III study to investigate the efficacy and safety of tislelizumab in combination with platinum-pemetrexed versus platinum-pemetrexed alone as first-line treatment for chemotherapy-naïve patients with locally advanced non-squamous NSCLC who were not candidates for surgical resection or platinum-based chemoradiation, or metastatic non-squamous NSCLC.

The study excluded patients with active brain or leptomeningeal metastases, known EGFR mutations or ALK translocations sensitive to available targeted inhibitor therapy, active autoimmune disease, or any condition requiring systemic treatment with either corticosteroids (>10 mg daily of prednisone or equivalent) or other immunosuppressants.

A total of 334 patients were randomised (2:1) to receive tislelizumab 200 mg combined with pemetrexed 500 mg/m^2 and carboplatin AUC 5 mg/ml/min or cisplatin 75 mg/m^2 (T+PP arm, n = 223) or pemetrexed 500 mg/m^2 and carboplatin AUC 5 mg/ml/min or cisplatin 75 mg/m^2 (PP arm, n = 111). The choice of platinum (cisplatin or carboplatin) was at the investigator's discretion.

The treatment was administered on a 3-week cycle. After the administration of 4, 5 or 6 cycles of chemotherapy or tislelizumab combined with chemotherapy at the investigator's discretion, patients in the T+PP arm received tislelizumab 200 mg combined with pemetrexed 500 mg/m^2 on a 3-week cycle until disease progression or unacceptable toxicity; patients in the PP arm received pemetrexed 500 mg/m^2 alone until disease progression or unacceptable toxicity, and those with disease progression confirmed by Independent Review Committee (IRC) were given the option to cross over to receive tislelizumab monotherapy on a 3-week cycle.

Randomisation was stratified by PD-L1 expression in tumour cells (TC) (<1% versus 1% to 49% versus ≥50%) and disease stage (IIIB versus IV), as classified according to American Joint Committee on Cancer (AJCC), 7th edition of Cancer Staging Manual. PD-L1 expression was evaluated at a central laboratory using the Ventana PD-L1 (SP263) assay that identified PD-L1 staining on tumour cells. Tumour assessments were conducted every 6 weeks for the first 6 months, then every 9 weeks for the second 6 months, then every 12 weeks.

The baseline characteristics for patients in study BGB-A317-304 were: median age 61 years (range: 25 to 75), 29% age 65 years or older; 74% male; 100% Asian (all enrolled in China); 23.4% with ECOG PS of 0 and 76.6% with ECOG PS of 1; 18.3% with disease stage IIIB; 26.6% with unknown status for ALK rearrangement and 73.4% with negative ALK rearrangement; 36.2% never-smokers; 5.4% with brain metastases. The characteristics of age, sex, ECOG PS, stage, smoking status, PD-L1 TC score and prior anticancer treatments were balanced between the treatment arms.

The primary efficacy endpoint was progression-free survival (PFS) per RECIST v1.1 by IRC in the intent-to-treat (ITT) analysis. The secondary efficacy endpoints included overall survival (OS), objective response rate (ORR) and duration of response (DoR) per IRC and per investigator.

The study met its primary endpoint at the interim analysis (data cut-off date of 23-Jan-2020 and a median duration of study follow-up of 9.8 months), showing a statistically significant improvement in PFS with T+PP compared with PP. The stratified hazard ratio was 0.65 (95% CI: 0.47, 0.91; p = 0.0054) with a median PFS of 9.7 months with T+PP and 7.6 months with PP.

The efficacy results of the final analysis (data cut-off date of 26-Oct-2020 and a median duration of study follow-up of 16.1 months) were consistent with those of the interim analysis.

Amongst the 334 patients in study BGB-A317-304, 110 (33%) patients had tumour cell PD-L1 expression ≥50%. Of these, 74 patients were in the tislelizumab plus chemotherapy group and 36 patients were in the placebo plus chemotherapy group. Efficacy results of the patients with tumour cell PD-L1 expression ≥50% from the final analysis are shown in Table 3 and the Kaplan-Meier curve for PFS and OS is presented in Figures 1 and 2, respectively.

Table 3 Efficacy results in BGB-A317-304 in patients with PD-L1 expression ≥50%

Endpoint	Tislelizumab + Pemetrexed + Platinum (n = 74)	Pemetrexed + Platinum (n = 36)
PFS		
Events, n (%)	33 (44.6)	22 (61.1)
Median PFS (months) (95% CI)	14.6 (11.5, NE)	4.6 (3.5, 9.7)
Stratified hazard ratio[a] (95% CI)	0.31 (0.18, 0.55)	
OS		
Deaths, n (%)	24 (32.4)	20 (55.6)
Median OS (months) (95% CI)	NE (NE, NE)	13.1 (5.6, NE)
Stratified hazard ratio[a] (95% CI)	0.39 (0.22, 0.71)	
Best overall response, n (%)[b]		
ORR[b], n (%)	52 (70.3)	11 (30.6)
95% CI[c]	(58.5, 80.3)	(16.3, 48.1)
CR, n (%)	7 (9.5)	0 (0.0)
PR, n (%)	45 (60.8)	11 (30.6)
DoR[b]		
Median DoR (months) (95% CI)	NE (13.2, NE)	8.5 (3.3, NE)

PFS = progression-free survival; CI = confidence interval; OS = overall survival; ORR = objective response rate; CR = complete response; PR = partial response; DoR = duration of response; NE = not estimable.
Medians were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley.

[a] Hazard ratio was estimated from stratified Cox model with pemetrexed+platinum group as reference group and stratified by disease stage (IIIB versus IV).

[b] PFS was based on IRC assessment, and ORR/DoR was based on the confirmed response by IRC.

[c] 95% CI was calculated using Clopper-Pearson method.

Figure 1 Kaplan Meier plot of PFS in BGB-A317-304 in patients with PD-L1 ≥50%

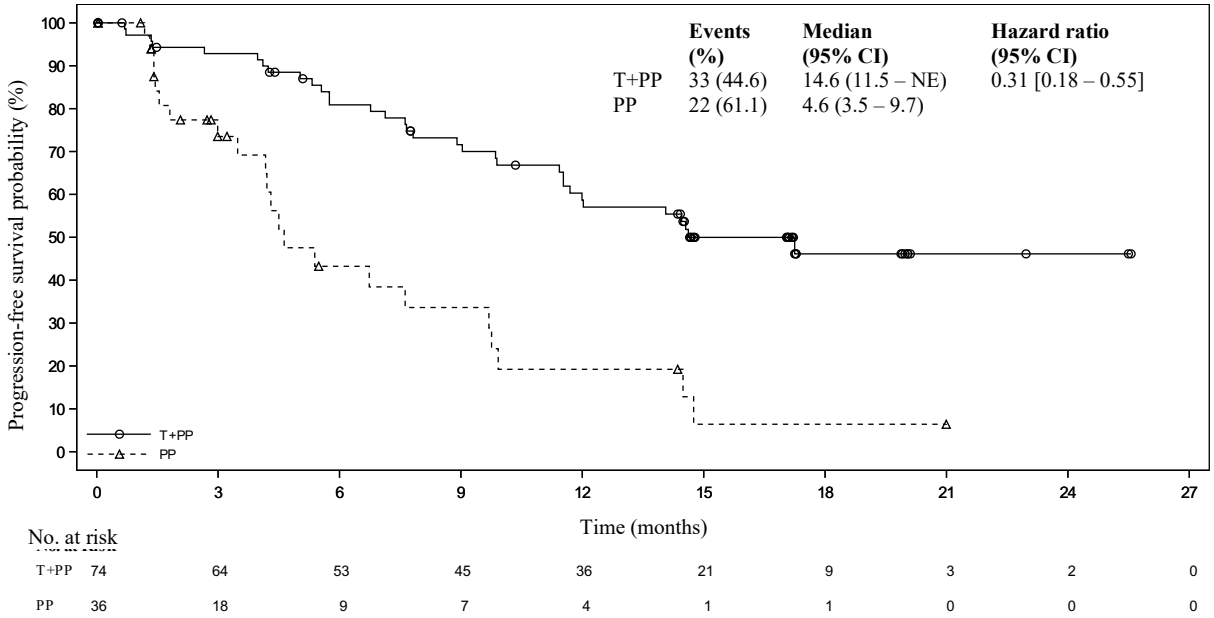
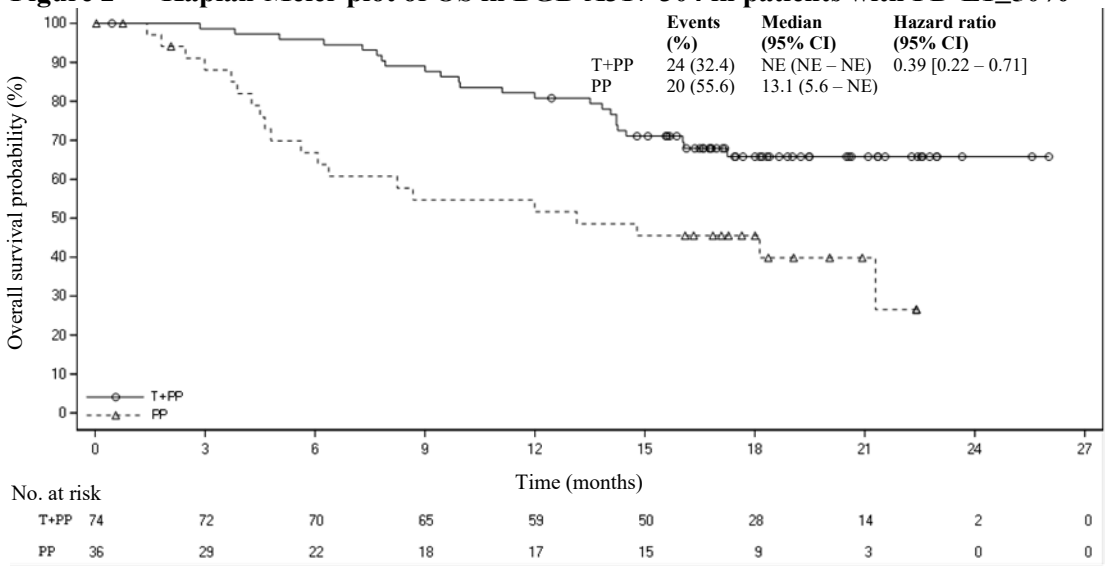


Figure 2 Kaplan-Meier plot of OS in BGB-A317-304 in patients with PD-L1≥50%



First-line treatment of squamous NSCLC: BGB-A317-307
BGB-A317-307 was a randomised, open-label, multicentre phase III study to compare the efficacy and safety of tislelizumab in combination with paclitaxel plus carboplatin or nab-paclitaxel plus carboplatin with that of paclitaxel plus carboplatin alone as first-line treatment for chemotherapy-naïve patients with locally advanced squamous NSCLC who were not candidates for surgical resection or platinum-based chemoradiation or metastatic squamous NSCLC.

The study excluded patients with active brain or leptomeningeal metastases, known EGFR mutations or ALK translocations sensitive to available targeted inhibitor therapy, active autoimmune disease, or any condition requiring systemic treatment with either corticosteroids (>10 mg daily of prednisone or equivalent) or other immunosuppressive treatments.

A total of 360 patients were randomised (1:1:1) to receive tislelizumab 200 mg combined with paclitaxel 175 mg/m^2 and carboplatin AUC 5 mg/ml/min (T+PC arm, n = 120), or tislelizumab 200 mg combined with nab-paclitaxel 100 mg/m^2 and carboplatin AUC 5 mg/ml/min (T+nPC arm, n = 119), or paclitaxel 175 mg/m^2 and carboplatin AUC 5 mg/ml/min (PC arm, n = 121).

The treatment was administered on a 3-week cycle, until the patient completed administration of 4 to 6 cycles of chemotherapy or tislelizumab combined with chemotherapy at the investigator's discretion. Patients in the T+nPC and T+PC arms received tislelizumab until disease progression or unacceptable toxicity. Patients in the PC arm with disease progression were given the option to cross over to receive tislelizumab monotherapy on a 3-week cycle.

Randomisation was stratified by PD-L1 expression in tumour cells (TC) (<1% versus 1% to 49% versus ≥50%) and tumour staging (IIIB versus IV), as classified according to American Joint Committee on Cancer (AJCC), 7th edition of Cancer Staging Manual. PD-L1 expression was evaluated at a central laboratory using the Ventana PD-L1(SP263) assay that identified PD-L1 staining on tumour cells. Tumour assessments were conducted every 6 weeks for the first 6 months, then every 9 weeks for the remainder of the first year, then every 12 weeks until disease progression.

The baseline characteristics for the study population were: median age 62.0 years (range: 34 to 74), 35.3% age 65 years or older; 91.7% male; 100% Asian (all enrolled in China), 23.6% with ECOG PS of 0 and 76.4% with ECOG PS of 1; 33.9% diagnosed with stage IIIB and 66.1% with stage IV at baseline; 16.4% never-smokers; 38.3% with PD-L1 TC score <1%, 25.3% with PD-L1 TC score ≥1% and ≤49%, 34.7% with PD-L1 TC score ≥50%. The characteristics of age, sex, ECOG PS, stage, smoking status, PD-L1 TC score and prior anticancer treatments were balanced between the treatment arms.

The primary efficacy endpoint was progression-free survival (PFS) as assessed by IRC per RECIST v1.1 in the ITT analysis which was to be tested sequentially in arms T+PC versus PC and arms T+nPC versus PC. The secondary efficacy endpoints included overall survival (OS), objective response rate (ORR) and duration of response (DoR) per IRC and per investigator.

The study met its primary endpoint at the interim analysis (data cut-off date of 06-Dec-2019 and a median duration of study follow-up of 8.4 months), showing statistically significant improvements in PFS with tislelizumab in combination with paclitaxel and carboplatin (T+PC arm) and tislelizumab in combination with nab-paclitaxel and carboplatin (T+nPC arm) compared with paclitaxel and carboplatin alone (PC arm). The stratified HR (T+PC arm versus PC arm) was 0.48 (95% CI: 0.34, 0.69; p <0.0001). The stratified HR (T+nPC arm versus PC arm) was 0.45 (95% CI: 0.32, 0.64; p <0.0001). Median PFS was 7.6 months in the T+PC arm, 7.6 months in the T+nPC arm and 5.4 months in the PC arm.

The final analysis (data cut-off date of 30-Sep-2020 and a median duration of study follow-up of 16.7 months) showed the consistent results from the interim analysis.

Efficacy results for the final analysis are shown in Table 4, Figure 3 and Figure 4.

Table 4 Efficacy results in BGB-A317-307

Endpoint	Tislelizumab + Paclitaxel + Carboplatin (n = 120)	Tislelizumab + nab-Paclitaxel + Carboplatin (n = 119)	Paclitaxel + Carboplatin (n = 121)
PFS			
Events, n (%)	80 (66.7)	79 (66.4)	86 (71.1)
Median PFS (months) (95% CI)	7.7 (6.7, 10.4)	9.6 (7.4, 10.8)	5.5 (4.2, 5.6)
Stratified hazard ratio[a] (95% CI)	0.45 (0.33, 0.62)	0.43 (0.31, 0.60)	-
OS			
Deaths, n (%)	48 (40.0)	47 (39.5)	52 (43.0)
Median OS (months) (95% CI)	22.8 (19.1, NE)	NE (18.6, NE)	20.2 (16.0, NE)
Stratified hazard ratio (95% CI)	0.68 (0.45, 1.01)	0.75 (0.50, 1.12)	-
ORR[b]			
ORR, n (%)	74 (61.7)	74 (62.2)	45 (37.2)
95% CI	(52.4, 70.4)	(52.8, 70.9)	(28.6, 46.4)
CR, n (%)	7 (5.8)	6 (5.0)	1 (0.8)
PR, n (%)	67 (55.8)	68 (57.1)	44 (36.4)
DoR[b]			
Median DoR (months) (95% CI)	13.2 (7.85, 18.79)	10.4 (8.34, 17.15)	4.8 (4.04, 5.72)

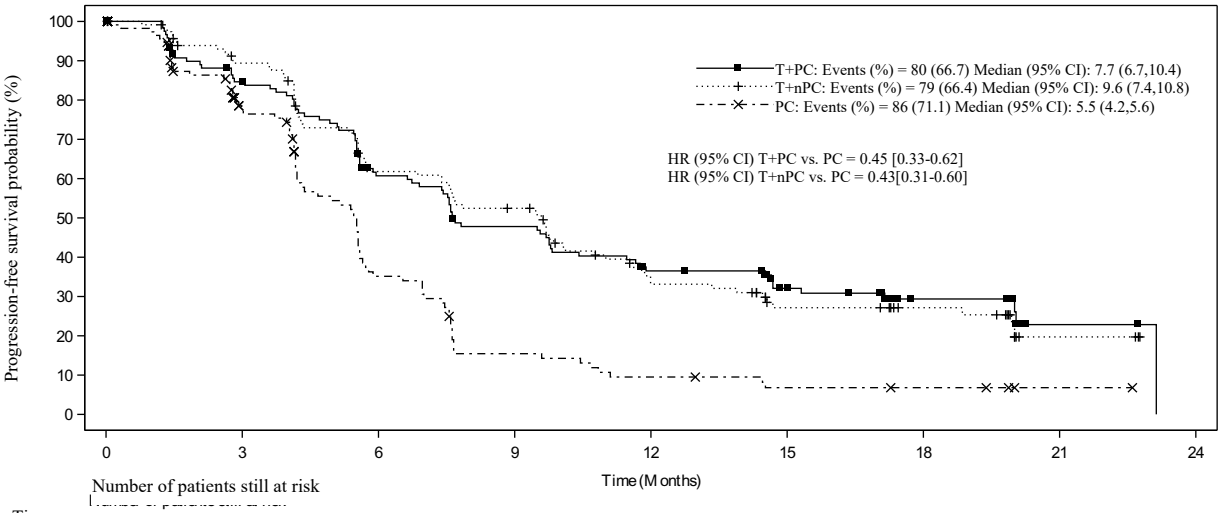
PFS = progression-free survival; CI = confidence interval; OS = overall survival; ORR = objective response rate; CR = complete response; PR = partial response; DoR = duration of response; NE = not estimable.

[a] Stratified by stratification factors: disease stage (IIIB versus IV) and PD-L1 expression in tumour cell (≥50% TC versus 1% to 49% TC versus <1% TC).

[b] PFS was based on IRC assessment, and ORR/DoR was based on the confirmed response by IRC.

Figure 3 Kaplan-Meier plot of PFS in BGB-A317-307 by IRC

T+PC arm versus T+nPC arm versus PC arm



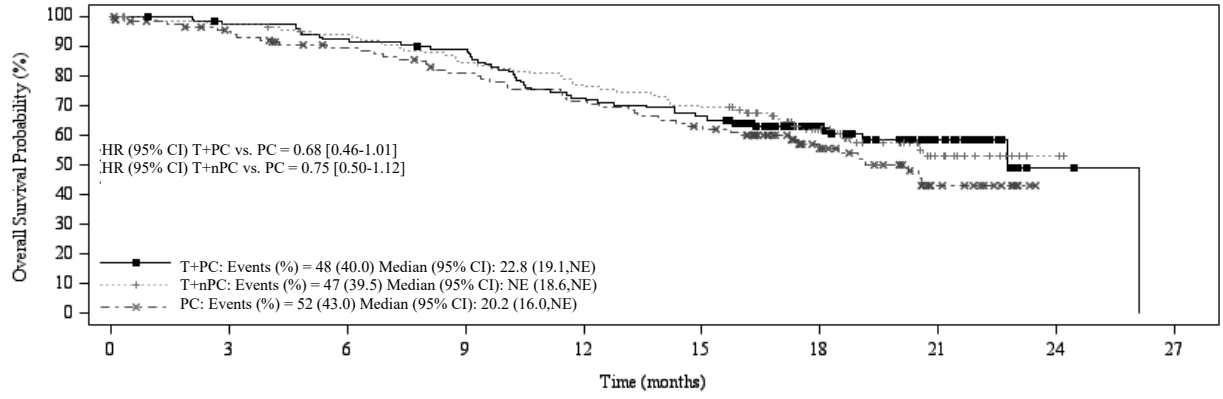
Number of patients still at risk

Time	0	3	6	9	12	15	18	21	24
T+PC	120	97	66	51	37	27	13	2	0
T+nPC	119	99	66	55	31	20	15	3	0
PC	121	74	31	13	8	5	4	1	0

CI = Confidence interval; T+PC = tislelizumab+paclitaxel+carboplatin; T+nPC = tislelizumab+nab-paclitaxel+carboplatin; PC = paclitaxel+carboplatin.

Figure 4 Kaplan-Meier plot of OS in BGB-A317-307

T+PC arm versus T+nPC arm versus PC arm



Number of patients still at risk

Time	0	3	6	9	12	15	18	21	24	27
T+PC	120	115	109	104	85	78	46	17	2	0
T+nPC	119	113	107	96	88	79	46	20	2	0
PC	121	108	96	85	75	65	35	13	0	0

CI = Confidence interval; T+PC = tislelizumab+paclitaxel+carboplatin; T+nPC = tislelizumab+nab-paclitaxel+carboplatin; PC = paclitaxel+carboplatin; NE = not estimable.

Subgroup analyses demonstrated consistent PFS treatment effect across major demographic and prognostic subgroups, including PD-L1 expression <1%, 1 to 49% and ≥50% and disease stages IIIB and IV:

- for T+PC, with PFS HR of 0.57 (95% CI, HR = 0.34, 0.94) for PD-L1 <1%, 0.40 (95% CI, HR = 0.21, 0.76) for 1 to 49% and 0.44 (95% CI, HR = 0.26, 0.75)) for ≥50%
- for T+nPC, with PFS HR of 0.65 (95% CI, HR = 0.40, 1.06) for PD-L1 <1%, 0.40 (95% CI, HR = 0.22, 0.74) for 1 to 49% and 0.33 (95% CI, HR = 0.18, 0.59)) for ≥50%

Second-line treatment of NSCLC: BGB-A317-303
BGB-A317-303 was a randomised, open-label, multicentre phase III study to investigate the efficacy and safety of tislelizumab compared with docetaxel in patients with locally advanced or metastatic NSCLC (squamous or non-squamous), who had experienced disease progression on or after a prior platinum-based regimen.

The study excluded patients with known EGFR mutation or ALK rearrangement, prior PD-(L)1 inhibitor or CTLA-4 inhibitor treatment, active autoimmune disease, or any condition requiring systemic treatment with either corticosteroids (>10 mg daily of prednisone or equivalent) or other immunosuppressive treatments.

A total of 805 patients were randomised (2:1) ratio to receive tislelizumab 200 mg intravenously every 3 weeks (n = 535) or docetaxel 75 mg/m^2 intravenously every 3 weeks (n = 270). Randomisation was stratified by histology (squamous versus non-squamous), lines of therapy (second- versus third-line), and PD-L1 expression in tumour cells (TC) (≥25% versus <25%). Administration of docetaxel and tislelizumab continued until disease progression, as assessed by investigator per RECIST v1.1, or unacceptable toxicity. PD-L1 expression was evaluated at a central laboratory using the Ventana PD-L1 (SP263) assay that identified PD-L1 staining on tumour cells. Tumour assessments were conducted every 9 weeks for 52 weeks after randomisation and continued every 12 weeks thereafter. Survival status was followed every 3 months after discontinuation of the study treatment.

The baseline characteristics for the study population were: median age 61 years (range: 28 to 88), 32.4% age 65 years or older, 3.2% age 75 years or older; 77.3% male; 17.0% White and 79.9% Asian; 20.6% with ECOG PS of 0 and 79.4% with ECOG PS of 1; 85.5% with metastatic disease; 30.3% never-smokers; 46.0% with squamous and 54.0% non-squamous histology; 65.8% with wild-type and 34% with unknown EGFR status; 46.1% with wild-type and 53.9% with unknown ALK status; 7.1% with previously treated brain metastases.

57.0% of the patients had a PD-L1 TC score <25% and 42.5% had a PD-L1 TC score ≥25%. All patients had received prior therapy with a platinum-doublet regimen: 84.7% patients received one prior therapy, 15.3% had received two prior therapies.

The dual-primary efficacy endpoints were OS in the ITT and PD-L1 TC score ≥25% analysis sets. Additional efficacy endpoints included investigator-assessed PFS, ORR and DoR.

BGB-A317-303 met both dual-primary endpoints of OS in the ITT analysis and PD-L1 ≥25% analysis sets. At the prespecified interim analysis (data cut-off date 10-Aug-2020 with a median duration of follow-up time of 11.7 months), a statistically significant improvement in OS was observed in the ITT population. Results favoured the tislelizumab arm (HR = 0.64; 95% CI: 0.53, 0.78; p < 0.0001). Median OS was 17.2 months for the tislelizumab arm and 11.9 months for the docetaxel arm. At the final analysis (data cutoff date 15-Jul-2021 with a median duration of follow-up of 14.2 months), a statistically significant improvement in OS was observed in the PD-L1 ≥25% analysis set favouring the tislelizumab arm (stratified HR = 0.53; 95% CI: 0.41, 0.70; p < 0.0001) with median OS being 19.3 months for the tislelizumab arm and 11.5 months for the docetaxel arm.

The final analysis (data cut-off date 15-Jul-2021 and a median duration of follow-up of 14.2 months) showed consistent efficacy results in the ITT population compared to the interim analysis.

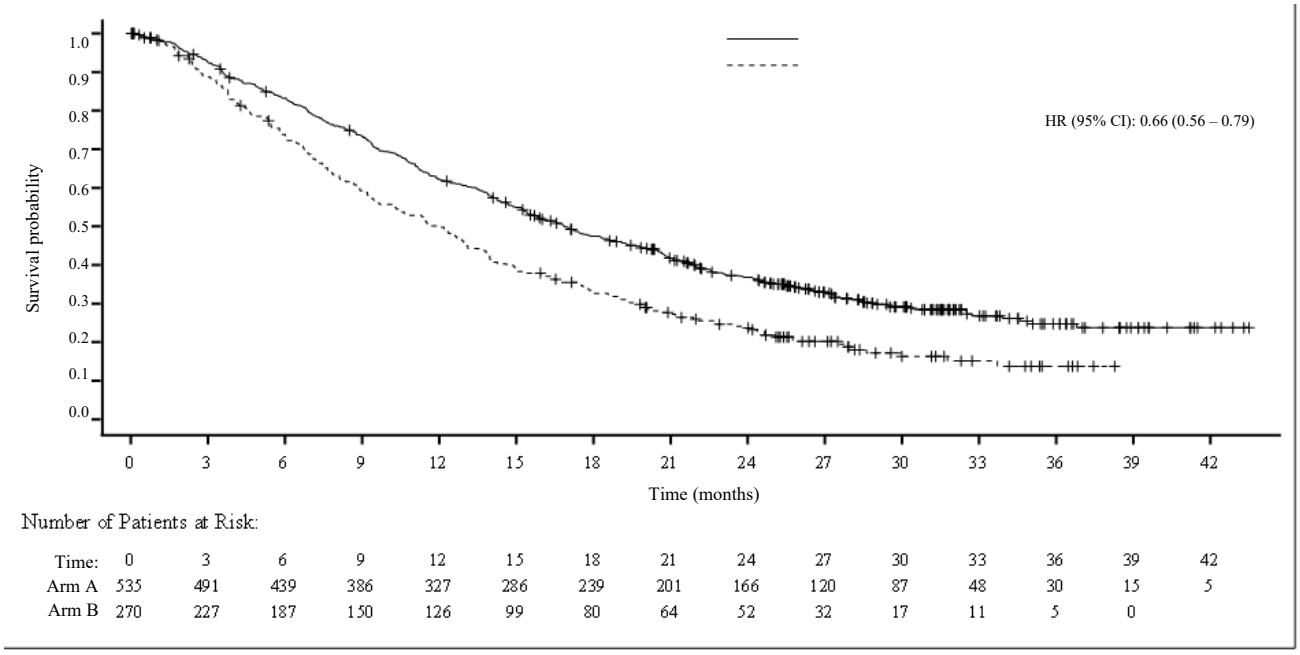
Table 5 and Figure 5 summarise the efficacy results for BGB-A317-303 (ITT analysis set) at the final analysis.

Table 5 Efficacy results in BGB-A317-303

Endpoint	Tislelizumab (n = 535)	Docetaxel (n = 270)
OS		
Deaths, n (%)	365 (68.2)	206 (76.3)
Median OS (months) (95% CI)	16.9 (15.24, 19.09)	11.9 (9.63, 13.54)
Hazard ratio (95% CI)[a, b]	0.66 (0.56, 0.79)	
PFS		
Events, n (%)	451 (84.3)	208 (77.0)
Median PFS (months) (95% CI)	4.2 (3.88, 5.52)	2.6 (2.17, 3.78)
Hazard ratio[a] (95% CI)	0.63 (0.53, 0.75)	
ORR (%) (95% CI)[c]	20.9 (17.56, 24.63)	3.7 (1.79, 6.71)
Best overall response[c]		
CR (%)	1.7	0.4
PR (%)	19.3	3.3
DoR[c]		
Median DoR (months) (95% CI)	14.7 (10.55, 21.78)	6.2 (4.11, 8.31)

OS = overall survival; CI = confidence interval; PFS = progression-free survival; ORR = objective response rate; CR = complete response; PR = partial response; DoR = duration of response.
Medians were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley.
[a] Hazard ratio was estimated from stratified Cox model with docetaxel group as reference group.
[b] Stratified by stratification factors: histology (squamous versus non-squamous), lines of therapy (second versus third), and PD-L1 expression in tumour cells (≥25% PD-L1 score versus <25% PD-L1 score).
[c] Confirmed by investigator.

Figure 5 Kaplan-Meier plot of OS in BGB-A317-303 (ITT Analysis Set)



Prespecified subgroup analyses demonstrated a consistent OS treatment effect in favour of tislelizumab across major demographic and prognostic subgroups.

Table 6 summarises efficacy results of OS by tumour PD-L1 (<25% TC, ≥25% TC) expression in prespecified subgroup analyses.

Table 6 Efficacy results of OS by tumour PD-L1 expression (<25% TC, ≥25% TC) in BGB-A317-303

	Tislelizumab arm	Docetaxel arm
	n = 535	**n = 270**
PD-L1 expression in tumour cells <25%, n	307	152
Events, n (%)	223 (72.6)	117 (77.0)
Median OS (months) (95% CI)	15.2 (13.4, 17.6)	12.3 (9.3, 14.3)
Hazard ratio [a] (95% CI)	0.79 (0.64, 0.99)	
PD-L1 expression in tumour cells ≥25%, n	227	115
Events, n (%)	141 (62.1)	86 (74.8)
Median OS (months) (95% CI)	19.3 (16.5, 22.6)	11.5 (8.2, 13.5)
Hazard ratio [a] (95% CI)	0.54 (0.41, 0.71)	
[a] Hazard ratio and its 95% CI were estimated from unstratified Cox model.		

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with tislelizumab in all subsets of the paediatric population in the treatment of malignant neoplasms (except central nervous system, haematopoietic and lymphoid tissue) (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetics (PK) of tislelizumab were assessed for Tizveni both as monotherapy and in combination with chemotherapy.

The PK of tislelizumab were characterised using population PK analysis with concentration data from 2 596 patients with advanced malignancies who received tislelizumab doses of 0.5 to 10 mg/kg every 2 weeks, 2.0 and 5.0 mg/kg every 3 weeks, and 200 mg every 3 weeks.

The time to reach 90% steady-state level is approximately 84 days (12 weeks) after 200 mg doses once every 3 weeks, and the steady-state accumulation ratio of tislelizumab PK exposure is approximately 2-fold.

Absorption

Tislelizumab is administered intravenously and therefore is immediately and completely bioavailable.

Distribution

A population pharmacokinetic analysis indicates that the steady-state volume of distribution is 6.42 l, which is typical of monoclonal antibodies with limited distribution.

Biotransformation

Tislelizumab is expected to be degraded into small peptides and amino acids via catabolic pathways.

Elimination

Based on population PK analysis, the clearance of tislelizumab was 0.153 l/day with an inter-individual variability of 26.3% and the geometrical mean terminal half-life was approximately 23.8 days with a coefficient variation (CV) of 31%.

Linearity/non-linearity

At the dosing regimens of 0.5 mg/kg to 10 mg/kg once every 2 or 3 weeks (including 200 mg once every 3 weeks), the PK of tislelizumab were observed to be linear and the exposure was dose proportional.

Special populations

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

Renal impairment
No dedicated studies of tislelizumab have been conducted in patients with renal impairment. In the population PK analyses of tislelizumab, no clinically relevant differences in the clearance of tislelizumab were found between patients with mild renal impairment (CL_{Cr} 60 to 89 ml/min, n = 1 046) or moderate renal impairment (CL_{Cr} 30 to 59 ml/min, n = 320) and patients with normal renal function (CL_{Cr} ≥90 ml/min, n = 1 223). Mild and moderate renal impairment had no effect on the exposure of tislelizumab (see section 4.2). Based on the limited number of patients with severe renal impairment (n = 5), the effect of severe renal impairment on the pharmacokinetics of tislelizumab is not conclusive.

Hepatic impairment
No dedicated studies of tislelizumab have been conducted in patients with hepatic impairment. In the population PK analyses of tislelizumab, no clinically relevant differences in the clearance of tislelizumab were found between patients with mild hepatic impairment (bilirubin ≤ ULN and AST >ULN or bilirubin >1.0 to 1.5 x ULN and any AST, n = 396) or moderate hepatic impairment (bilirubin >1.5 to 3 x ULN and any AST; n = 12), compared to patients with normal hepatic function (bilirubin ≤ ULN and AST = ULN, n = 2 182) (see section 4.2). Based on the limited number of patients with severe hepatic impairment (bilirubin >3 x ULN and any AST, n = 2), the effect of severe hepatic impairment on the pharmacokinetics of tislelizumab is unknown.

5.3 Preclinical safety data

In repeat-dose toxicology studies in cynomolgus monkeys with intravenous dose administration at doses of 3, 10, 30 or 60 mg/kg every 2 weeks for 13 weeks (7 dose administrations), no apparent treatment-related toxicity or histopathological changes were observed at doses up to 30 mg/kg every 2 weeks, corresponding to 4.3 to 6.6 times the exposure in humans with the clinical dose of 200 mg.

No developmental and reproductive toxicity studies or animal fertility studies have been conducted with tislelizumab.

No studies have been performed to assess the potential of tislelizumab for carcinogenicity or genotoxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium citrate dihydrate
Citric acid monohydrate
L-histidine hydrochloride monohydrate
L-histidine
Trehalose dihydrate
Polysorbate 20
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial

3 years.

After opening

Once opened, the medicinal product should be diluted and infused immediately (see section 6.6 for instructions on dilution of the medicinal product before administration).

After preparation of solution for infusion

Tizveni does not contain a preservative. Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C to 8°C. The 24 hours include storage of the diluted solution under refrigeration (2°C to 8°C) for no more than 20 hours, time required for returning to room temperature (25°C or below) and time to complete the infusion within 4 hours.

From a microbiological point of view, unless the method of dilution precludes the risk of microbial contamination, the product should be used immediately.

If not used immediately, in-use storage times and conditions are the responsibility of the user. The diluted solution must not be frozen.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

Do not freeze.

Store in the original carton in order to protect from light.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

10 ml of Tizveni concentrate is provided in a clear Type 1 glass vial, with a grey chlorobutyl stopper with FluroTec coating and seal cap with a flip-off button.

Tizveni is available in unit packs containing 1 vial and in multipacks containing 2 (2 packs of 1) vials.

6.6 Special precautions for disposal and other handling

The diluted solution for infusion should be prepared by a healthcare professional using aseptic technique.

Preparation of solution for infusion

- Two Tizveni vials are required for each dose.
- Remove the vials from the refrigerator, taking care not to shake them.
- Inspect each vial visually for particulate matter and discolouration prior to administration. The concentrate is a clear to slightly opalescent, colourless to slightly yellowish solution. Do not use a vial if the solution is cloudy, or if visible particles or discolouration are observed.
- Invert the vials gently without shaking. Withdraw the solution from the two vials (a total of 200 mg in 20 ml) into a syringe and transfer into an intravenous infusion bag containing sodium chloride 9 mg/ml (0.9%) solution for infusion, to prepare a diluted solution with a final concentration ranging from 2 to 5 mg/ml. Mix diluted solution by gentle inversion to avoid foaming or excessive shearing of the solution.

Administration

- Administer the diluted Tizveni solution by infusion through an intravenous administration line with a sterile, non-pyrogenic, low-protein-binding 0.2 micron or 0.22 micron in-line or add-on filter with a surface area of approximately 10 cm^2.
- The first infusion should be delivered over 60 minutes. If well tolerated, subsequent infusions may be administered over 30 minutes.
- Other medicinal products should not be co-administered through the same infusion line.
- Tizveni must not be administered as an intravenous push or single bolus injection.
- The intravenous line must be flushed at the end of the infusion.
- Discard any unused portion left in the vial.
- Tizveni vials are for single use only.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Beigene Ireland Limited
10 Earlsfort Terrace
Dublin 2
D02 T380
Ireland
Tel. +353 1 566 7660
E-mail: bg.ireland@beigene.com

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1797/001-002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)

Boehringer Ingelheim Biopharmaceuticals (China) Ltd.
1090 Halei Road
Pilot Free Trade Zone
201203 Shanghai
China

Name and address of the manufacturer(s) responsible for batch release

Novartis Farmacéutica, S.A.
Gran Via de les Corts Catalanes, 764
08013 Barcelona
Spain

Novartis Pharma GmbH
Roonstrasse 25
90429 Nuremberg
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

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

The Patient Card is aimed at increasing the awareness of patients on the signs and symptoms relevant to the early recognition/identification of the potential immune-related ARs and prompt them about when to seek medical attention. It also contains prompts to enter the contact details of the physician and to alert other physicians that the patient is being treated with Tizveni. The Patient Card is designed to be carried by the patient at all times and presented to any healthcare professional who may help them.

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

The Patient Card shall contain the following key elements:

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

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Tizveni 100 mg concentrate for solution for infusion
tislelizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One 10 ml vial contains 100 mg tislelizumab.

3. LIST OF EXCIPIENTS

Also contains: sodium-citrate dihydrate, citric acid monohydrate, L-histidine hydrochloride monohydrate, L-histidine, trehalose dihydrate, polysorbate 20, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion.

1 vial
100 mg/10 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use after dilution.
Single use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Beigene Ireland Limited
10 Earlsfort Terrace
Dublin 2
D02 T380
Ireland
Tel. +353 1 566 7660
E-mail: bg.ireland@beigene.com

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1797/001 1 vial

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACKS (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Tizveni 100 mg concentrate for solution for infusion
tislelizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One 10 ml vial contains 100 mg tislelizumab.

3. LIST OF EXCIPIENTS

Also contains: sodium citrate dihydrate, citric acid monohydrate, L-histidine hydrochloride monohydrate, L-histidine, trehalose dihydrate, polysorbate 20, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion

Multipack: 2 (2 x 1) vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use after dilution.
Single use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the vials in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Beigene Ireland Limited
10 Earlsfort Terrace
Dublin 2
D02 T380
Ireland
Tel. +353 1 566 7660
E-mail: bg.ireland@beigene.com

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1797/002 2 (2 x 1) vials

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACKS (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Tizveni 100 mg concentrate for solution for infusion
tislelizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One 10 ml vial contains 100 mg tislelizumab.

3. LIST OF EXCIPIENTS

Also contains: sodium citrate dihydrate, citric acid monohydrate, L-histidine hydrochloride monohydrate, L-histidine, trehalose dihydrate, polysorbate 20, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion

1 vial. Component of a multipack. Not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use after dilution.
Single use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Beigene Ireland Limited
10 Earlsfort Terrace
Dublin 2
D02 T380
Ireland
Tel. +353 1 566 7660
E-mail: bg.ireland@beigene.com

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1797/002 2 (2 x 1) vials

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT

Tizveni 100 mg sterile concentrate
tislelizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One 10 ml vial contains 100 mg tislelizumab.

3. LIST OF EXCIPIENTS

Also contains: sodium-citrate dihydrate, citric acid monohydrate, L-histidine hydrochloride monohydrate, L-histidine, trehalose dihydrate, polysorbate 20, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion

100 mg/10 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

IV after dilution
Single use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Beigene Ireland Limited

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1797/001	1 vial
EU/1/24/1797/002	2 (2x1) vials

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Tizveni 100 mg concentrate for solution for infusion
tislelizumab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- It is important that you keep the Patient Card with you during treatment.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Tizveni is and what it is used for

Tizveni is a cancer medicine that contains the active substance tislelizumab. It is a monoclonal antibody, a type of protein that is designed to recognise and attach to a specific target in the body called programmed death-1 receptor (PD-1) which is found on the surface of T and B cells (types of white blood cells that form part of the immune system, the body's natural defences). When PD-1 is activated by cancer cells it can switch off the activity of T cells. By blocking PD-1, Tizveni prevents it from switching off your T cells which helps your immune system fight the cancer.

Tizveni is used in adults to treat:
- non-small cell lung cancer that has spread to other parts of the body, has not already been treated with chemotherapy and cannot be removed by surgery. When used to treat this type of cancer, Tizveni is given in combination with chemotherapy.
- non-small cell lung cancer that has spread to other parts of the body and has already been treated with chemotherapy. When used to treat this type of cancer, Tizveni is given alone.

If you have any questions about how Tizveni works or why this medicine has been prescribed for you, ask your doctor.

Tizveni may be given in combination with other anti-cancer medicines. It is important that you also read the package leaflet for these other medicines. If you have any questions about these medicines, ask your doctor.

2. What you need to know before you are given Tizveni

You must not be given Tizveni
- if you are allergic to tislelizumab or any of the other ingredients of this medicine (listed in section 6). Talk to your doctor if you are not sure.

Warnings and precautions
Talk to your doctor before you are given Tizveni if you have or have had:
- autoimmune disease (a condition where the body's own defence system attacks normal cells)
- inflammation of the liver (hepatitis) or other liver problems
- inflammation of the kidney (nephritis)
- pneumonia or inflammation of the lungs (pneumonitis)
- inflammation of the large bowel (colitis)
- serious rash
- problems with hormone-producing glands (including the adrenal, pituitary and thyroid glands)
- type 1 diabetes mellitus
- a solid organ transplant
- infusion-related reaction

If any of the above apply to you, or you are not sure, talk to your doctor before you are given Tizveni.

Look out for serious side effects
Tizveni can have serious side effects, which can sometimes become life-threatening and can lead to death. Tell your doctor immediately if you get any of these serious side effects during treatment with Tizveni:
- inflammation of the liver (hepatitis) or other liver problems
- inflammation of the kidney (nephritis)
- inflammation of the lungs (pneumonitis)
- inflammation of the large bowel (colitis)
- severe skin reactions: symptoms may include fever, flu-like symptoms, rash, itching, skin blistering or ulcers in the mouth or on other moist surfaces
- problems with hormone-producing glands (especially the adrenal, pituitary or thyroid glands): symptoms may include fast heart rate, extreme tiredness, weight gain or weight loss, dizziness or fainting, hair loss, feeling cold, constipation, headaches that will not go away or unusual headaches
- type 1 diabetes mellitus
- infusion-related reaction
- inflammation of the muscles (myositis)
- inflammation of the heart muscle (myocarditis)
- inflammation of the membrane around the heart (pericarditis)
- inflammation of the joints (arthritis)
- inflammatory disorder that causes muscle pain and stiffness, especially in the shoulders and hips (polymyalgia rheumatica): symptoms may include pain in the shoulders, neck, upper arms, buttocks, hips or thighs, stiffness in affected areas, pain or stiffness in the wrists, elbows or knees
- inflammation of the nerves: symptoms may include pain, weakness and paralysis in the extremities (Guillain-Barré syndrome)

➢ For more information on the symptoms of any of the above, read section 4 ("Possible side effects"). Talk to your doctor if you have any questions or concerns.

Patient Card
You will also find key information from this package leaflet in the Patient Card that you have been given by your doctor. It is important that you carry the Patient Card with you at all times and show it to a healthcare professional in case of signs and symptoms that may indicate immune-related adverse reactions (listed above under "Look out for serious side effects"), for a prompt diagnosis and adequate treatment.

Monitoring during your treatment with Tizveni
Your doctor will carry out regular tests (liver function tests, kidney function tests, radiographic imaging tests) before and during treatment.

Your doctor will also carry out regular blood tests before and during treatment with Tizveni to monitor the blood sugar and hormone levels in your body. This is because blood sugar and hormone levels can be affected by Tizveni.

Children and adolescents
Tizveni should not be used in children and adolescents below 18 years of age.

Other medicines and Tizveni
Tell your doctor if you are taking, have recently taken or might take any other medicines. This includes herbal medicines and medicines obtained without a prescription.

In particular, tell your doctor if you are taking any medicines that suppress your immune system, including corticosteroids (such as prednisone), since these medicines may interfere with the effect of Tizveni. However, once you have started treatment with Tizveni, your doctor may give you corticosteroids to reduce any side effects that you may have.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before you are given this medicine.

You should not be given Tizveni if you are pregnant unless your doctor specifically prescribes it for you. The effects of Tizveni in pregnant women are not known, but it is possible that the active substance, tislelizumab, could harm an unborn baby.
- If you are a woman who could become pregnant, you must use effective contraception while you are being treated with Tizveni and for at least 4 months following the last dose of Tizveni.
- If you are pregnant, think you may be pregnant or are planning to have a baby, tell your doctor.

It is not known whether Tizveni passes into breast milk. A risk to the breast-fed infant cannot be ruled out. If you are breast-feeding, tell your doctor. You should not breast-feed during treatment with Tizveni and for at least 4 months after the last dose of Tizveni.

Driving and using machines
Tizveni has a minor effect on your ability to drive or use machines.

Feeling tired or weak are possible side effects of Tizveni. Do not drive or use machines after you have been given Tizveni unless you are sure you are feeling well.

Tizveni contains sodium
Tell your doctor if you are on a low-sodium (low-salt) diet before you are given Tizveni. This medicine contains 1.6 mg sodium (main component of cooking/table salt) in each ml of concentrate. A single infusion of Tizveni contains 32 mg sodium in two 10 ml vials. This is equivalent to 1.6% of the recommended maximum daily dietary intake of sodium for an adult.

3. How Tizveni is given

Tizveni will be given to you in a hospital or clinic under the supervision of an experienced doctor.
- The usual daily dose of Tizveni is 200 mg, which is given as an intravenous infusion (drip into a vein) every 3 weeks.The first dose of Tizveni will be given by an infusion over a period of 60 minutes. If you tolerate the first dose well, then the next infusion may be given over a period of 30 minutes.
- When Tizveni is given in combination with chemotherapy, you will be given Tizveni first and then the chemotherapy.
- Please refer to the package leaflet of the other anti-cancer medicines in order to understand the use of these medicines. If you have questions, ask your doctor.
- Your doctor will decide how many treatments you need.

If you miss a dose of Tizveni
- Call your doctor immediately to reschedule your appointment.
- It is very important that you do not miss a dose of this medicine.

If you stop Tizveni treatment
Stopping your treatment may stop the effect of the medicine. Do not stop treatment with Tizveni unless you have discussed this with your doctor.

If you have any further questions about your treatment or the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some of the side effects of Tizveni may be serious (see the list under "Look out for serious side effects" in section 2 of this leaflet). If you experience any of these serious side effects, **tell your doctor immediately.**

The following side effects have been reported with Tizveni alone:

Very common (may affect more than 1 in 10 people)
- Hypothyroidism (an underactive thyroid gland which can cause tiredness, weight gain, skin and hair changes)
- Cough
- Rash
- Itching (pruritus)
- Tiredness (fatigue)
- Decreased appetite
- Weakness (spontaneous bleeding or bruising and frequent infections, fever, chills and sore throat (anaemia)
- High blood level of bilirubin, a breakdown product of red blood cells, which can cause yellowing of the skin and eyes, indicating liver problems
- Increased blood level of the liver enzyme aspartate aminotransferase
- Increased blood level of the liver enzyme alanine aminotransferase

Common (may affect up to 1 in every 10 people)
- Pneumonia
- Diarrhoea
- Nausea
- Spontaneous bleeding or bruising (thrombocytopenia)
- Frequent infections, fever, chills, sore throat or mouth ulcers due to infections (neutropenia or lymphopenia)
- Feeling sick (nausea), vomiting, loss of appetite, pain on the right side of the stomach, yellowing of the skin or the whites of the eyes, drowsiness, dark-coloured urine, bleeding or bruising more easily than normal – possible symptoms of liver problems (hepatitis)
- Joint pain (arthralgia)
- Muscle pain (myalgia)
- Shortness of breath, cough or chest pain - possible symptoms of lung problems (pneumonitis)
- Fatigue, swelling at the base of the neck, pain in front of the throat – possible symptoms of thyroid gland problems (thyroiditis)
- Increased blood sugar level, thirst, dry mouth, need to pass urine more frequently, tiredness, increased appetite with weight loss, confusion, nausea, vomiting, fruity smelling breath, difficulty breathing and dry or flushed skin – possible symptoms of hyperglycaemia
- Tiredness, confusion, muscle twitching, convulsions (hyponatraemia)
- Muscle weakness, muscle spasms, abnormal heart rhythm (hypokalaemia)

- Hyperthyroidism (an overactive thyroid gland which can cause hyperactivity, sweating, weight loss and thirst)
- Difficulty breathing (dyspnoea)
- Increased blood pressure (hypertension)
- Mouth sores or ulcers with inflammation of the gums (stomatitis)
- Increased blood level of the liver enzyme alkaline phosphatase
- High blood level of the enzyme creatine kinase
- High blood level of creatinine

Uncommon (may affect up to 1 in every 100 people)
- Changes in the amount or colour of the urine, pain while urinating, pain in kidney area – possible symptoms of kidney problems (nephritis)
- Diarrhoea or more bowel movements than normal, black tarry, sticky stools, blood or mucus in stools, severe pain or tenderness in the stomach – possible symptoms of intestine problems (colitis)
- Severe upper stomach pain, nausea, vomiting, fever, tender abdomen – possible symptoms of pancreas problems (pancreatitis)
- High blood sugar, feeling more hungry or thirsty than normal, passing urine more often than normal - possible symptoms of diabetes mellitus
- Muscle pain, stiffness, weakness, chest pain or severe tiredness – possible symptoms of muscle problems (myositis)
- 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, tiredness - possible symptoms of heart muscle problems (myocarditis)
- Joint pain, stiffness, swelling or redness, decreased range of motion in the joints – possible symptoms of joint problems (arthritis)
- Eye redness, eye pain and swelling - possible symptoms of problems affecting the uvea, the layer beneath the white of the eyeball (uveitis)
- Adrenal insufficiency (disorder in which the adrenal glands do not make enough of certain hormones)
- Inflammation of the nerves: symptoms may include pain, weakness and paralysis in the extremities (Guillain-Barré syndrome)
- Chills or shaking, itching or rash, flushing, shortness of breath or wheezing, dizziness or fever which may occur during infusion or up to 24 hours after infusion – possible symptoms of infusion-related reaction
- Low blood level of leukocytes
- High blood levels of haemoglobin, potassium and sodium
- Low blood level of albumin

Rare (may affect up to 1 in every 1 000 people)
- Chest pain, fever, cough, palpitations - possible symptoms of problems affecting the membrane around the heart (pericarditis)
- Frequent headaches, vision changes (either low vision or double vision), fatigue and/or weakness, confusion, decreased blood pressure, dizziness - possible symptoms of pituitary gland problems (hypophysitis)
- Itching or peeling skin, skin sores - possible symptoms of severe skin reactions

The following side effects have been reported with Tizveni when Tizveni is given together with other anti-cancer medicines

Note that it is important that you also read the package leaflets for the other anti-cancer medicines that you receive as they may also cause side effects.

Very common (may affect more than 1 in 10 people)
- Shortness of breath, cough or chest pain – possible symptoms of lung problems (pneumonitis)

- Increased blood sugar levels, thirst, dry mouth, need to pass urine more frequently, tiredness, increased appetite with weight loss, confusion, nausea, vomiting, fruity smelling breath, difficulty breathing and dry or flushed skin - possible symptoms of hyperglycaemia
- Underactive thyroid gland which can cause tiredness, weight gain, skin and hair changes (hypothyroidism)
- Overactive thyroid gland which can cause hyperactivity, sweating, weight loss and thirst (hyperthyroidism)
- Cough
- Difficulty breathing (dyspnoea)
- Diarrhoea
- Rash
- Joint pain (arthralgia)
- Tiredness (fatigue)
- Increased blood level of the liver enzyme aspartate aminotransferase
- Increased blood level of the liver enzyme alanine aminotransferase
- Increased blood level of bilirubin, a breakdown product of red blood cells
- Increased blood level of the liver enzyme alkaline phosphatase
- Low levels of haemoglobin
- Low levels of the following blood cells: leukocytes, neutrophils, platelets
- High levels of the following enzymes: alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase
- High levels of bilirubin
- High levels of creatine kinase and creatinine
- High levels of potassium
- Low levels of potassium and sodium

Common (may affect up to 1 in every 10 people)
- Nausea, vomiting, loss of appetite, pain on the right side of the stomach, yellowing of the skin or the whites of the eyes, drowsiness, dark-coloured urine, bleeding or bruising more easily than normal – possible symptoms of liver problems (hepatitis)
- Diarrhoea or more bowel movements than normal, black tarry, sticky stools, blood or mucus in stools, severe pain or tenderness in the stomach – possible symptoms of intestine problems (colitis)
- High blood sugar, feeling more hungry or thirsty than normal, passing urine more often than normal - possible symptoms of diabetes mellitus
- Chills or shaking, itching or rash, flushing, shortness of breath or wheezing, dizziness or fever which may occur during infusion or up to 24 hours after infusion – possible symptoms of infusion-related reaction
- Chest pain, rapid or abnormal heartbeat, shortness of breath at rest or during activity, fluid buildup with swelling of the legs, ankles and feet, tiredness - possible symptoms of heart muscle problems (myocarditis)
- Joint pain, stiffness, swelling or redness, decreased range of motion in the joints - possible symptoms of joint problems (arthritis)
- Mouth sores or ulcers with inflammation of the gums (stomatitis)
- Itching (pruritus)
- Muscle pain (myalgia)
- High levels of haemoglobin
- High levels of sodium

Uncommon (may affect up to 1 in every 100 people)
- Changes in the amount or colour of the urine, pain while urinating, pain in kidney area – possible symptoms of kidney problems (nephritis)
- Fatigue, swelling at the base of the neck, pain in front of the throat - possible symptoms of thyroid gland problems (thyroiditis)
- Severe upper stomach pain, nausea, vomiting, fever, tender abdomen – possible symptoms of pancreas problems (pancreatitis)

- Muscle pain, stiffness, weakness, chest pain, or severe tiredness – possible symptoms of muscle problems (myositis)
- Serious problems of the nerves, 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 - possible symptoms of Guillain-Barré syndrome

Tell your doctor immediately if you experience any of the serious side effects listed above.

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Tizveni

Your doctor, pharmacist or nurse is responsible for storing this medicine and disposing of any unused product correctly. The following information is intended for healthcare professionals.

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and vial label after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C to 8°C).

Do not freeze.

Store in the original carton in order to protect from light.

Tizveni does not contain a preservative. Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C to 8°C. The 24 hours include storage of the diluted solution under refrigeration (2°C to 8°C) for no more than 20 hours, time required for returning to room temperature (25°C or below) and time to complete the infusion within 4 hours.

From a microbiological point of view, unless the method of dilution precludes the risk of microbial contamination, the product should be used immediately.

If not used immediately, in-use storage times and conditions are the responsibility of the user. The diluted solution must not be frozen.

Do not store any unused portion of the infusion solution for reuse. Any unused medicine or waste material should be disposed of in accordance with local requirements.

6. Contents of the pack and other information

What Tizveni contains
- The active substance is tislelizumab. Each ml of concentrate for solution for infusion contains 10 mg of tislelizumab.
- Each vial contains 100 mg of tislelizumab in 10 ml of concentrate.

The other ingredients are sodium citrate dihydrate (see section 2, “Tizveni contains sodium”), citric acid monohydrate, L-histidine hydrochloride monohydrate, L-histidine, trehalose dihydrate, polysorbate 20 and water for injections.

What Tizveni looks like and contents of the pack
Tizveni concentrate for solution for infusion (sterile concentrate) is a clear to slightly opalescent, colourless to slightly yellowish solution.

Tizveni is available in packs containing 1 vial and in multipacks containing 2 (2 packs of 1) vials.

Marketing Authorisation Holder
Beigene Ireland Limited
10 Earlsfort Terrace
Dublin 2
D02 T380
Ireland
Tel. +353 1 566 7660
E-mail: bg.ireland@beigene.com

Manufacturer
Novartis Farmacéutica, S.A.
Gran Via de les Corts Catalanes, 764
08013 Barcelona
Spain

Novartis Pharma GmbH
Roonstrasse 25
90429 Nuremberg
Germany

This leaflet was last revised in

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

The following information is for healthcare professionals only:

Tizveni vials are for single use only. Each vial contains 100 mg of tislelizumab.

The diluted solution for infusion should be prepared by a healthcare professional using aseptic technique.

Preparation of solution for infusion

- Two Tizveni vials are required for each dose.
- Remove the vials from the refrigerator, taking care not to shake them.
- Inspect each vial visually for particulate matter and discolouration prior to administration. The concentrate is a clear to slightly opalescent, colourless to slightly yellowish solution. Do not use a vial if the solution is cloudy, or if visible particles or discolouration are observed.
- Invert the vials gently without shaking. Withdraw the solution from the two vials (a total of 200 mg in 20 ml) into a syringe and transfer into an intravenous infusion bag containing sodium chloride 9 mg/ml (0.9%) solution for injection, to prepare a diluted solution with a final concentration ranging from 2 to 5 mg/ml. Mix the diluted solution by gentle inversion to avoid foaming or excessive shearing of the solution.

Administration

- Administer the diluted Tizveni solution by infusion through an intravenous administration line with a sterile, non-pyrogenic, low-protein-binding 0.2 micron or 0.22 micron in-line or add-on filter with a surface area of approximately 10 cm^2.
- The first infusion should be delivered over 60 minutes. If well tolerated, subsequent infusions may be administered over 30 minutes.
- Other medicinal products should not be co-administered through the same infusion line.
- Tizveni must not be administered as an intravenous push or single bolus injection.
- Tizveni does not contain a preservative. Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C to 8°C. The 24 hours include storage of the diluted solution under refrigeration (2°C to 8°C) for no more than 20 hours, time required for returning to room temperature (25°C and below) and time to complete the infusion within 4 hours. From a microbiological point of view, unless the method of dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.
- The diluted solution must not be frozen.
- Discard any unused portion left in the vial.
- The intravenous line must be flushed at the end of the infusion.
- Tizveni vials are for single use only.