1. NAME OF THE MEDICINAL PRODUCT

TEVIMBRA (tislelizumab) concentrate for solution for infusion 100mg/ 10mL

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Each vial of 10 ml contains 100 mg tislelizumab.

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

Excipient with known effect

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate)

Clear to slightly opalescent, colourless to slightly yellowish solution.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Non-small cell lung cancer (NSCLC)

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 patients with locally advanced or metastatic NSCLC after prior chemotherapy.

Esophageal squamous cell carcinoma (ESCC)

TEVIMBRA in combination with platinum-based chemotherapy, is indicated for the first-line treatment of adult patients with unresectable, locally advanced or metastatic esophageal squamous cell carcinoma (ESCC) with a PD-L1 expression ≥ 1%.

TEVIMBRA as monotherapy is indicated for the treatment of patients with unresectable, recurrent,locally advanced, or metastatic esophageal squamous cell carcinoma (ESCC) after prior chemotherapy.

Nasopharyngeal cancer (NPC)

TEVIMBRA, in combination with gemcitabine and cisplatin is indicated for the first-line treatment of patients with recurrent, not amenable to curative surgery or radiotherapy, or metastatic NPC.

Gastric or gastroesophageal junction (G/GEJ) adenocarcinoma

TEVIMBRA, in combination with platinum and fluoropyrimidine-based chemotherapy, isindicated for the first-line treatment of adult patients with human epidermal growth factor receptor-2 (HER-2)- negative locally advanced unresectable or metastatic gastric or gastroesophageal junction (G/GEJ) adenocarcinoma with a PD-L1 expression ≥ 1%.

4.2 Posology and method of administration

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

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 Package Leaflet 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.

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

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

Table 1 Recommended treatment modifications for 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 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

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, Guillain-Barré syndrome and aplastic anaemia (see section 4.8).

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

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

Infusion-related reactions

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

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

Patients excluded from clinical studies

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

Patients on controlled sodium diet

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

4.5 Interaction with other medicinal products and other forms of interaction

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

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception

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

Pregnancy

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

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

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

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

Breast-feeding

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

Because of the potential for serious adverse drug reactions in breast-fed newborns/infants from 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 1 952 patients across multiple tumour types who received 200 mg tislelizumab every 3 weeks. The most common adverse reactions were anaemia (27.7%), fatigue (24.7%) and increased alanine aminotransferase (22.0%).
The most common grade 3/4 adverse reactions were anaemia (4.8%), increased aspartate aminotransferase (3.7%), pneumonia (3.6%), hyponatremia (2.9%), increased blood bilirubin (2.8%), hypertension (2.4%) and fatigue (2.1%). The adverse reactions leading to death were pneumonia (0.6%), thrombocytopenia (0.1%), decreased appetite (0.1%), hepatitis (0.1%), dyspnoea (0.1%) and pneumonitis (0.1%). Among the 1 952 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 in combination with chemotherapy is based on data in 1 950 patients treated with tislelizumab in combination with chemotherapy.
The most common adverse reactions were neutropenia (71.6%), anaemia (67.2%), thrombocytopenia (48.7%), nausea (43.3%), fatigue (40.8%), decreased appetite (40.1%), increased alanine aminotransferase (30.6%), increased aspartate aminotransferase (30.3%), rash (21.4%) and diarrhoea (20.3%). The most common grade 3/4 adverse reactions were neutropenia (45.2%), anaemia (14.5%), thrombocytopenia (14.1%), hyponatremia (4.6%), hypokalemia (4.5%), fatigue (4.2%), pneumonia (4.0%), lymphopenia (3.1%), rash (2.9%), decreased appetite (2.6%), increased aspartate aminotransferase (2.2%), and increased alanine aminotransferase (2.1%). The adverse reactions leading to death were pneumonia (0.5%), pneumonitis (0.3%), dyspnoea (0.2%), myocarditis (0.2%), thrombocytopenia (0.1%), colitis (0.1%), hepatitis (0.1%), hypokalemia (0.1%) and myositis (0.1%), Among the 1 950 patients, 56.5% were exposed to tislelizumab for longer than 6 months, and 31.9% were exposed for longer than 12 months.

Tabulated list of adverse reactions

Adverse reactions reported in the pooled dataset for patients treated with Tislelizumab monotherapy(n = 1 952) and in combination with chemotherapy (n = 1 950) 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 Tislelizumab as monotherapy (n = 1 952) and in combinationwith chemotherapy (n = 1 950)

Adverse reactions	Tislelizumab monotherapy n = 1 952	Tislelizumab + chemotherapy n = 1 950
	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
Immune system disorders		
Sjögren's syndrome	-	Uncommon
Immune-mediated cystitis[#]	Not known	Not known
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		
Encephalitis[15]	-	Rare
Guillain-Barré syndrome	Rare	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	Uncommon
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[#]	Not known*	Not known*
Musculoskeletal and connective tissue disorders		
Arthralgia	Common	Very common
Myalgia	Common	Common
Myositis[27]	Uncommon	Uncommon
Arthritis[28]	Uncommon	Common
Renal and urinary disorders		
Nephritis[29]	Uncommon	Uncommon
General disorders and administration site conditions		
Fatigue[30]	Very common	Very common
Pyrexia[31]	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[32]	Very common	Very common
Blood alkaline phosphatase Increased	Common	Common
Blood creatinine increased	Common	Very common
Injury, poisoning and procedural complications		
Infusion-related reaction[33]	Common	Common

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

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

[3] Thrombocytopenia includes PTs of immune thrombocytopenia, platelet count decreased and 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 anti-thyroid antibody increased, central hypothyroidism, hypothyroidism, immune-mediated hypothyroidism, primary hypothyroidism, thyroid hormones decreased, thyroxine decreased, thyroxine free decreased, tri-iodothyronine decreased and tri-iodothyronine free 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 autoimmune thyroiditis, immune-mediated thyroiditis, silent thyroiditis, 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 hypopituitarism and hypophysitis.

[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, latent autoimmune diabetes in adults and type 1 diabetes mellitus.

[15] Encephalitis includes the PT of immune-mediated encephalitis.

[16] Uveitis includes PTs of uveitis, iritis, iridocyclitis and chorioretinitis.

[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 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 autoimmune hepatitis, drug-induced liver injury, hepatic function abnormal, hepatitis, hepatotoxicity, immune-mediated hepatitis and liver injury.
[25] Rash includes PTs of acute febrile neutrophilic dermatosis, autoimmune dermatitis, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis exfoliative, drug eruption, eczema, erythema, erythema nodosum, hand dermatitis, immune-mediated dermatitis, lichenoid keratosis, pemphigoid, psoriasis, rash, rash erythematous, rash follicular, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, skin exfoliation and urticaria.
[26] Vitiligo includes PTs of vitiligo, skin hypopigmentation, skin depigmentation and leukoderma.
[27] Myositis includes PTs of myositis, rhabdomyolysis and immune-mediated myositis.
[28] Arthritis includes PTs of arthritis, immune-mediated arthritis and polyarthritis.
[29] Nephritis includes PTs of focal segmental glomerulosclerosis, glomerulonephritis membranous, immune mediated nephritis, immune-mediated renal disorder, nephritis and tubulointerstitial nephritis.
[30] Fatigue includes PTs of asthenia, fatigue, lethargy, malaise and physical deconditioning.
[31] Blood bilirubin increased includes PTs of bilirubin conjugated increased, blood bilirubin increased, blood bilirubin unconjugated increased and hyperbilirubinaemia.
[32] Pyrexia includes the PTs of body temperature increased and pyrexia.
[33] Infusion-related reaction includes PTs of anaphylactic reaction, chills, corneal oedema, dermatitis allergic, drug eruption, drug hypersensitivity, face oedema, gingival swelling, hypersensitivity, infusion related reaction, 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 and urticaria.
[#]Post-marketing experience.
*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.

Immune-related pneumonitis

In patients treated with tislelizumab as monotherapy, immune-related pneumonitis occurred in 5.1% ofpatients, 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 waspermanently 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 patientswith a history of prior thoracic radiation (8.4%) than in patients who did not receive prior thoracic radiation (3.6%).

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 days 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%) and 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) and 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 patient 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: 1.0 month 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. Tislelizumab was neither interrupted nor permanently discontinued in any patient. Hypophysitis resolved in 20% 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. 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.

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.

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, 0.1% for increased lymphocytes, 17.9% for decreased lymphocytes, 47.2% for decreased neutrophils, 14.1% for decreased platelets, 3.5% for increased alanine aminotransferase, 0.5% for albumin decreased, 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, 1.2% for increased glucose, 0.5% for decreased 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 monotherapy between patients aged <65 years and patients aged between 65 and 74 years. Data for patients aged 75 years and above are too limited to draw conclusions on this population.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

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

Clinical efficacy and safety

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

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

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

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

Randomisation was stratified by PD-L1 expression in tumour cells (TC) (<1% versus 1% to 49% versus ≥50%) and disease stage (IIIB versus IV), as classified according to American Joint Committee

on Cancer (AJCC), 7th edition of Cancer Staging Manual. PD-L1 expression was evaluated at a central laboratory using the Ventana PD-L1 (SP263) assay that identified PD-L1 staining on tumour cells. Tumour assessments were conducted every 6 weeks for the first 6 months, then every 9 weeks for the second 6 months, then every 12 weeks.

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

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

The study met its primary endpoint at the interim analysis (data cut-off date of 23-Jan-2020 and a median duration of study follow-up of 9.0 months), showing a statistically significant improvement in PFS with T+PP compared with PP. The stratified hazard ratio was 0.65 (95% CI: 0.47, 0.91; $p = 0.0054$) with a median PFS of 9.7 months with T+PP and 7.6 months with PP.

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

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

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

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

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

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

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

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

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

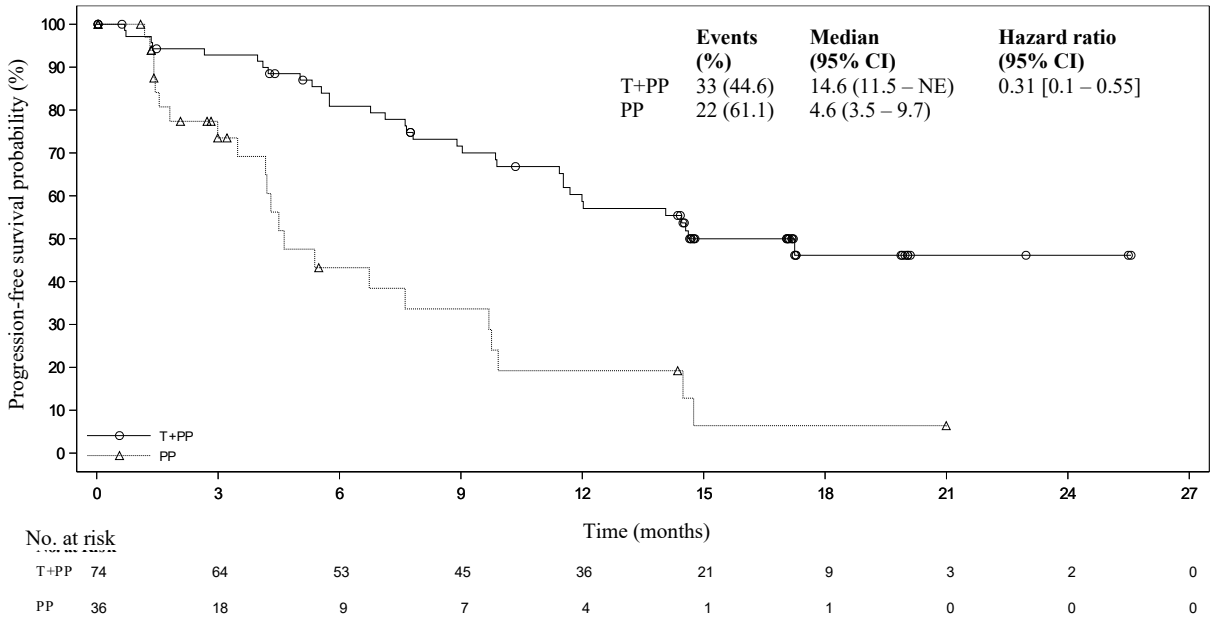
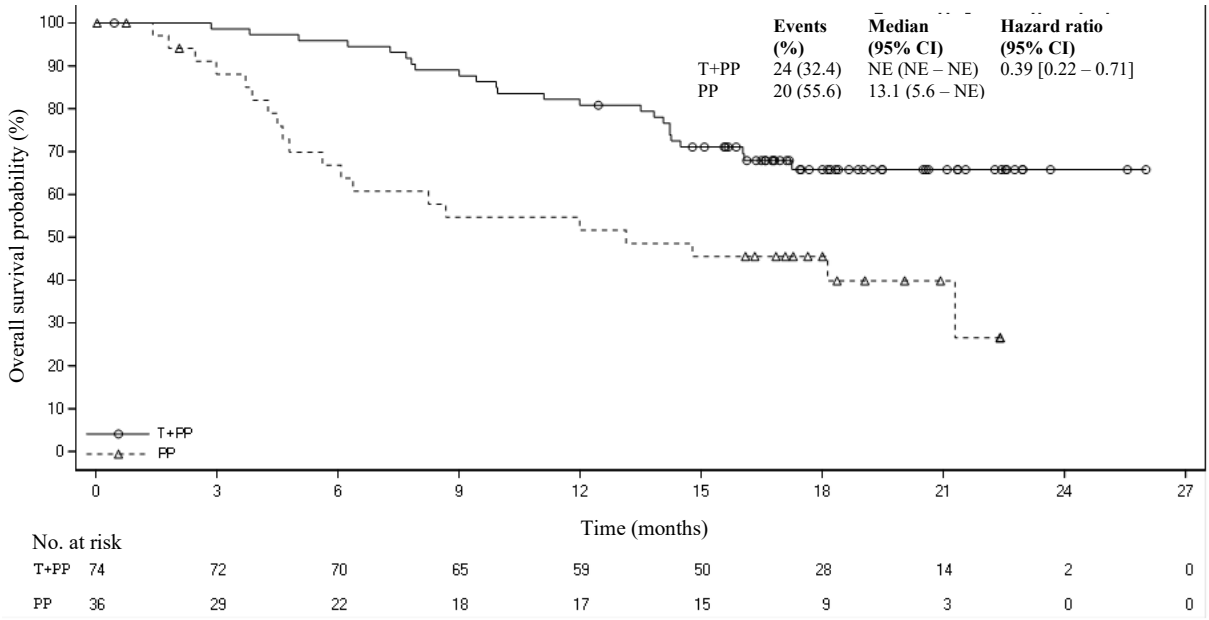


Figure 2 Kaplan-Meier plot of OS in BGB-A317-304 in patients with PD-L1 ≥50%



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

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

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

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

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

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

smoking status, PD-L1 TC score and prior anticancer treatments were balanced between the treatment arms.

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

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

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

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

Table 4 Efficacy results in BGB-A317-307

Endpoint	Tislelizumab + Paclitaxel + Carboplatin (N = 120)	Tislelizumab + nab-Paclitaxel + Carboplatin (N = 119)	Paclitaxel + Carboplatin (N = 121)
PFS			
Events, n (%)	80 (66.7)	79 (66.4)	86 (71.1)
Median PFS (months) (95% CI)	7.7 (6.7, 10.4)	9.6 (7.4, 10.8)	5.5 (4.2, 5.6)
Stratified hazard ratio[a] (95% CI)	0.45 (0.33, 0.62)	0.43 (0.31, 0.60)	-
OS			
Deaths, n (%)	48 (40.0)	47 (39.5)	52 (43.0)
Median OS (months) (95% CI)	22.8 (19.1, NE)	NE (18.6, NE)	20.2 (16.0, NE)
Stratified hazard ratio (95% CI)	0.68 (0.45, 1.01)	0.752 (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)
CR, n (%)	7 (5.8)	6 (5.0)	1 (0.8)
PR, n (%)	67 (55.8)	68 (57.1)	44 (36.4)
DoR[b]			
Median DoR (months) (95% CI)	13.2 (7.85, 18.79)	10.4 (8.34, 17.15)	4.8 (4.04, 5.72)

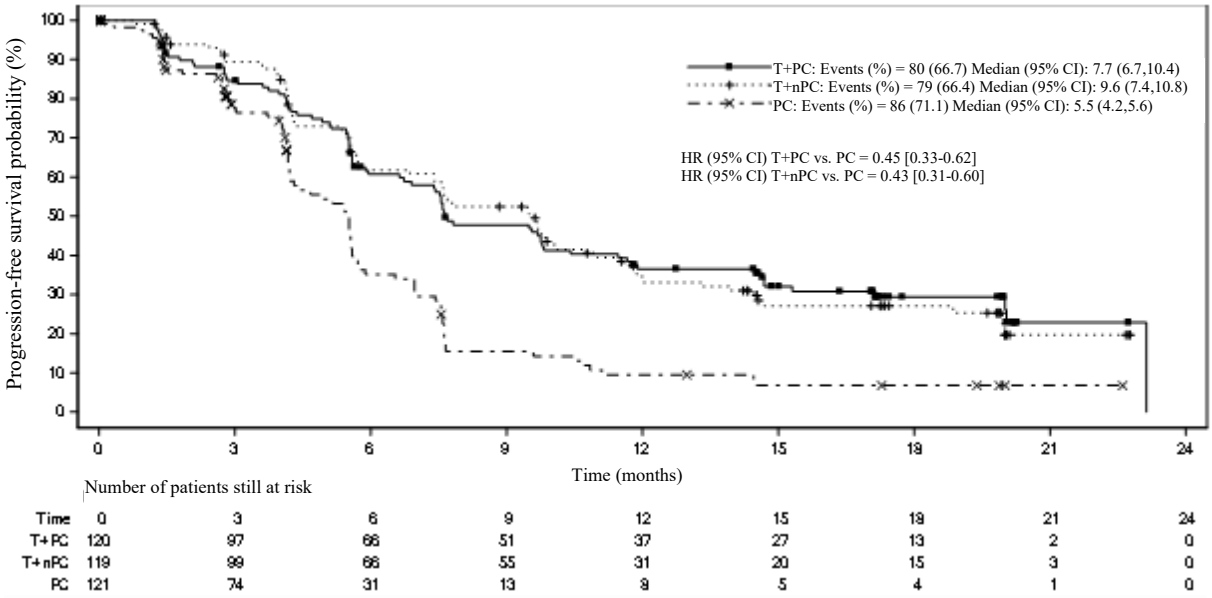
PFS = progression-free survival; CI = confidence interval; OS = overall survival; ORR = objective response rate; CR = complete response; PR = partial response; DoR = duration of response; NE = not estimable.

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

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

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

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



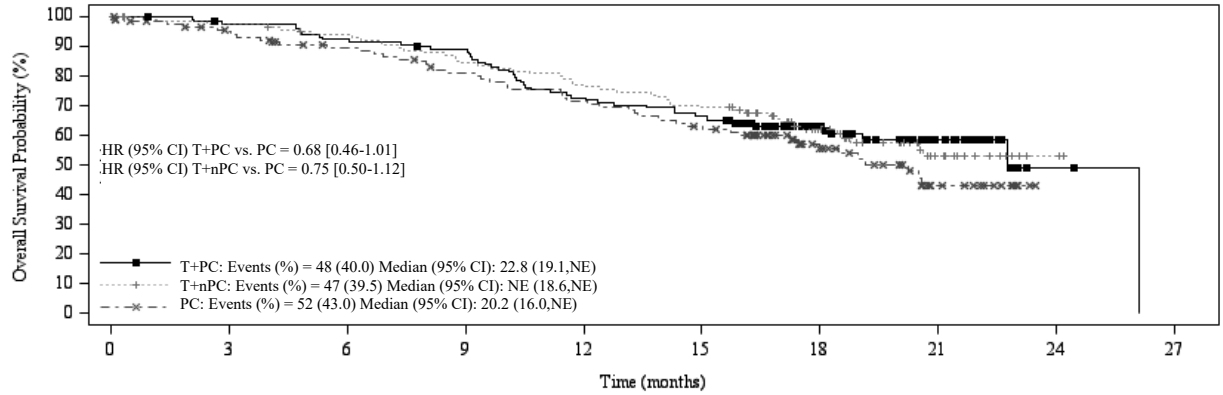
Number of patients still at risk

Time	0	3	6	9	12	15	18	21	24
T+PC	120	97	68	51	37	27	13	2	0
T+nPC	119	99	68	55	31	20	15	3	0
PC	121	74	31	13	9	5	4	1	0

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

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

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



Number of patients still at risk

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

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

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

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

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

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

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

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

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

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

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

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

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

Table 5 Efficacy results in BGB-A317-303

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

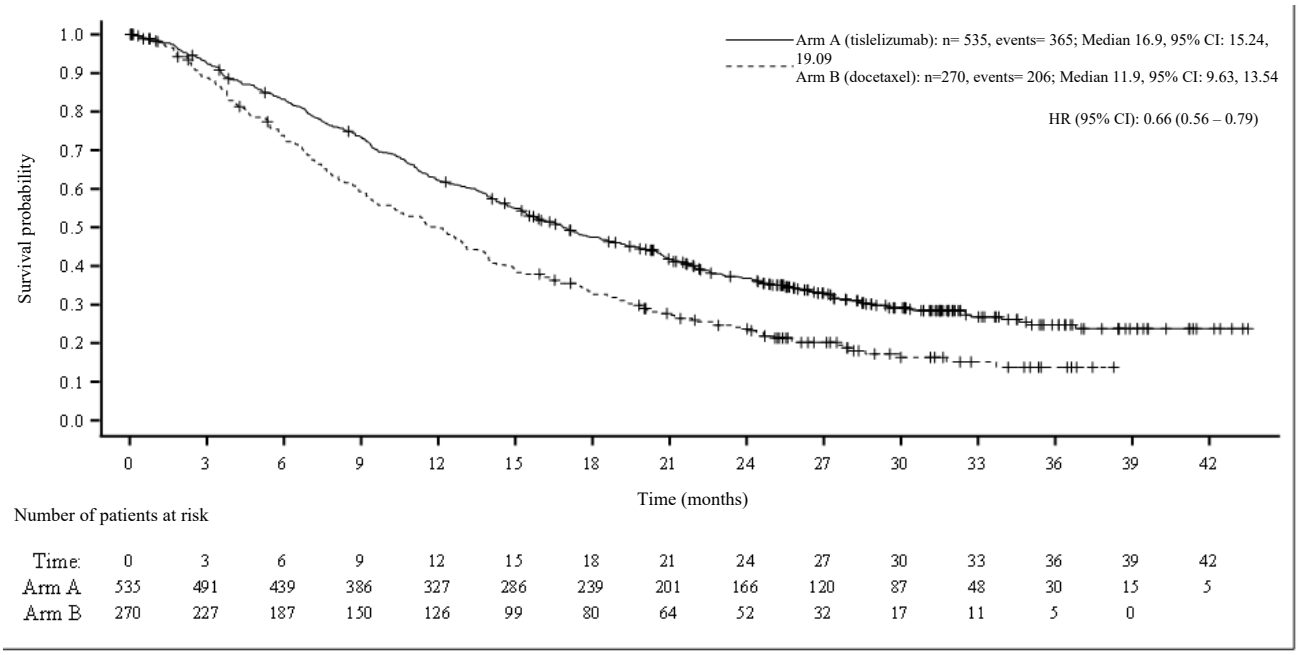
OS = overall survival; CI = confidence interval; PFS = progression-free survival; ORR = objective response rate; CR = complete response; PR = partial response; DoR = duration of response.
Medians were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley.

[a] Hazard ratio was estimated from stratified Cox model with docetaxel group as reference group.

[b] Stratified by stratification factors: histology (squamous versus non-squamous), lines of therapy (second versus third), and PD-L1 expression in tumour cells (≥25% PD-L1 score versus <25% PD-L1 score).

[c] Confirmed by investigator.

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



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

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

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

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

[a] Hazard ratio and its 95% CI were estimated from unstratified Cox model.

Esophageal squamous cell carcinoma (ESCC)

BGB-A317-306:
BGBA-317-306 is a randomised, double-blind placebo-controlled, global phase III study to compare the efficacy of tislelizumab in combination with chemotherapy versus placebo in combination with chemotherapy in patients with unresectable, locally advanced recurrent or metastatic ESCC.

The study enrolled patients who were not amenable to chemoradiation or surgery with curative intent. 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.

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 active leptomeningeal disease or uncontrolled brain metastasis, active autoimmune disease, a medical condition requiring systemic corticosteroids or immunosuppressants, or evidence of fistula or complete esophageal 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 every 3 weeks or placebo 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).

Cross-over between treatment arms or between fluoropyrimidine and paclitaxel during the study treatment period was not allowed.

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.

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 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, 223 patients had PD-L1 score ⩾10%, 319 patients had PD-L1 score <10% and 107 patients had PD-L1 status unknown.

The baseline characteristics for the study population were: median age 64.0 years (range: 26 to 84), 48.1% age 65 years or older; 86.7% male; 23.9% White and 74.9% Asian. 86.4% had metastatic disease at study entry and 13.6% had locally advanced disease. Patients had histological confirmation of squamous cell carcinoma (99.8%). Baseline ECOG performance status was 0 (32.8%) or 1 (67.2%).

BGB-A317-306 showed a statistically significant improvement in OS for patients randomised to the tislelizumab in combination with chemotherapy arm as compared to the placebo in combination with chemotherapy arm. As of the data cut-off date of interim analysis, the median follow-up times by reverse Kaplan-Meier methodology were 23.9 months in the tislelizumab in combination with chemotherapy arm and 23.5 months in the placebo in combination with chemotherapy arm.

Efficacy results are shown in Table 7 and Figure 6.

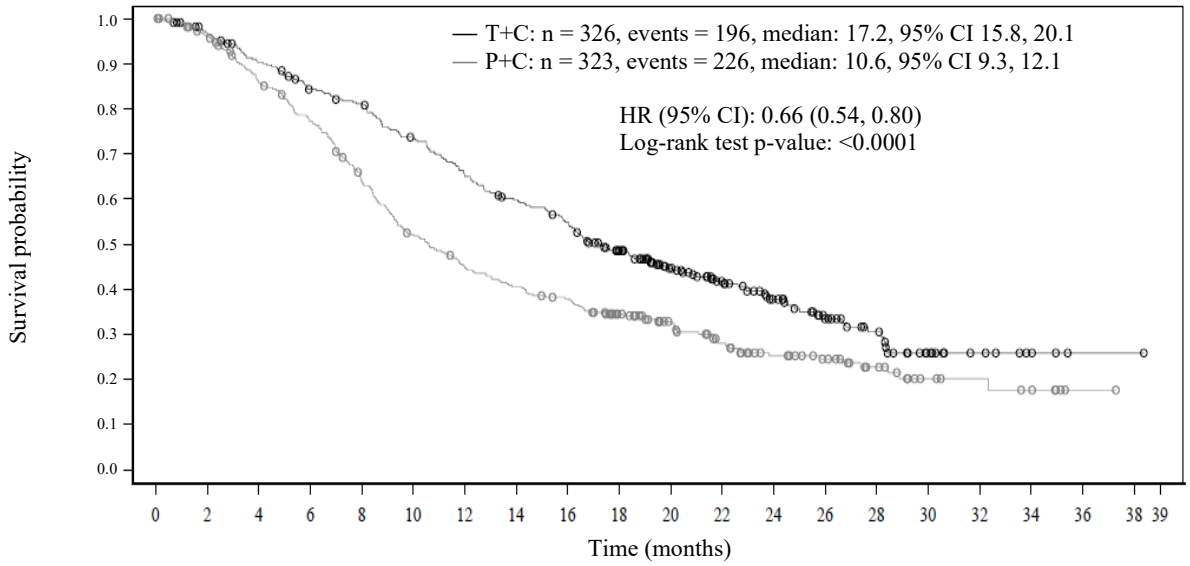
Table 7 Efficacy results in BGB-A317-306

Endpoint	Tislelizumab + chemotherapy (N = 326)	Placebo + chemotherapy (N = 323)
OS		
Deaths, n (%)	196 (60.1)	226 (70.0)
Median (months) (95% CI)	17.2 (15.8, 20.1)	10.6 (9.3, 12.1)
HR (95% CI)[a]	0.66 (0.54, 0.80)	
p-value[b]	<0.0001	
PFS		
Events, n (%)	220 (67.5)	254 (78.6)
Median (months) (95% CI)	7.3 (6.9, 8.3)	5.6 (4.9, 6.0)
HR (95% CI)[a]	0.62 (0.52, 0.75)	
p-value[b]	< 0.0001	
ORR[c]		
ORR, n	207	137
ORR, % (95% CI)[d]	63.5 (58.0, 68.7)	42.4 (37.0, 48.0)
CR, n (%)	15 (4.6)	8 (2.5)
PR, n (%)	192 (58.9)	129 (39.9)
Odds ratio for ORR (95%CI)[e]	2.38 (1.73, 3.27)	
p-value[e]	<0.0001	
DOR[c]		
Median DoR rate (months) (95% CI)	7.1 (6.1, 8.1)	5.7 (4.4, 7.1)
6 months (95% CI)	57.6 (50.2, 64.3)	46.0 (36.9, 54.6)
12 months (95% CI)	31.3 (24.6, 38.2)	18.7 (11.9, 26.7)
18 months (95% CI)	23.2 (17.0, 29.9)	10.7 (5.4, 18.0)

OS = overall survival; CI = confidence interval; HR = hazard ratio; PFS = progression-free survival; ORR = objective response rate; CR = complete response; PR = partial response; DOR = duration of response

[a] Based on a stratified Cox regression model.
[b] One-sided p-value from a stratified log rank test.
[c] ORR and DoR are unconfirmed.
[d] Exact Clopper-Person-2-sided confidence interval.
[e] Odds ratio and two-sided p-value were based on a stratified Cochran-Mantel-Haenszel test.

Figure 6 Kaplan-Meier plot of OS in BGB-A317-306 (ITT analysis set)



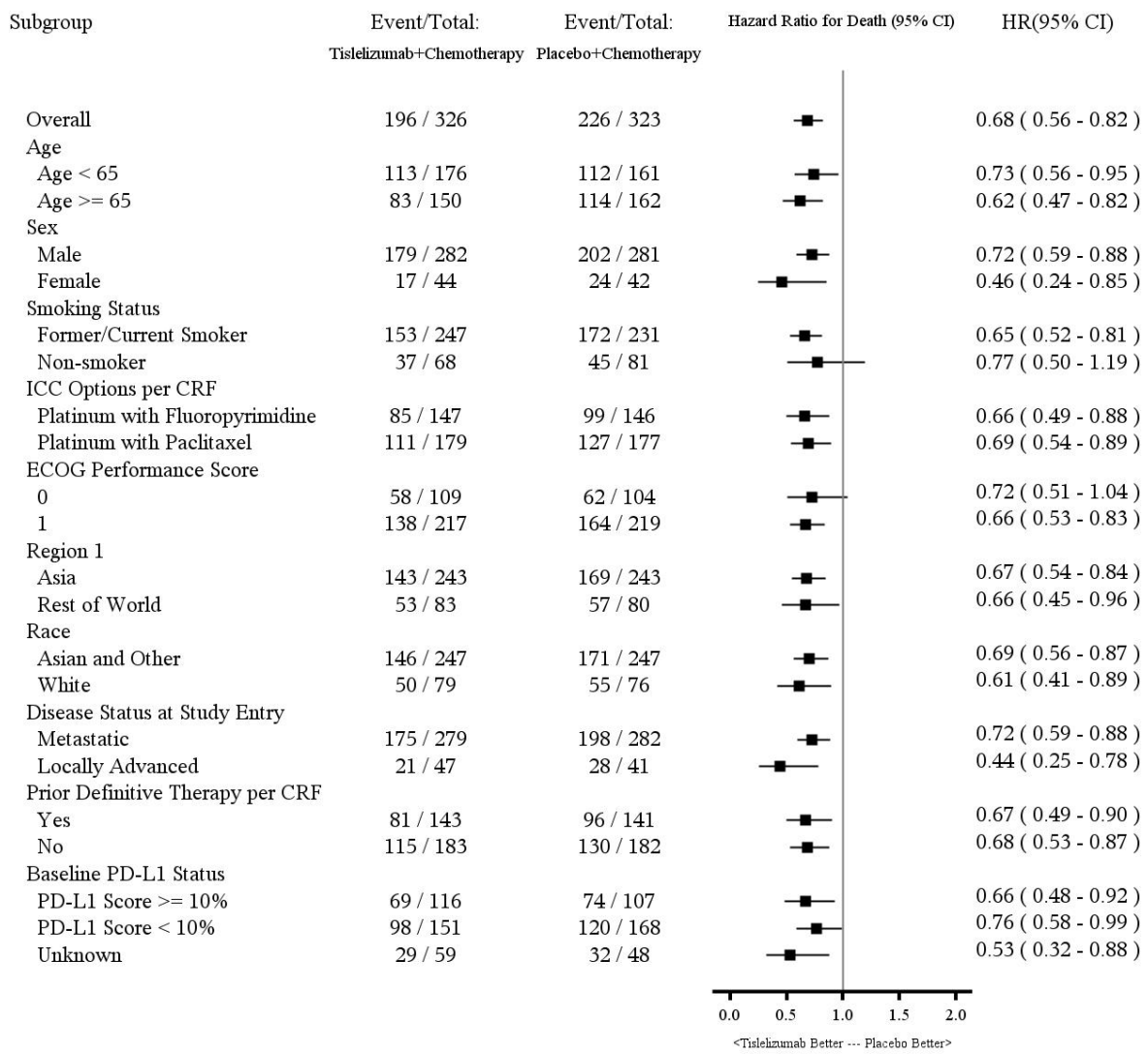
Number of patients at risk

Time:	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39
T+C	326	320	311	300	287	277	264	256	253	236	227	216	201	190	183	178	167	150	136	120	101	90	79	70	58	50	41	34	28	19	14	9	8	6	4	2	1	1	1	0
P+C	323	315	304	285	268	254	239	217	195	176	158	147	135	129	122	115	112	102	91	80	71	63	54	45	40	36	32	25	22	15	11	8	8	7	6	3	1	1	0	0

P+C = placebo in combination with chemotherapy; T+C = tislelizumab in combination with chemotherapy.
One-sided p-value was estimated from a log-rank test stratified on geographical region, prior definitive therapy and ICC option.
Hazard ratio was based on a Cox regression model including treatment as covariate, and stratified by pooled geographical region, prior definitive therapy and ICC option.

OS benefit with tislelizumab plus chemotherapy over placebo plus chemotherapy was consistent across pre-specified subgroups, including age, gender, investigator's choice of chemotherapy options (platinum with fluoropyrimidine and platinum with paclitaxel), smoking status, ECOG performance status, geographical region (Asia versus ROW), race (Asian and other versus White), disease status at study entry (metastatic versus locally advanced), prior definitive therapy (yes versus no), and baseline PD-L1 status. Results are provided in Figure 7.

Figure 7 Forest plot of OS by subgroups based on demographics and baseline characteristicsin RATIONALE-306 (ITT analysis set) (data cut-off date of 28-Feb-2022)



***** Hazard ratio was based on unstratified Cox regression model, including treatment as covariate.

At an updated descriptive analysis with a median follow-up by reverse Kaplan-Meier methodology of 37.8 months for tislelizumab in combination with chemotherapy and 36.2 months for placebo in combination with chemotherapy, OS improvements were consistent with the primary analysis.

Efficacy and PD-L1 subgroups
In a pre-defined analysis in patients with PD-L1 score ≥10%, the stratified HR for OS was 0.62 (95% CI: 0.44 to 0.87). The one-sided stratified log-rank test p-value of 0.0029 was statistically significant. The median OS was 16.6 months (95% CI: 15.3 to 24.4 months) for the tislelizumab in combination with chemotherapy arm and 10 months (95% CI: 8.6 to 13.3 months) for the placebo in combination with chemotherapy arm.

In a pre-defined analysis in patients with PD-L1 score <10%, the stratified HR for OS was 0.77 (95% CI: 0.59 to 1.01), and the median OS was 15.8 months (95% CI: 12.3 to 19.6 months) for the tislelizumab in combination with chemotherapy arm and 10.4 months (95% CI: 9.0 to 13.6 months) for the placebo in combination with chemotherapy arm.

In a pre-defined analysis in patients with unknown PD-L1 status (n = 107), the stratified HR for OS was 0.54 (95% CI: 0.32 to 0.91), and the median OS was 23.7 months (95% CI: 16.6 to 28.4 months) for the tislelizumab in combination with chemotherapy arm and 11.7 months (95% CI: 7.4 to 21.7 months) for the placebo in combination with chemotherapy arm.

Patient-reported outcomes
Patient-reported outcomes (PROs) were collected using EORTC QLQ-C30, EORTC QLQ-OES18 and EQ-5D-5L questionnaires. Adjusted completion rate from baseline to cycle 6 and cycle 8 was ≥93% and ≥91%, respectively, for each questionnaire in both treatment arms.

Based on the mixed-effect model analysis for measuring clinically meaningful changes compared to baseline, no significant differences between treatment arms from baseline to the key clinical cycles 6 and 8 were observed in Global Health Status (GHS), fatigue, pain or in the disease-specific symptoms of dysphagia, eating, pain and reflux. These results indicated that overall HRQoL did not worsen with the addition of tislelizumab to chemotherapy compared to placebo plus chemotherapy in this population of patients with ESCC.

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 ESCC 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 inhibitor treatment and tumour invasion into organs located adjacent to the oesophageal disease site (e.g. aorta or respiratory tract).

Randomisation was stratified by geographic 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 PD-L1 Positive Analysis Set (PD-L1 score of visually-estimated Combined Positive Score, now known as Tumour Area Positivity score [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 62 years (range: 35 to 86), 37.9% 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.

BGB-A317-302 showed a statistically significant improvement in OS for patients randomised to the tislelizumab arm as compared to 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.

Efficacy results are shown in Table 8 and Figure 8.

Table 8 Efficacy results in BGB-A317-302

Endpoint	**Tevimbra (N = 256)**	**Chemotherapy (N = 256)**
OS		
Deaths, n (%)	197 (77.0)	213 (83.2)
Median (months)[a] (95% CI)	8.6 (7.5, 10.4)	6.3 (5.3, 7.0)
Hazard ratio (95% CI)[b]	0.70 (0.57, 0.85)	
p-value[c]	p = 0.0001	
PFS assessed by investigator[d]		
Disease progression or death, n (%)	223 (87.1)	180 (70.3)
Median (months) (95% CI)	1.6 (1.4, 2.7)	2.1 (1.5, 2.7)
Hazard ratio (95% CI)	0.83 (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)
CR, n (%)	5 (2.0)	1 (0.4)
PR, n (%)	34 (13.3)	16 (6.3)
SD, n (%)	81 (31.6)	90 (35.2)
Median duration of response with confirmation by investigator (months) (95% CI)	10.3 (6.5, 13.2)	6.3 (2.8, 8.5)

OS = overall survival; CI = confidence interval; PFS = progression-free survival; ORR = objective response rate; CR = complete response; PR = partial response; SD = stable disease

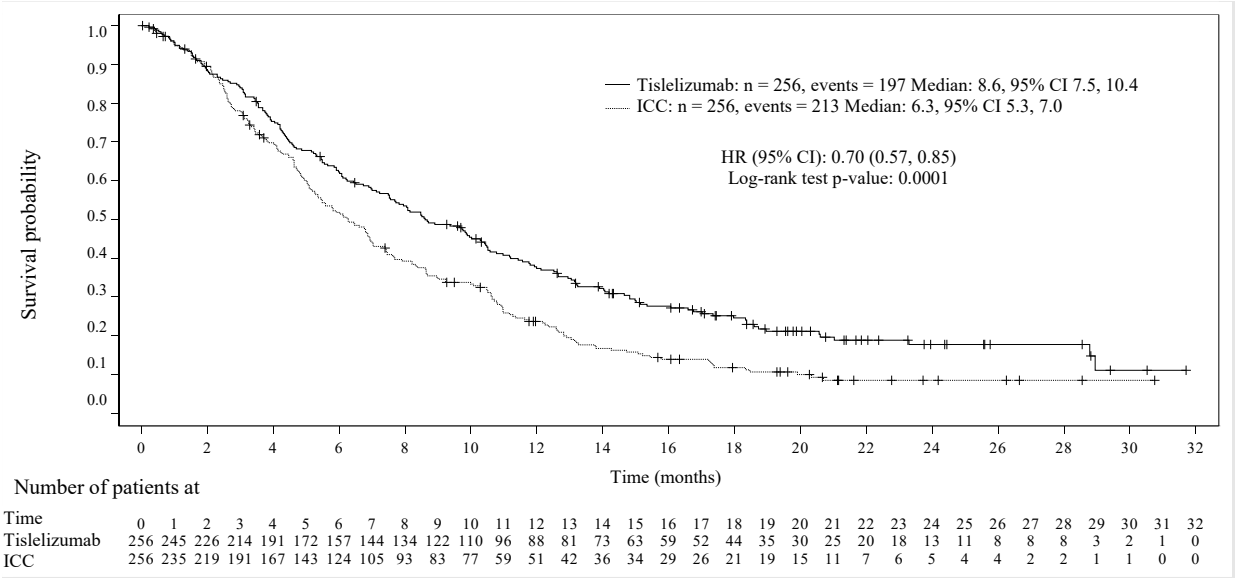
[a] Estimated using Kaplan-Meier method.

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

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

[d] Based on ad hoc analysis.

Figure 8 Kaplan-Meier plot of OS in BGB-A317-302 (ITT analysis set)



Efficacy and PD-L1 subgroups:
In a pre-specified analysis of OS in the PD-L1 positive subgroup (PD-L1 score ≥10%), the stratified hazard ratio (HR) for OS was 0.49 (95% CI: 0.33 to 0.74), with a 1-sided stratified log-rank test p-value of 0.0003. The median survival was 10.0 months (95% CI: 8.5 to 15.1 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 0.83 (95% CI: 0.62 to 1.12), 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.
First-Line Treatment of Recurrent or Metastatic Nasopharyngeal Cancer RATIONALE-309 (NCT03924986)

A randomized, multicenter, double-blind, placebo-controlled Phase 3 study comparing the efficacy and safety of tislelizumab in combination with gemcitabine and cisplatin versus placebo in combination with gemcitabine and cisplatin as first-line treatment in patients with recurrent or metastatic nasopharyngeal cancer (NPC).

A total of 263 patients randomized (1:1) to receive either tislelizumab 200 mg in combination with gemcitabine and cisplatin (N=131) or placebo in combination with gemcitabine and cisplatin (N=132).

The study included patients with pathologically confirmed recurrent, not amenable to surgery or radiotherapy, or metastatic NPC who have not received prior systemic treatment and an ECOG performance status of 0 or 1. Patients with recurrent NPC after treatment with curative intent were required to have an interval of at least 6 months between the last dose of radiotherapy or chemotherapy and recurrence.

The study excluded patients who received any approved systemic anticancer therapy including hormonal therapy within 28 days before initiation of study treatment, prior therapies targeting PD-1 or PD-L1, or who have active leptomeningeal disease or uncontrolled, untreated brain metastasis.

The baseline characteristics for the study population were: median age of 50 years (range: 23 to 74 years); 91.6% of patients < 65 years old; 78.3% of patients were male; 63.1% with baseline ECOG PS score of 1; 100% Asian (from China, Thailand, and Taiwan); and 95% were never or former smokers. The baseline demographic and disease characteristics in the ITT Analysis Set were generally well-balanced between the 2 arms.

Randomization was stratified by gender and metastatic status (with versus without liver metastases). Patients were randomized (1:1) to receive either tislelizumab 200 mg or placebo plus cisplatin 80 mg/m^2 on Day 1 plus gemcitabine 1 g/m^2 on Day 1 and Day 8 of each 21-day cycle for 4 to 6 cycles. Tislelizumab or placebo was administered until disease progression or unacceptable toxicity.
The primary endpoint was progression-free survival (PFS) as assessed by the Independent Review Committee (IRC) per RECIST v1.1 in the Intention-to-Treat (ITT) Analysis Set. The secondary endpoints were Overall Survival (OS), Objective Response Rate (ORR), and Duration of Response (DOR).

The study demonstrated a statistically significant improvement in PFS for patients randomized to tislelizumab in combination with gemcitabine and cisplatin arm compared with the placebo plus gemcitabine and cisplatin arm. Table 9 and Figure 9 summarize the efficacy results for the study.

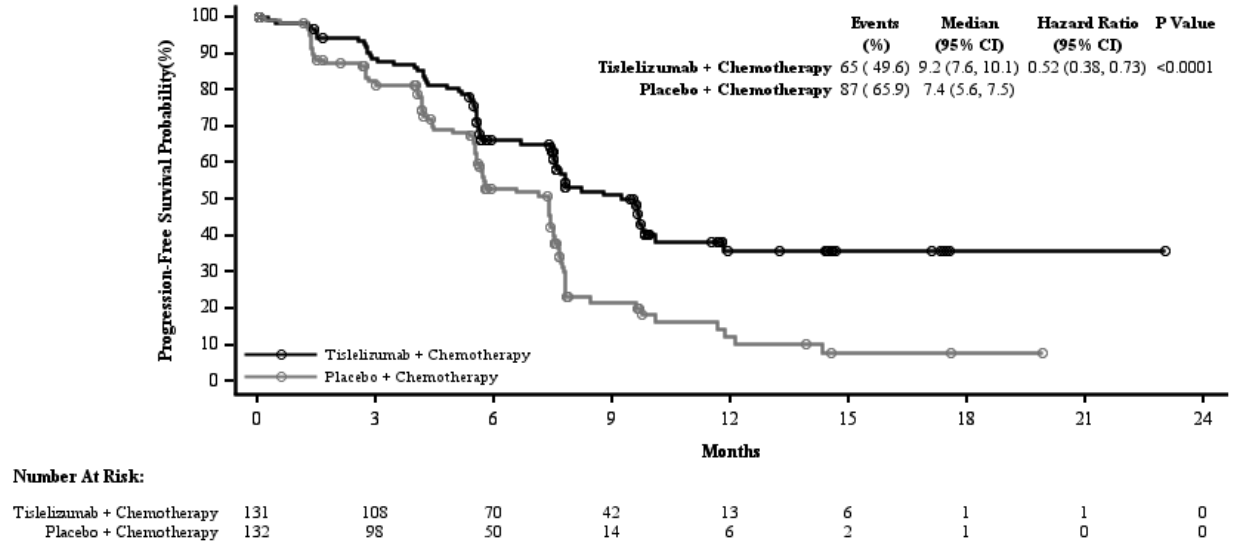
Table 9 Efficacy Results in RATIONALE-309 per RECIST version 1.1 by IRC (ITT analysis set) (data cut-off date of 26-Mar-2021)

End Point	Tislelizumab + Gemcitabine + Cisplatin (N = 131)	Placebo + Gemcitabine + Cisplatin (N = 132)
Progression Free Survival		
Events, n (%)	65 (49.6)	87 (65.9)
Median PFS (months) (95% CI) [a]	9.2 (7.6, 10.1)	7.4 (5.6, 7.5)
Stratified Hazard Ratio (95% CI) [b, c]	0.52 (0.38, 0.73)	
p-value[c, d]	<0.0001	
Overall Survival		
Deaths, n (%)	18 (13.7)	16 (12.1)
Median (months) (95% CI) [a]	NR (NE, NE)	NR (NE, NE)
HR (95% CI) [b, c]	0.97 (0.49, 1.92)	
Objective Response Rate		
Objective Response Rate, n (%)	91 (69.5)	73 (55.3)
95% CI[e]	(60.8, 77.2)	(46.4, 64)
Complete Response, n(%)	21 (16)	9 (6.8)
Partial Response, n (%)	70 (53.4)	64 (48.5)
Duration of Response (months)		
Median DOR (95% CI) [a]	8.5 (6.5, NE)	6.1 (4.7, 6.2)

Abbreviations: NR= not reached; NE = not estimable.

[a] Medians and other quartiles were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley
[b] estimated from stratified Cox model
[c] stratified by gender and liver metastases status (with versus without)
[d] one-sided p-value from log-rank test
[e] 95% CI was calculated using Clopper-Pearson method.

Figure 9: Kaplan-Meier Plot of Progression-Free Survival in BGB-A317- 309 per RECIST version 1.1 by Independent Review Committee (ITT Analysis Set)*



**Chemotherapy = Gemcitabine + Cisplatin*

An updated analysis (data cut-off date of 08-Dec-2023) showed consistent efficacy results with the interim analysis (Table 10 and Figure 10). At this time, 52.3% of patients in the control arm had crossed over to receive tislelizumab monotherapy. The median OS follow-up times by reverse Kaplan-Meier method were 41.4 months in the tislelizumab plus chemotherapy arm and 40.8 months in the placebo plus chemotherapy arm. Data from NPC patients aged 65 years or older are too limited to draw conclusions in this population.

Table 10: Efficacy results in BGB-A317-309 (ITT Analysis Set) – Updated Analysis

Endpoint	**Tislelizumab + Chemotherapy (N=131)**	**Placebo + Chemotherapy (N=132)**
PFS by IRC		
Events, n (%)	95 (72.5)	106 (80.3)
Median PFS (months) (95% CI)[a]	9.6 (7.6, 11.6)	7.4 (5.6, 7.6)
Stratified Hazard Ratio (95% CI)[b]	0.53 (0.39, 0.71)	
OS		
Deaths, n (%)	55 (42.0)	64 (48.5)
Median (months) (95% CI) [a]	45.3 (33.4, NE)	31.8 (25.0, NE)
Stratified Hazard Ratio (95% CI) [b]	0.73 (0.51, 1.05)	
ORR by IRC (%) (95% CI)[c]	68.7 (60.0, 76.5)	55.3 (46.4, 64.0)

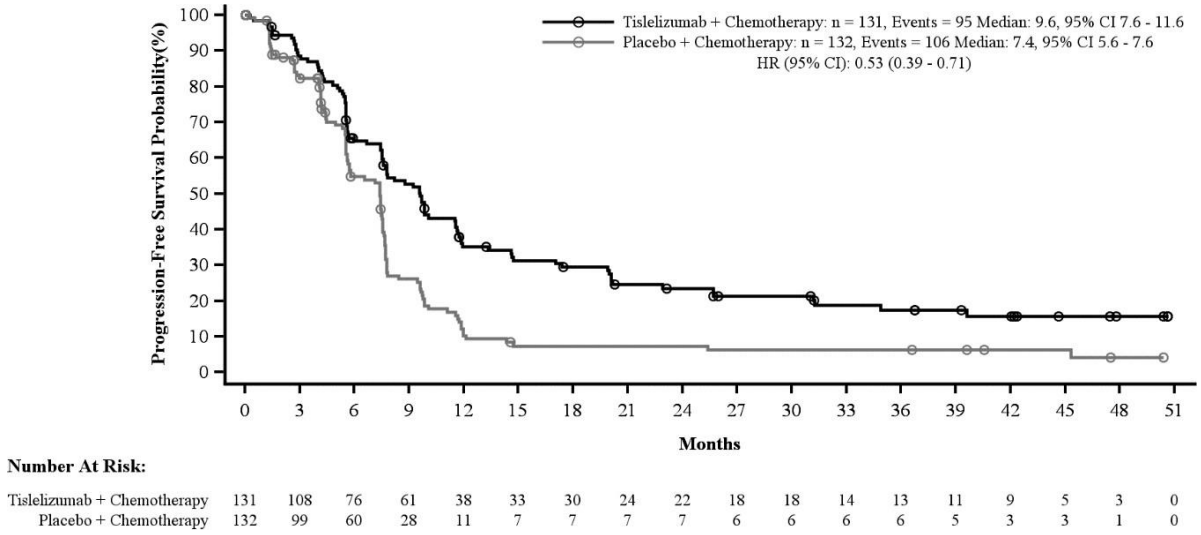
Abbreviations: NE = not estimable; OS = overall survival; CI = confidence interval; PFS = progression-free survival; ORR = objective response rate.

[a] Medians were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley.

[b] Stratified by gender (male versus female) and liver metastases status (with versus without).

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

Figure 10 Kaplan-Meier plot of PFS in BGB-A317-309 by IRC (ITT Analysis Set) – Updated Analysis



** Chemotherapy = Gemcitabine + Cisplatin.*

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-linetreatment 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 were enrolled regardless of their tumour PD-L1 expression level, which was evaluated prospectively using the Ventana PD-L1(SP263) assay that identified PD-L1 staining on both tumour and tumour-associated immune cells at a central laboratory.

The study excluded patients who had squamous cell or undifferentiated or other histological type G/GEJ cancer; patients who had known HER-2 positive tumours; patients who had active leptomeningeal disease or uncontrolled brain metastasis; patients with active autoimmune disease or history of autoimmune disease that may relapse.

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 score ≥5% versus PD-L1 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 every 3 weeks or placebo in combination with platinum and fluoropyrimidine-based chemotherapy on a 21-day cycle. Tislelizumab (or placebo) was administered until disease progression or unacceptable toxicity.

Chemotherapy consisted of:

- oxaliplatin 130 mg/m² IV on day 1 and capecitabine 1 000 mg/m^2 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/m^2/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.

Cross-over between treatment arms was not allowed.

The primary efficacy endpoints were overall survival (OS) in the PD-L1 Positive Analysis Set (PD-L1score ≥5%) and ITT analysis set (all randomized 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 score ≥5%(tislelizumab + chemotherapy: n = 274; placebo + chemotherapy: n = 272).

The baseline characteristics for the study population were: median age of 61 years (range: 23 to 86),34.5% age 65 years or older; 69.4% male; 22.4% White and 75% Asian; 32.4% with ECOG PS of 0 and 67.6% with ECOG PS of 1. A total of 80.2% patients had primary tumour location of stomach;98.7% of patients had metastatic disease at baseline; 37.9% and 43.5% patients had liver metastasis and peritoneal metastasis, respectively.

At prespecified interim analysis, with a minimum study follow-up of 7.9 months, BGB-A317-305 demonstrated a statistically significant and clinically meaningful improvement in OS for patients randomised to the tislelizumab + chemotherapy arm as compared to the placebo + chemotherapy armin patients with PD-L1 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 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 plus chemotherapy compared to 5.9 months for placebo plus chemotherapy.

At prespecified final analysis, with a minimum study follow-up of 24.6 months, BGB-A317-305 demonstrated a statistically significant and clinically meaningful improvement for all randomized 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. At final analysis, the updated results of OS in patients with PD-L1 score ≥5% were consistent with its primary analysis results (stratified HR 0.71, 95% CI: 0.58 to 0.86).

The final analysis efficacy results from patients with PD-L1 score ≥5% and all randomized patients are shown in Table 11 and in Figures 11 and 12.

Table 11 Efficacy results in BGB-A317-305 (final analysis)

	Tislelizumab + chemotherapy (N = 274)	Placebo + chemotherapy (N = 272)	Tislelizumab + chemotherapy (N = 501)	Placebo + chemotherapy (N = 496)
	Patients with PD-L1 score ≥5%		**All randomized patients**	
Minimum study follow-up (months)	24.6		24.6	
OS				
Death, n (%)	192 (70.1)	219 (80.5)	370 (73.9)	406 (81.9)
Median[a] (months) (95% CI)	16.4 (13.6, 19.1)	12.8 (12.0, 14.5)	15.0 (13.6, 16.5)	12.9 (12.1, 14.1)
Hazard ratio[b] (95% CI)	0.71 (0.58, 0.86)		0.80 (0.70, 0.92)	
p-value[b,c]	0.0003[d]		0.0011	
OS event free rate[e]				
12 months (95% CI)	59.3 (53.2, 65.0)	56.4 (50.2, 62.2)	57.9 (53.4, 62.2)	55.3 (50.8, 59.7)
24 months (95% CI)	37.8 (31.9, 43.6)	21.1 (16.3, 26.3)	32.7 (28.5, 36.9)	23.4 (19.7, 27.3)
PFS				
Disease progression or death,n (%)	189 (69.0)	216 (79.4)	361 (72.1)	391 (78.8)
Median[a] (months) (95% CI)	7.2 (5.8, 8.4)	5.9 (5.6, 7.0)	6.9 (5.7, 7.2)	6.2 (5.6, 6.9)
Hazard ratio[b] (95% CI)	0.68 (0.56, 0.83)		0.78 (0.67, 0.90)	
PFS event-free rate[e]				
12 months (%), (95% CI)	34.2 (28.1, 40.3)	19.4 (14.6, 24.8)	30.7 (26.4, 35.1)	21.5 (17.6, 25.5)
24 months (%), (95% CI)	21.5 (16.3, 27.2)	9.8 (6.3, 14.2)	17.6 (14.0, 21.5)	9.1 (6.5, 12.3)
ORR				
ORR, n (%) (95% CI)	141 (51.5) (45.4, 57.5)	116 (42.6) (36.7, 48.8)	237 (47.3) (42.9, 51.8)	201 (40.5) (36.2, 45.0)
CR, n (%)	12 (4.4)	7 (2.6)	19 (3.8)	19 (3.8)
PR, n (%)	129 (47.1)	109 (40.1)	218 (43.5)	182 (36.7)
SD, n (%)	90 (32.8)	104 (38.2)	185 (36.9)	197 (39.7)
DoR				
Median[a] (months) (95% CI)	10.0 (8.2, 16.8)	6.9 (5.7, 8.5)	8.6 (7.9, 11.1)	7.2 (6.0, 8.5)
DoR event-free rate[e]				
12 months (95% CI)	46.0 (37.2, 54.2)	29.8 (21.2, 38.8)	40.1 (33.6, 46.6)	33.8 (26.9, 40.8)
24 months (95% CI)	32.4 (24.4, 40.6)	19.6 (12.4, 28.1)	29.2 (23.1, 35.5)	19.1 (13.5, 25.4)

OS = overall survival; CI = confidence interval; PFS = progression-free survival; ORR = objective response rate; CR = complete response; PR = partial response; SD = stable disease; DoR = duration of response.

[a] Medians were estimated using Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley.

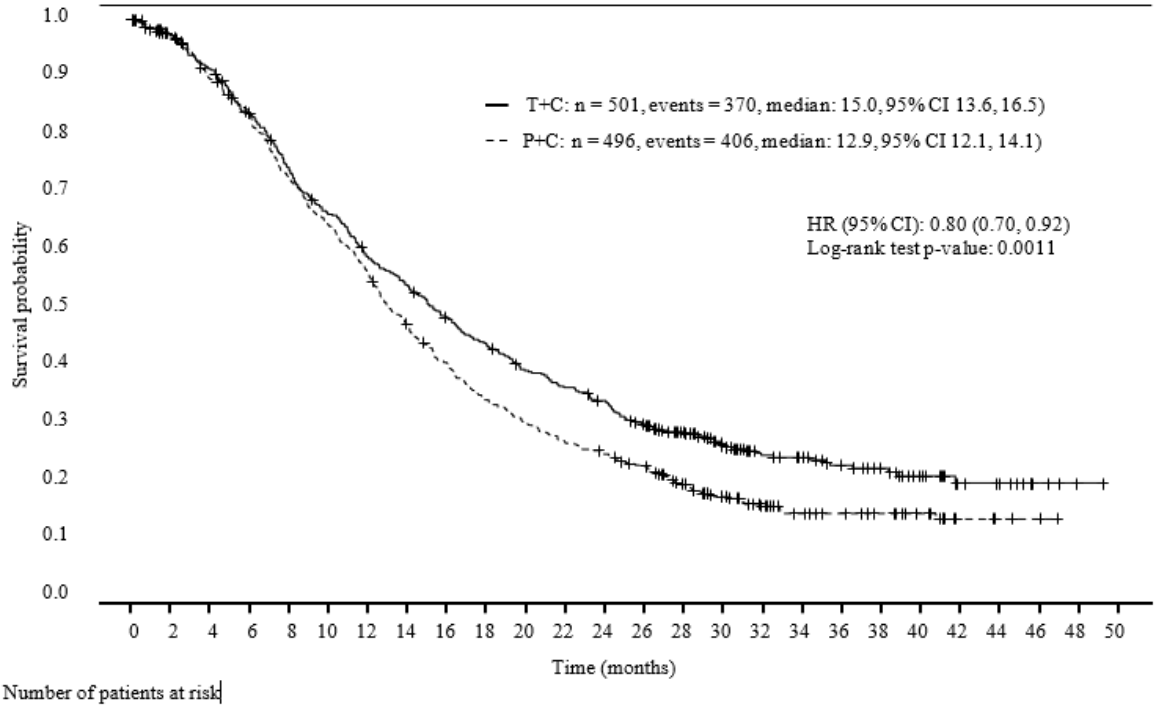
[b] Stratified by regions (east Asia versus ROW including US, Europe, and other regions) and peritoneal metastasis, and for the ITT analysis by PD-L1 expression.

[c] One-sided p-value from stratified log-rank test.

[d] Nominal p-value.

[e] Event-free rates were estimated using Kaplan-Meier method with 95% CIs estimated using Greenwood's formula.

Figure 11 Kaplan-Meier plot of OS in BGB-A317-305 (all randomized patients, final analysis)

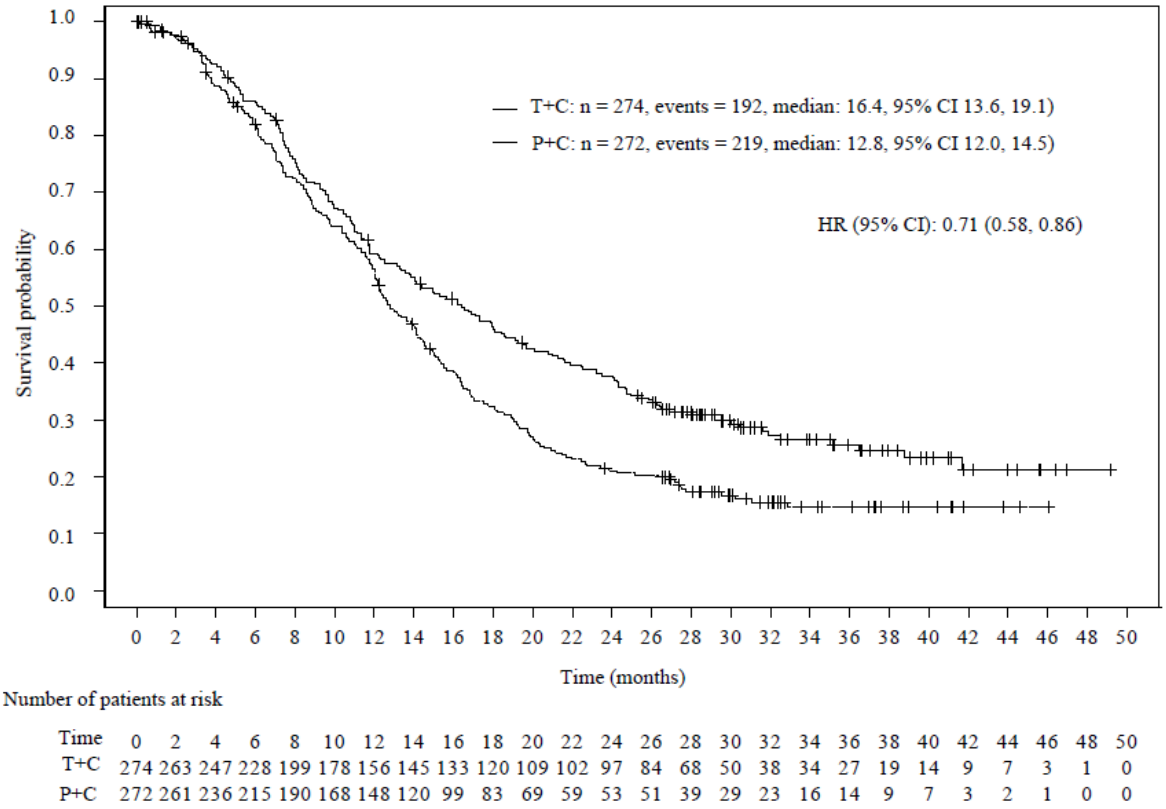


Number of patients at risk

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	501	477	445	404	355	316	278	254	226	202	179	165	152	130	107	77	59	53	43	31	22	13	10	4	1	0
P+C	496	472	431	398	344	304	264	218	186	155	136	119	109	96	73	52	39	29	25	20	15	6	3	2	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 other regions) and presence of peritoneal metastasis. P-value is one sided and is based on the stratified log rank test.

Figure 12 Kaplan-Meier plot of OS in BGB-A317-305 (patients with PD-L1 score ≥5%, final analysis)



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 other regions) and presence of peritoneal metastasis.

Subgroup analyses demonstrated a consistent OS benefit with tislelizumab + chemotherapy over placebo + chemotherapy across subgroups, including age, gender, investigator choice of chemotherapyoptions (oxaliplatin + capecitabine or cisplatin + 5-fluorouracil), ECOG status, geographical region (Asia versus rest of the world (ROW) including US and Europe), baseline PD-L1 status and race.

In a pre-specified analysis of OS in patients with PD-L1 score <5% (n = 451), the stratified HR for OS was 0.92 (95% CI: 0.75 to 1.13). Median OS was 14.1 months and 12.9 months for the tislelizumab + chemotherapy and placebo + chemotherapy arms, respectively.

HRQoL was assessed using the validated questionnaires, including EORTC QLQ-C30 (specific to cancer and cancer treatment), QLQ-STO22 (specific to gastric cancer) and EQ-5D-5L (comprising adescriptive module and a visual analogue scale, VAS). Completion rates for all three questionnaires were high, and were similar for both arms at baseline, cycle 4 and cycle 6, with adjusted completionrates all above 91% at cycle 4, and all above 96% at cycle 6.

Changes in scores from baseline to cycles 4 and 6 indicated improved HRQoL outcomes as indicated by improvements in mean change from baseline for Global Health Status (GHS)/QoL, physical functioning, fatigue, pain/discomfort, upper gastrointestinal symptoms, and general gastric cancer (GC) symptoms in the tislelizumab + chemotherapy arm as compared to the placebo + chemotherapy arm. Both arms had similar decreases in dysphagia/odynophagia and dietary restrictions scores at cycle 4 which were maintained at cycle 6.

Results of the mixed-effects model analyses showed that patients in the tislelizumab + chemotherapy arm reported improved HRQoL outcomes in key patient reported outcome (PRO) endpoints comparedto the placebo + chemotherapy arm, as indicated by the difference in LS mean change for GHS/QoL, physical function, fatigue and general GC symptom index score by cycle 6. In addition, upper gastrointestinal symptoms and pain/discomfort scores were maintained in the tislelizumab + chemotherapy arm. Patients in both arms experienced similar changes in the symptoms of dysphagia/odynophagia and dietary restrictions.

The analysis results for time to deterioration (TTD), indicated by stratified HR (95% CI), showed that tislelizumab plus chemotherapy treatment was associated with a numerically lower risk for deteriorating events in GHS/QoL (0.77 [95% CI: 0.60 to 0.98]), physical functioning (0.72 [95% CI: 0.57 to 0.92]), general GC symptoms (0.64 [95% CI: 0.45 to 0.92]), pain/discomfort (HR: 0.74 [95% CI: 0.58 to 0.96]) and upper gastrointestinal symptoms (0.73 [95% CI: 0.56 to 0.95]). There were no numerical differences between the arms in risk of deterioration for fatigue, dysphagia/odynophagia, and dietary restrictions.

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 2 596 patients with advanced malignancies who received tislelizumab doses of 0.5 to 10 mg/kg every 2 weeks, 2.0 and 5.0 mg/kg every 3 weeks, and 200 mg every 3 weeks.

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

Absorption

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

Distribution

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

Biotransformation

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

Elimination

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

Linearity/non-linearity

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

Special populations

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

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

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

5.3 Preclinical safety data

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

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vial

3 years.

After opening

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

After preparation of solution for infusion

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, unless the method of dilution precludes the risk of microbial contamination, the product should be used immediately.

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

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

Do not freeze.

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

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

6.5 Nature and contents of container

10 ml of 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.

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. PRODUCT OWNER

BeiGene Switzerland GmbH
Aeschengraben 27, 4051 Basel
Switzerland

8. DATE OF REVISION OF THE TEXT

30 June 2025