TEVIMBRA

Prescribing Information

Patient Card
The marketing of TEVIMBRA is subject to a risk management plan (RMP) including a Patient Card. The Patient Card emphasizes important safety information that the patient should be aware of before and during treatment. Please explain to the patient the need to review the card before starting treatment.

1. NAME OF THE MEDICINAL PRODUCT

Tevimbra 100 mg

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.

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 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

Oesophageal squamous cell carcinoma (OSCC)

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

Gastric cancer

Tevimbra in combination with platinum and fluoropyrimidine-based chemotherapy, is indicated for the first-line treatment of adults with unresectable or metastatic HER2-negative gastric or gastroesophageal junction adenocarcinoma (G/GEJ) whose tumors express PD-L1 (≥1).

4.2 Posology and method of administration

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

Patient selection

Select patients for the first-line treatment of unresectable or metastatic HER2-negative gastric or gastroesophageal junction adenocarcinoma (G/GEJ) based on the presence of PD-L1 in tumor specimens.

Refer to the respective Prescribing Information for each therapeutic agent administered in combination with TEVIMBRA for the recommended dosage information, as appropriate.

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.

Refer to the respective Prescribing Information for dosage modifications for platinum and fluoropyrimidine agent administered in combination with TEVIMBRA.

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]
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 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.

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, 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 characterized 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 1534 patients across multiple tumour types who received 200 mg tislelizumab every 3 weeks. The most common adverse reactions were anaemia (29.8%), fatigue (23.9%) and aspartate aminotransferase increased (21.3%). The most common Grade 3/4 adverse reactions were anaemia (5.1%), pneumonia (4.4%), hyponatraemia (2.9%), aspartate aminotransferase increased (2.6%), hypertension (2.3%), blood bilirubin increased (2.1%), pneumonitis (2.0%) and fatigue (2.0%). 1.1% of patients experienced adverse reactions leading to death. The adverse reactions leading to death were pneumonia (0.72%), hepatitis (0.07%), abnormal hepatic function (0.07%), pneumonitis (0.07%), dyspnoea (0.07%), decreased appetite (0.07%) and decreased platelet count (0.07%). Among the 1534 patients, 40.8% were exposed to tislelizumab for 6 months or longer, and 24.0% were exposed for 12 months or longer.

The safety of tislelizumab given in combination with chemotherapy is based on data in 1319 patients with G/GEJ adenocarcinoma, OSCC or NSCLC. The most common adverse reactions were neutropenia (65.6%), anaemia (63.6%), thrombocytopenia (48.4%), nausea (44.0%), fatigue (43.1%), decreased appetite (41.8%), aspartate aminotransferase increased (31.7%), alanine aminotransferase increased (30.4%), diarrhoea (22.7%), and rash (20.8%). The most common Grade 3/4 adverse reactions were neutropenia (38.4%), thrombocytopenia (13.3%), anaemia (13.3%), fatigue (5.0%), hypokalaemia (4.4%), hyponatraemia (3.9%), pneumonia (3.8%), decreased appetite (3.3%), rash (2.6%), lymphopenia (2.5%), alanine aminotransferase increased (2.4%), aspartate aminotransferase increased (2.4%), diarrhoea (2.4%), pneumonitis (2.0%), and hepatitis (2.0%). 1.1% of patients

experienced adverse reactions leading to death. The adverse reactions leading to death were pneumonia (0.5%), pneumonitis (0.2%), dyspnoea (0.2%), myocarditis (0.2%), colitis (0.1%), hypokalaemia (0.1%), and myositis (0.1%). Among the 1319 patients, 57.1% were exposed to tislelizumab for 6 months or longer, and 29.7% 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 = 1534) and in combination with chemotherapy (N = 1319) 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 (≥1/1000 to <1/100); rare (≥1/10000 to <1/1000); very rare (<1/10000); 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 = 1534) and in combination with chemotherapy (N = 1319)

	Tislelizumab monotherapy N = 1534	**Tislelizumab plus chemotherapy N = 1319**
Adverse reactions	**Frequency category (All grades)**	**Frequency category (All grades)**
Infections and infestations		
Pneumonia[1]	Very common*	Very common*
Blood and lymphatic system disorders		
Anaemia[2]	Very common	Very common
Thrombocytopenia[3]	Common*	Very common
Neutropenia[4]	Common	Very common
Lymphopenia[5]	Common	Very common
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]	Rare	Uncommon
Metabolism and nutrition disorders		
Hyperglycaemia[11]	Common	Common
Hyponatraemia[12]	Common	Very common
Hypokalaemia[13]	Common	Very common*
Diabetes mellitus[14]	Uncommon	Common
Nervous system disorders		
Encephalitis[15]	-	Rare
Guillain-Barré syndrome	-	Rare
Myasthenia gravis	-	Rare
Eye disorders		
Uveitis[16]	Uncommon	Uncommon
Cardiac disorders		
Myocarditis[117]	Uncommon	Common*
Pericarditis	Rare	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]	Common	Very common
Stomatitis[21]	Common	Very common
Pancreatitis[22]	Common	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	common
Vitiligo[26]	Uncommon	Uncommon
Severe skin reactions[27]	Uncommon	Rare
Stevens Johnson Syndrome[28]	Not known	Not known
Toxic epidermal necrolysis[28]	Not known*	Not known*
Musculoskeletal and connective tissue disorders		
Arthralgia	Common	Common
Myalgia	Common	Common
Myositis[29]	Uncommon	Uncommon
Arthritis[30]	Uncommon	Common
Renal and urinary disorders		
Nephritis[31]	Uncommon	Uncommon
Cystitis noninfective[32]	Rare	-
General disorders and administration site conditions		
Fatigue[33]	Very common	Very common
Pyrexia[34]	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[35]	Very common	Very common
Blood alkaline phosphatase increased	Common	Common
Blood creatinine increased	Common	Common
Injury, poisoning and procedural complications		
Infusion-related reaction[36]	Common	Common

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

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

[3] Thrombocytopenia includes PTs of thrombocytopenia, immune thrombocytopenia and platelet count decreased.

[4] Neutropenia includes PTs of neutropenia and neutrophil count decreased.

[5] Lymphopenia includes PTs of lymphopenia, lymphocyte count decreased and lymphocyte percentage decreased.

[6] Hypothyroidism includes PTs of hypothyroidism, thyroxine free decreased, tri-iodothyronine free decreased, tri-iodothyronine decreased, primary hypothyroidism, central hypothyroidism and thyroxine decreased.

[7] Hyperthyroidism includes PTs of hyperthyroidism, blood thyroid stimulating hormone decreased, tri-iodothyronine free increased, thyroxine free increased, thyroxine increased and tri-iodothyronine increased.

[8] Thyroiditis includes PTs of thyroiditis, autoimmune thyroiditis and thyroiditis subacute.

[9] Adrenal insufficiency includes PTs of adrenal insufficiency, glucocorticoid deficiency, immune-mediated adrenal insufficiency and secondary adrenocortical insufficiency.

[10] Hypophysitis includes PT of hypopituitarism.

[11] Hyperglycaemia includes PTs of hyperglycaemia and blood glucose increased.
[12] Hyponatraemia includes PTs of hyponatraemia and blood sodium decreased.
[13] Hypokalaemia includes PTs of hypokalaemia and blood potassium decreased.
[14] Diabetes mellitus includes PTs of diabetes mellitus, type 1 diabetes mellitus, diabetic ketoacidosis and latent autoimmune diabetes in adults.
[15] Encephalitis includes the PT of immune-mediated encephalitis.
[16] Uveitis includes PTs of uveitis iritis, chorioretinitis and iridocyclitis.
[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, aphthous ulcer and oral mucosa erosion.
[22] Pancreatitis includes PTs of pancreatitis, amylase increased, lipase increased, and pancreatitis acute.
[23] Colitis includes PTs of colitis and immune-mediated enterocolitis.
[24] Hepatitis includes PTs of hepatitis, hepatic function abnormal, immune-mediated hepatitis, liver injury, drug-induced liver injury, hepatotoxicity and autoimmune hepatitis.
[25] Rash includes PTs of rash, rash maculo-papular, eczema, rash erythematous, dermatitis, dermatitis allergic, rash papular, urticaria, erythema, skin exfoliation, drug eruption, rash macular, psoriasis, rash pustular, dermatitis acneiform, rash pruritic, lichenoid keratosis, hand dermatitis, immune mediated dermatitis, rash follicular, acute febrile neutrophilic dermatosis, erythema nodosum and pemphigoid.
[26] Vitiligo includes PTs of vitiligo, skin hypopigmentation, skin depigmentation and leukoderma.
[27] Severe skin reaction includes erythema multiforme.
[28] Post-marketing experience.
[29] Myositis includes PTs of myositis, rhabdomyolysis and immune-mediated myositis.
[30] Arthritis includes PTs of arthritis, immune-mediated arthritis and polyarthritis.
[31] Nephritis includes PTs of nephritis, focal segmental glomerulosclerosis, immune-mediated nephritis, tubulointerstitial nephritis.[32] Cystitis noninfective includes PTs of cystitis noninfective and immune-mediated cystitis. Cases of immune-mediated cystitis have been reported in the post-marketing setting.
[33] Fatigue includes PTs of fatigue, asthenia, malaise and lethargy.
[34] Pyrexia includes the PTs of pyrexia and body temperature increased.
[35] Blood bilirubin increased includes PTs of blood bilirubin increased, bilirubin conjugated increased, blood bilirubin unconjugated increased and hyperbilirubinaemia.
[36] Infusion-related reaction includes PTs of infusion-related reaction rash, chills, rhinitis allergic, urticaria, drug hypersensitivity, type I hypersensitivity, laryngeal oedema, rash erythematous, rash pruritic, lip oedema, lip swelling, mouth swelling, swelling face, tongue oedema, anaphylactic reaction, corneal oedema, dermatitis allergic, drug eruption, face oedema, gingival swelling and pruritus allergic. Cases of anaphylaxis, including anaphylactic reaction and anaphylactic shock, have been reported in the post-marketing setting.
* including fatal outcomes

Description of selected adverse reactions

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

Immune-related pneumonitis
In patients treated with tislelizumab as monotherapy, immune-related pneumonitis occurred in 5.4% of patients, including Grade 1 (1.3%), Grade 2 (2.2%), Grade 3 (1.6%), Grade 4 (0.3%) and Grade 5 (0.1%) events.

The median time from first dose to onset of the event was 3.2 months (range: 1.0 day to 26.2 months), and the median duration from onset to resolution was 6.1 months (range: 1.0+ day to 33.9+ months). + denotes a censored observation, with ongoing events at the time of the analysis. Tislelizumab was permanently discontinued in 2.0% of patients and tislelizumab treatment was interrupted in 1.9% of patients. Pneumonitis resolved in 48.2% of patients.

In patients treated with tislelizumab as monotherapy, pneumonitis occurred more frequently in patients with a history of prior thoracic radiation (7.8%) than in patients who did not receive prior thoracic radiation (3.8%).

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

Immune-related hepatitis
In patients treated with tislelizumab as monotherapy, immune-related hepatitis occurred in 1. 1% of patients, including Grade 1 (0.1%), Grade 2 (0.2%), Grade 3 (0.5%), Grade 4 (0.3%) and Grade 5 (0.1%) events.

The median time from first dose to onset of the event was 22.0 days (range: 4.0 days to 2.7 months), and the median duration from onset to resolution was 1.9 months (range: 6.0 days to 6.6 months). Tislelizumab was permanently discontinued in 0.41% of patients and tislelizumab treatment was interrupted in 0.6% of patients for immune-related hepatitis. Hepatitis resolved in 64.7% of patients.

Immune-related skin adverse reactions
In patients treated with tislelizumab as monotherapy, immune-related skin adverse reactions occurred in 13.4% of patients, including Grade 1 (9.0%), Grade 2 (3.7%), Grade 3 (0.7%) and Grade 4 (0.1%) events.

The median time from first dose to onset of the event was 1.6 months (range: 1.0 days to 25.8 months). The median duration from onset to resolution was 1.7 months (range: 1.0 days to 35.0+ months). + denotes a censored observation, with ongoing events at the time of the analysis. Tislelizumab was permanently discontinued in 0.1% of patients, and tislelizumab treatment was interrupted in 0.8% of patients. Skin adverse reactions resolved in 68.9% 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 0.5% of patients, including Grade 1 (0.1%), Grade 2 (0.3%) and Grade 3 (0.1%) events.

The median time from first dose to onset of the event was 10.1 months (range: 12.0 days to 28.2 months), and the median duration from onset to resolution was 27.0 days (range: 2.0 days to 6.5 months). Tislelizumab was permanently discontinued in 0.1% of patients and tislelizumab treatment was interrupted in 0.2% of patients. Colitis resolved in 87.5% of patients.

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

The median time from first dose to onset of the event was 1.5 months (range: 15.0 days to 11.7 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 0.3% of patients and tislelizumab treatment was interrupted in 0.5% of patients. Myositis/rhabdomyolysis resolved in 71.4% of patients.

Immune-related endocrinopathies
Thyroid disorders
Hypothyroidism:
In patients treated with tislelizumab as monotherapy, hypothyroidism occurred in 14.3% of patients, including Grade 1 (6.6%), Grade 2 (7.6%) and Grade 4 (0.1%) events.

The median time from first dose to onset of the event was 3.5 months (range: 1.0 days to 29.0 months). The median duration from onset to resolution was 12.5 months (range: 1.0 days to 37.3+ months). + denotes a censored observation, with ongoing events at the time of the analysis. Tislelizumab was not permanently discontinued in any patient and tislelizumab treatment was interrupted in 0.5% of patients. Hypothyroidism resolved in 33.6% of patients.

Hyperthyroidism:
In patients treated with tislelizumab as monotherapy, hyperthyroidism occurred in 5.0% of patients, including Grade 1 (4.4%) and Grade 2 (0.6%) events.

The median time from first dose to onset of the event was 2.1 months (range: 6.0 days to 25.6 months). The median duration from onset to resolution was 1.4 months (range: 5.0 days to 29.0+ months). + denotes a censored observation, with ongoing events at the time of the analysis. Tislelizumab was permanently discontinued in 0.1% of patients and tislelizumab treatment was interrupted in 0.1% of patients. Hyperthyroidism resolved in 76.3% of patients.

Thyroiditis:
In patients treated with tislelizumab as monotherapy, thyroiditis occurred in 1.2% of patients, including Grade 1 (0.6%) and Grade 2 (0.6%) events.

The median time from first dose to onset of the event was 2.1 months (range: 20.0 days to 20.7 months). The median duration from onset to resolution was 4.9 months (range: 20.0 days to 26.1+ months). + denotes a censored observation, with ongoing events at the time of the analysis. Tislelizumab was not permanently discontinued in any patient and tislelizumab treatment was interrupted in 0.1% of patients. Thyroiditis resolved in 50.0% of patients.

Adrenal insufficiency
In patients treated with tislelizumab as monotherapy, adrenal insufficiency occurred in 0.4% of patients, including Grade 2 (0.2%), Grade 3 (0.1%) and Grade 4 (0.1%) events.

The median time from first dose to onset of the event was 7.9 months (range: 1.3 months to 16.9 months). The median duration from onset to resolution was not evaluable based on currently available data (range: 1.0 month to 18.2+ months). + denotes a censored observation, with ongoing events at the time of the analysis. Tislelizumab was not permanently discontinued in any patient and tislelizumab treatment was interrupted in 0.3% of patients. Adrenal insufficiency resolved in 33.3% of patients.

Hypophysitis
In patients treated with tislelizumab as monotherapy, hypopituitarism (Grade 2) occurred in 0.2% of patients.

The median time from first dose to onset of the event was 8.3 months (range: 22.0 days to 9.0 months). The median duration from onset to resolution was not evaluable based on currently available data (range: 13.0+ months to 23.3+ months). + denotes a censored observation, with ongoing events at the time of the analysis. Tislelizumab was neither interrupted nor permanently discontinued in any patient. Hypophysitis did not resolve in any patient.

Type 1 diabetes mellitus
In patients treated with tislelizumab as monotherapy, type 1 diabetes mellitus occurred in 0.9% of patients, including Grade 1 (0.1%), Grade 2 (0.5%) and Grade 3 (0.3%) events.

The median time from first dose to onset of the event was 5.3 months (range: 8.0 days to 33.2 months). The median duration from onset to resolution was 3.3 months (range: 5.0 days to 30.1+ months). + denotes a censored observation, with ongoing events at the time of the analysis. Tislelizumab was permanently discontinued in 0.1% of patients and tislelizumab treatment was interrupted in 0.1% of patients. Type 1 diabetes mellitus resolved in 28.6% of patients.

Immune-related nephritis and renal dysfunction
In patients treated with tislelizumab as monotherapy, immune-related nephritis and renal dysfunction occurred in 0.3% of patients, including Grade 1 (0.1%), Grade 2 (0.1%), 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 not evaluable based on currently available data (range: 9.0 days to 12.1 months). + denotes a censored observation, with ongoing events at the time of the analysis. Tislelizumab was permanently discontinued in 0.1% of patients and tislelizumab treatment was interrupted in 0.1% of patients. 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 (0.3%), 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 1.6 months (range: 14.0 days to 6.1 months), and the median duration from onset to resolution was 5.1 months (range: 4.0 days to 26.4 months). + denotes a censored observation, with ongoing events at the time of the analysis. Tislelizumab was permanently discontinued in 0.5% of patients and tislelizumab treatment was interrupted in 0.4% of patients. Myocarditis resolved in 53.8% of patients.

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

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 2.9% of patients, including grade 3 (0.1%) events. Tislelizumab was permanently discontinued in 0.07% of patients and tislelizumab treatment was interrupted in 0.07% 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, 4.8% for decreased haemoglobin, 0.9% for decreased leukocytes, 9.7% for decreased lymphocytes, 0.07% for increased lymphocytes, 1.9% for decreased neutrophils, 1.2% for decreased platelets, 2.2% for increased alanine aminotransferase, 0.7% for decreased albumin, 2.5% for increased alkaline phosphatase, 3.4% for increased aspartate aminotransferase, 2.3% for increased bilirubin, 2.1% for increased creatine kinase, 0.9% for increased creatinine, 0.9% for increased potassium, 2.5% for decreased potassium, 0.1% for increased sodium, 6.0% 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: 12.9% for decreased haemoglobin, 18.8% for decreased leukocytes, 14.8% for decreased lymphocytes, 0.1% for increased lymphocytes, 39.8% for decreased neutrophils, 13.2% for decreased platelets, 4.4% for increased alanine aminotransferase, 0.6% for decreased albumin, 0.9% for increased alkaline phosphatase, 4.0% for increased aspartate aminotransferase, 2.1% for increased bilirubin, 2.1% for increased creatine kinase, 2.4% for increased creatinine, 0.4% for decreased glucose, 1.8% for increased glucose, 1.8% for increased potassium, 8.6% for decreased potassium, 0.4% for increased sodium, 11.7% for decreased sodium.

Immunogenicity
Of 2686 antidrug antibodies (ADA)-evaluable patients treated at the recommended dose of 200 mg once every 3 weeks with tislelizumab as monotherapy or in combination with chemotherapies, 19.5% of patients tested positive for treatment-emergent ADA, and neutralising antibodies (NAbs) were detected in 1.0% 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, 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 51.7% vs. 41.2%, serious adverse events (SAEs) 37.9% vs. 31.0%, AEs leading to tislelizumab treatment discontinuation 12.1% vs 10.7% (for monotherapy); Grade ≥ 3 AEs 78.5% vs. 74.5%, SAEs 44.7% vs. 41.5%, AEs leading to tislelizumab treatment discontinuation 14.4% vs. 13.8% (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 authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: 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

First-line treatment of squamous NSCLC: BGB-A317-307
BGB-A317-307 was a randomised, open-label, multicentre phase III study to compare the efficacy and safety of tislelizumab in combination with paclitaxel plus carboplatin or nab-paclitaxel plus

carboplatin with that of paclitaxel plus carboplatin alone as first-line treatment for chemotherapy-naïve patients with locally advanced squamous NSCLC who were not candidates for surgical resection or platinum-based chemoradiation or metastatic squamous NSCLC.

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

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

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

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

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

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

The study met its primary endpoint at the interim analysis (data cut-off date of 06-Dec-2019), 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)

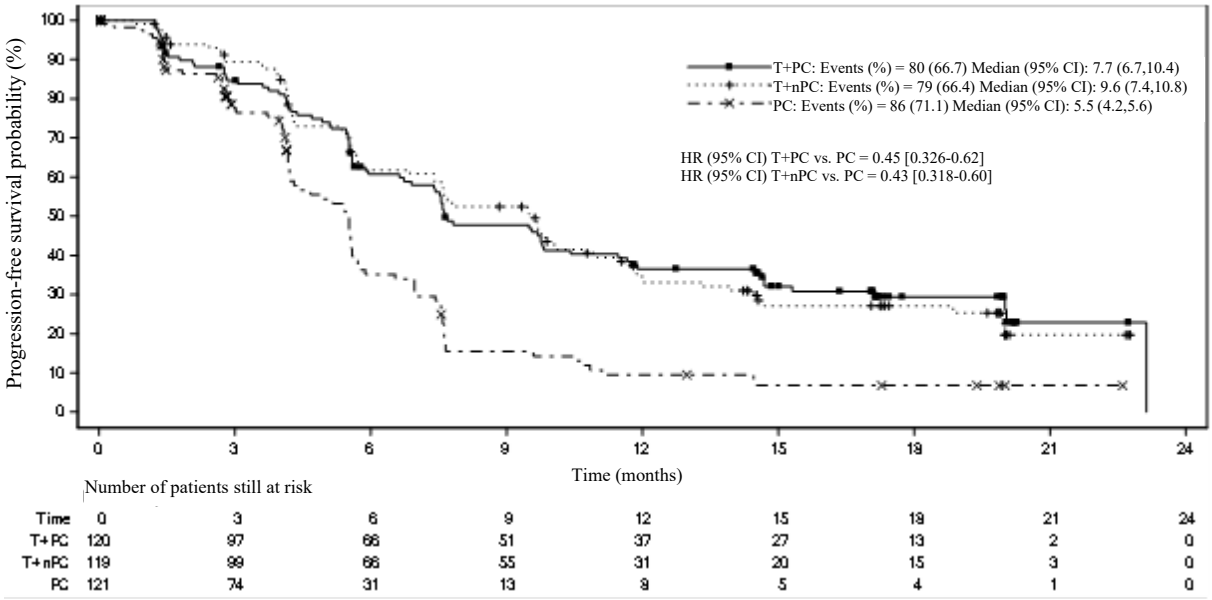
PFS = progression-free survival; CI = confidence interval; OS = overall survival; ORR = objective response rate; DoR = duration of response; NE = not estimable.

[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

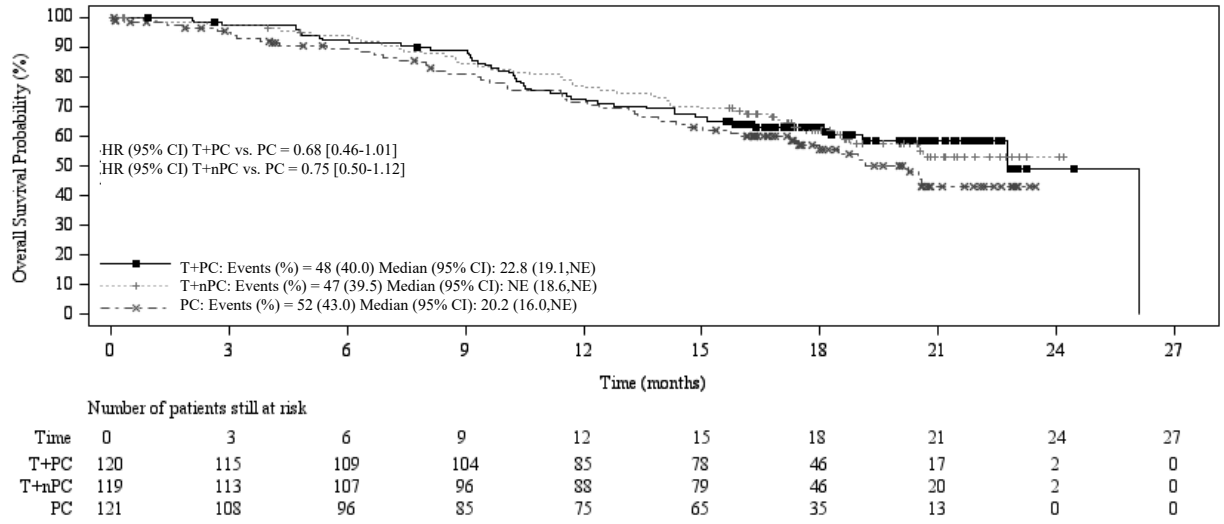
T+PC arm versus T+nPC arm versus PC arm



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)
Best overall response[c]		
DoR[c]		
Median DoR (months) (95% CI)	14.7 (10.55, 21.78)	6.2 (4.11, 8.31)

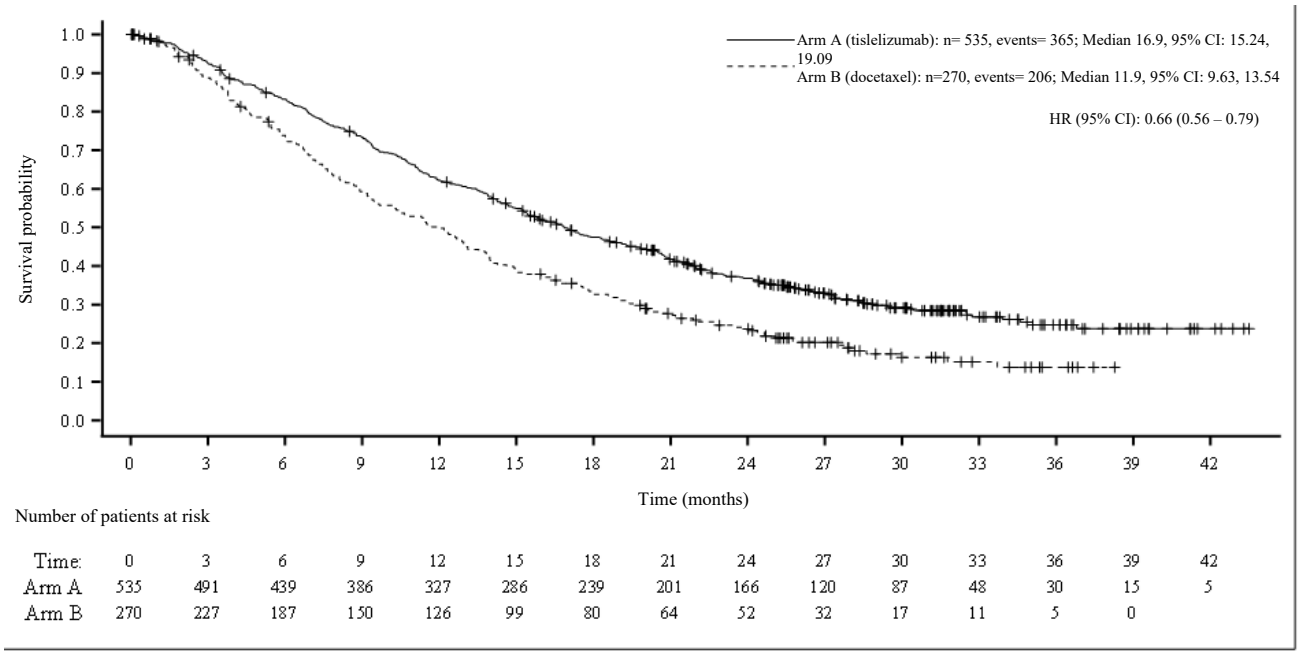
OS = overall survival; CI = confidence interval; PFS = progression-free survival; ORR = objective response rate; DoR = duration of response.
Medians were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley.

[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.

Previously treated Oesophageal squamous cell carcinoma (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 7 and Figure 6.

Table 7 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

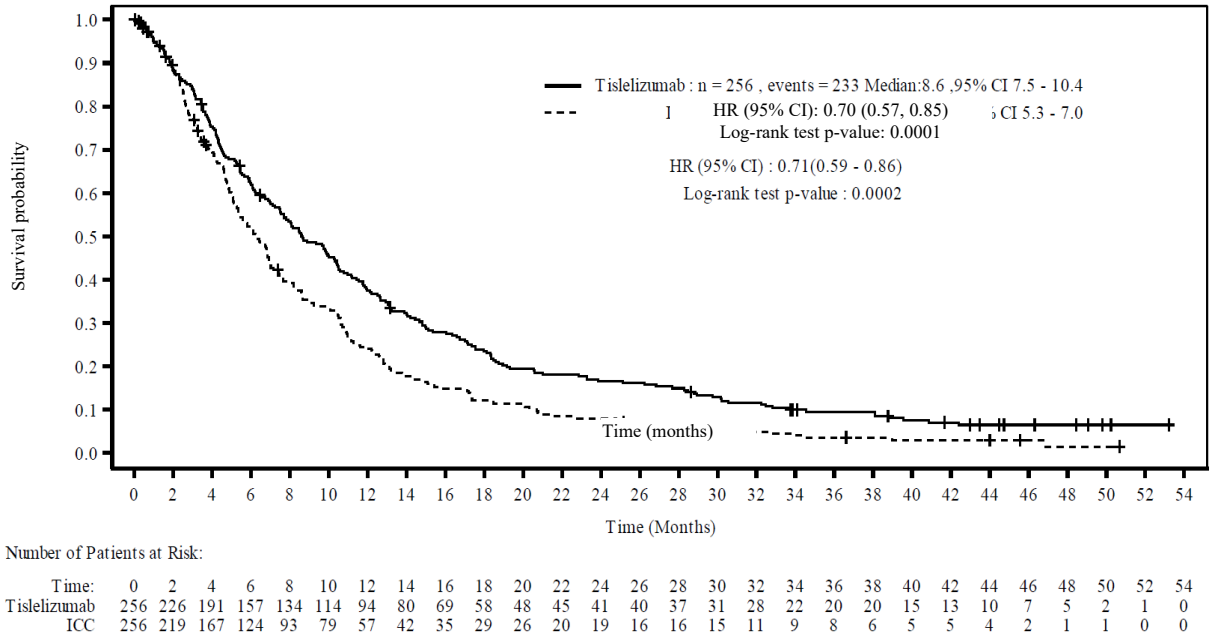
[a] Estimated using Kaplan-Meier method.

[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 6 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.

Gastric cancer

Previously Untreated, Unresectable, or Metastatic HER2-Negative Gastric or Gastroesophageal Junction (G/GEJ) Adenocarcinoma Whose Tumors Express PD-L1 (≥1)

RATIONALE-305 (NCT03777657) was a randomized, multicenter, placebo-controlled, double-blind trial in patients with HER2-negative previously untreated unresectable or metastatic G/GEJ adenocarcinoma.

Patients were enrolled regardless of their tumor PD-L1 expression level, which was evaluated prospectively at a central laboratory using the VENTANA PD-L1 (SP263) assay that identified PD-L1 staining on both tumor and tumor-associated immune cells (TAP). A retrospective scoring of tumor PD-L1 status using Combined Positive Score (CPS) was also conducted using the PD-L1-stained tumor specimens used for randomization.

The trial excluded patients who had active leptomeningeal disease or uncontrolled brain metastasis, and patients with active autoimmune disease or history of autoimmune diseases, or a medical condition requiring systemic corticosteroids or immunosuppressants.

Patients were randomized to receive either TEVIMBRA 200 mg every 3 weeks or placebo in combination with investigator's choice of chemotherapy on a 21-day cycle. TEVIMBRA (or placebo) was administered until disease progression or unacceptable toxicity.

The chemotherapy doublets regimen consisted of:

- CAPOX: Oxaliplatin 130 mg/m^2 IV on Day 1 for up to 6 cycles and capecitabine 1000 mg/m^2 orally twice daily for 14 consecutive days. Capecitabine treatment could be continued beyond 6 cycles.

or

- FP: Cisplatin 80 mg/m^2 IV, Day 1, and 5-FU 800 mg/m^2/day IV continuous infusion over 24 hours daily Day 1-5. Cisplatin and 5-FU were given for up to 6 cycles.

Cross-over between treatment arms was not allowed.

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

Tumor assessments were performed every 6 weeks for the first 48 weeks and thereafter approximately every 9 weeks.

The primary efficacy outcome measures were OS in the PD-L1 TAP score ≥5% population and in the Intent-to-Treat (ITT) population. Secondary outcome measures included progression-free survival (PFS), objective response rate (ORR), and duration of response (DoR) as assessed by the investigator per RECIST v1.1. Additional analyses of efficacy outcome measures were also conducted based on PD-L1 TAP ≥1% and CPS ≥1.

A total of 997 patients were randomized. The trial population characteristics were median age 61 years (range, 23 to 86 years), 35% ≥65 years of age, 69% male; 75% Asian, 22% White, and 0% Black or African American. Eighty percent had primary stomach tumor; 89% had PD-L1 TAP ≥1% and 86% had PD-L1 CPS ≥1, and 99% of patients had metastatic disease at baseline. Baseline ECOG performance status was 0 (32%) or 1 (68%). Ninety-three percent of patients received CAPOX and 7% received FP.

RATIONALE-305 demonstrated a statistically significant improvement in OS for patients randomized to TEVIMBRA in combination with chemotherapy compared with placebo plus chemotherapy in the PD-L1 TAP ≥5% population and in the ITT population. Exploratory analyses of OS in the TAP <1% population and in the CPS <1 population showed hazard ratios of 0.98 (95% CI: 0.64, 1.50) and 1.01 (95% CI: 0.66, 1.52) respectively, indicating that the improvement in the ITT population was primarily attributed to the results observed in the subgroup of patients with PD-L1 ≥1.

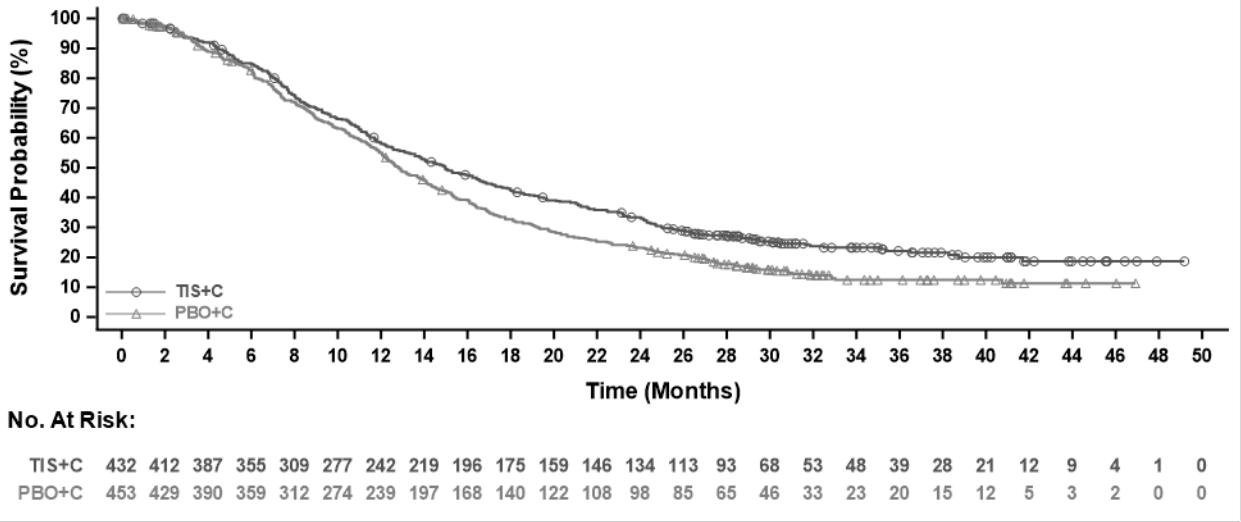
Efficacy results are summarized in Table 8, Figure 7, and Figure 8.

Table 8: Efficacy Results in RATIONALE-305

Endpoint	TEVIMBRA + Chemotherapy (N=432)	Placebo + Chemotherapy (N=453)	TEVIMBRA + Chemotherapy (N=420)	Placebo + Chemotherapy (N=434)
	PD-L1 TAP ≥1%		PD-L1 CPS ≥1	
Overall Survival				
Deaths n (%)	318 (74)	370 (82)	308 (73)	356 (82)
Median (months)[a] (95% CI)	15.0 (13.3, 16.7)	12.8 (12.1, 14.1)	15.1 (13.6, 17.2)	12.9 (12.1, 14.1)
HR[b] (95% CI)	0.78 (0.67, 0.90)		0.78 (0.67, 0.91)	
Progression-Free Survival				
Events, n (%)	316 (73)	364 (80)	303 (72)	348 (80)
Median[c] (months) (95% CI)	6.9 (5.7, 7.2)	5.9 (5.6, 6.9)	7.0 (5.7, 7.7)	6.4 (5.6, 6.9)
HR[b] (95% CI)	0.78 (0.67, 0.91)		0.77 (0.66, 0.90)	
Objective Response Rate[c]				
ORR, n	206	186	204	183
ORR, %	48	41	49	42
95% CI (%)[d]	(43, 53)	(37, 46)	(44, 53)	(37, 47)
Complete response, n (%)	15 (3.5)	15 (3.3)	16 (3.8)	16 (3.7)
Partial response, n (%)	191 (44)	171 (38)	188 (45)	167 (38)
Duration of Response				
Median (months)[a] (95% CI)	8.6 (7.8, 10.4)	7.2 (5.8, 8.3)	8.6 (7.8, 10.4)	7.2 (5.8, 8.5)

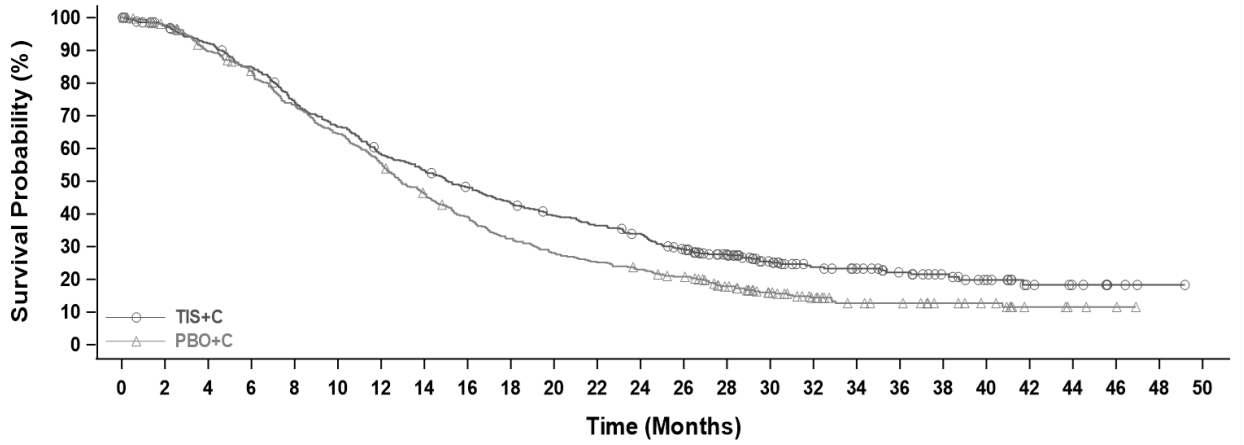
Abbreviations: CI, confidence interval; HR, hazard ratio; ORR, objective response rate.
[a] Medians were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley.
[b] Estimated by Cox proportional hazards model.
[c] Based on confirmed response.
[d] Exact Clopper-Pearson 2-sided confidence interval.

Figure 7: Kaplan-Meier Curve for Overall Survival in RATIONALE-305 (PD-L1 TAP ≥1%)



TIS+C, Tislelizumab + Chemotherapy; PBO+C, Placebo + Chemotherapy.

Figure 8: Kaplan-Meier Curve for Overall Survival in RATIONALE-305 (PD-L1 CPS ≥1)



No. At Risk:

TIS+C	420	400	376	345	301	270	235	215	193	173	156	144	132	111	89	64	51	46	37	26	19	10	7	3	1	0
PBO+C	434	417	379	351	307	270	233	192	162	134	116	104	94	83	63	44	32	22	20	15	12	5	3	2	0	0

TIS+C, Tislelizumab + Chemotherapy; PBO+C, Placebo + Chemotherapy;

An exploratory subgroup analysis of OS in 40 patients with MSI-H tumors irrespective of PD-L1 status showed a HR of 0.66 (0.3, 1.43).

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 = 1046) 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 = 1223). 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 = 2182) (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

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

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vial

The expiry date of the product is indicated on the packaging materials.

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.

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

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

6.5 Nature and contents of container

10 ml of 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.

Not all pack sizes may be marketed.

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. REGISTRATION HOLDER

BeOne Medicines Israel Ltd.
89 Medinat HaYehudim St.,
Herzliya.

8. REGISTRATION NUMBER

172-72-37815-00

9. DATE OF REVISION OF THE TEXT

Revised in August 2025.