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

Tevimbra 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 10 ml vial contains 100 mg tislelizumab (100 mg/10 ml).

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 1.6 mg sodium and 0.2 mg polysorbate 20 (E432).

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)

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

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

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

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

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

Small Cell Lung Cancer (SCLC)

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

Gastric or gastroesophageal junction (G/GEJ) adenocarcinoma

Tevimbra, in combination with platinum and fluoropyrimidine-based chemotherapy, is indicated for the first-line treatment of adult patients with HER-2-negative locally advanced unresectable or metastatic gastric or gastroesophageal junction (G/GEJ) adenocarcinoma whose tumours express PD-L1 with a tumour area positivity (TAP) score ≥ 5% (see section 5.1).

Oesophageal squamous cell carcinoma (OSCC)

Tevimbra, in combination with platinum-based chemotherapy, is indicated for the first-line treatment of adult patients with unresectable, locally advanced or metastatic OSCC whose tumours express PD-L1 with a TAP score ≥ 5% (see section 5.1).

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

4.2 Posology and method of administration

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

PD-L1 testing

If specified in the indication, patient selection for treatment with Tevimbra based on the tumour expression of PD-L1 should be assessed by a CE-marked IVD with the corresponding intended purpose. If the CE-marked IVD is not available, an alternative validated test should be used (see sections 4.1, 4.4, and 5.1).

Posology

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

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

When Tevimbra and chemotherapy are administered on the same day, Tevimbra should be administered before chemotherapy. The 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 Tevimbra until disease progression or unacceptable toxicity (see section 5.1).

Dose delay or discontinuation (see also section 4.4)
Dose reductions of Tevimbra as monotherapy or in combination therapy are not recommended. Tevimbra should be withheld or discontinued based on safety and tolerability 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 Tevimbra

Immune-related adverse reaction	**Severity[1]**	**Tevimbra 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 Tevimbra 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 Tevimbra 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 Tevimbra may be considered after corticosteroid taper. Otherwise, treatment should be discontinued.[3]

Immune-related adverse reaction	Severity[1]	Tevimbra treatment modification
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 Tevimbra 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 of 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 Tevimbra 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

Tevimbra 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.

Assessment of PD-L1 status

When assessing the PD-L1 status of the tumour, it is important that a well validated methodology is chosen to minimise false negative or false positive determinations.

Patient Card

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

The prescriber must discuss the risks of immune-related adverse reactions during Tevimbra 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) including erythema multiforme (EM), Stevens-Johnson syndrome (SJS) and Toxic epidermal necrolysis (TEN), some of them with fatal outcome, have been reported in patients receiving tislelizumab (see section 4.8). 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 SCAR, tislelizumab should be withheld and the patient should be referred to specialised care for assessment and treatment. If SCAR 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, cystitis noninfective, immune thrombocytopenia, encephalitis, myasthenia gravis, Sjögren's syndrome 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.

Haemophagocytic lymphohistiocytosis
Haemophagocytic lymphohistiocytosis (HLH) has been reported in patients receiving tislelizumab (see section 4.8). HLH is a life-threatening syndrome characterised by fever, skin rash, lymphadenopathy, hepato- and/or splenomegaly and cytopenias. Patients should be monitored for clinical signs and symptoms of HLH. For suspected HLH, tislelizumab must be interrupted for diagnostic workup and treatment for HLH initiated. If HLH is confirmed, administration of tislelizumab should be discontinued.

Infusion-related reactions

Severe infusion-related reactions (Grade 3 or higher) have been reported in patients receiving tislelizumab (see section 4.8). Cases of anaphylaxis, including anaphylactic reaction and anaphylactic shock, have been reported in the post-marketing setting. 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 status 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.

Tevimbra is to be diluted in sodium chloride 9 mg/mL (0.9%) solution for infusion. This should be taken into consideration for patients on a controlled sodium diet (see section 6.6).

Polysorbate 20
This medicinal product contains 0.2 mg of polysorbate 20 in each ml of concentrate, which is equivalent to 4 mg in two 10 ml vials of a single infusion of Tevimbra. Polysorbates may cause allergic reactions. Patients with known allergies should be taken into consideration.

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 low doses of systemic corticosteroid (10 mg/day prednisone or equivalent), should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of tislelizumab. 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 Tevimbra, women should be advised not to breast-feed during treatment and for at least 4 months after the last dose of Tevimbra.

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

Tevimbra 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 1952 patients across multiple tumour types who received 200 mg tislelizumab every 3 weeks. The most common adverse reactions (≥ 20%) were anaemia (27.7%), aspartate aminotransferase increased (24.7%), fatigue (24.6%), and alanine aminotransferase increased (22.0%). The most common Grade 3/4 adverse reactions (≥ 2%) were anaemia (4.8%), aspartate aminotransferase increased (3.7%), pneumonia (3.6%), hyponatraemia (2.9%), blood bilirubin increased (2.8%), hypertension (2.4%), and fatigue (2.1%). 1.0% of patients experienced adverse reactions leading to death. The adverse reactions leading to death were pneumonia (0.61%), pneumonitis (0.10%), hepatitis (0.10%), thrombocytopenia (0.05%), dyspnoea (0.05%) and decreased appetite (0.05%). Among the 1952 patients, 40.7% were exposed to tislelizumab for longer than 6 months, and 24.7% were exposed for longer than 12 months.

The safety of tislelizumab given in combination with chemotherapy is based on data in 1950 patients across multiple tumour types who received 200 mg tislelizumab every 3 weeks, with the exception of study BGB A317-315 where patients also received tislelizumab at a dose of 400 mg once every 6 weeks as adjuvant treatment after neoadjuvant therapy and surgery. The most common adverse

reactions (≥ 20%) were neutropenia (71.6%), anaemia (67.2%), thrombocytopenia (48.7%), nausea (43.3%), fatigue (40.8%), decreased appetite (40.1%), alanine aminotransferase increased (30.6%), aspartate aminotransferase increased (30.3%), rash (21.4%) and diarrhoea (20.3%). The most common Grade 3/4 adverse reactions (≥ 2%) were neutropenia (45.2%), anaemia (14.5%), thrombocytopenia (14.1%), hyponatraemia (4.6%), hypokalaemia (4.5%), fatigue (4.2%), pneumonia (4.0%), lymphopenia (3.1%), rash (2.9%), decreased appetite (2.6%), aspartate aminotransferase increased (2.2%), alanine aminotransferase increased (2.1%). 1.3% of patients experienced adverse reactions leading to death. The adverse reactions leading to death were pneumonia (0.50%), pneumonitis (0.30%), dyspnoea (0.20%), myocarditis (0.20%), hepatitis (0.05%), thrombocytopenia (0.05%), colitis (0.05%), hypokalaemia (0.05%), and myositis (0.05%). Among the 1950 patients, 56.5% were exposed to tislelizumab for 6 months or longer, and 31.9% were exposed for 12 months or longer.

Tabulated list of adverse reactions

Adverse reactions reported in the pooled dataset for patients treated with Tevimbra monotherapy (N= 1952) and in combination with chemotherapy (N = 1950) 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 Tevimbra as monotherapy (N = 1952) and in combination with chemotherapy (N = 1950)

	Tislelizumab monotherapy N = 1952	**Tislelizumab plus chemotherapy N = 1950**
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]	Very common*	Very common*
Neutropenia[4]	Common	Very common
Lymphopenia[5]	Common	Very common
Haemophagocytic lymphohistiocytosis	Not known	Rare
Immune system disorders		
Sjögren's syndrome	#	Uncommon
Endocrine disorders		
Hypothyroidism[6]	Very common	Very common
Hyperthyroidism[7]	Common	Common
Thyroiditis[8]	Common	Uncommon
Adrenal insufficiency[9]	Uncommon	Uncommon
Hypophysitis[10]	Uncommon	Uncommon
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	Rare	Rare
Encephalitis[15]	#	Rare

Myasthenia gravis	#	Rare
Eye disorders		
Uveitis[16]	Uncommon	Uncommon
Cardiac disorders		
Myocarditis[17]	Uncommon	Common*
Pericarditis	Uncommon	Rare
Vascular disorders		
Hypertension[18]	Common	Common
Respiratory, thoracic and mediastinal disorders		
Cough	Very common	Very common
Dyspnoea	Common*	Common*
Pneumonitis[19]	Common*	Common*
Gastrointestinal disorders		
Nausea	Very common	Very common
Diarrhoea[20]	Very common	Very common
Stomatitis[21]	Common	Common
Pancreatitis[22]	Uncommon	Common
Colitis[23]	Uncommon	Common
Coeliac disease	Rare	#
Hepatobiliary disorders		
Hepatitis[24]	Common*	Common*
Skin and subcutaneous tissue disorders		
Rash[25]	Very common	Very common
Pruritus	Very common	Very common
Vitiligo[26]	Uncommon	Uncommon
Erythema multiforme	Uncommon	Rare
Stevens-Johnson syndrome	Rare	#
Toxic epidermal necrolysis[27]	Not known*	Not known*
Musculoskeletal and connective tissue disorders		
Arthralgia	Common	Very common
Myalgia	Common	Common
Myositis[28]	Uncommon	Uncommon*
Arthritis[29]	Uncommon	Common
Renal and urinary disorders		
Nephritis[30]	Uncommon	Uncommon
Cystitis noninfective[31]	Rare	#
General disorders and administration site conditions		
Fatigue[32]	Very common	Very common
Pyrexia[33]	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[34]	Very common	Very common
Blood alkaline phosphatase increased	Common	Common
Blood creatinine increased	Common	Very common
Injury, poisoning and procedural complications		
Infusion-related reaction[35]	Common	Common

[1] Pneumonia includes preferred terms (PTs) of pneumonia, lower respiratory tract infection, lower respiratory tract infection bacterial, pneumonia bacterial, pneumonia fungal, pneumocystis jirovecii pneumonia, bronchopulmonary aspergillosis, candida pneumonia, pneumonia mycoplasmal, pneumonia staphylococcal and pneumonia viral.

[2] Anaemia includes PTs of anaemia and haemoglobin decreased.

[3] Thrombocytopenia includes PTs of thrombocytopenia, platelet count decreased and immune thrombocytopenia.
[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 PTs of hypothyroidism, anti-thyroid antibody increased, immune-mediated hypothyroidism, thyroid hormones decreased, thyroxine decreased, thyroxine free decreased, tri-iodothyronine free decreased, tri-iodothyronine decreased, primary hypothyroidism, central hypothyroidism and thyroxine decreased.
[7] Hyperthyroidism includes PTs of blood thyroid stimulating hormone decreased, hyperthyroidism, immune-mediated hyperthyroidism, thyroxine free increased, thyroxine increased, tri-iodothyronine free increased, and tri-iodothyronine increased.
[8] Thyroiditis includes PTs of thyroiditis, autoimmune thyroiditis, immune-mediated thyroiditis, silent thyroiditis and thyroiditis subacute.
[9] Adrenal insufficiency includes PTs of Addison's disease, adrenal insufficiency, glucocorticoid deficiency, immune-mediated adrenal insufficiency, primary 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, diabetic ketoacidosis, diabetic ketosis, ketoacidosis, type 1 diabetes mellitus and latent autoimmune diabetes in adults.
[15] Encephalitis includes the PT of immune-mediated encephalitis.
[16] Uveitis includes PTs of chorioretinitis, iridocyclitis, uveitis and iritis.
[17] Myocarditis includes PTs of myocarditis, immune-mediated myocarditis and autoimmune myocarditis.
[18] Hypertension includes PTs of hypertension, blood pressure increased and essential hypertension.
[19] Pneumonitis includes PTs of pneumonitis, immune-mediated lung disease, interstitial lung disease and organising pneumonia.
[20] Diarrhoea includes PTs of diarrhoea and frequent bowel movements.
[21] Stomatitis includes PTs of stomatitis, mouth ulceration, oral mucosa erosion and aphthous ulcer.
[22] Pancreatitis includes PTs of, amylase increased, lipase increased, pancreatitis and pancreatitis acute.
[23] Colitis includes PTs of autoimmune colitis, colitis, colitis ulcerative and immune-mediated enterocolitis.
[24] Hepatitis includes PTs of hepatitis, drug-induced liver injury, hepatotoxicity, hepatic function abnormal, immune-mediated hepatitis, liver injury and autoimmune hepatitis.
[25] Rash includes PTs of rash, rash maculo-papular, eczema, rash erythematous, dermatitis, acute febrile neutrophilic dermatosis, autoimmune dermatitis, dermatitis allergic, dermatitis exfoliative, 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, erythema nodosum and pemphigoid.
[26] Vitiligo includes PTs of, leukoderma skin depigmentation, skin hypopigmentation and vitiligo.
[27] Post-marketing experience.
[28] Myositis includes PTs of myositis, rhabdomyolysis and immune-mediated myositis.
[29] Arthritis includes PTs of arthritis, polyarthritis and immune-mediated arthritis.
[30] Nephritis includes PTs of nephritis, focal segmental glomerulosclerosis, glomerulonephritis membranous, immune-mediated renal disorder, tubulointerstitial nephritis and immune-mediated nephritis.
[31] Cystitis noninfective includes PTs of cystitis noninfective and immune-mediated cystitis. Cases of immune-mediated cystitis have been reported in the post-marketing setting.
[32] Fatigue includes PTs of fatigue, asthenia, malaise, physical deconditioning and lethargy.
[33] Pyrexia includes the PTs of body temperature increased and pyrexia.
[34] Blood bilirubin increased includes PTs of blood bilirubin increased, bilirubin conjugated increased, blood bilirubin unconjugated increased and hyperbilirubinaemia.
[35] Infusion-related reaction includes PTs of anaphylactic reaction, chills, corneal oedema, dermatitis allergic, drug eruption, drug hypersensitivity, face oedema, gingival swelling, hypersensitivity,

	laryngeal obstruction, laryngeal oedema, lip oedema, lip swelling, mouth swelling, pruritus allergic, rash, rash erythematous, rash macular, rash pruritic, rhinitis allergic, swelling face, tongue oedema, type I hypersensitivity, urticaria, infusion-related reaction and infusion-related hypersensitivity reaction.
*	Including fatal outcomes
#	Not reported in this pooled setting

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 5.1% of patients, including Grade 1 (1.3%), Grade 2 (2.1%), Grade 3 (1.3%), Grade 4 (0.3%) and Grade 5 (0.1%) events.

The median time from first dose to onset of the event was 4.1 months (range: 1.0 day to 55.0 months), and the median duration from onset to resolution was 2.8 months (range: 7.0 days to 33.7 months). Tislelizumab was permanently discontinued in 1.8% of patients and tislelizumab treatment was interrupted in 1.9% of patients. Pneumonitis resolved in 47.0% of patients.

In patients treated with tislelizumab as monotherapy, pneumonitis occurred more frequently in patients with a history of prior thoracic radiation (8.4%) than in patients who did not receive prior thoracic radiation (3.6%).

Pneumonitis occurred in 11.2% of patients with NSCLC treated with tislelizumab in combination with chemotherapy. In patients with NSCLC treated with tislelizumab as monotherapy, pneumonitis occurred in 8.3% of patients.

Immune-related hepatitis
In patients treated with tislelizumab as monotherapy, immune-related hepatitis occurred in 1.2% of patients, including Grade 1 (0.1%), Grade 2 (0.2%), Grade 3 (0.6%) and Grade 4 (0.3%) events.

The median time from first dose to onset of the event was 22.0 days (range: 1.0 day to 4.1 months), and the median duration from onset to resolution was 1.1 months (range: 6.0 days to 6.6 months). Tislelizumab was permanently discontinued in 0.3% of patients and tislelizumab treatment was interrupted in 0.8% of patients for immune-related hepatitis. Hepatitis resolved in 60.9% of patients.

Immune-related skin adverse reactions
In patients treated with tislelizumab as monotherapy, immune-related skin adverse reactions occurred in 12.6% of patients, including Grade 1 (7.7%), Grade 2 (3.7%), Grade 3 (1.0%) and Grade 4 (0.1%) events.

The median time from first dose to onset of the event was 1.5 months (range: 1.0 day to 36.1 months). The median duration from onset to resolution was 1.1 months (range: 1.0 day to 36.7 months). Tislelizumab was permanently discontinued in 0.1% of patients, and tislelizumab treatment was interrupted in 1.3% of patients. Skin adverse reactions resolved in 72.0% of patients.

Cases of SJS and TEN have been reported from post-marketing experience, some with fatal outcome (see section 4.2 and 4.4).

Immune-related colitis
In patients treated with tislelizumab as monotherapy, immune-related colitis occurred in 0.6% of patients, including Grade 2 (0.4%) and Grade 3 (0.2%) events.

The median time from first dose to onset of the event was 6.0 months (range: 6.0 days to 26.5 months), and the median duration from onset to resolution was 28.0 days (range: 9.0 days to 26.7 months). Tislelizumab was permanently discontinued in 0.1% of patients and tislelizumab treatment was interrupted in 0.4% 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 0.8% of patients, including Grade 1 (0.3%), Grade 2 (0.3%), Grade 3 (0.2%) and Grade 4 (0.1%) events.

The median time from first dose to onset of the event was 1.5 months (range: 15.0 days to 39.3 months), and the median duration from onset to resolution was 1.2 months (range: 5.0 days to 5.2 months). Tislelizumab was permanently discontinued in 0.2% of patients and tislelizumab treatment was interrupted in 0.5% of patients. Myositis/rhabdomyolysis resolved in 75.0% of patients.

Immune-related endocrinopathies
Thyroid disorders
Hypothyroidism:
In patients treated with tislelizumab as monotherapy, hypothyroidism occurred in 13.8% of patients, including Grade 1 (6.4%), Grade 2 (7.3%), Grade 3 (0.1%) and Grade 4 (0.1%) events.

The median time from first dose to onset of the event was 4.0 months (range: 1.0 day to 29.9 months). The median duration from onset to resolution was 2.1 months (range: 2.0 days to 27.0 months). Tislelizumab was permanently discontinued in 0.1% of patients and tislelizumab treatment was interrupted in 0.6% of patients. Hypothyroidism resolved in 36.4% of patients.

Hyperthyroidism:
In patients treated with tislelizumab as monotherapy, hyperthyroidism occurred in 5.1% of patients, including Grade 1 (4.4%) and Grade 2 (0.7%) events.

The median time from first dose to onset of the event was 2.1 months (range: 6.0 days to 39.4 months). The median duration from onset to resolution was 1.4 months (range: 8.0 days to 22.1 months). Tislelizumab was permanently discontinued in 0.1% of patients and tislelizumab treatment was interrupted in 0.3% of patients. Hyperthyroidism resolved in 77.0% of patients.

Thyroiditis:
In patients treated with tislelizumab as monotherapy, thyroiditis occurred in 1.1% of patients, including Grade 1 (0.5%) and Grade 2 (0.6%) events.

The median time from first dose to onset of the event was 2.0 months (range: 14.0 days to 20.7 months). The median duration from onset to resolution was 2.0 months (range: 20.0 days to 15.3 months). Tislelizumab was not permanently discontinued in any patient and tislelizumab treatment was interrupted in 0.2% of patients. Thyroiditis resolved in 38.1% of patients.

Adrenal insufficiency
In patients treated with tislelizumab as monotherapy, adrenal insufficiency occurred in 0.5% of patients, including Grade 2 (0.3%), Grade 3 (0.2%) and Grade 4 (0.1%) events.

The median time from first dose to onset of the event was 10.3 months (range: 1.4 months to 16.9 months). The median duration from onset to resolution was 1.9 months (range: 30.0 days to 13.6 months). Tislelizumab was not permanently discontinued in any patient and tislelizumab treatment was interrupted in 0.4% of patients. Adrenal insufficiency resolved in 30.0% of patients.

Hypophysitis
In patients treated with tislelizumab as monotherapy, hypophysitis (Grade 2) occurred in 0.3% of patients.

The median time from first dose to onset of the event was 9.0 months (range: 22.0 days to 16.2 months). The median duration from onset to resolution was 2.3 months (only 1 resolved event). Tislelizumab was not permanently discontinued in any patients and tislelizumab treatment was not interrupted in any patients. Hypophysitis resolved in 20.0% of patients.

Type 1 diabetes mellitus
In patients treated with tislelizumab as monotherapy, type 1 diabetes mellitus occurred in 0.6% of patients, including Grade 1 (0.1%), Grade 2 (0.3%), Grade 3 (0.2%) and Grade 4 (0.1%) events.

The median time from first dose to onset of the event was 6.5 months (range: 1.1 months to 36.1 months). The median duration from onset to resolution was 22.0 days (range: 5.0 days to 3.6 months). Tislelizumab was permanently discontinued in 0.2% of patients and tislelizumab treatment was interrupted in 0.2% of patients. Type 1 diabetes mellitus resolved in 8.3% of patients.

Immune-related nephritis and renal dysfunction
In patients treated with tislelizumab as monotherapy, immune-related nephritis and renal dysfunction occurred in 0.2% of patients, including Grade 1 (0.1%), Grade 2 (0.1%) and Grade 3 (0.1%) events.

The median time from first dose to onset of the event was 1.5 months (range: 15.0 days to 12.1 months). The median duration from onset to resolution was 9.0 days (the same for 2 resolved events). Tislelizumab was permanently discontinued in 0.1% of patients and tislelizumab treatment was interrupted in 0.1% 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 0.8% of patients, including Grade 1 (0.4%), Grade 2 (0.2%), 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 33.6 months), and the median duration from onset to resolution was 1.2 months (range: 4.0 days to 15.6 months). Tislelizumab was permanently discontinued in 0.4% of patients and tislelizumab treatment was interrupted in 0.4% of patients. Myocarditis resolved in 60.0% of patients.

Myocarditis occurred in 1.2% of patients treated with tislelizumab in combination with chemotherapy, including Grade 5 (0.2%) events.

Immune checkpoint inhibitor class effects
There have been cases of the following adverse reactions reported during treatment with other immune checkpoint inhibitors which might also occur during treatment with tislelizumab: pancreatic exocrine insufficiency.

Infusion-related reactions
In patients treated with tislelizumab as monotherapy, infusion-related reactions occurred in 3.0% of patients, including Grade 3 (0.1%) events. Tislelizumab was permanently discontinued in 0.1% of patients and tislelizumab treatment was interrupted in 0.1% of patients.

Cases of anaphylaxis, including anaphylactic reaction and anaphylactic shock, have been reported in the post-marketing setting.

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, 8.9% for decreased

lymphocytes, 0.2% for increased lymphocytes, 2.1% for decreased neutrophils, 1.3% for decreased platelets, 2.6% for increased alanine aminotransferase, 0.3% for decreased albumin, 2.7% for increased alkaline phosphatase, 4.8% for increased aspartate aminotransferase, 2.8% for increased bilirubin, 1.9% for increased creatine kinase, 1.2% for increased creatinine, 4.4% for increased glucose, 0.5% for decreased glucose, 0.9% for increased potassium, 2.9% for decreased potassium, 0.1% for increased sodium, 6.5% 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, 23.3% for decreased leukocytes, 17.9% for decreased lymphocytes, 0.1% for increased lymphocytes, 47.2% for decreased neutrophils, 14.1% for decreased platelets, 3.5% for increased alanine aminotransferase, 0.5% for decreased albumin, 0.8% for increased alkaline phosphatase, 3.1% for increased aspartate aminotransferase, 2.0% for increased bilirubin, 2.3% for increased creatine kinase, 1.8% for increased creatinine, 0.5% for decreased glucose, 1.2% for increased glucose, 1.3% for increased potassium, 7.6% for decreased potassium, 0.3% for increased sodium, 11.5% for decreased sodium.

Immunogenicity
Of 3614 antidrug antibodies (ADA)-evaluable patients, 21.1% 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 receiving 200 mg once every 3 weeks monotherapy or in combination with chemotherapies (including adjuvant 400 mg once every 6 weeks in resectable NSCLC) 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 52.5% vs. 42.1%, serious adverse events (SAEs) 39.0% vs. 31.8%, AEs leading to tislelizumab treatment discontinuation 12.3% vs 11.4% (for monotherapy); Grade ≥ 3 AEs 80.0% vs. 78.6%, SAEs 43.3% vs. 41.0%, AEs leading to tislelizumab treatment discontinuation 13.6% vs 13.5% (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 as monotherapy or in combination with chemotherapy 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.

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 should be instituted immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, 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), 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 median OS follow-up times by reverse Kaplan-Meier methodology were 9.9 months in the T+PP arm and 9.7 months in the PP arm.

The efficacy results of the final analysis (data cut-off date of 26-Oct-2020) were consistent with those of the interim analysis. At the final analysis, the median OS follow-up times by reverse Kaplan-Meier methodology were 18.4 months in the T+PP arm and 18.0 months in the PP arm.

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)
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; 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%

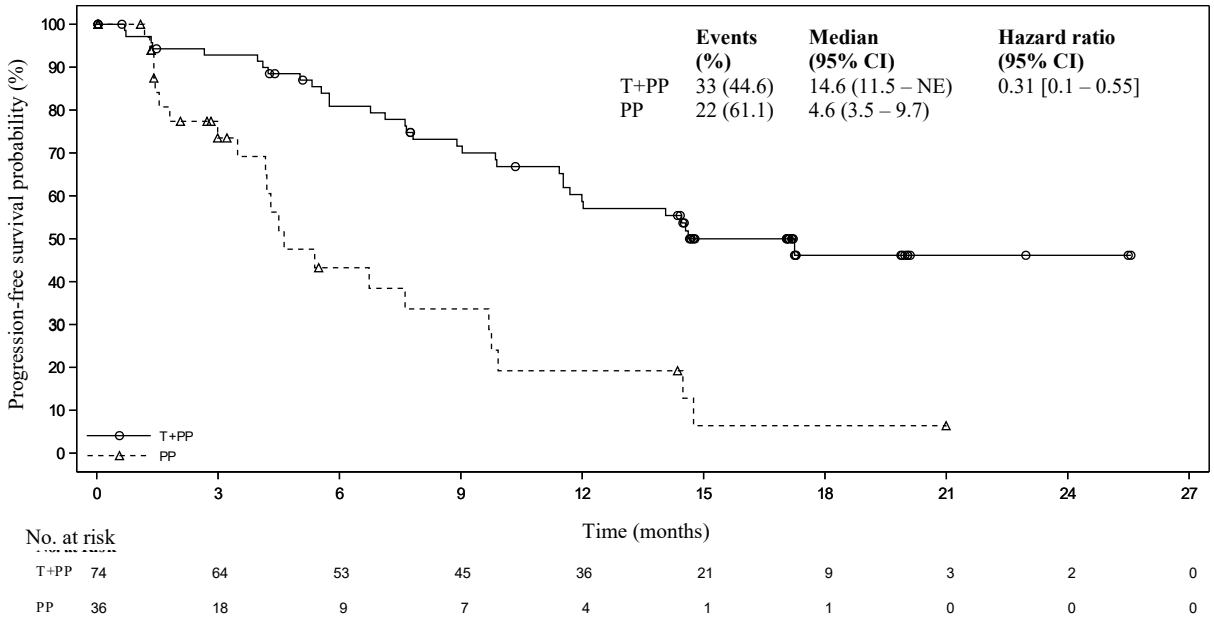
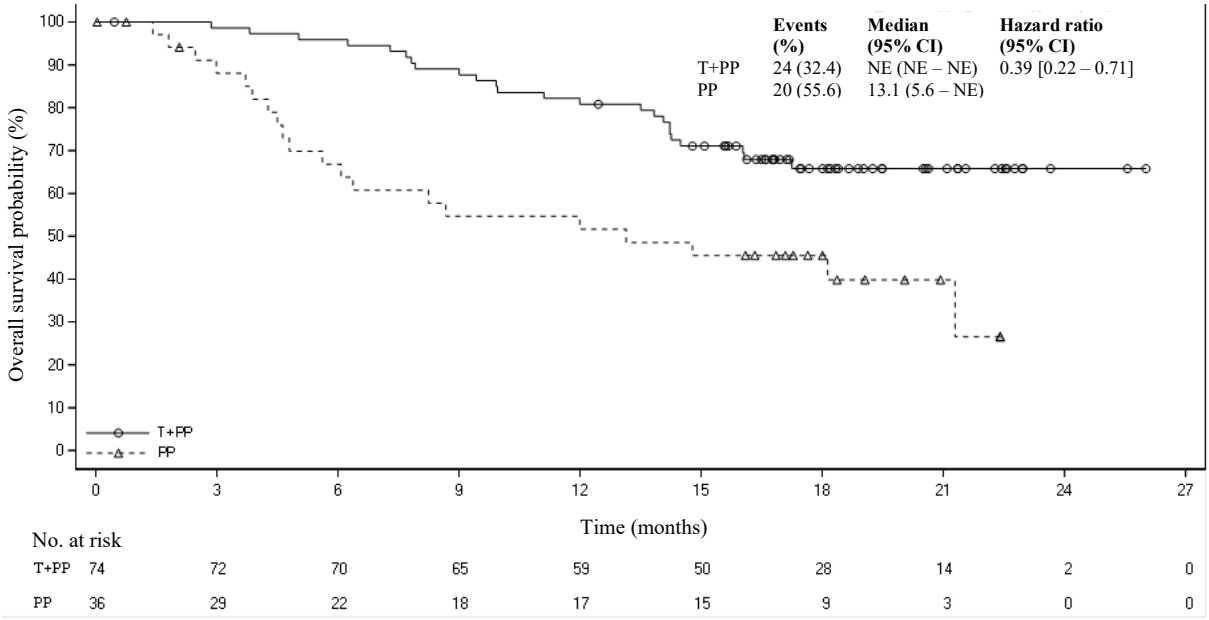


Figure 2 Kaplan-Meier plot of OS in BGB-A317-304 in patients with PD-L1 ≥50%



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 versus 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), 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 median OS follow-up times by reverse Kaplan-Meier methodology were 8.8 months in the T+PC arm, 8.8 months in the T+nPC arm, and 8 months in the PC arm.

The final analysis (data cut-off date of 30-Sep-2020) showed the consistent results from the interim analysis. At the final analysis, the median OS follow-up times by reverse Kaplan-Meier methodology were 18.8 months in the T+PC arm, 18.9 months in the T+nPC arm, and 18.1 months in the PC arm.

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)	0.752 (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)
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)

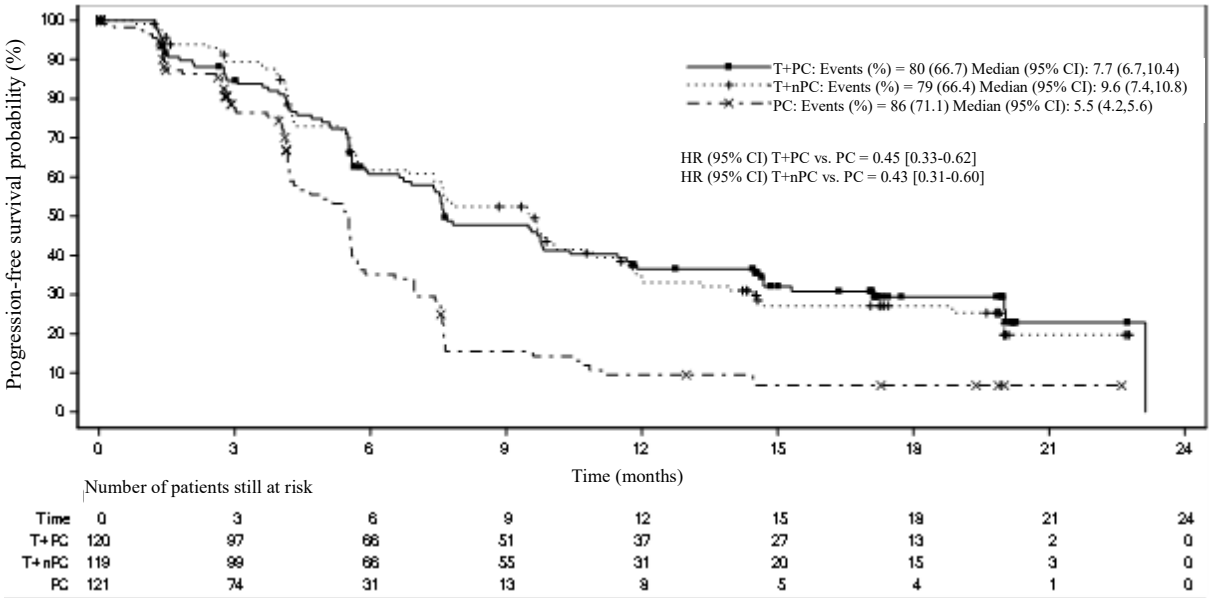
PFS = progression-free survival; CI = confidence interval; OS = overall survival; ORR = objective response rate; DoR = duration of response; NE = not estimable.

[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

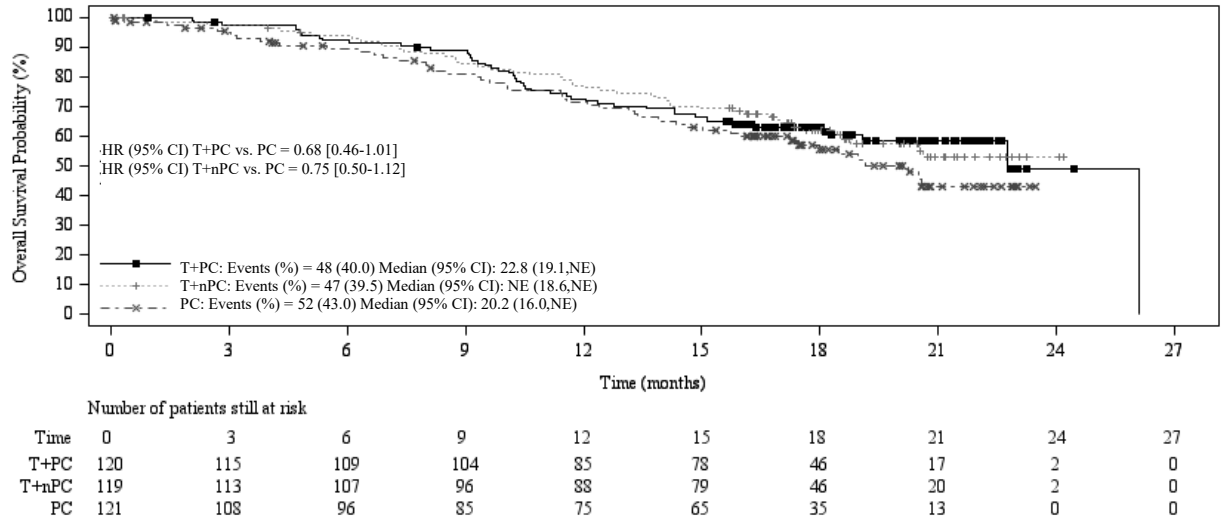
T+PC arm versus T+nPC arm versus PC arm



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%

Previously treated 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), 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. The median follow-up times by reverse Kaplan-Meier methodology were 19.5 months in the tislelizumab arm and 17.0 months in the docetaxel arm. At the final analysis (data cutoff date 15-Jul-2021), 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 median follow-up time by reverse Kaplan-Meier methodology at the final analysis were 31.1 months in the tislelizumab arm and 27.9 months in the docetaxel arm.

The final analysis (data cut-off date 15-Jul-2021) showed consistent efficacy results in the ITT population compared to the interim analysis.

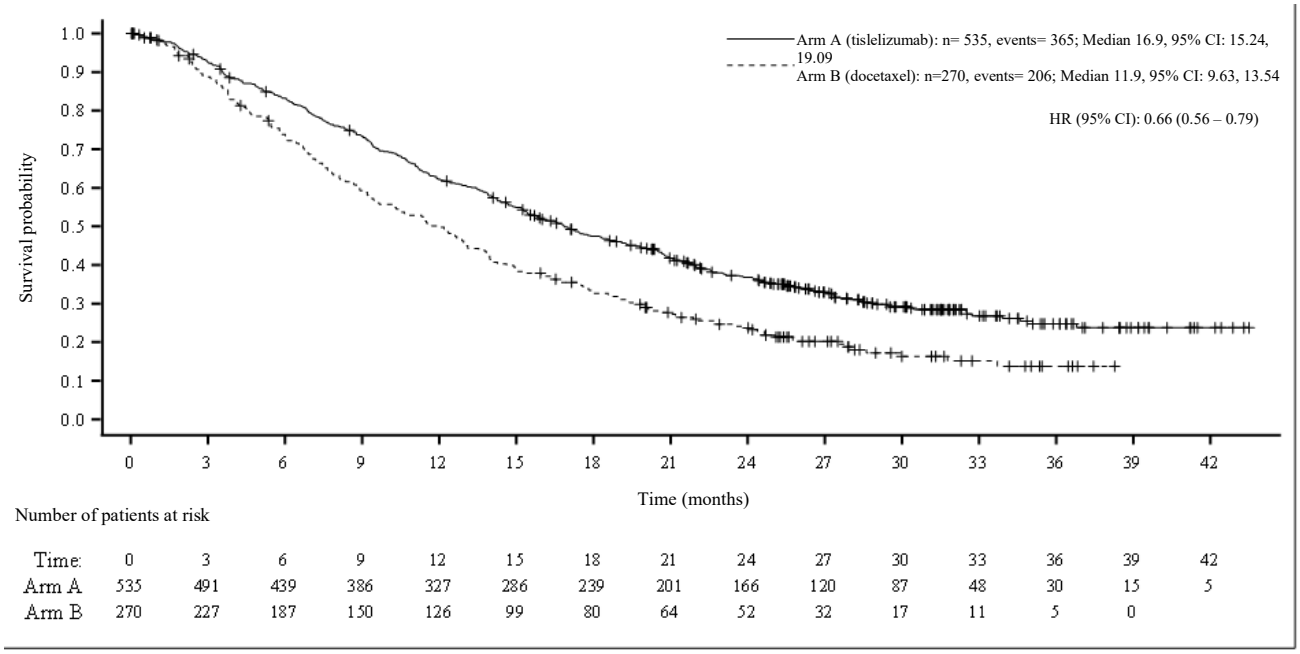
Table 5 and Figure 5 summarise the efficacy results for BGB-A317-303 (ITT analysis set) at the final analysis.

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)
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; 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.

<u>*Small cell lung cancer*</u>

First-line treatment of extensive-stage SCLC: BGB-A317-312
BGB-A317-312 was a randomised, double-blind, multicentre phase III study to compare the efficacy and safety of tislelizumab in combination with cisplatin or carboplatin plus etoposide versus placebo in combination with cisplatin or carboplatin plus etoposide as first-line treatment in patients with extensive-stage small cell lung cancer (ES-SCLC).

The study included patients with histologically or cytologically confirmed diagnosis of ES-SCLC who had not received any prior systemic treatment for ES-SCLC and ECOG performance status 0 or 1.

A total of 457 patients were randomised (1:1) to receive:

- Arm tislelizumab + chemotherapy: tislelizumab 200 mg plus carboplatin AUC 5 mg/mL/min or cisplatin 75 mg/m^2 on Day 1 and etoposide 100 mg/m^2 intravenously on Days 1, 2, and 3 of each 21-day cycle for a maximum of 4 cycles.
- Arm placebo + chemotherapy: placebo plus carboplatin AUC 5 mg/mL/min or cisplatin 75 mg/m^2 on Day 1 and etoposide 100 mg/m^2 intravenously on Days 1, 2, and 3 of each 21-day cycle for a maximum of 4 cycles.

The choice of platinum agent (cisplatin or carboplatin) was at the investigator's discretion. Tislelizumab 200 mg monotherapy or placebo continued every 3 weeks until disease progression, loss of clinical benefit, unacceptable toxicity.

Randomisation was stratified by ECOG performance status (0 versus 1), investigator-chosen chemotherapy (carboplatin versus cisplatin), and brain metastasis (yes versus no).

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

Demographics and baseline characteristics were generally balanced between the 2 treatment arms. The baseline characteristics for all 457 randomised patients were: median age of 62 years (range: 31 to 78 years); 37.2% were ≥65 years of age; 81.4% male; 100% Asian (all enrolled in China), 84.9% with ECOG PS of 1; 1.1% had a history of brain metastases; 79% received carboplatin per investigator's choice; 62.6% were current smokers; and 89.3% had disease Stage IV defined by AJCC 7th Edition.

At the time of the prespecified final analysis (data cut-off 19 April 2023), BGB-A317-312 showed a statistically significant improvement in OS for patients randomised to the tislelizumab plus chemotherapy arm as compared to the placebo plus chemotherapy arm. The stratified HR was 0.75 (95% CI: 0.61, 0.93; 1-sided p-value of 0.004), with a median OS of 15.5 months in the tislelizumab plus chemotherapy arm compared to 13.5 months in the placebo plus chemotherapy arm.

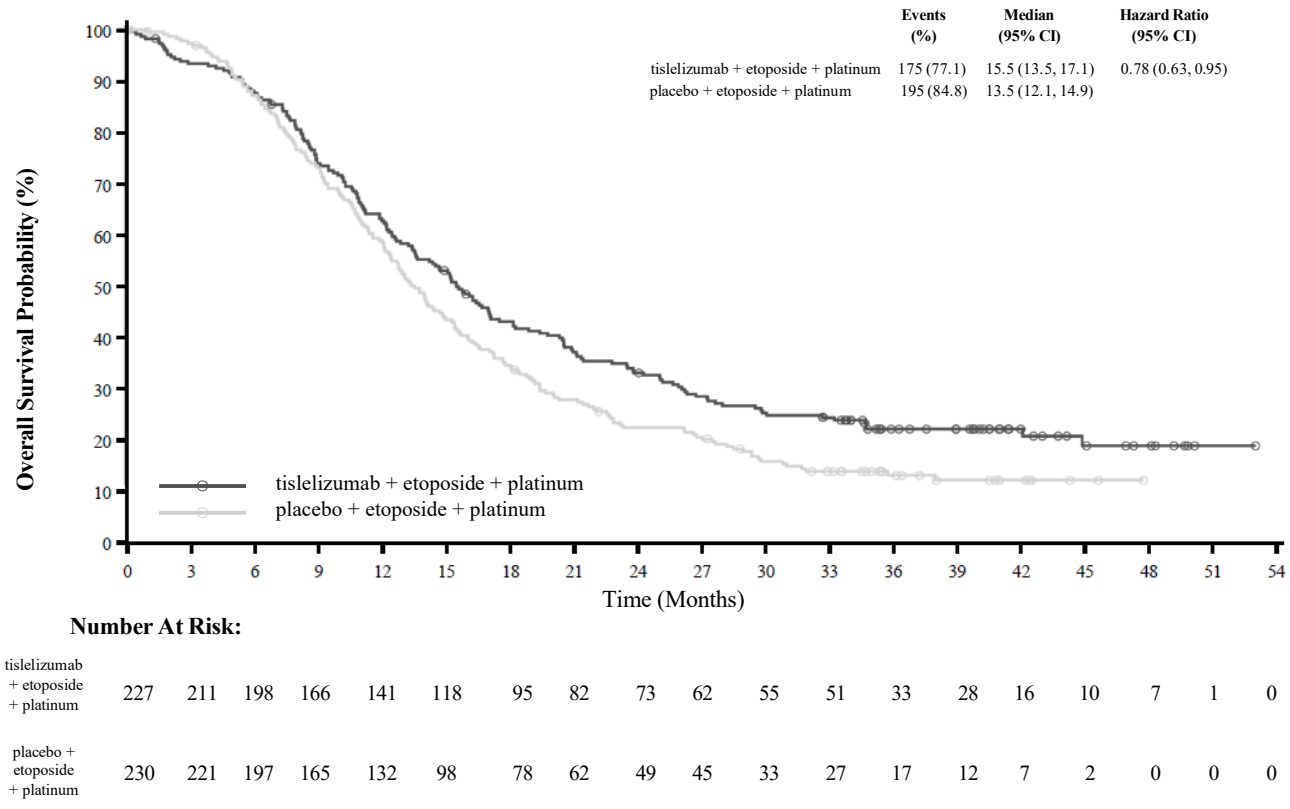
A descriptive updated analysis (data cut-off 29 December 2023) showed consistent efficacy results with the final analysis. The median OS follow-up times by reverse Kaplan-Meier methodology were 39.8 months (95% CI: 36.2 to 41.4 months) in the tislelizumab plus chemotherapy arm and 36.4 months (95% CI: 35.0 to 40.9 months) in the placebo plus chemotherapy arm.
Efficacy results of the updated analysis are shown in Table 7 and Figure 6. Data for patients with brain metastases are too limited to draw conclusions on this population.

Table 7 Efficacy results in BGB-A317-312 – Updated analysis

	Tislelizumab + Chemotherapy (N = 227)	Placebo + Chemotherapy (N = 230)
Overall Survival		
Deaths, n (%)	175 (77.1)	195 (84.8)
Median (months) (95% CI)[a]	15.5 (13.5, 17.1)	13.5 (12.1, 14.9)
Stratified Hazard Ratio (95% CI)[b]	0.78 (0.63, 0.95)	
Progression-Free Survival		
Events, n (%)	178 (78.4)	207 (90.0)
Median (months) (95% CI)[a]	4.7 (4.3, 5.5)	4.3 (4.2, 4.4)
Stratified Hazard Ratio (95% CI)[b]	0.65 (0.53, 0.80)	
Overall Response Rate[c], (%) (95% CI)[d]	68.3 (61.8, 74.3)	61.7 (55.1, 68.0)
Median Duration of Response (Months)[c] (95% CI)[a]	4.3 (4.1, 5.6)	3.7 (3.0, 4.1)

[a] Median was estimated using Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley with log-log transformation.
[b] Hazard ratio and 95% CI were estimated using a Cox regression model stratified by ECOG performance (1 vs 0) and platinum (Carboplatin vs Cisplatin) with placebo + chemotherapy as the reference group.
[c] Objective responses were confirmed per RECIST v1.1.
[d] The 95% CI was estimated using the Clopper-Pearson method.

Figure 6: Kaplan-Meier plot of OS in BGB-A317-312



Number At Risk:

tislelizumab + etoposide + platinum	227	211	198	166	141	118	95	82	73	62	55	51	33	28	16	10	7	1	0
placebo + etoposide + platinum	230	221	197	165	132	98	78	62	49	45	33	27	17	12	7	2	0	0	0

Gastric or gastroesophageal junction (G/GEJ) adenocarcinoma

First-line treatment of G/GEJ adenocarcinoma: BGB-A317-305

BGB-A317-305 is a randomised, multicentre, double-blind, placebo-controlled phase III study comparing the efficacy and safety of tislelizumab plus platinum and fluoropyrimidine-based chemotherapy versus placebo plus platinum and fluoropyrimidine-based chemotherapy as first-line treatment in patients with locally advanced unresectable or metastatic G/GEJ adenocarcinoma.

The study included only patients with histologically confirmed adenocarcinoma and with no prior systemic therapy for advanced disease. Patients may have received prior neoadjuvant or adjuvant therapy as long as it was completed and have no recurrence or disease progression for at least 6 months.

Patients were enrolled regardless of their tumour PD-L1 expression level, which was evaluated prospectively at a central laboratory by Tumour Area Positivity (TAP) score, which is defined as total percentage of tumor area (tumor and any desmoplastic stroma) covered by tumor cells with PD-L1 membrane staining (any intensity), and tumor associated immune cells with PD-L1 staining (any intensity), visually estimated by pathologists using Ventana PD-L1 (SP263) assay.

The study excluded patients who had squamous cell or undifferentiated or other histological type G/GEJ cancer and patients who had known HER-2 positive tumours.

Randomisation was stratified by geographical region (China [including Taiwan] versus Japan and South Korea versus rest of the world [ROW, including US and Europe]), PD-L1 expression (PD-L1 TAP score ≥5% versus PD-L1 TAP score <5%), presence of peritoneal metastasis (yes versus no) and ICC option (oxaliplatin plus capecitabine versus cisplatin plus 5-FU).

Patients were randomised (1:1) to receive tislelizumab 200 mg or placebo every 3 weeks in combination with platinum and fluoropyrimidine-based chemotherapy on a 21-day cycle. Tislelizumab (or placebo) was administered until disease progression or unacceptable toxicity. After 24 months of treatment, study therapy could be continued beyond two years if the investigator considered this to be in the best interest of the patient based on an assessment of clinical benefit and potential risks.

Chemotherapy consisted of:

- oxaliplatin 130 mg/m² IV on day 1 and capecitabine 1 000 mg/m2 orally twice daily for 14 consecutive days, repeated every 3 weeks. Oxaliplatin was administered for up to 6 cycles and capecitabine was administered as maintenance therapy at investigator's discretion until disease progression or unacceptable toxicity.

or

- cisplatin 80 mg/m² IV on day 1, and 5-FU 800 mg/m2/day by continuous IV infusion over 24 hours daily on days 1 to 5, repeated every 3 weeks. Cisplatin and 5-FU were given for up to 6 cycles.

The primary efficacy endpoints were overall survival (OS) in the PD-L1 Positive Analysis Set (PD-L1 TAP score ≥5%) and ITT analysis set (all randomised patients). The secondary efficacy endpoints were PFS, ORR and DoR, as assessed by the investigator per RECIST v1.1, and health-related quality of life (HRQoL).

Tumour assessment was performed approximately every 6 weeks during the first 48 weeks and thereafter approximately every 9 weeks.

A total of 997 patients were randomised to either the tislelizumab + chemotherapy arm (n = 501) or the placebo + chemotherapy arm (n = 496). Of the 997 patients, 546 (54.8%) had PD-L1 TAP score ≥5% (tislelizumab + chemotherapy: n = 274; placebo + chemotherapy: n = 272), 931 (93.4%) received oxaliplatin + capecitabine treatment (tislelizumab + chemotherapy: n = 466; placebo + chemotherapy: n = 465).

In patients whose tumours expressed PD-L1 with a TAP score ≥ 5%, the baseline characteristics for the study population were: median age of 62 years (range: 23 to 84), 39.2% age 65 years or older; 72.2% male; 23.1% White and 73.8% Asian; 33.7% with ECOG PS of 0 and 66.3% with ECOG PS of 1. A total of 79.9% patients had primary tumour location of stomach; 98.5% of patients had metastatic disease at baseline; 43.6% and 39.7% and patients had liver metastasis and peritoneal metastasis, respectively.

At prespecified interim analysis, BGB-A317-305 demonstrated a statistically significant improvement in OS for patients randomised to the tislelizumab + chemotherapy arm as compared to the placebo + chemotherapy arm in patients with PD-L1 TAP score ≥5%. The stratified HR was 0.74 (95% CI: 0.59 to 0.94; 1-sided p-value of 0.0056), with a median OS of 17.2 months in the tislelizumab + chemotherapy arm compared to 12.6 months in the placebo + chemotherapy arm. The study also demonstrated a statistically significant improvement in PFS in patients with PD-L1 TAP score ≥5%. The stratified HR was 0.67 (95% CI: 0.55 to 0.83; 1-sided p-value < 0.0001), with a median PFS of 7.2 months for tislelizumab + chemotherapy compared to 5.9 months for placebo + chemotherapy.

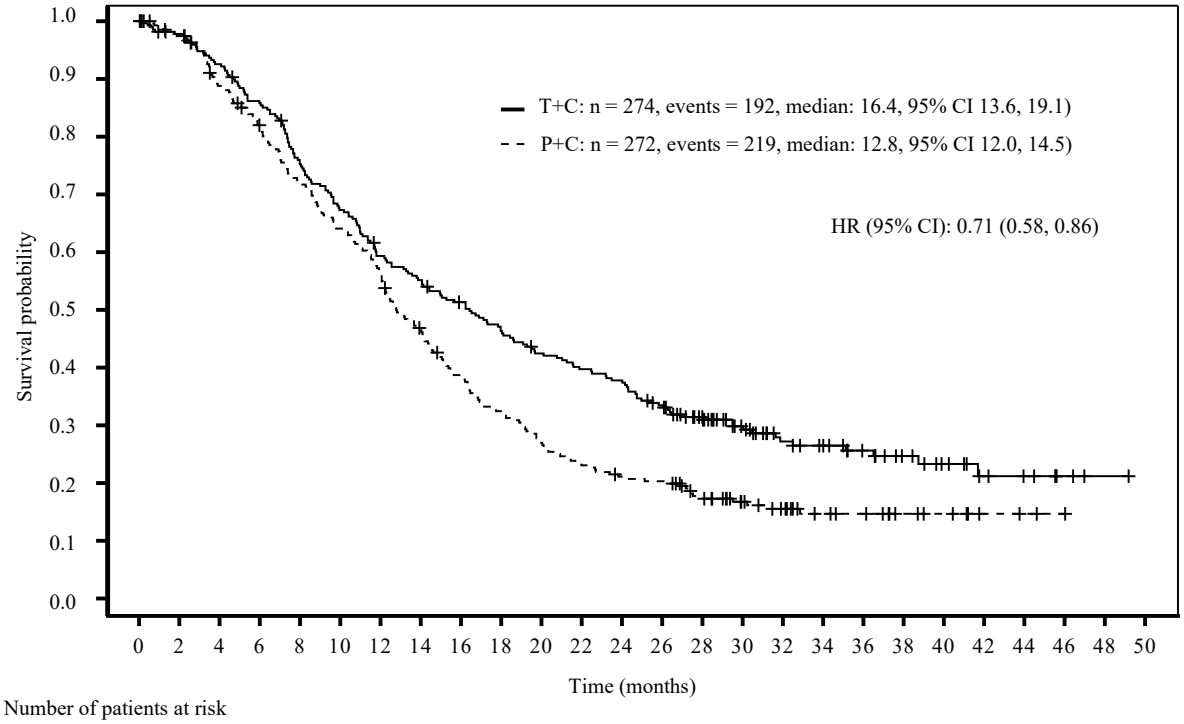
At prespecified final analysis, BGB-A317-305 demonstrated a statistically significant improvement for all randomised patients. The stratified HR was 0.80 (95% CI: 0.70 to 0.92; 1-sided p-value of 0.0011), with a median OS of 15.0 months in the tislelizumab + chemotherapy arm compared to 12.9 months in the placebo + chemotherapy arm. The updated results of OS in patients with PD-L1 TAP score ≥5% were consistent with its primary analysis results.
The final analysis efficacy results from patients with PD-L1 TAP score ≥5% are shown in Table 8 and in Figure 7.

Table 8 Efficacy results in BGB-A317-305 patients with PD-L1 TAP score ≥ 5% (final analysis)

	Tislelizumab + chemotherapy (N = 274)	**Placebo + chemotherapy (N = 272)**
	Patients with PD-L1 score ≥ 5%	
Median study follow-up (months)[a]	32.5	32.2
OS		
Death, n (%)	192 (70.1)	219 (80.5)
Median[b] (months) (95% CI)	16.4 (13.6, 19.1)	12.8 (12.0, 14.5)
Hazard ratio[c] (95% CI)	0.71 (0.58, 0.86)	
p-value[c,d]	0.0003[e]	
PFS		
Disease progression or death, n (%)	189 (69.0)	216 (79.4)
Median[b] (months) (95% CI)	7.2 (5.8, 8.4)	5.9 (5.6, 7.0)
Hazard ratio[c] (95% CI)	0.68 (0.56, 0.83)	
ORR (%) (95% CI)	51.5 (45.4, 57.5)	42.6 (36.7, 48.8)

OS = overall survival; CI = confidence interval; PFS = progression-free survival; ORR = objective response rate.
[a] Median follow-up time was estimated by the reverse Kaplan-Meier method.
[b] Medians were estimated using Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley.
[c] Stratified by regions (east Asia versus US, Europe) and peritoneal metastasis.
[d] One-sided p-value from stratified log-rank test.
[e] Nominal p-value.

Figure 7 Kaplan-Meier plot of OS in BGB-A317-305 patients with PD-L1 TAP score ≥ 5% (final analysis)



Number of patients at risk

Time	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50
T+C	274	263	247	228	199	178	156	145	133	120	109	102	97	84	68	50	38	34	27	19	14	9	7	3	1	0
P+C	272	261	236	215	190	168	148	120	99	83	69	59	53	51	39	29	23	16	14	9	7	3	2	1	0	0

T+C = Tislelizumab + Chemotherapy, P+C = Placebo + Chemotherapy
Both log-rank and Cox regression model were stratified by regions (east Asia versus US, Europe) and presence of peritoneal metastasis.

Oesophageal squamous cell carcinoma (OSCC)
First-line treatment of OSCC: BGB-A317-306
BGB-A317-306 is a randomised, double-blind placebo-controlled, global phase III study to compare the efficacy of tislelizumab in combination with platinum-based chemotherapy versus placebo in combination with platinum-based chemotherapy in patients with unresectable, locally advanced recurrent or metastatic OSCC.

The study enrolled patients who were not amenable to chemoradiation or surgery with curative intent. Patients were enrolled regardless of their tumour PD-L1 expression level. Where available, the archival/fresh tumour tissue specimens taken were retrospectively tested for PD-L1 expression status. PD-L1 expression was evaluated using TAP (tumour area positivity) score, defined as the total percentage of the tumour area (tumour and any desmoplastic stroma) covered by tumour cells with PD-L1 membrane staining at any intensity and tumour-associated immune cells with PD-L1 staining at any intensity, as visually estimated using the VENTANA PD-L1 (SP263) Assay.

Patients who had received prior systemic therapy for advanced or metastatic disease were excluded. A treatment-free interval of at least 6 months was required if the patient had received prior neoadjuvant/adjuvant therapy with platinum-based chemotherapy.

The study excluded patients who had evidence of fistula or complete oesophageal obstruction not amenable to treatment.

Randomisation was stratified by geographical region (Asia [excluding Japan] versus Japan versus rest of world [ROW]), prior definitive therapy (yes versus no) and investigator choice of chemotherapy (ICC; platinum with fluoropyrimidine or platinum with paclitaxel).

Patients were randomised (1:1) to receive either tislelizumab 200 mg or placebo every 3 weeks in combination with investigator's choice of chemotherapy (ICC) on a 21-day cycle. The chemotherapy doublet regimen consisted of:

- platinum (cisplatin [60 to 80 mg/m^2 IV on day 1] or oxaliplatin [130 mg/m^2 IV on day 1]) and a fluoropyrimidine (5-FU [750 to 800 mg/m^2 IV on days 1 to 5] or capecitabine [1000 mg/m^2 orally twice daily on days 1 to 14]), or
- platinum (cisplatin [60 to 80 mg/m^2 IV on day 1 or 2] or oxaliplatin [130 mg/m^2 IV on day 1 or 2]) and paclitaxel (175 mg/m^2 IV on day 1).

Patients were treated with tislelizumab in combination with chemotherapy or placebo in combination with chemotherapy until disease progression, as assessed by the investigator per RECIST version 1.1 or unacceptable toxicity. After 24 months of treatment, study therapy could be continued beyond two years if the investigator considered this to be in the best interest of the patient based on an assessment of clinical benefit and potential risks.

The tumour assessments were conducted every 6 weeks for the first 48 weeks, and every 9 weeks thereafter.

The primary efficacy endpoint was overall survival (OS) in the intent-to-treat (ITT) population. Secondary efficacy endpoints were progression-free survival (PFS), objective response rate (ORR) and duration of response (DoR) as assessed by the investigator per RECIST v1.1, OS in the PD-L1 positive (PD-L1 TAP score ⩾10%) subgroup and health-related quality of life (HRQoL).

A total of 649 patients were randomised to receive tislelizumab in combination with chemotherapy (n = 326) or placebo in combination with chemotherapy (n = 323). Of the 649 patients, 293 (45.1%) patients received platinum + fluoropyrimidine, 358 patients had PD-L1 TAP score ≥ 5%, 184 patients had PD-L1 TAP score < 5% and 107 patients had PD-L1 status unknown.

In patients whose tumours expressed PD-L1 with a TAP score ≥ 5%, the baseline characteristics were: median age 63.0 years (range: 40 to 84), 44.7% age 65 years or older; 84.9% male; 20.9% White and 78.2% Asian. 87.7% had metastatic disease at study entry and 12.3% had locally advanced disease. All patients had histological confirmation of squamous cell carcinoma. Baseline ECOG performance status was 0 (29.9%) or 1 (70.1%).

As of the data cut-off date of interim analysis (28 February 2022), BGB-A317-306 showed a statistically significant improvement in OS for all randomised patients. The stratified HR was 0.66 (95% CI, 0.54-0.80, 1-sided p-value of < 0.0001), with a median OS of 17.2 months for the tislelizumab with chemotherapy arm vs. 10.6 months for the placebo with chemotherapy arm.

An updated analysis (up to 3-year follow-up; data cut-off date of 24 November 2023) showed consistent efficacy results with the interim analysis. The median follow-up times by reverse Kaplan-Meier methodology were 44.2 months in the tislelizumab in combination with chemotherapy arm and 43.8 months in the placebo in combination with chemotherapy arm.

Efficacy results for patients with PD-L1 TAP score ≥ 5%, at 3-year follow-up, are shown in Table 9 and Figure 8.

Table 9 Efficacy results in BGB-A317-306 patients with PD-L1 TAP score ≥ 5% - 3-year follow-up (data cut-off 24 November 2023)

Endpoint	Tislelizumab + chemotherapy (N = 172)	Placebo + chemotherapy (N = 186)
OS		
Deaths, n (%)	128 (74.4)	151 (81.2)
Median (months) (95% CI)	19.1 (16.1, 24.1)	10.0 (8.6, 11.9)
HR (95% CI)[a]	0.62 (0.49, 0.79)	
p-value[b]	< 0.0001	
PFS		
Events, n (%)	119 (69.2)	153 (82.3)
Median (months) (95% CI)	8.2 (7.0, 9.8)	5.5 (4.3, 6.4)
HR (95% CI)[a]	0.50 (0.39, 0.65)	
p-value[b]	< 0.0001	
ORR % (95% CI)[c]	64.0 (56.3, 71.1)	36.0 (29.1, 43.4)

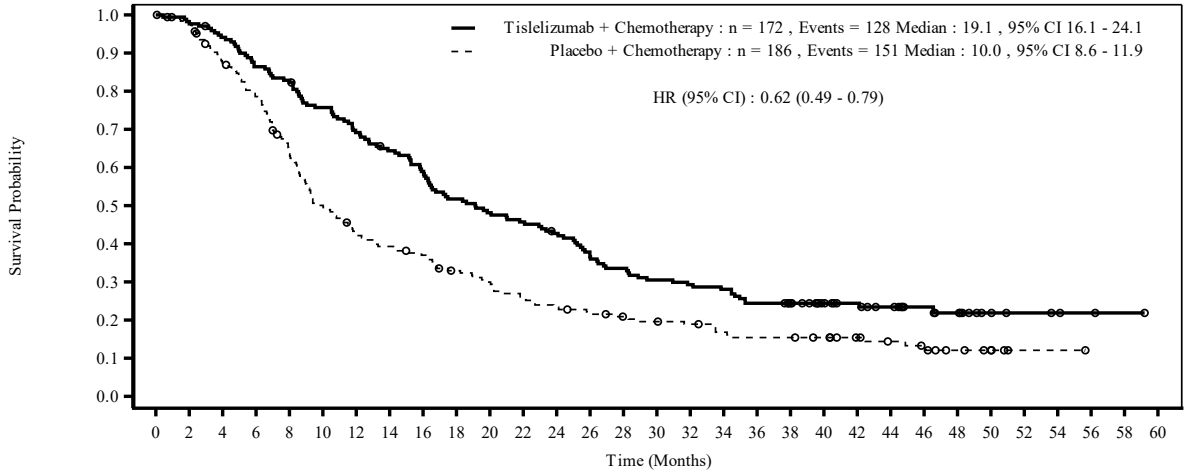
OS = overall survival; CI = confidence interval; HR = hazard ratio; PFS = progression-free survival; ORR = objective response rate

[a] Based on a stratified Cox regression model.

[b] One-sided nominal p-value from a stratified log rank test.

[c] Exact Clopper-Person-2-sided confidence interval.

Figure 8 Kaplan-Meier plot of OS in BGB-A317-306 patients with PD-L1 TAP score ≥ 5% - 3-year follow-up (data cut-off 24 November 2023)



Number of Patients at Risk:

Time:	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52	54	56	58	60
Tislelizumab +Chemotherapy	172	167	159	146	140	127	116	107	98	86	80	76	70	60	55	50	48	46	40	37	29	25	21	15	12	6	4	3	2	1	0
Placebo +Chemotherapy	186	181	159	142	113	89	74	69	64	55	50	43	39	35	32	30	28	24	22	22	20	16	13	11	7	5	1	1	0	0	0

Hazard ratio was based on a stratified Cox regression model.

Previously treated OSCC: BGB-A317-302

BGB-A317-302 was a randomised, controlled, open-label, global phase III study to compare the efficacy of tislelizumab versus chemotherapy in patients with unresectable, recurrent, locally advanced or metastatic OSCC who progressed on or after prior systemic treatment. Patients were enrolled regardless of their tumour PD-L1 expression level. Where available, the archival/fresh tumour tissue specimens taken were retrospectively tested for PD-L1 expression status. PD-L1 expression was evaluated at a central laboratory using the Ventana PD-L1 (SP263) assay that identified PD-L1 staining on both tumour and tumour-associated immune cells.

The study excluded patients with prior anti-PD-1/PD-L1 inhibitor treatment and tumour invasion into organs located adjacent to the oesophageal disease site (e.g. aorta or respiratory tract).

Randomisation was stratified by geographical region (Asia [excluding Japan] versus Japan versus USA/EU), ECOG PS (0 versus 1) and investigator choice of chemotherapy (ICC) option (paclitaxel versus docetaxel versus irinotecan). The choice of ICC was determined by the investigator before randomisation.

Patients were randomised (1:1) to receive tislelizumab 200 mg every 3 weeks or investigator's choice of chemotherapy (ICC), selected from the following, all given intravenously:

- paclitaxel 135 to 175 mg/m² on day 1, given every 3 weeks (also at doses of 80 to 100 mg/m^2 on a weekly schedule according to local and/or country-specific guidelines for standard of care), or
- docetaxel 75 mg/m^2 on day 1, given every 3 weeks, or
- irinotecan 125 mg/m^2 on days 1 and 8, given every 3 weeks.

Patients were treated with Tevimbra or one of the ICC until disease progression as assessed by the investigator per RECIST version 1.1 or unacceptable toxicity.

The tumour assessments were conducted every 6 weeks for the first 6 months, and every 9 weeks thereafter.

The primary efficacy endpoint was overall survival (OS) in the intent-to-treat (ITT) population. Secondary efficacy endpoints were OS in the PD-L1 Positive Analysis Set (PD-L1 score of visually-estimated Combined Positive Score, now known as Tumour Area Positivity [TAP] PD-L1 score ≥10%), objective response rate (ORR), progression-free survival (PFS) and duration of response (DoR), as assessed by the investigator per RECIST v1.1.

A total of 512 patients were enrolled and randomised to tislelizumab (N = 256) or ICC (N = 256; paclitaxel [N = 85], docetaxel [N = 53] or irinotecan [N = 118]). Of the 512 patients, 142 (27.7%) had PD-L1 score ≥10%, 222 (43.4%) had PD-L1 score <10%, and 148 (28.9%) had unknown baseline PD-L1 status.

The baseline characteristics for the study population were median age 63 years (range: 35 to 86), 39.5% age 65 years or older; 84% male; 19% White and 80% Asian; 25% with ECOG PS of 0 and 75% with ECOG PS of 1. Ninety-five percent of the study population had metastatic disease at study entry. All patients had received at least one prior anti-cancer chemotherapy, which was a platinum-based combination chemotherapy for 97% of patients.

At the time of the prespecified final analysis, BGB-A317-302 showed a statistically significant improvement in OS for patients randomised to the tislelizumab arm as compared to the ICC arm. The stratified HR was 0.70 (95% CI: 0.57, 0.85; 1-sided p-value of 0.0001), with a median OS of 8.6 months (95% CI: 7.5, 10.4) in the tislelizumab arm compared to 6.3 months (95% CI: 5.3, 7.0) in the ICC arm. The median follow-up times by reverse Kaplan-Meier methodology were 20.8 months in the tislelizumab arm and 21.1 months in the ICC arm.

An updated analysis with additional 24 months follow-up after the prespecified final analysis showed consistent efficacy results with the final analysis. The median follow-up times by reverse Kaplan-Meier methodology were 44.7 months in the tislelizumab arm and 44.0 months in the ICC arm.

Efficacy results of the updated analysis are shown in Table 10 and Figure 9.

Table 10 Efficacy results in BGB-A317-302 – Updated analysis

Endpoint	Tevimbra (N = 256)	Chemotherapy (N = 256)
OS		
Deaths, n (%)	233 (91.0)	233 (91.0)
Median (months)[a] (95% CI)	8.6 (7.5, 10.4)	6.3 (5.3, 7.0)
Hazard ratio (95% CI)[b]	0.71 (0.59, 0.86)	
p-value[c]	p = 0.0002	
PFS assessed by investigator[d]		
Disease progression or death, n (%)	229 (89.5)	181 (70.7)
Median (months) (95% CI)	1.6 (1.4, 2.7)	2.1 (1.5, 2.7)
Hazard ratio (95% CI)	0.82 (0.67, 1.01)	
ORR with confirmation by investigator[d]		
ORR (%) (95% CI)	15.2 (11.1, 20.2)	6.6 (3.9, 10.4)
Median duration of response with confirmation by investigator (months) (95% CI)	11.3 (6.5, 14.4)	6.3 (2.8, 8.5)

OS = overall survival; CI = confidence interval; PFS = progression-free survival; ORR = objective response rate

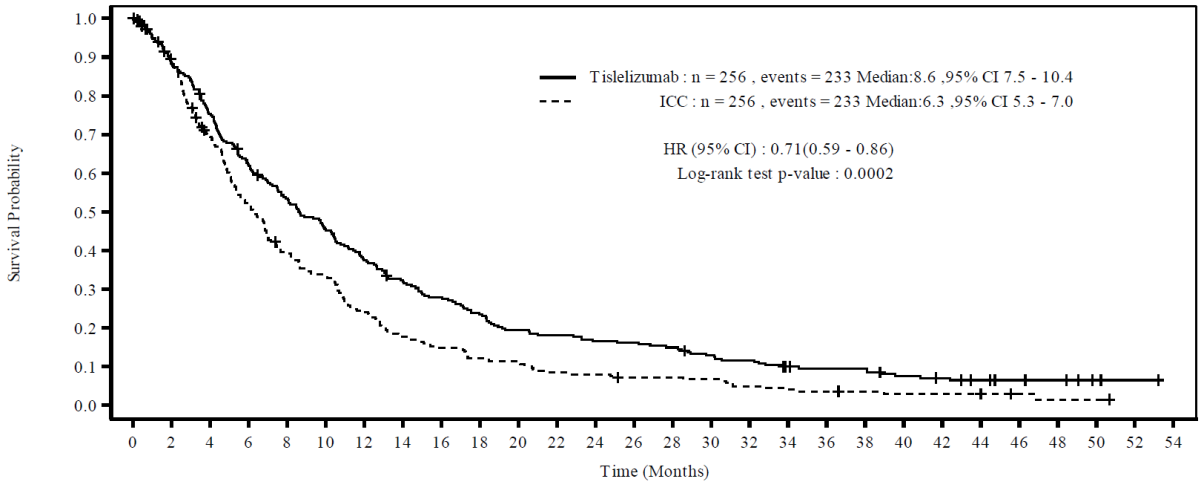
[a] Estimated using Kaplan-Meier method.

[b] Based on Cox regression model including treatment as covariate, and stratified by baseline ECOG status and investigator's choice of chemotherapy.

[c] Nominal one-sided p-value based on a log-rank test stratified by ECOG performance status and investigator's choice of chemotherapy.

[d] Based on ad hoc analysis.

Figure 9 Kaplan-Meier plot of OS in BGB-A317-302 (ITT analysis set) – updated analysis



Nominal one-sided p-value is based on a log-rank test stratified by ECOG performance status and investigator's choice of chemotherapy.

Efficacy and PD-L1 subgroups (Updated analysis):
At the updated analysis of OS in the PD-L1 positive subgroup (PD-L1 score ≥10%), the stratified HR for OS was 0.54 (95% CI: 0.36 to 0.79. The median survival was 10.2 months (95% CI: 8.5 to 14.5 months) and 5.1 months (95% CI: 3.8 to 8.2 months) for the tislelizumab and ICC arms, respectively.

In the PD-L1 negative subgroup (PD-L1 score <10%), the stratified HR for OS was 0.86 (95% CI: 0.65 to 1.14), with median overall survival of 7.5 months (95% CI: 5.5 to 8.9 months) and 5.8 months (95% CI: 4.8 to 6.9 months) for the tislelizumab and ICC arms, respectively.

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 Tevimbra both as monotherapy and in combination with chemotherapy.

The PK of tislelizumab were characterised using population PK analysis with concentration data from 2596 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 body weight 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 (E 432)
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

Tevimbra 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, once diluted, 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.

Keep the vial in the outer 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 Tevimbra 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.

Tevimbra 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 Tevimbra 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 diluted solution by gentle inversion to avoid foaming or excessive shearing of the solution.

Administration

- Administer the diluted Tevimbra 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.
- Tevimbra 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.
- Tevimbra 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

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

8. MARKETING AUTHORISATION NUMBERS

EU/1/23/1758/001-002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 September 2023

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER 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. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance

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

Novartis Pharmaceutical Manufacturing LLC.
Kolodvorska Cesta 27
Mengeš, 1234
Slovenia

Name and address of the manufacturer responsible for batch release

BeiGene Switzerland GmbH Dutch Branch
Evert Van De Beekstraat 1/104
Schiphol
1118 CL
Netherlands

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 Tevimbra 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 Tevimbra. 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 Tevimbra is marketed, all healthcare professionals and patients/carers who are expected to prescribe and use Tevimbra 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 Tevimbra.
- A reminder that all known or suspected adverse drug reactions (ADRs) can also be reported to local regulatory authorities.
- The contact details of their Tevimbra prescriber.

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

Tevimbra 100 mg concentrate for solution for infusion
tislelizumab

2. STATEMENT OF ACTIVE SUBSTANCE

Each 10 ml vial contains 100 mg tislelizumab (100 mg/10 ml).

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 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

BeOne Medicines Ireland Limited
10 Earlsfort Terrace
Dublin 2
D02 T380
Ireland

12. MARKETING AUTHORISATION NUMBER

EU/1/23/1758/001 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

Tevimbra 100 mg concentrate for solution for infusion
tislelizumab

2. STATEMENT OF ACTIVE SUBSTANCE

Each 10 ml vial contains 100 mg tislelizumab (100 mg/10 ml).

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 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

BeOne Medicines Ireland Limited
10 Earlsfort Terrace
Dublin 2
D02 T380
Ireland

12. MARKETING AUTHORISATION NUMBER

EU/1/23/1758/002 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

Tevimbra 100 mg concentrate for solution for infusion
tislelizumab

2. STATEMENT OF ACTIVE SUBSTANCE

Each 10 ml vial contains 100 mg tislelizumab (100 mg/10 ml).

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 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

BeOne Medicines Ireland Limited
10 Earlsfort Terrace
Dublin 2
D02 T380
Ireland

12. MARKETING AUTHORISATION NUMBER

EU/1/23/1758/002 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

Tevimbra 100 mg sterile concentrate
tislelizumab

2. STATEMENT OF ACTIVE SUBSTANCE

Each 10 ml vial contains 100 mg tislelizumab (100 mg/10 ml).

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 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

BeOne Medicines Ireland Limited

12. MARKETING AUTHORISATION NUMBERS

EU/1/23/1758/001	1 vial
EU/1/23/1758/002	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

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Tevimbra 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 Tevimbra is and what it is used for

Tevimbra 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, Tevimbra prevents it from switching off your T cells which helps your immune system fight the cancer.

Tevimbra is used in adults to treat:
- a type of lung cancer called non-small cell lung cancer.
- a type of lung cancer called extensive-stage small cell lung cancer.
- a type of stomach cancer called advanced gastric or gastroesophageal junction adenocarcinoma
- a type of oesophageal cancer called oesophageal squamous cell carcinoma

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

Tevimbra 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 Tevimbra

You must not be given Tevimbra
- 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 Tevimbra 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
- A rare condition in which the immune system makes too many of otherwise normal infection fighting cells called histiocytes and lymphocytes. It can lead to enlarged liver and/or spleen, heart problems and kidney abnormalities. Symptoms may include fever, skin rash, swollen lymph glands, breathing problems and easy bruising. Tell your doctor immediately if you experience these symptoms at the same time (haemophagocytic lymphohistiocytosis)

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

Look out for serious side effects
Tevimbra can cause 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 Tevimbra:
- 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 (including Stevens-Johnson syndrome (SJS) or Toxic epidermal necrolysis (TEN): 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 Tevimbra
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 Tevimbra to monitor the blood sugar and hormone levels in your body. This is because blood sugar and hormone levels can be affected by Tevimbra.

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

Other medicines and Tevimbra
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 Tevimbra. However, once you have started treatment with Tevimbra, 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 Tevimbra if you are pregnant unless your doctor specifically prescribes it for you. The effects of Tevimbra 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 Tevimbra and for at least 4 months following the last dose of Tevimbra.
- If you are pregnant, think you may be pregnant or are planning to have a baby, tell your doctor.

It is not known whether Tevimbra 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 Tevimbra and for at least 4 months after the last dose of Tevimbra.

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

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

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

Tevimbra contains polysorbate
This medicine contains 0.2 mg of polysorbate 20 in each ml of concentrate, which is equivalent to 4.0 mg in two 10 ml vials of a single infusion of Tevimbra. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

3. How Tevimbra is given

Tevimbra will be given to you in a hospital or clinic under the supervision of an experienced doctor.
- The usual dose of Tevimbra is 200 mg, which is given as an intravenous infusion (drip into a vein) every 3 weeks.
- The first dose of Tevimbra 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 Tevimbra is given in combination with chemotherapy, you will be given Tevimbra 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 Tevimbra
- 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 Tevimbra treatment
Stopping your treatment may stop the effect of the medicine. Do not stop treatment with Tevimbra 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 Tevimbra 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 Tevimbra alone:

Very common (may affect more than 1 in 10 people)
- Weakness, rapid heart rate, shortness of breath (anaemia)
- Spontaneous bleeding or bruising (thrombocytopenia)
- Underactive thyroid gland, which can cause tiredness, weight gain, skin and hair changes (hypothyroidism)
- Cough
- Nausea
- Diarrhoea
- Rash
- Itching (pruritus)
- Tiredness (fatigue)
- Fever
- Decreased appetite
- 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, which can cause yellowing of the skin and eyes, indicating liver problems

Common (may affect up to 1 in every 10 people)
- Pneumonia

- Frequent infections, fever, chills, sore throat or mouth ulcers due to infections (neutropenia or lymphopenia)
- Overactive thyroid gland, which can cause hyperactivity, sweating, weight loss and thirst (hyperthyroidism)
- 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)
- Increased blood pressure (hypertension)
- Difficulty breathing (dyspnoea)
- Shortness of breath, cough or chest pain – possible symptoms of lung problems (pneumonitis)
- Mouth sores or ulcers with inflammation of the gums (stomatitis)
- 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)
- Increased blood level of the liver enzyme alkaline phosphatase
- Increased blood level of creatinine
- 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 haemoglobin
- Low blood levels of the following blood cells: lymphocytes, neutrophils and platelets
- High blood levels of the following enzymes: alanine aminotransferase, alkaline aminotransferase, aspartate aminotransferase and creatine kinase
- High blood level of alkaline phosphatase
- High blood level of bilirubin
- High blood level of creatinine
- High blood level of glucose
- Low blood levels of potassium and sodium

Uncommon (may affect up to 1 in every 100 people)
- Disorder in which the adrenal glands do not make enough of certain hormones (adrenal insufficiency)
- 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)
- High blood sugar, feeling more hungry or thirsty than normal, passing urine more often than normal – possible symptoms of diabetes mellitus
- Eye redness, eye pain and swelling – possible symptoms of problems affecting the uvea, the layer beneath the white of the eyeball (uveitis)
- 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)
- Chest pain, fever, cough, palpitations – possible symptoms of problems affecting the membrane around the heart (pericarditis)
- Severe upper stomach pain, nausea, vomiting, fever, tender abdomen – possible symptoms of pancreas problems (pancreatitis)
- 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 intestinal problems (colitis)
- Skin discolouration (vitiligo)
- Itching or peeling skin, skin sores – possible symptoms of severe skin reactions

- Muscle pain, stiffness, weakness, chest pain or severe tiredness – possible symptoms of muscle problems (myositis)
- Joint pain, stiffness, swelling or redness, decreased range of motion in the joints – possible symptoms of joint problems (arthritis)
- Changes in the amount or colour of the urine, pain while urinating, pain in kidney area – possible symptoms of kidney problems (nephritis)
- High blood levels of haemoglobin
- Low blood level of leukocytes
- High blood level of lymphocytes
- Low blood level of albumin
- Low blood level of glucose
- High blood levels of potassium and sodium

Rare (may affect up to 1 in every 1 000 people)
- 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
- Coeliac disease (characterised by symptoms such as stomach pain, diarrhoea, and bloating after consuming gluten-containing foods)
- Serious rash and reddening of the skin on upper body and quickly spreading to other body parts, blistering of the lips, eyes or mouth, skin peeling, sometimes with flu-like symptoms such as fever, sore throat, cough, and joint pain (Stevens-Johnson syndrome)
- Inflammation of the bladder. Signs and symptoms may include frequent and/or painful urination, urge to pass urine, blood in urine, pain or pressure in lower abdomen (noninfective cystitis)

Other side effects that have been reported (frequency not known):
- A condition where the immune system makes too many of otherwise normal infection-fighting cells called histiocytes and lymphocytes. Symptoms can include fever, skin rash, swollen lymph glands, breathing problems, easy bruising (haemophagocytic lymphohistiocytosis)
- Lack or reduction of digestive enzymes made by the pancreas (pancreatic exocrine insufficiency)

The following side effects have been reported with Tevimbra when Tevimbra 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)
- Pneumonia
- Weakness, rapid heart rate, shortness of breath (anaemia)
- Spontaneous bleeding or bruising (thrombocytopenia)
- Frequent infections, fever, chills, sore throat or mouth ulcers due to infections (neutropenia or lymphopenia)
- Underactive thyroid gland which can cause tiredness, weight gain, skin and hair changes (hypothyroidism)
- 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)
- Cough
- Nausea

- Diarrhoea
- Rash
- Itching (pruritus)
- Joint pain (arthralgia)
- Tiredness (fatigue)
- Fever
- Decreased appetite
- 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, which can cause yellowing of the skin and eyes, indicating liver problems
- Increased blood level of creatinine, a substance normally eliminated by the kidneys into the urine. This may mean that your kidneys are not functioning properly.
- Low blood level of haemoglobin
- Low blood levels of the following blood cells: leukocytes, lymphocytes, neutrophils and platelets
- Low blood level of sodium

Common (may affect up to 1 in every 10 people)
- Overactive thyroid gland, which can cause hyperactivity, sweating, weight loss and thirst (hyperthyroidism)
- High blood sugar, feeling more hungry or thirsty than normal, passing urine more often than normal – possible symptoms of diabetes mellitus
- 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)
- Increased blood pressure (hypertension)
- Difficulty breathing (dyspnoea)
- Shortness of breath, cough or chest pain – possible symptoms of lung problems (pneumonitis)
- Severe upper stomach pain, nausea, vomiting, fever, tender abdomen – possible symptoms of pancreas problems (pancreatitis)
- Mouth sores or ulcers with inflammation of the gums (stomatitis)
- 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)
- 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)
- Muscle pain (myalgia)
- Joint pain, stiffness, swelling or redness, decreased range of motion in the joints – possible symptoms of joint problems (arthritis)
- Increased blood level of the liver enzyme alkaline phosphatase
- 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
- High blood levels of the following enzymes: alanine aminotransferase and aspartate aminotransferase
- High blood level of bilirubin
- High blood levels of creatine kinase and creatinine
- High blood level of glucose
- High blood level of potassium
- Low blood level of potassium

Uncommon (may affect up to 1 in every 100 people)
- Disease in which the immune system attacks the glands that make moisture for the body, such as tears and saliva (Sjögren's syndrome).

- Fatigue, swelling at the base of the neck, pain in front of the throat – possible symptoms of thyroid gland problems (thyroiditis)
- Adrenal insufficiency (disorder in which the adrenal glands do not make enough of certain hormones)
- 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)
- Eye redness, eye pain and swelling – possible symptoms of problems affecting the uvea, the layer beneath the white of the eyeball (uveitis)
- Changes in the amount or colour of the urine, pain while urinating, pain in kidney area – possible symptoms of kidney problems (nephritis)
- Muscle pain, stiffness, weakness, chest pain, or severe tiredness – possible symptoms of muscle problems (myositis)
- Skin discolouration (vitiligo)
- High blood level of lymphocytes
- Low blood level of albumin
- High blood level of alkaline phosphatase
- Low blood level of glucose
- High blood level of sodium

Rare (may affect up to 1 in every 1 000 people)
- A condition where the immune system makes too many of otherwise normal infection-fighting cells called histiocytes and lymphocytes. Symptoms can include fever, skin rash, swollen lymph glands, breathing problems, easy bruising (haemophagocytic lymphohistiocytosis)
- Inflammation of the brain, which may cause confusion, fever, memory problems or seizures (encephalitis)
- 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
- Muscle weakness and tiredness (myasthenia gravis)
- Chest pain, fever, cough, palpitations – possible symptoms of problems affecting the membrane around the heart (pericarditis)
- Itching or peeling skin, skin sores – possible symptoms of severe skin reactions

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

Using Tevimbra should be stopped and medical attention should be sought immediately if you notice any of the following symptoms:

Frequency not known (cannot be estimated from the available data)
- Reddish non-elevated, target-like or circular patches on the trunk, often with central blisters, skin peeling, ulcers of mouth, throat, nose, genitals and eyes. These serious skin rashes can be preceded by fever and flu-like symptoms (TEN)

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 Tevimbra

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 - 8 °C).

Do not freeze.

Keep the vial in the outer carton in order to protect from light.

Tevimbra 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, once diluted, 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 Tevimbra 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, “Tevimbra contains sodium”), citric acid monohydrate, L-histidine hydrochloride monohydrate, L-histidine, trehalose dihydrate, polysorbate 20 and water for injections.

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

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

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

Manufacturer
BeiGene Switzerland GmbH Dutch Branch
Evert Van De Beekstraat 1/104
Schiphol
1118 CL

Netherlands

This leaflet was last revised in

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

The following information is for healthcare professionals only:

Tevimbra 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 Tevimbra 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 Tevimbra 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.
- Tevimbra must not be administered as an intravenous push or single bolus injection.
- Tevimbra 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, once diluted, 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.
- Tevimbra vials are for single use only.