NEW ZEALAND DATA SHEET
TEVIMBRA® (tislelizumab (rch))

1 PRODUCT NAME

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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each TEVIMBRA 10 mL single dose vial contains 100 mg of tislelizumab in 10 mL solution, with a concentration of 10 mg/mL.

Tislelizumab is produced in Chinese hamster ovary cells by recombinant DNA technology.

Excipient(s) 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 List of excipients.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear to slightly opalescent, colorless to slightly yellow solution.

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

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Oesophageal squamous cell carcinoma (OSCC)

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

Non-small cell lung cancer (NSCLC)

TEVIMBRA in combination with pemetrexed and platinum containing chemotherapy is indicated for the first-line treatment of patients with locally advanced or metastatic non-squamous non-small cell lung cancer (NSCLC), with PD-L1 expression ≥ 50% but no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumour aberrations.

TEVIMBRA in combination with carboplatin and either paclitaxel or nab-paclitaxel is indicated for the first-line treatment of patients with locally advanced or metastatic squamous NSCLC.

TEVIMBRA as monotherapy is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy.

4.2 DOSE AND METHOD OF ADMINISTRATION

TEVIMBRA should be administered under the supervision of a physician experienced in the use of cancer therapy.

TEVIMBRA is for single use in one patient only. Discard any residue after use.

Dosage

The recommended dose of TEVIMBRA is 200 mg administered as an intravenous infusion once every 3 weeks.

The first infusion should be administered over 60 minutes. If this is well tolerated, the subsequent infusions may be administered over a period of 30 minutes.

When TEVIMBRA is used in combination, refer to the full prescribing information of the combination therapy. When administering TEVIMBRA in combination with chemotherapy, administer TEVIMBRA before chemotherapy when both are given on the same day.

Table 1 Recommended dose for TEVIMBRA

Indication	**Recommended dose and schedule**	**Duration of treatment**
Tradename monotherapy		
Second-line OSCC	200 mg every 3 weeks	Until disease progression or unacceptable toxicity. For patients who are considered to be deriving clinical benefit despite initial evidence of disease progression, it is recommended to continue TEVIMBRA treatment until disease progression is confirmed.
Second-line NSCLC		
Tradename combination therapy		
First-line NSCLC	200 mg every 3 weeks	Until disease progression or unacceptable toxicity. For patients who are considered to be deriving clinical benefit despite initial evidence of disease progression, it is recommended to continue TEVIMBRA treatment until disease progression is confirmed.

Treatment modifications for adverse drug reactions

No dose reductions of TEVIMBRA as monotherapy or in combination therapy are recommended. Withhold or permanently discontinue TEVIMBRA depending on the severity of the adverse drug reaction (ADR).

Recommended treatment modifications to manage immune-related ADRs are provided in Table 2.

Detailed guidelines for the management of immune-related adverse reactions are described in section 4.4 Special warnings and precautions for use.

Table 2 Recommended treatment modifications for TEVIMBRA

Immune-related ADR	**Severity[1]**	**TEVIMBRA treatment modification**
Pneumonitis	Grade 2	Withhold[2]
	Recurrent Grade 2; Grade 3 or 4	Permanently discontinue
Hepatitis	ALT or AST >3 and up to 8 times ULN (or) total bilirubin >1.5 and up to 3 times ULN	Withhold[2]
	ALT or AST >8 times ULN (or)	Permanently discontinue

Immune-related ADR	**Severity[1]**	**TEVIMBRA treatment modification**
	total bilirubin >3 times ULN	
Rash	Grade 3	Withhold[2]
	Grade 4	Permanently discontinue
Severe cutaneous adverse reactions (SCARs)	Suspected SCARs, including SJS or TEN	Withhold[2] For suspected SCARs (SJS or TEN), do not resume unless SJS/TEN has been ruled out in consultation with appropriate specialist.
	Confirmed SCARs, including SJS or TEN	Permanently discontinue
Colitis	Grade 2 or 3	Withhold[2]
	Recurrent Grade 3; Grade 4	Permanently discontinue
Myositis/Rhabdomyolysis	Grade 2 or 3	Withhold[2]
	Recurrent Grade 3; Grade 4	Permanently discontinue
Endocrinopathies	Hypothyroidism	Hypothyroidism may be managed with replacement therapy without treatment interruption
	Grade 3 or 4 adrenal insufficiency or symptomatic hypophysitis; Hyperthyroidism Grade ≥3	Withhold[2] Grade 3 or Grade 4 that improved to Grade ≤2 and are controlled with HRT, if indicated, continuation of TEVIMBRA may be considered after corticosteroid taper, if needed. Otherwise, treatment should be discontinued.
	Diabetes mellitus associated with Grade ≥3 hyperglycemia (glucose >250 mg/dL or >13.9 mmol/L) or associated with ketoacidosis	Withhold[2] Grade 3 or 4 that 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.
	Grade 2 adrenal insufficiency and hypophysitis	Consider withholding treatment until controlled by HRT.
Nephritis with renal dysfunction	Grade 2 (creatinine >1.5 to 3 times baseline or >1.5 to 3 times ULN)	Withhold[2]
	Grade 3 (creatinine >3 times baseline or >3 to 6 times ULN) Grade 4 (creatinine >6 times ULN)	Permanently discontinue
Myocarditis	Grade 2, 3, or 4	Permanently discontinue
Neurological toxicities	Grade 2	Withhold[2]
	Grade 3 or 4	Permanently discontinue

Immune-related ADR	Severity[1]	TEVIMBRA treatment modification
Pancreatitis	Grade 3 pancreatitis or Grade 3 or Grade 4 serum amylase or lipase levels increased (>2 times ULN)	Withhold[2]
	Grade 4	Permanently discontinue
Other immune-related ADRs	Grade 3	Withhold[2]
	Recurrent Grade 3; Grade 4	Permanently discontinue
Other ADRs		
Infusion-related reactions	Grade 1	Consider premedication for prophylaxis of subsequent infusion reactions. Slow the rate of infusion by 50%.
	Grade 2	Interrupt infusion[3]
	Grade 3 or 4	Permanently discontinue

ALT = alanine aminotransferase, AST = aspartate aminotransferase, BSA = body surface area, 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 4.03 (NCI-CTCAE v4).

[2] Resume in patients with complete or partial resolution (Grades 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating corticosteroids or inability to reduce prednisone to 10 mg per day or less (or equivalent) within 12 weeks of initiating corticosteroids.

[3] Resume infusion if resolved or decreased to Grade 1 and slow the rate of infusion by 50%.

Special populations

Patients with Renal Impairment

Based on population pharmacokinetic analysis, no dose adjustment of TEVIMBRA is necessary in patients with mild or moderate renal impairment. Data from patients with severe renal impairment are too limited to draw conclusions for this population (see section 5.2 Pharmacokinetic properties).

Patients with Hepatic Impairment

Based on population pharmacokinetic analysis, no dose adjustment of TEVIMBRA is necessary in patients with mild or moderate hepatic impairment. Data from patients with severe hepatic impairment are too limited to draw conclusions for this population (see section 5.2 Pharmacokinetic properties).

Use in Children

The efficacy and safety of TEVIMBRA has not been established in patients below 18 years.

Use in the Elderly

No dose adjustment of TEVIMBRA is required in patients ages 65 years or above (see section 5.2 Pharmacokinetic properties).

Method of administration

TEVIMBRA is for intravenous infusion use only. The diluted solution must be administered by infusion, 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.

The initial TEVIMBRA infusion should be administered over a period of 60 minutes. If this is well-tolerated, subsequent infusions may be administered over a period of 30 minutes.

TEVIMBRA must not be administered as an intravenous push or bolus injection.

For instructions on the dilution of TEVIMBRA before administration, see section 6.6 Special precautions for disposal.

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

When TEVIMBRA is administered in combination with chemotherapy, it should be administered before chemotherapy when both are given on the same day. Refer to the New Zealand Data Sheet(s) for the chemotherapy administered in combination with TEVIMBRA.

4.3 CONTRAINDICATIONS

Hypersensitivity to tislelizumab or any of the excipients listed in section 6.1 List of excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Immune-related adverse drug reactions

Immune-related ADRs, including severe and fatal cases, have been reported in patients treated with immune checkpoint inhibitors, including tislelizumab. Most immune-related adverse reactions occurring during treatment with tislelizumab were reversible and managed with interruptions of tislelizumab, administration of corticosteroids and/or supportive care. Immune-related adverse reactions have also occurred 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. Administration of other systemic immunosuppressants can be considered in patients whose immune-related adverse reactions are not controlled with corticosteroid therapy (see sections 4.2 Dose and method of administration and 4.8 Adverse effects (Undesirable effects)).

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 ruled out. Patients with immune-related pneumonitis should be managed according to treatment modifications in Table 2 (see section 4.2 Dose and method of administration) as well as applicable current local treatment guidelines.

Immune-related hepatitis

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

Patients with immune-related hepatitis should be managed according to treatment modifications in Table 2 (see section 4.2 Dose and method of administration) as well as applicable current local treatment guidelines.

Immune-related skin reactions

Immune-related skin rash or dermatitis have been reported in patients receiving tislelizumab. Patients should be monitored for signs and symptoms of 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 2 (see section 4.2 Dose and method of administration) as well as per applicable current local treatment guidelines.

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

Immune-related colitis

Immune-related colitis, frequently associated with diarrhea, 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 treatment modifications in Table 2 (see section 4.2 Dose and method of administration) as well as per applicable current local treatment guidelines.

Immune-related endocrinopathies

Immune-related endocrinopathies, including thyroid disorders, adrenal insufficiency, and hypophysitis have been reported with tislelizumab, which may require supportive treatment.

Patients with immune-related endocrinopathies should be managed according to treatment modifications as recommended in Table 2 (see section 4.2 Dose and method of administration) as well as applicable local treatment guidelines.

Thyroid disorders

Thyroid disorders, including hyperthyroidism, hypothyroidism and thyroiditis have been reported in patients treated with tislelizumab. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Patients should be monitored for changes in thyroid function (at the start of treatment, periodically during treatment and as indicated based on clinical evaluation) and clinical signs and symptoms of thyroid disorders. Hypothyroidism may be managed with hormone replacement therapy without treatment interruption and without corticosteroids. Hyperthyroidism may be managed symptomatically.

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 hormone replacement should be administered as clinically indicated.

Hypophysitis/hypopituitarism

Hypophysitis/hypopituitarism has been reported in patients treated with tislelizumab. Hypophysitis can cause hypopituitarism. Patients should be monitored for signs and symptoms of hypophysitis/hypopituitarism. Monitoring of pituitary function and hormone levels should be considered. Corticosteroids and hormone replacement should be administered as clinically indicated.

Diabetes mellitus

Diabetes mellitus, including diabetic ketoacidosis has been reported in patients treated with tislelizumab. Patients should be monitored for hyperglycaemia or other signs and symptoms of diabetes. Insulin should be administered as clinically indicated for 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 Dose and method of administration). Treatment with tislelizumab should be resumed when metabolic control is achieved.

Immune-related nephritis with renal dysfunction

Immune-related nephritis with renal disfunction 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 treatment modifications in Table 2 (see section 4.2 Dose and method of administration) as well as applicable current local treatment guidelines.

Other immune-related adverse reactions

Other clinically important immune-related adverse reactions were reported in patients treated with tislelizumab: myositis, myocarditis, arthritis, polymyalgia rheumatica, pericarditis, immune thrombocytopenia, encephalitis, myasthenia gravis, Sjogren’s syndrome and Guillain-Barré syndrome (see 4.8 Adverse effects (Undesirable effects)).

Patients with other immune-related adverse reactions should be managed according to treatment modifications Table 2 (see section 4.2 Dose and method of administration) as well as applicable current local treatment guidelines.

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. Cases of anaphylaxis, including anaphylactic reaction and anaphylactic shock, have been reported in the post-marketing setting. Patients should be monitored for signs and symptoms of infusion-related reactions.

Infusion-related reactions should be managed as recommended in Table 2 (see section 4.2 Dose and method of administration).

Embryo-fetal toxicity

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

Animal studies have demonstrated that inhibition of PD-1/PD-L1 pathway can lead to increased risk of immune-related rejection of the developing fetus resulting in fetal death.

Women should be advised of the potential risk to a fetus. Tislelizumab should not be used during pregnancy and in women of childbearing potential not using effective contraception unless the clinical condition of the woman requires treatment with tislelizumab.

Sexually-active females of reproductive potential should be advised to use effective contraception (methods that result in less than 1% pregnancy rates) during treatment with tislelizumab and for at least 4 months after the last dose of tislelizumab (see section 4.6 Fertility, pregnancy and lactation).

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, which is equivalent to 0.8% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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 TEVIMBRA. TEVIMBRA is not expected to inhibit or induce CYP or other drug metabolising enzymes.

The use of systemic corticosteroids and other immunosuppressants at baseline, before starting TEVIMBRA, 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 TEVIMBRA to treat immune-related adverse reactions (see section 4.4 Special warnings and precautions for use).

Corticosteroids can also be used as pre-medication when TEVIMBRA is used in combination with chemotherapy, as antiemetic prophylaxis and/or to alleviate chemotherapy-related adverse reactions.

4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy

There are no available data on the use of tislelizumab in pregnant women. Based on its mechanism of action, there is a potential risk that administration of tislelizumab during pregnancy may result in foetal harm.

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. Tislelizumab is not recommended during pregnancy unless the clinical benefit is expected to outweigh the potential risk to the foetus. Effective contraception (methods that result in less than 1% pregnancy rates) should be used for at least 4 months following the last dose of tislelizumab.

Breast-feeding

It is unknown whether tislelizumab is excreted in human milk but it is known that antibodies (including IgG4) are excreted in human milk. The effects of tislelizumab on breast-fed newborns/infants and on milk production are also unknown.

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

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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

TEVIMBRA has a minor influence on the ability to drive and use machines. In some patients, fatigue has been reported following administration of TEVIMBRA (see section 4.8 Adverse effects (Undesirable effects)).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile

Tislelizumab as monotherapy

The safety of TEVIMBRA 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 drug reactions (ADR) (reported at a frequency >20%, with TEVIMBRA as monotherapy) were anaemia, increased aspartate aminotransferase, fatigue and increased alanine aminotransferase. The most common grade 3/4 ADRs (reported at a frequency >2%, with TEVIMBRA as monotherapy) were anaemia, increased aspartate aminotransferase, pneumonia, hyponatraemia, increased blood bilirubin, hypertension and fatigue.

ADRs leading to death were reported in 1.0% of patients. The ADRs leading to death were pneumonia (0.6%), thrombocytopenia (0.1%), decreased appetite (0.1%), hepatitis (0.1%), pneumonitis (0.1%) and dyspnoea (0.1%).

Tislelizumab as combination therapy

The safety of TEVIMBRA given in combination with chemotherapy is based on data in 1,950 patients treated with tislelizumab in combination with chemotherapy. TEVIMBRA was administered at a dose of 200 mg every 3 weeks in combination with chemotherapy. The most common ADRs (reported at a frequency >20%, with TEVIMBRA in combination with chemotherapy) were neutropenia, anaemia, thrombocytopenia, nausea, fatigue. decreased appetite, increased alanine aminotransferase, increased aspartate aminotransferase, rash, and diarrhoea. The most common Grade 3/4 ADRs (reported at a frequency >2%, with TEVIMBRA in combination with chemotherapy) were neutropenia, anaemia,

thrombocytopenia, hyponatraemia, hypokalemia, fatigue, pneumonia, lymphopenia, rash, decreased appetite, increased alanine aminotransferase and increased aspartate aminotransferase.

ADRs leading to death were reported in 0.8% of patients. The ADRs leading to death were pneumonitis (0.3%), myocarditis (0.2%), dyspnoea (0.2%), hepatitis (0.1%), colitis (0.1%), hypokalaemia (0.1%) and myositis (0.1%).

Tabulated list of adverse reactions

Table 3 lists the incidence of adverse reactions in the monotherapy safety dataset and in patients treated with TEVIMBRA in combination with chemotherapy. ADRs are listed according to system organ class in MedDRA. Within each system organ class, the adverse drug reactions are presented in decreasing frequency.

Table 3 Adverse drug reactions with TEVIMBRA as monotherapy (N = 1,952) and in combination with chemotherapy (N = 1,950)

	Tislelizumab monotherapy N = 1,952	**Tislelizumab combination therapy N = 1,950**
Adverse drug reactions	**All Grades n (%)**	**All Grades n (%)**
Infections and infestations		
Pneumonia[1]	186 (9.5)*	227 (11.6)
Blood and lymphatic system disorders		
Anaemia[2]	541 (27.7)	1311 (67.2)
Thrombocytopenia[3]	212 (10.9)*	949 (48.7)
Neutropenia[4]	136 (7.0)	1397 (71.6)
Lymphopenia[5]	88 (4.5)	200 (10.3)
Immune system disorders		
Sjogren's syndrome	-	2 (0.1)
Immune-mediated cystitis[#]	-	-
Endocrine disorders		
Hypothyroidism[6]	276 (14.1)	311 (15.9)
Hyperthyroidism[7]	128 (6.6)	152 (7.8)
Thyroiditis[8]	21 (1.1)	14 (0.7)
Adrenal insufficiency[9]	11 (0.6)	17 (0.9)
Hypophysitis[10]	3 (0.2)	9 (0.5)
Metabolism and nutrition disorders		
Hyperglycaemia[11]	186 (9.5)	204 (10.5)
Hyponatraemia[12]	182 (9.3)	364 (18.7)
Hypokalaemia[13]	158 (8.1)	334 (17.1)*
Diabetes mellitus[14]	19 (1.0)	32 (1.6)
Nervous system disorders		
Guillain-Barré syndrome	1 (0.1)	1 (0.1)
Encephalitis[15]	-	1 (0.1)
Myasthenia gravis	-	1 (0.1)
Eye disorders		
Uveitis[16]	5 (0.3)	3 (0.2)
Cardiac disorders		
Myocarditis[17]	14 (0.7)	23 (1.2)*
Pericarditis	-	1 (0.05)
Vascular disorders		

Hypertension[18]	117 (6.0)	115 (5.9)
Respiratory, thoracic and mediastinal disorders		
Cough	298 (15.3)	293 (15.0)
Dyspnoea	136 (7.0)*	180 (9.2)*
Pneumonitis[19]	101 (5.2)*	151 (7.7)*
Gastrointestinal disorders		
Diarrhoea[20]	197 (10.1)	395 (20.3)
Nausea	196 (10.0)	844 (43.3)
Stomatitis[21]	64 (3.3)	181 (9.3)
Pancreatitis[22]	18 (0.9)	54 (2.8)
Colitis[23]	14 (0.7)	20 (1.0)*
Hepatobiliary disorders		
Hepatitis[24]	54 (2.8)*	73 (3.7)*
Skin and subcutaneous tissue disorders		
Rash[25]	319 (16.3)	418 (21.4)
Pruritus	215 (11.0)	198 (10.2)
Vitiligo[26]	13 (0.7)	6 (0.3)
Erythema multiforme	3 (0.2)	1 (0.1)
Stevens-Johnson syndrome	1 (0.1)	-
Toxic epidermal necrolysis[#]	-*	-*
Musculoskeletal and connective tissue disorders		
Arthralgia	180 (9.2)	227 (11.6)
Myalgia	35 (1.8)	80 (4.1)
Myositis[27]	16 (0.8)	14 (0.7)*
Arthritis[28]	18 (0.9)	21 (1.1)
Renal and urinary disorders		
Nephritis[29]	4 (0.2)	8 (0.4)
General disorders and administration site conditions		
Fatigue[30]	481 (24.6)	796 (40.8)
Pyrexia[31]	314 (16.1)	360 (18.5)
Decreased appetite	290 (14.9)*	782 (40.1)
Investigations		
Aspartate aminotransferase increased	482 (24.7)	590 (30.3)
Alanine aminotransferase increased	430 (22.0)	597 (30.6)
Blood bilirubin increased[32]	303 (15.5)	271 (13.9)
Blood alkaline phosphatase increased	165 (8.5)	132 (6.8)
Blood creatinine increased	104 (5.3)	214 (11.0)
Injury, poisoning and procedural complications		
Infusion-related reaction[33]	58 (3.0)	123 (6.3)

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

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

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

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

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

[6] Hypothyroidism includes preferred terms (PTs) of hypothyroidism, immune-mediated hypothyroidism, anti-thyroid antibody increased, thyroxine free decreased, tri-iodothyronine free decreased, tri-iodothyronine decreased, anti-thyroid antibody increased, thyroid hormones decreased, primary hypothyroidism and thyroxine decreased.

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

[8] Thyroiditis includes PTs of thyroiditis, autoimmune thyroiditis, immune-mediated thyroiditis, silent thyroiditis, and thyroiditis subacute.

[9] Adrenal insufficiency includes PTs of adrenal insufficiency, Addison's disease, glucocorticoid deficiency, immune-mediated adrenal insufficiency, primary adrenal insufficiency, and secondary adrenocortical insufficiency.

[10] Hypophysitis includes PTs of hypopituitarism and lymphocytic 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, type 1 diabetes mellitus, diabetic ketoacidosis, diabetic ketosis, ketoacidosis and latent autoimmune diabetes in adults.

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

[16] Uveitis includes PTs of uveitis and iritis.

[17] Myocarditis includes PTs of myocarditis, immune-mediated myocarditis and autoimmune myocarditis.

[18] Hypertension includes PTs of hypertension and 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 and aphthous ulcer.

[22] Pancreatitis includes PTs of amylase increased, lipase increased, pancreatitis, autoimmune pancreatitis and pancreatitis acute.

[23] Colitis includes PTs of colitis, immune-mediated enterocolitis, colitis ulcerative and autoimmune colitis.

[24] Hepatitis includes PTs of hepatitis, hepatitis function abnormal, immune-mediated hepatitis and liver injury and autoimmune hepatitis.

[25] Rash includes PTs of rash, rash maculo-papular, eczema, rash erythematous, dermatitis, dermatitis exfoliative, dermatitis allergic, rash papular, urticaria, erythema, skin exfoliation, drug eruption, rash macular, psoriasis, rash pustular, dermatitis acneiform, rash pruritic, lichenoid keratosis, hand dermatitis, immune mediated dermatitis, autoimmune dermatitis, rash follicular, acute febrile neutrophilic dermatosis, erythema nodosum, granulomatous dermatitis, nodular rash, pemphigoid and transient acantholytic dermatosis.

[26] Vitiligo includes PTs of vitiligo, skin hypopigmentation, skin depigmentation, and leukoderma.

[27] Myositis includes PTs of myositis, immune-mediated myositis and polymyalgia rheumatica.

[28] Arthritis includes PTs of arthritis, immune-mediated arthritis and polyarthritis.

[29] Nephritis includes PTs of nephritis, focal segmental glomerulosclerosis, glomerulonephritis membranous, tubulointerstitial nephritis immune-mediated renal disorder and immune-mediated nephritis.

[30] Fatigue includes PTs of fatigue, asthenia, malaise, physical deconditioning and lethargy.

[31] Pyrexia included reports of body temperature increased and pyrexia.

[32] Blood bilirubin increased includes PTs of blood bilirubin increased, bilirubin conjugated increased, blood bilirubin unconjugated increased and hyperbilirubinaemia.

[33] Infusion-related reaction includes PTs of infusion-related reaction and infusion-related hypersensitivity reaction.

[*] Including fatal outcomes

[#] Reported in the post-marketing setting.

Adverse events by indication

Oesophageal squamous cell carcinoma (OSCC)

The data described below reflect exposure to tislelizumab in 255 patients with oesophageal squamous cell carcinoma in RATIONALE-302. Patients received 200 mg of tislelizumab via intravenous infusion every 3 weeks [see 5.1 Pharmacodynamic properties (Clinical trials)]. The median duration of exposure to tislelizumab was 2.8 months (range: 0.2 to 28.3 months).

The most common adverse events (≥20%) were anaemia, fatigue (including asthenia, fatigue, and malaise), and weight decreased.

The most common ≥ Grade 3 adverse events (≥2%) were dysphagia, anaemia, hyponatremia, pneumonia, dyspnoea, lymphocyte count decreased, hypertension, fatigue (including asthenia, fatigue, and malaise), and pneumonitis (including pneumonitis and interstitial lung disease).

Serious adverse events occurred in 41.2% of patients; the most frequent serious adverse events (≥2%) were pneumonia, dysphagia, pneumonitis (including pneumonitis and immune-mediated pneumonitis), and oesophageal obstruction.

Fatal adverse events (excluding death due to disease under study) occurred in 5.5% of patients who received tislelizumab, including bronchiectasis, hemoptysis, pulmonary arterial hypertension, pulmonary embolism, pulmonary hemorrhage, sudden death, cardio-respiratory arrest, upper gastrointestinal hemorrhage, platelet count decreased (1 patient each), death due to an unknown cause (2 patients), and pneumonia (3 patients).

Adverse events leading to discontinuation of tislelizumab occurred in 19.2% of patients; the most common adverse events resulting in permanent discontinuation (≥1%) were pneumonitis (including pneumonitis and immune-mediated pneumonitis), pneumonia, and upper gastrointestinal hemorrhage.

Adverse events leading to the interruption of tislelizumab occurred in 22.7% of patients; the most common adverse events leading to interruption of tislelizumab (≥2%) were pneumonia, pneumonitis (including pneumonitis, interstitial lung disease, and immune-mediated pneumonitis) and fatigue (including asthenia and fatigue).

Adverse events are listed in Table 4.

Table 4 Adverse events (≥ 10%) in Patients Receiving tislelizumab in RATIONALE-302

	Tislelizumab (N = 255)		**ICC (N = 240)**	
System Organ Class Preferred Term	**All Grades n (%)**	**≥ Grade 3 n (%)**	**All Grades n (%)**	**≥ Grade 3 n (%)**
Blood and Lymphatic system disorders	92 (36.1)	18 (7.1)	139 (57.9)	55 (22.9)
Anaemia	78 (30.6)	15 (5.9)	107 (44.6)	26 (10.8)
Endocrine Disorders	39 (15.3)	1 (0.4)	2 (0.8)	0 (0.0)
Hypothyroidism	29 (11.4)	1 (0.4)	1 (0.4)	0 (0.0)
Gastrointestinal Disorders	149 (58.4)	36 (14.1)	171 (71.3)	43 (17.9)

	Tislelizumab (N = 255)		ICC (N = 240)	
System Organ Class Preferred Term	**All Grades n (%)**	**≥ Grade 3 n (%)**	**All Grades n (%)**	**≥ Grade 3 n (%)**
Constipation	39 (15.3)	0 (0.0)	45 (18.8)	1 (0.4)
Nausea	36 (14.1)	1 (0.4)	72 (30.0)	8 (3.3)
Diarrhoea	32 (12.5)	3 (1.2)	77 (32.1)	15 (6.3)
Dysphagia	28 (11.0)	16 (6.3)	20 (8.3)	7 (2.9)
Vomiting	27 (10.6)	2 (0.8)	48 (20.0)	9 (3.8)
General Disorders and administration site conditions	116 (45.5)	9 (3.5)	147 (61.3)	18 (7.5)
Fatigue [a]	72 (28.2)	5 (2.0)	110 (45.8)	15 (6.3)
Pyrexia	41 (16.1)	1 (0.4)	34 (14.2)	0 (0.0)
Infections and Infestations	75 (29.4)	17 (6.7)	75 (31.3)	24 (10.0)
Pneumonia	36 (14.1)	11 (4.3)	27 (11.3)	14 (5.8)
Investigations	129 (50.6)	25 (9.8)	166 (69.2)	90 (37.5)
Weight decreased	59 (23.1)	3 (1.2)	45 (18.8)	0 (0.0)
Aspartate aminotransferase increased	37 (14.5)	3 (1.2)	11 (4.6)	1 (0.4)
Alanine aminotransferase	33 (12.9)	2 (0.8)	18 (7.5)	4 (1.7)
Metabolism and nutrition disorders	116 (45.5)	26 (10.2)	141 (58.8)	31 (12.9)
Decreased appetite	40 (15.7)	1 (0.4)	84 (35.0)	10 (4.2)
Hypoalbuminemia	34 (13.3)	2 (0.8)	30 (12.5)	2 (0.8)
Hyponatremia	32 (12.5)	14 (5.5)	33 (13.8)	10 (4.2)
Musculoskeletal and connective tissue disorders	66 (25.9)	5 (2.0)	61 (25.4)	4 (1.7)
Back pain	26 (10.2)	0 (0.0)	18 (7.5)	1 (0.4)
Respiratory, thoracic, and mediastinal disorders	104 (40.8)	20 (7.8)	81 (33.8)	16 (6.7)
Cough	43 (16.9)	0 (0.0)	28 (11.7)	1 (0.4)
Skin and subcutaneous tissue disorders	59 (23.1)	1 (0.4)	67 (27.9)	0 (0.0)
Rash [b]	33 (12.9)	1 (0.4)	15 (6.3)	0 (0.0)

ICC = Investigator chosen chemotherapy: paclitaxel vs docetaxel vs irinotecan
Adverse event Grades are evaluated based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v.4.03. Patients with multiple events for a given grouping term and system organ class are counted only once at the worst toxicity grade for the grouping term, and system organ class, respectively.

[a] Fatigue includes Asthenia, Fatigue, Malaise.

[b] Rash includes Dermatitis, Dermatitis acneiform, Dermatitis allergic, Eczema, Erythema, Psoriasis, Rash, Rash follicular, Rash maculo-papular, Rash pruritic.

Non-small cell lung cancer (NSCLC)

First-line treatment of metastatic non-squamous NSCLC in combination with pemetrexed and platinum chemotherapy

The data described below reflect exposure to tislelizumab in 222 patients with untreated locally advanced or metastatic non-squamous NSCLC in RATIONALE-304. Patients received tislelizumab 200 mg combined with pemetrexed 500 mg/m2 and carboplatin AUC 5 mg/mL/min or cisplatin 75 mg/m2 (T+PP arm) [see 5.1 Pharmacodynamic properties (Clinical trials)]. The median duration of exposure to tislelizumab was 34.14 weeks (range: 3.0 to 118.0 weeks).

The most common adverse events (≥50%) were anaemia, white blood cell count decreased, neutrophil count decreased, platelet count decreased, and alanine aminotransferase increased.

The most common ≥Grade 3 adverse events (≥5%) were neutropenia, anaemia, thrombocytopenia, leukopenia, neutrophil count decreased, white blood cell count decreased, platelet count decreased, and pneumonia.

Serious adverse events occurred in 39.2% of patients; the most frequent serious adverse events (≥2%) were pneumonitis, pneumonia, thrombocytopenia, platelet count decreased, pyrexia, and dyspnoea.

Fatal adverse events occurred in 4.1% of patients who received tislelizumab, including asphyxia, dyspnoea, atrial fibrillation, myocarditis, death, and cerebellar haemorrhage (1 patient each), and pneumonitis (3 patients).

Adverse events leading to discontinuation of tislelizumab occurred in 14.4% of patients; the most common adverse events resulting in permanent discontinuation (≥1%) were pneumonitis, and immune-mediated enterocolitis.

Adverse events leading to the treatment modification of tislelizumab occurred in 64.0% of patients; the most common adverse events leading to treatment modification of tislelizumab (≥5%) were anaemia, neutropenia, white blood cell count decreased, neutrophil count decreased, alanine aminotransferase increased, pneumonia, and pneumonitis.

Adverse events are listed in Table 5.

Table 5 Adverse Events (≥20%) in Patients Receiving tislelizumab in RATIONALE-304

	T+PP (N = 222)		**PP (N = 110)**	
System Organ Class Preferred Term	**All Grades n (%)**	**≥Grade 3 n (%)**	**All Grades n (%)**	**≥Grade 3 n (%)**
Investigations	209 (94.1)	85 (38.3)	101 (91.8)	22 (20.0)
White blood cell count decreased	158 (71.2)	30 (13.5)	62 (56.4)	5 (4.5)
Neutrophil count decreased	146 (65.8)	57 (25.7)	55 (50.0)	14 (12.7)
Platelet count decreased	121 (54.5)	19 (8.6)	46 (41.8)	6 (5.5)
Alanine aminotransferase increased	115 (51.8)	8 (3.6)	50 (45.5)	3 (2.7)
Aspartate aminotransferase increased	102 (45.9)	4 (1.8)	51 (46.4)	0 (0.0)
Blood and lymphatic system disorders	201 (90.5)	87 (39.2)	97 (88.2)	38 (34.5)
Anaemia	186 (83.8)	33 (14.9)	85 (77.3)	13 (11.8)
Neutropenia	84 (37.8)	53 (23.9)	39 (35.5)	25 (22.7)
Thrombocytopenia	66 (29.7)	25 (11.3)	33 (30.0)	10 (9.1)
Leukopenia	65 (29.3)	24 (10.8)	32 (29.1)	12 (10.9)
Gastrointestinal disorders	155 (69.8)	10 (4.5)	74 (67.3)	1 (0.9)
Nausea	101 (45.5)	1 (0.5)	46 (41.8)	1 (0.9)
Vomiting	61 (27.5)	1 (0.5)	26 (23.6)	1 (0.9)
Constipation	54 (24.3)	0 (0.0)	26 (23.6)	0 (0.0)
Metabolism and nutrition disorders	145(65.3)	17 (7.7)	65 (59.1)	4 (3.6)
Decreased appetite	79 (35.6)	3 (1.4)	36 (32.7)	2 (1.8)
General disorders and administration site conditions	135 (60.8)	6 (2.7)	59 (53.6)	6 (5.5)
Malaise	42 (18.9)	1 (0.5)	23 (20.9)	3 (2.7)

	T+PP (N = 222)		PP (N = 110)	
System Organ Class Preferred Term	**All Grades n (%)**	**≥Grade 3 n (%)**	**All Grades n (%)**	**≥Grade 3 n (%)**
Respiratory, thoracic and mediastinal disorders	113 (50.9)	20 (9.0)	38 (34.5)	2 (1.8)
Skin and subcutaneous tissue disorders	74 (33.3)	3 (1.4)	29 (26.4)	1 (0.9)
Infections and infestations	70 (31.5)	20 (9.0)	26 (23.6)	9 (8.2)
Nervous system disorders	52 (23.4)	6 (2.7)	19 (17.3)	3 (2.7)
Musculoskeletal and connective tissue disorders	73 (32.9)	1(0.5)	24 (21.8)	2 (1.8)

Abbreviations: T+PP, Tislelizumab+Pemetrexed+Platinum; PP, Pemetrexed+Platinum;
Adverse event Grades were evaluated based on NCI-CTCAE (version 5.0). Patients with multiple events for a given Preferred Term and System Organ Class were counted only once at the maximum Grade for the preferred term and system organ class, respectively. First-line treatment of locally advanced or metastatic squamous NSCLC in combination with carboplatin and either paclitaxel or nab-paclitaxel chemotherapy

First-line treatment of metastatic squamous NSCLC in combination with paclitaxel and platinum chemotherapy

The data described below reflect exposure to tislelizumab in 238 patients with locally advanced or metastatic squamous NSCLC in RATIONALE-307. Patients receive tislelizumab 200 mg combined with paclitaxel 175 mg/m2 and carboplatin AUC 5 mg/ml/min (T+PC arm, N=120), or tislelizumab 200 mg combined with nab-paclitaxel 100 mg/m2 and carboplatin AUC 5 mg/mL/min (T+nPC arm, N=118) [see 5.1 Pharmacodynamic properties (Clinical trials)]. The median duration of exposure to tislelizumab was 40.21 weeks (range: 3.0 to 100.9 weeks) in Arm T+PC and 44.21 weeks (range: 3.0 to 105.0 weeks) in Arm T+nPC.

The most common adverse events (≥50%) were anaemia, neutrophil count decreased, white blood cell count decreased, and alopecia in Arm T+PC, and anaemia, leukopenia, neutrophil count decreased, white blood cell count decreased, and alopecia in Arm T+nPC.

The most common ≥Grade 3 adverse events (≥5%) were neutrophil count decreased, white blood cell count decreased, platelet count decreased, neutropenia, anaemia, thrombocytopenia, leukopenia, and pneumonia in both Arm T+PC and Arm T+nPC.

Serious adverse events occurred in 43.3% of patients in Arm T+PC and 42.4% of patients in Arm T+nPC. The most frequent serious adverse events (≥2%) were pneumonitis, pneumonia, haemoptysis, and neutrophil count decreased in Arm T+PC, and pneumonitis, pneumonia, haemoptysis, febrile neutropenia, and neutrophil count decreased in Arm T+nPC.

Fatal adverse events occurred in 3.3% of patients in Arm T+PC and 5.9% of patients in Arm T+nPC, including cerebrovascular accident, hydrocephalus, haemoptysis, and respiratory failure (1 patient each) in Arm T+PC, and haemoptysis, respiratory failure, hepatic failure, pneumonia, and hypokalaemia (1 patient each) and death (2 patients) in Arm T+nPC.

Adverse events leading to discontinuation of tislelizumab occurred in 14.2% of patients in Arm T+PC and 12.7% of patients in Arm T+nPC; the most common adverse events resulting in permanent discontinuation (≥2 patients) were pneumonitis, and pneumonia in Arm T+PC, and immune-mediated pneumonitis, pneumonia, blood creatine phosphokinase increased, myocarditis, and death in Arm T+nPC.

Adverse events leading to the treatment modification of tislelizumab occurred in 47.5% of patients in Arm T+PC, and 79.7% of patients in Arm T+nPC; the most common adverse events leading to treatment modification of tislelizumab (≥5%) were anaemia, thrombocytopenia, leukopenia, platelet count decreased, neutrophil count decreased, alanine aminotransferase increased, white blood cell count decreased, aspartate aminotransferase increased, hypothyroidism, and pneumonia in Arm T+PC, and anaemia, thrombocytopenia, leukopenia, neutropenia, platelet count decreased, neutrophil count decreased, alanine aminotransferase increased, and white blood cell count decreased in Arm T+nPC.

Adverse events are listed in Table 6.

Table 6 Adverse Events (≥ 20%) in Patients Receiving tislelizumab in RATIONALE-307

	T+PC (N = 120)		**T+*n*PC (N = 118)**		**PC (N = 117)**	
System Organ Class Preferred Term	**All Grades n (%)**	**≥Grade 3 n (%)**	**All Grades n (%)**	**≥Grade 3 n (%)**	**All Grades n (%)**	**≥Grade 3 n (%)**
Blood and lymphatic system disorders	112 (93.3)	56 (46.7)	115 (97.5)	68 (57.6)	106 (90.6)	63 (53.8)
Anaemia	107 (89.2)	12 (10.0)	111 (94.1)	27 (22.9)	94 (80.3)	15 (12.8)
Leukopenia	58 (48.3)	19 (15.8)	66 (55.9)	30 (25.4)	57 (48.7)	22 (18.8)
Neutropenia	53 (44.2)	40 (33.3)	50 (42.4)	32 (27.1)	56 (47.9)	47 (40.2)
Thrombocytopenia	35 (29.2)	8 (6.7)	49 (41.5)	15 (12.7)	33 (28.2)	7 (6.0)
Investigations	111 (92.5)	77 (64.2)	110 (93.2)	69 (58.5)	101 (86.3)	58 (49.6)
Neutrophil count decreased	78 (65.0)	64 (53.3)	72 (61.0)	54 (45.8)	68 (58.1)	53 (45.3)
White blood cell count decreased	67 (55.8)	28 (23.3)	68 (57.6)	32 (27.1)	62 (53.0)	28 (23.9)
Alanine aminotransferase increased	56 (46.7)	3 (2.5)	43 (36.4)	2 (1.7)	27 (23.1)	0 (0.0)
Aspartate aminotransferase increased	49 (40.8)	2 (1.7)	42 (35.6)	1 (0.8)	14 (12.0)	0 (0.0)
Platelet count decreased	44 (36.7)	6 (5.0)	52 (44.1)	16 (13.6)	29 (24.8)	2 (1.7)
Blood bilirubin increased	30 (25.0)	0 (0.0)	18 (15.3)	0 (0.0)	15 (12.8)	0 (0.0)
Metabolism and nutrition disorders	95 (79.2)	11 (9.2)	91 (77.1)	7 (5.9)	72 (61.5)	8 (6.8)
Decreased appetite	54 (45.0)	2 (1.7)	55 (46.6)	2 (1.7)	37 (31.6)	1 (0.9)
Hypoalbuminaemia	30 (25.0)	1 (0.8)	25 (21.2)	0 (0.0)	19 (16.2)	0 (0.0)
Hypokalaemia	26 (21.7)	3 (2.5)	20 (16.9)	2 (1.7)	16 (13.7)	2 (1.7)
Hyponatraemia	26 (21.7)	2 (1.7)	25 (21.2)	2 (1.7)	20 (17.1)	3 (2.6)
Skin and subcutaneous tissue disorders	89 (74.2)	6 (5.0)	94 (79.7)	4 (3.4)	74 (63.2)	0 (0.0)
Alopecia	78 (65.0)	0 (0.0)	82 (69.5)	0 (0.0)	72 (61.5)	0 (0.0)
Rash	26 (21.7)	4 (3.3)	28 (23.7)	2 (1.7)	4 (3.4)	0 (0.0)
Gastrointestinal disorders	77 (64.2)	5 (4.2)	90 (76.3)	2 (1.7)	60 (51.3)	3 (2.6)
Constipation	40 (33.3)	0 (0.0)	36 (30.5)	0 (0.0)	27 (23.1)	0 (0.0)
Nausea	37 (30.8)	1 (0.8)	54 (45.8)	0 (0.0)	35 (29.9)	1 (0.9)
Vomiting	28 (23.3)	1 (0.8)	27 (22.9)	0 (0.0)	20 (17.1)	2 (1.7)
General disorders and administration site	77 (64.2)	5 (4.2)	70 (59.3)	3 (2.5)	62 (53.0)	5 (4.3)

	T+PC (N = 120)		T+*n*PC (N = 118)		PC (N = 117)	
System Organ Class Preferred Term	**All Grades n (%)**	**≥Grade 3 n (%)**	**All Grades n (%)**	**≥Grade 3 n (%)**	**All Grades n (%)**	**≥Grade 3 n (%)**
conditions						
Asthenia	30 (25.0)	0 (0.0)	24 (20.3)	0 (0.0)	24 (20.5)	1 (0.9)
Pyrexia	25 (20.8)	0 (0.0)	24 (20.3)	0 (0.0)	18 (15.4)	0 (0.0)
Malaise	24 (20.0)	3 (2.5)	19 (16.1)	1 (0.8)	19 (16.2)	0 (0.0)
Musculoskeletal and connective tissue disorders	74 (61.7)	5 (4.2)	59 (50.0)	1 (0.8)	51 (43.6)	1 (0.9)
Pain in extremity	40 (33.3)	3 (2.5)	18 (15.3)	0 (0.0)	27 (23.1)	0 (0.0)
Arthralgia	26 (21.7)	0 (0.0)	23 (19.5)	0 (0.0)	20 (17.1)	0 (0.0)
Nervous system disorders	68 (56.7)	7 (5.8)	38 (32.2)	1 (0.8)	45 (38.5)	2 (1.7)
Hypoaesthesia	27 (22.5)	0 (0.0)	13 (11.0)	0 (0.0)	20 (17.1)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	59 (49.2)	9 (7.5)	69 (58.5)	13 (11.0)	39 (33.3)	3 (2.6)
Haemoptysis	24 (20.0)	2 (1.7)	20 (16.9)	4 (3.4)	13 (11.1)	0 (0.0)
Infections and infestations	52 (43.3)	13 (10.8)	45 (38.1)	13 (11.0)	27 (23.1)	6 (5.1)
Pneumonia	26 (21.7)	6 (5.0)	19 (16.1)	6 (5.1)	13 (11.1)	3 (2.6)

Abbreviations: PC, Paclitaxel+Carboplatin; T+PC, Tislelizumab+Paclitaxel+Carboplatin; T+nPC, Tislelizumab+nab-Paclitaxel+Carboplatin.
Adverse event Grades were evaluated based on NCI-CTCAE (version 5.0).
Patients with multiple events for a given preferred term and system organ class were counted only once at the maximum Grade for the preferred term and system organ class, respectively.

Previously Treated Non-Small Cell Lung Cancer

The data described below reflect exposure to tislelizumab in 534 patients with locally advanced or metastatic NSCLC (squamous or non-squamous) in RATIONALE-303. Patients received 200 mg of TEVIMBRA via intravenous infusion every 3 weeks [see 5.1 Pharmacodynamic properties (Clinical trials)]. The median duration of exposure to tislelizumab was 23.3 weeks (range: 1 to 140 weeks).

The most common adverse events (≥15%) were anaemia, decreased appetite, cough, weight decreased, alanine aminotransferase increased, and aspartate aminotransferase increase.

The most common ≥Grade 3 adverse events (≥5%) were pneumonia.

Serious adverse events occurred in 32.6% of patients; the most frequent serious adverse events (≥1%) were pneumonia, pneumonitis, immune-mediated pneumonitis, interstitial lung disease, haemoptysis, dyspnoea, and pleural effusion.

Fatal adverse events related to tislelizumab occurred in 1.5% of patients, including multiple organ dysfunction syndrome, pneumonitis, and hepatic function abnormal (1 patient each), death, respiratory failure, and pneumonia (2 patients each).

Adverse events leading to discontinuation of tislelizumab occurred in 10.5% of patients; the most common adverse events resulting in permanent discontinuation (≥1%) were pneumonitis, interstitial lung disease and pneumonia.

Adverse events leading to the interruption of tislelizumab occurred in 22.3% of patients; the most common adverse events leading to interruption of tislelizumab (≥2%) were pneumonia, and blood creatine phosphokinase increased.

Adverse events are listed in Table 7.

Table 7 Adverse Events (≥ 10%) in Patients Receiving tislelizumab in RATIONALE-303

	TEVIMBRA (N = 534)		Docetaxel (N = 258)	
System Organ Class Preferred Term	**All Grades n (%)**	**≥ Grade 3 n (%)**	**All Grades n (%)**	**≥ Grade 3 n (%)**
Investigations	311 (58.2)	40 (7.5)	174 (67.4)	82 (31.8)
Alanine aminotransferase increased	106 (19.9)	4 (0.7)	38 (14.7)	0 (0.0)
Aspartate aminotransferase increased	101 (18.9)	5 (0.9)	31 (12.0)	1 (0.4)
Weight decreased	81 (15.2)	4 (0.7)	26 (10.1)	0 (0.0)
White blood cell count decreased	20 (3.7)	1 (0.2)	74 (28.7)	47 (18.2)
Neutrophil count decreased	15 (2.8)	3 (0.6)	95 (36.8)	71 (27.5)
Respiratory, thoracic and mediastinal disorders	253 (47.4)	58 (10.9)	111 (43.0)	19 (7.4)
Cough	104 (19.5)	5 (0.9)	40 (15.5)	1 (0.4)
Dyspnoea	61 (11.4)	9 (1.7)	32 (12.4)	6 (2.3)
Haemoptysis	57 (10.7)	6 (1.1)	22 (8.5)	3 (1.2)
Metabolism and nutrition disorders	252 (47.2)	37 (6.9)	118 (45.7)	27 (10.5)
Decreased appetite	82 (15.4)	5 (0.9)	59 (22.9)	3 (1.2)
Hypoalbuminaemia	70 (13.1)	0 (0.0)	41 (15.9)	1 (0.4)
Hyperglycaemia	56 (10.5)	8 (1.5)	29 (11.2)	3 (1.2)
Hyponatraemia	49 (9.2)	8 (1.5)	29 (11.2)	11 (4.3)
General disorders and administration site conditions	215 (40.3)	24 (4.5)	132 (51.2)	28 (10.9)
Asthenia	67 (12.5)	6 (1.1)	56 (21.7)	14 (5.4)
Pyrexia	56 (10.5)	1 (0.2)	26 (10.1)	0 (0.0)
Gastrointestinal disorders	194 (36.3)	12 (2.2)	127 (49.2)	11 (4.3)
Constipation	65 (12.2)	0 (0.0)	42 (16.3)	0 (0.0)
Nausea	59 (11.0)	0 (0.0)	41 (15.9)	1 (0.4)
Diarrhoea	35 (6.6)	4 (0.7)	35 (13.6)	5 (1.9)
Blood and lymphatic system disorders	179 (33.5)	26 (4.9)	174 (67.4)	111 (43.0)
Anaemia	152 (28.5)	18 (3.4)	112 (43.4)	16 (6.2)
Leukopenia	15 (2.8)	1 (0.2)	69 (26.7)	41 (15.9)
Neutropenia	9 (1.7)	3 (0.6)	81 (31.4)	72 (27.9)
Febrile neutropenia	0 (0.0)	0 (0.0)	33 (12.8)	33 (12.8)
Infections and infestations	151 (28.3)	47 (8.8)	77 (29.8)	38 (14.7)
Pneumonia	61 (11.4)	38 (7.1)	36 (14.0)	24 (9.3)
Skin and subcutaneous tissue disorders	102 (19.1)	3 (0.6)	135 (52.3)	4 (1.6)
Alopecia	5 (0.9)	0 (0.0)	122 (47.3)	2 (0.8)
Endocrine disorders	79 (14.8)	3 (0.6)	2 (0.8)	0 (0.0)
Hypothyroidism	57 (10.7)	0 (0.0)	2 (0.8)	0 (0.0)

Adverse event Grades were evaluated based on NCI-CTCAE (version 4.03).
Patients with multiple events for a given preferred term and system organ class were counted only once at the maximum Grade for the preferred term and system organ class, respectively.

Laboratory abnormalities

Clinically relevant abnormalities of routine haematological or biochemical laboratory values from the data set of the 9 pooled studies of TEVIMBRA as monotherapy and the 9 pooled studies of TEVIMBRA in combination with chemotherapy are presented in Table 8.

Table 8 Laboratory abnormalities worsening from baseline with TEVIMBRA as monotherapy (N = 1,952) and in combination with chemotherapy (N = 1,950)

	Tislelizumab monotherapy N = 1,952	Tislelizumab combination therapy N = 1,950
Laboratory abnormality parameter*	**All Grades n (%)**	**All Grades n (%)**
Hematological parameters		
Haemoglobin increased	86 (4.5)	39 (2.1)
Haemoglobin decreased	752 (39.3)	1559 (82)
Leukocytes decreased	321 (16.8)	1454 (76.5)
Lymphocytes increased	40 (2.1)	38 (3.3)
Lymphocytes decreased	776 (41.1)	714 (61.5)
Neutrophils decreased	258 (13.6)	1499 (79.7)
Platelets decreased	315 (16.5)	1148 (60.4)
Biochemical parameters		
Alanine aminotransferase increased	628 (32.9)	794 (41.8)
Albumin decreased	639 (33.4)	887 (46.7)
Alkaline phosphatase increased	610 (31.9)	593 (31.3)
Aspartate aminotransferase increased	708 (37.0)	883 (46.5)
Bilirubin increased	452 (23.7)	500 (26.3)
Creatine kinase increased	259 (20.7)	433 (23.9)
Creatinine increased	253 (13.2)	420 (22.1)
Potassium increased	191 (10.0)	263 (13.8)
Potassium decreased	296 (15.5)	571 (30)
Sodium increased	131 (6.9)	127 (6.7)
Sodium decreased	662 (34.7)	1025 (53.9)

*Each test incidence is based on the number of patients who had both baseline and at least one post-baseline laboratory measurement available: Monotherapy (range: 1,254 to 1,914 patients), combination therapy (range: 1,161 to 1,901 patients).

Description of selected adverse drug reactions

Immune-related ADRs

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

Immune-related pneumonitis

In patients treated with TEVIMBRA as monotherapy, immune-related pneumonitis occurred in 4.7% of patients, including Grade 1 (1.0%), Grade 2 (1.9%), Grade 3 (1.4%), Grade 4 (0.3%) and Grade 5 (0.1%) events.

The median time from first dose to onset of the event was 3.9 months (range: 1.0 day to 55 months), and the median duration of the event was 6 months (range: 1+ day to 48.3+ months). + denotes a censored observation, with ongoing events at the time of the analysis. TEVIMBRA was permanently discontinued in 1.8% of patients and TEVIMBRA treatment was interrupted in 1.7% of patients.

81 (71.7%) of the 113 patients received systemic corticosteroids. + denotes a censored observation. 74 (65.5%) of the 113 patients received high-dose (defined as a dose ≥40 mg/day of prednisone or equivalent) systemic corticosteroids. Two (1.8%) of 113 patients received immunosuppressive treatment. Pneumonitis resolved in 55 (48.7%) of the 113 patients.

Immune-related hepatitis

In patients treated with tislelizumab as monotherapy, immune--related hepatitis occurred in 30 (1.3%) of 2,390 patients, including Grade 1 (2 patients, 0.1%), Grade 2 (7 patients, 0.3%), Grade 3 (15 patients, 0.6%), and Grade 4 (4 patients, 0.3%) events.

The median time from first dose to onset of the event was 1.1 months (range: 14 days to 34.8 months), and the median duration of the event was 1.9 months (range: 6 days to 6.6 months). + denotes a censored observation. Tislelizumab was permanently discontinued in 0.3% of patients and tislelizumab treatment was interrupted in 19 (0.8%) of patients for immune-related hepatitis. Twenty-five (83.3%) out of 30 patients received systemic corticosteroids. Twenty-four (80%) of the 30 patients received high-dose systemic corticosteroids. Two (6.7%) of the 30 patients received other immunosuppressive treatment. Hepatitis resolved in 20 (66.7%) of the 30 patients.

Immune-related skin adverse reactions

In patients treated with tislelizumab as monotherapy, immune-related skin adverse reactions occurred in 13% of patients, including Grade 1 (8.4%), Grade 2 (3.4%), Grade 3 (1.1%) and Grade 4 (0.1%) events.

The median time from first dose to onset of the event was 1.5 months (range: 1 day to 36.1 months). The median duration of the event was 2.1 months (range: 1 day to 61.6+ months). + denotes a censored observation. TEVIMBRA was permanently discontinued in 0.1% of patients, and tislelizumab treatment was interrupted in 1.3% of patients. Forty-four (14.1%) of the 311 patients received systemic corticosteroids. Nineteen (6.1%) of the 311 patients received high-dose systemic corticosteroids. Two out of 311 patients (0.6%) received immunosuppressive treatment. Skin adverse reactions resolved in 208 (66.9%) of the 311 patients.

Immune-related colitis

In patients treated with tislelizumab as monotherapy, immune-related colitis occurred in 0.8% of patients, including Grade 1 (0.04%), Grade 2 (0.4%) and Grade 3 (0.3%) events.

The median time from first dose to onset of the event was 6 months (range: 6 days to 26.5 months), and the median duration of the event was 26 days (range: 5 days to 26.7 months). Tislelizumab was permanently discontinued in 0.2% of patients and tislelizumab treatment was interrupted in 0.4% of patients.

All 19 patients received systemic corticosteroids. Twelve (63.2%) of the 19 patients were treated with high-dose systemic corticosteroids. Two (10.5%) of the 19 patients received immunosuppressive treatment. Colitis resolved in 17 (89.5%) of the 19 patients.

Immune-related myositis/rhabdomyolysis

In patients treated with tislelizumab as monotherapy, immune-related myositis/rhabdomyolysis occurred in 0.7% of patients, including Grade 1 (0.3%), Grade 2 (0.2%), Grade 3 (0.2%) and Grade 4 (0.04%) events.

The median time from first dose to onset of the event was 1.6 months (range: 15 days to 39.3 months), and the median duration of the event was 45 days (range: 5 days to 5.2 months). Tislelizumab was

permanently discontinued in 0.2% of patients and tislelizumab treatment was interrupted in 0.4% of patients.

Nine (52.9%) of the 17 patients received systemic corticosteroids. Eight (47.1%) of the 17 patients were treated with high-dose systemic corticosteroids. One (5.9%) out of the 17 patients received immunosuppressive treatment. Myositis/rhabdomyolysis resolved in 13 (76.5%) of the 17 patients.

Immune-related endocrinopathies

Thyroid disorders

Hypothyroidism

In patients treated with tislelizumab as monotherapy, hypothyroidism occurred in 12.5% of patients, including Grade 1 (5.7%), Grade 2 (6.7%), Grade 3 (0.04%), and Grade 4 (0.04%) events.

The median time from first dose to onset of the event was 3.7 months (range: 1 day to 29.9 months). The median duration of the event was 10.3 months (range: 1+ day to 56+ months). + denotes a censored observation. Tislelizumab was permanently discontinued in 0.1% of patients and tislelizumab treatment was interrupted in 0.5% of patients. Two (0.7%) of the 299 patients received systemic corticosteroids. No patient received high-dose systemic corticosteroids. One hundred ninety-five patients received hormone replacement therapy. Hypothyroidism resolved in 103 (34.4%) of the 299 patients.

Hyperthyroidism

In patients treated with tislelizumab as monotherapy, hyperthyroidism occurred in 4.9% of patients, including Grade 1 (4.0%), Grade 2 (0.9%) and Grade 3 (0.04%) events.

The median time from first dose to onset of the event was 2.1 months (range: 6 days to 39.4 months). The median duration of the event was 2.1 months (range: 8 days to 48.4+ months). + denotes a censored observation. Tislelizumab was permanently discontinued in 0.04% of patients and tislelizumab treatment was interrupted in 0.3% of patients. Two (2.5%) of the 118 patients received systemic corticosteroids. One patient received high-dose systemic corticosteroids. Nineteen (16.1%) of the 118 patients received hormone replacement therapy. Hyperthyroidism resolved in 90 (76.3%) of the 118 patients.

Thyroiditis

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

The median time from first dose to onset of the event was 2 months (range: 14 days to 20.7 months). The median duration of the event was 7.3 months (range: 20 days to 34.5+ months). + denotes a censored observation. Tislelizumab was not permanently discontinued in any patient and tislelizumab treatment was interrupted in 0.2% of patients. Two (8%) of the 25 patients received systemic corticosteroids. No patients received high-dose systemic corticosteroids. Sixteen (64%) of the 25 patients received hormone replacement therapy. Thyroiditis resolved in 9 (36%) of the 25 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 (0.04%) events.

The median time from first dose to onset of the event was 9.7 months (range: 1.4 months to 16.9 months). The median duration of the event was not reached (range: 1 month to 27.9+ months). + denotes a censored observation. Tislelizumab was not permanently discontinued in any patient and tislelizumab treatment was interrupted in 0.4% of patients. All 12 patients received systemic corticosteroids. Three (25%) of the 12 patients received high-dose systemic corticosteroids. Adrenal insufficiency resolved in 3 (25%) of the 12 patients.

Hypophysitis

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

The median time from first dose to onset of the event was 8.7 months (range: 22 days to 16.2 months). The median duration of the event was not reached (range: 70 days to 30+ months). + denotes a censored observation. Tislelizumab was not permanently discontinued in any patients and treatment was interrupted in 0.04% of patients. Five (83.3%) of the 6 patients received systemic corticosteroids. One (16.7%) of the 6 patients received high-dose systemic corticosteroids. Hypophysitis resolved in 1 (16.7%) of the 6 patients.

Diabetes mellitus

In patients treated with tislelizumab as monotherapy, diabetes mellitus occurred in 16 (0.7%) patients, including Grade 1 (1 patient, 0.04%), Grade 2 (6 patients, 0.3%), Grade 3 (6 patients, 0.3%) and Grade 4 (3 patients, 0.1%) events.

The median time from first dose to onset of the event was 6.5 months (range: 22 days to 36.1 months). The median duration of the event was not reached (range: 2 days to 44.5+ months). + denotes a censored observation. Tislelizumab was permanently discontinued in 0.2% of patients and tislelizumab treatment was interrupted in 0.2% of patients. Diabetes mellitus resolved in 2 (12.5%) of 16 patients. The median duration for all resolved events was 22 days (range: 2 days to 3.6 months). Fourteen (87.5%) of the 16 patients received insulin therapy for diabetes mellitus.

Immune-related nephritis and renal dysfunction

In patients treated with tislelizumab as monotherapy, immune-related nephritis and renal dysfunction occurred in 5 (0.2%) patients, including Grade 1 (1 patient, 0.04%), Grade 2 (3 patients, 0.1%), and Grade 3 (1 patient, 0.04%) events.The median time from first dose to onset of the event was 2.1months (range: 15 days to 34.5months). The median duration of the event was not reached (range: 9 days to 16.2+ months). + denotes a censored observation. Tislelizumab was permanently discontinued in 1 (0.04%) of patients and tislelizumab treatment was interrupted in 3 (0.1%) of patients. Three (60%) out of 5 patients received systemic corticosteroids. All 3 patients received high-dose systemic corticosteroids. One (20%) of the 5 patients received immunosuppressive treatment. Immune-related nephritis and renal dysfunction resolved in 2 (40%) of the 5 patients.

Immune-related myocarditis

In patients treated with tislelizumab as monotherapy, immune-related myocarditis occurred in 15 (0.6%) patients, including Grade 1 (8 patients, 0.3%), Grade 2 (3 patients, 0.1%), Grade 3 (3 patients, 0.1%) and Grade 4 (1 patient, 0.04%) events.

The median time from first dose to onset of the event was 1.6 months (range: 14 days to 33.6 months), and the median duration of the event was 5.1 months (range: 4 days to 26.4+ months). + denotes a censored observation. Tislelizumab was permanently discontinued in 7 (0.3%) of patients and

tislelizumab treatment was interrupted in 8 (0.3%) of patients. Ten (66.7%) of the 15 patients received systemic corticosteroids, with a median initial dose of 75 mg/day (range: 20 to 200 mg/day) for a median duration of 28.5 days (range: 1 day to 2.4+ months). + denotes a censored observation. Nine (60%) of the 15 patients received high-dose corticosteroids. One (6.7%) of the 15 patients received immunosuppressive treatment. Myocarditis resolved in 9 (60%) of the 15 patients.

Infusion related reactions

In patients treated with tislelizumab as monotherapy, infusion-related reactions occurred in 113 (4.7%) patients, including Grade 1 (74 patients, 3.1%), Grade 2 (36 patients, 1.5 %), Grade 3 (2 patients, 0.1%) and Grade 4 (1 patient, 0.04%) events. Twenty-three (20.4%) of the 113 patients received treatment with corticosteroids. Tislelizumab was permanently discontinued in 4 (0.2%) patients, and tislelizumab treatment was interrupted in 17 (0.7%) patients. Cases of anaphylaxis, including anaphylactic reaction and anaphylactic shock, have been reported in the post-marketing setting.

Immunogenicity

Overall, a 20.8% incidence (839 of 4035 anti-drug antibody (ADA) evaluable patients) of treatment-emergent ADA was observed following tislelizumab administration across all dose levels, including 0.5 to 10 mg/kg once every 2 weeks, 2 to 5 mg/kg once every 3 weeks, and 200 mg once every 3 weeks (including 200 mg once every 3 weeks in neoadjuvant phase followed by 400 mg once every 6 weeks in adjuvant phase). Neutralizing antibodies were detected in 45 of these 4035 patients (1.1%).

Of 3,674 antidrug antibodies (ADA)-evaluable patients treated at the recommended dose of 200 mg once every 3 weeks with tislelizumab as monotherapy or in combination with chemotherapies, 776 (21.1%) of patients tested positive for treatment-emergent ADAs, the incidence of treatment-emergent ADA was 16.8% (307 of 1822 patients) for monotherapy and 25.3% (469 of 1852 patients) for combination therapy. Neutralising antibodies (NAbs) were detected in 45 (1.2%) of patients. The incidence of neutralizing antibodies was 1.3% (23 of 1822 patients) for monotherapy and 1.2% (22 of 1852 patients) for combination therapy. 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, efficacy, or safety.

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 are too limited to draw conclusions on this population.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions at https://pophealth.my.site.com/carmreportnz/s/.

4.9 OVERDOSE

There is no information on overdose with tislelizumab. No cases of overdose have been reported in clinical trials. In case of overdose, patients should be closely monitored for signs or symptoms of adverse drug reactions, and appropriate symptomatic treatment instituted immediately.

For information on the management of overdose, contact the National Poisons Centre on 0800 POISON (0800 764 766).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies. ATC code: L01FF09.

Mechanism of action

Binding of the PD-1 ligands PD-L1 and PD-L2, to the PD-1 receptor found on T-cells, inhibits T-cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumours and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumours.

Tislelizumab is a humanized immunoglobulin G4 (IgG4) variant monoclonal antibody against PD-1, binding to the extracellular domain of human PD-1 with high specificity and affinity (KD = 0.15 nM). It competitively blocks the binding of both PD-L1 and PD-L2, inhibiting PD-1-mediated negative signaling and enhancing the functional activity in T-cells in *in vitro* cell-based assays. Tislelizumab does not bind to Fc gamma receptors (FcγRs) and *C1q*, and therefore not induce antibody-dependent cellular cytotoxicity (ADCC), antibody dependent cellular phagocytosis (ADCP) or complement-dependent cytotoxicity (CDC). In addition, tislelizumab demonstrated decreased tumour growth in several human cancer allogeneic xenograft models and a human PD-1 transgenic mouse model.

Clinical trials

Oesophageal squamous cell carcinoma (OSCC)

RATIONALE-302 was a randomised, controlled, open-label, global phase III study to compare the efficacy of tislelizumab versus chemotherapy in patients with unresectable, recurrent, locally advanced or metastatic OSCC who progressed on or after prior systemic treatment. Patients were enrolled regardless of their tumour PD-L1 expression level. Where available, the archival/fresh tumour tissue specimens taken were retrospectively tested for PD-L1 expression status. Patients with inactive or asymptomatic carrier chronic or active HBV status and patients with detectable HCV receiving antivirals at screening were also enrolled in the study.

The study excluded patients with active brain or leptomeningeal tumour invasion into organs located adjacent to the oesophageal disease site (e.g., aorta or respiratory tract), active autoimmune disease or history of autoimmune diseases, or any condition requiring systemic treatment with either corticosteroids or other immunosuppressive treatments. 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 were randomized (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, also administered as 100 mg/m^2 on Days 1, 8, 15, 22, 29, and 36, followed by 1 week of rest in Japan),
- docetaxel 75 mg/m^2 on day 1, given every 3 weeks (70 mg/m^2 on Day 1, given every 21 days in Japan), or

- irinotecan 125 mg/m^2 on days 1 and 8, given every 3 weeks.

Crossover between the tislelizumab arm and ICC arm was not permitted. In the ICC arm, switching between the different chemotherapy options was not permitted.

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

Patients were treated with tislelizumab or one of the ICC until disease progression or unacceptable toxicity.

The tumour assessments were conducted every 6 weeks for the first 6 months, and every 9 weeks thereafter. Treatment beyond initial investigator-assessed progression was permitted in patients receiving tislelizumab with no rapid progression, investigator-assessed benefit, tolerance to treatment, stable performance status, and for whom treatment beyond progression would not delay an imminent intervention to prevent serious complications associated with disease progression (e.g., brain metastasis).

The primary efficacy outcome measure was overall survival (OS) in the intent-to-treat (ITT) population. Key secondary efficacy outcome measure was OS in PD-L1 Positive Analysis Set (PD-L1 score ≥10%).

Additional secondary efficacy endpoints included objective response rate (ORR), progression-free survival (PFS) and duration of response (DoR), as assessed by the investigator per RECIST v 1.1 and health related quality of life.

A total of 512 patients were enrolled and randomized 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 of 62 years (range: 35 to 86 years), 37.9% with 65 years of age or older; 84% male; 19% White and 80% Asian; 25% with an eastern cooperative oncology group performance status (ECOG PS) of 0 and 75% with an 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 systemic therapy.

RATIONALE-302 demonstrated a statistically significant improvement in OS for patients randomized to tislelizumab arm as compared with 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 9 and Figure 1.

Table 9 Efficacy results in RATIONALE-302 (ITT analysis set)

Endpoint	**Tislelizumab (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		
Disease progression or death, n (%)	223 (87.1)	180 (70.3)

Endpoint	Tislelizumab (N = 256)	Chemotherapy (N = 256)
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		
ORR, n	39	17
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 DoR with confirmation by investigator (months) (95% CI)	10.3 (6.5, 13.2)	6.3 (2.8, 8.5)

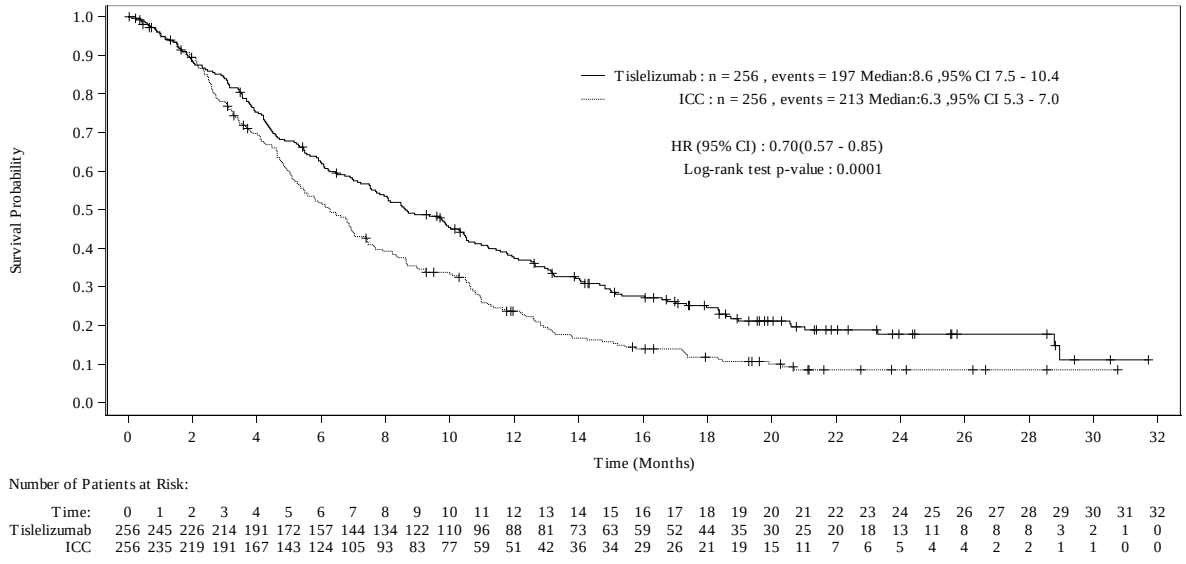
Abbreviations: OS = overall survival; CI = confidence interval; PFS = progression-free survival; ORR = objective response rate; CR = complete response; PR = partial response; SD = stable disease; DoR = duration of response.

[a] 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 log rank test stratified by ECOG performance status and investigator's choice of chemotherapy.

Figure 1 Kaplan-Meier plot of OS in RATIONALE-302 (ITT analysis set)



One-sided p-value was estimated from log-rank test stratified on ECOG status and ICC option. Hazard ratio was based on Cox regression model including treatment as covariate stratified by ECOG status and ICC option

Overall survival benefit with tislelizumab over ICC was consistent across subgroups, including age, gender, investigators choice of chemotherapy options (paclitaxel, docetaxel and irinotecan), smoking status, ECOG performance status, region (Asia versus America/Europe), baseline PD-L1 status, and race (Asian versus White).

PD-L1 subgroups

Of the 512 patients, 142 (27.7%) had PD-L1 positive ESCC, defined as PD-L1 score ≥10%. The remaining 222 (43.4%) had PD-L1 negative ESCC defined as PD-L1 score<10% and 148 (28.9%) had baseline PD-L1 status missing.

In a pre-specified analysis of OS in the PD-L1 positive sub-group (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 arm and ICC arms, respectively.

Non-small cell lung cancer

First-line treatment of metastatic non-squamous NSCLC in combination with pemetrexed and platinum chemotherapy

The efficacy of tislelizumab was evaluated in RATIONALE-304 (NCT03663205), a multicenter, randomized, open-label, phase 3 study evaluating the efficacy and safety of tislelizumab combined with chemotherapy in untreated locally advanced non-squamous NSCLC patients who were not candidates for surgical resection or platinum based chemoradiation, or metastatic non-squamous NSCLC patients.

The study excluded patients with active brain or leptomeningeal metastases; with 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 334 patients were randomized (2:1) to receive tislelizumab 200 mg combined with pemetrexed 500 mg/m2 and carboplatin AUC 5 mg/mL/min or cisplatin 75 mg/m2 (T+PP arm, N = 223), or pemetrexed 500 mg/m2 and carboplatin AUC 5 mg/mL/min or cisplatin 75 mg/m2 (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 arm T+PP received tislelizumab 200 mg combined with pemetrexed 500 mg/m2 on a 3-week cycle until disease progression or unacceptable toxicity. Tislelizumab monotherapy was continued beyond disease progression if the patient was deriving clinical benefit as assessed by the investigator; patients in arm PP received pemetrexed 500 mg/m2 alone until disease progression is confirmed or unacceptable toxicity, and those with disease progression confirmed by IRC given the option to cross over to receive tislelizumab monotherapy on a 3-week cycle.

Randomization was stratified by PD-L1 expression in tumour cells (TC) (<1% vs 1% to 49% vs ≥50%) and disease stage (IIIB vs 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 the study population were: median age of 61 years (range: 25 to 75 years), 29% with 65 years of age or older; 74% male; 100% Asian; 23.4% had an ECOG PS of 0 and 76.6% had an ECOG PS of 1; 18.3% had disease stage IIIb; 26.6% of the patients were unknown status on ALK rearrangement whereas 73.4% with negative ALK rearrangement; 36.2% of the patients were never-smokers; 5.4% with brain metastases, 4.6% PD-L1 TC score < 1%, 24.0% with PD-L1 TC score ≥1% and ≤49%, 32.9% with PD-L1 TC score ≥50%. The characteristics of age, sex,

ECOG PS, stage, smoking status, PD-L1 expression and prior anticancer treatments were well balanced.

The primary efficacy endpoint was progression-free survival (PFS) per RECIST v.1.1 per IRC in the intent to treat (ITT) analysis. The secondary endpoints included overall survival (OS), PFS per investigator, 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 tislelizumab in combination with PP as compared with PP. The hazard ratio (HR) was 0.65 (95% CI: 0.47, 0.91; p = 0.0054) indicating a 35% reduction in the risk of experiencing disease progression or death, with a median PFS of 9.7 months with tislelizumab in combination with PP and 7.6 months with PP.

The final analysis (data cut-off date of 26-Oct-2020 and a median duration of study follow-up of 16.1 months) confirmed the results from the interim analysis. Efficacy results in the final analysis are shown in Table 10 and Figure 2.

Table 10 Efficacy results in RATIONALE-304 by IRC

Endpoint	**Tislelizumab + Pemetrexed + Platinum (N = 223)**	**Pemetrexed + Platinum (N = 111)**
PFS		
Events, n (%）	133 (59.6)	68 (61.3)
Median PFS (months）（95% CI）	9.8 (8.94, 11.70)	7.6 (5.55, 8.02)
Stratified Hazard Ratio [a,b]（95% CI）	0.63 (0.47, 0.86)	
Event-free rate		
12 months (%), (95% CI)	39.9 (32.8, 46.8)	20.1 (11.6, 30.2)
18 months (%), (95% CI)	26.6 (19.5, 34.3)	11.3 (4.6, 21.1)
OS		
Deaths n (%)	96 (43.0)	46 (41.4)
Median OS (months) (95% CI)	21.4 (17.68, NE)	21.3 (15.08, NE)
Stratified Hazard ratio (95% CI)	0.90 (0.63, 1.28)	
Event-free rate [c] (%), (95% CI)		
12 months [c]	76.4 (70.2, 81.5)	69.4 (59.4, 77.4)
18 months	55.4 (48.0, 62.2)	55.3 (44.6, 64.8)
Best Overall Response, n (%) [d]		
ORR, n (%) [d]	113 (50.7)	31 (27.9)
95% CI [e]	(43.9, 57.4)	(19.8, 37.2)
CR, n (%）	9 (4.0)	2 (1.8)
PR, n (%）	104 (46.6)	29 (26.1)
DoR [d]		
Median DoR（months）（95% CI）	14.5 (10.09, NE)	8.4 (5.95, 15.47)
Event-free rate		
6-months (%), (95% CI) [f]	78.5 (69.47, 85.19)	63.8 (41.78, 79.35)
12-months (%), (95% CI) [f]	53.9 (43.63, 63.11)	37.2 (18.32, 56.24)
18-months (%), (95% CI) [f]	42.0 (30.35, 53.17)	20.7 (4.86, 43.97)

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

Endpoint	Tislelizumab + Pemetrexed + Platinum (N = 223)	Pemetrexed + Platinum (N = 111)

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

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

[b] Hazard ratio was estimated from stratified Cox model with pemetrexed + platinum group as reference group.

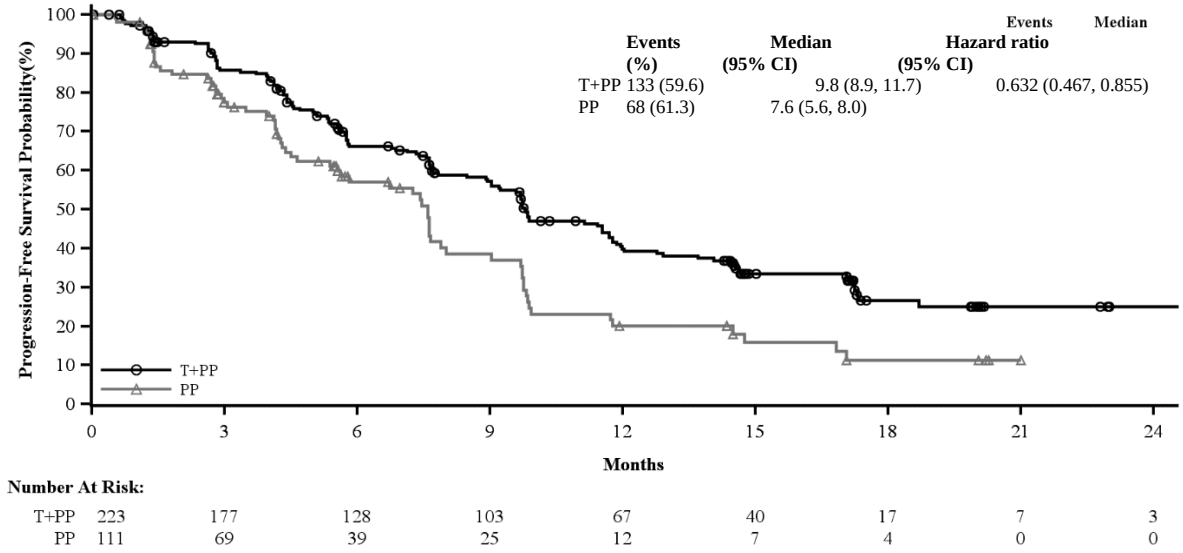
[c] The median time from randomization to crossover was 35.1 weeks and from end of study treatment to crossover is 2.6 weeks.

[d] Confirmed response by independent review committee.

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

[f] Event free rates were estimated by Kaplan-Meier method with 95% CI evaluated using Greenwood's formula.

Figure 2 Kaplan-Meier plot of PFS in RATIONALE-304 by IRC



Abbreviations: CI = Confidence Interval; T+PP = Tislelizumab + Pemetrexed + Platinum; PP = Pemetrexed + Platinum.

Subgroup analyses demonstrated a consistently beneficial PFS treatment effect for Arm T+PP over Arm PP irrespective of tumour stage, and across major demographic and prognostic subgroups.

In addition, generally consistent treatment benefit was observed for Arm T+PP over Arm PP for disease stages, with PFS HR of 0.63 (95% CI, HR = 0.31, 1.26) for stage IIIB and PFS HR of 0.59 (95% CI, 0.42, 0.82) for stage IV.

The benefit for PFS was observed in both PD-L1 TC score <1% (HR=0.83, 95% CI: 0.53, 1.28) and PD-L1 TC score ≥1% (HR=0.48, 95% CI: 0.32, 0.72). Within the PD-L1 positive group, the results from both PD-L1 TC score 1% to49% subgroup (HR=0.90, 95% CI: 0.49, 1.63) and PD-L1 TC score ≥50% subgroup (HR=0.29, 95% CI: 0.16, 0.50) need to be interpreted with caution considering the small sample size . In addition, generally consistent treatment effect was observed for disease stages IIIB and IV.

Table 11 Efficacy results of PFS by tumour PD-L1 expression in RATIONALE-304

	T +PP arm	PP arm
	N = 223	N = 111
PD-L1 expression in tumour cell <1%, n	91	48

	T +PP arm	PP arm
	N = 223	**N = 111**
Events, n (%)	64 (70.3)	30 (62.5)
Median PFS (months), (95% CI)	7.6 (5.0, 9.7)	7.6 (4.3, 7.9)
Hazard ratio (95% CI)	0.83 (0.53, 1.28)	
PD-L1 expression in tumour cell ≥1%, n	127	63
Events, n (%)	66 (52.0)	38 (60.3)
Median PFS (months), (95% CI)	11.9 (9.9, 17.3)	7.4 (4.5, 9.8)
Hazard ratio (95% CI)	0.48 (0.32, 0.72)	
PD-L1 expression in tumour cell 1%-49%, n	53	27
Events, n (%)	33 (62.3)	16 (59.3)
Median PFS (months)	9.7 (6.9, 11.7)	9.7 (5.6, 16.8)
Hazard ratio (95% CI)	0.90 (0.49, 1.63)	
PD-L1 expression in tumour cell ≥50%, n	74	36
Events, n (%)	33 (44.6)	22 (61.1)
Median PFS (months)	14.6 (11.5, NE)	4.6 (3.5, 9.7)
Hazard ratio[a] (95% CI)	0.29 (0.16, 0.50)	

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

Patient-reported outcomes (PROs) were collected using EORTC-QLQ-C30 and QLQ-LC13 questionnaires. QLQ-C30 and QLQ-LC13 completion rates among all treatment arms were 100% at baseline and remained ≥95% up to end of cycle 7.

The addition of tislelizumab to platinum-pemetrexed trended towards improvements in health-related quality of life (HRQoL) compared to platinum-pemetrexed alone in patients with previously untreated stage IIIB or IV non-squamous NSCLC. The median TTD (time to deterioration) for QLQ-C30 GHS/QoL was not reached in either treatment arms; the median TTD for the composite of cough, chest pain, and dyspnea in the QLQ LC13 was 5.8 months (95% CI: 4.40, NE) in T+PP arm and 4.3 months (95 %CI: 3.09, NE) in PP arm.

First-line treatment of locally advanced or metastatic squamous NSCLC in combination with carboplatin and either paclitaxel or nab-paclitaxel chemotherapy

The efficacy of tislelizumab was evaluated in RATIONALE-307 (NCT03594747), a multicenter, randomized, open-label, phase 3 study comparing the efficacy and safety of tislelizumab combined with paclitaxel plus carboplatin or nab-paclitaxel plus carboplatin versus paclitaxel plus carboplatin alone as first-line treatment for untreated locally advanced squamous NSCLC patients who were not candidates for surgical resection or platinum based chemoradiation or metastatic NSCLC patients.

The study excluded patients who have 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 randomized (1:1:1) to receive tislelizumab 200 mg combined with paclitaxel 175 mg/m2 and carboplatin AUC 5 mg/ml/min (T+PC arm, N = 120), or tislelizumab 200 mg combined with nab-paclitaxel 100 mg/m2 and carboplatin AUC 5 mg/mL/min (T+nPC arm, N = 119), or paclitaxel 175 mg/m2 and carboplatin AUC 5 mg/mL/min (PC, N = 121 arm).

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 T+nPC and T+PC arms received tislelizumab until disease progression or

unacceptable toxicity; while tislelizumab monotherapy could continue beyond disease progression if the patient was deriving clinical benefit as assessed by the investigator. Patients in the PC arm with disease progression were given the option to cross over to receive tislelizumab monotherapy on a 3-week cycle.

Randomization was stratified by PD-L1 tumour cell (TC) score (<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 VentanaPD-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 next 6 months, then every 12 weeks until disease progression.

The baseline characteristics for the study population were: median age 62.0 years (range: 34 to 74 years), 35.3% with 65 years of age or older; 91.7% male; 100% Asian, 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; 38.8% 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 well balanced.

The primary efficacy endpoint was progression-free survival (PFS) as assessed by IRC per RECIST v1.1 in the intention-to-treat (ITT) analysis which was to be tested sequentially in arms T+PC versus PC and arms T+nPC versus PC. The secondary 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), showingstatistically significant improvement 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), indicating a 52% risk reduction in disease progression or death. The stratified HR was 0.45 (95% CI: 0.32, 0.64; p <0.0001), a 55% risk reduction in disease progression or death was observed when comparing T+nPC arm with PC arm, with a median PFS of 7.6 months with T+PC arm and 7.6 months with T+nPC arm and 5.4 months with P+C arm.

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

Efficacy results for the final analysis are shown in Table 12, Figure 3 and Figure 4.

Table 12 Efficacy results in RATIONALE-307 by IRC

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)	-
PFS event-free rate, (%) (95% CI)			
12 months	36.5 (27.6, 45.4)	33.1 (24.2, 42.3)	9.5 (4.5, 16.8)
18 months	29.4 (20.8, 38.4)	27.1 (18.7, 36.2)	6.8 (2.7, 13.6)
OS			

Endpoint	tislelizumab + Paclitaxel + Carboplatin (N = 120)	tislelizumab + nab-Paclitaxel + Carboplatin (N = 119)	Paclitaxel + Carboplatin (N = 121)
Deaths n (%)	48 (40.0)	47 (39.5)	52 (43.0)
Median OS (months) (95% CI)	22.8 (19.1, 26.1)	NE (18.6, NE)	20.2 (16.0, NE)
Stratified hazard ratio (95% CI)	0.68 (0.46, 1.010)	0.75 (0.50, 1.12)	-
OS event-free rate, (%) (95% CI)			
12 months	72.7 (63.7, 79.9)	77.3 (68.4, 83.9)	71.4 (61.9, 79.0)
18 months	63.2 (53.8, 71.2)	62.0 (52.1, 70.4)	55.7 (45.3, 64.8)
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)
Event-free rate, (%) (95% CI) [c]			
6-months	68.3 (56.23, 77.66)	77.9 (66.44, 85.81)	35.2 (20.94, 49.74)
12-months	51.0 (38.87, 61.92)	45.8 (33.79, 57.09)	19.8 (9.14, 33.37)
18-months	44.8 (32.31, 56.48)	30.4 (18.61, 42.97)	11.9 (3.56, 25.62)

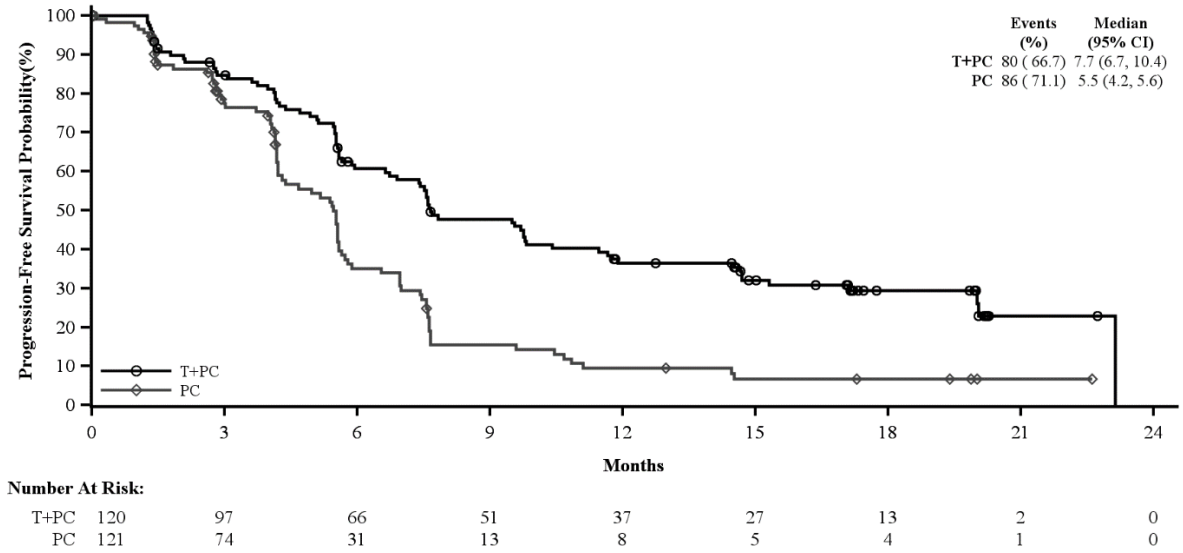
Abbreviations: PFS = progression-free survival; CI = confidence interval; ORR = objective response rate; CR = complete response; PR = partial response; DoR = duration of response; NE = not estimable.

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

[b] Confirmed response by independent review committee

[c] Event free rates evaluated by Kaplan-Meier method with 95% CI estimated using Greenwood's formula.

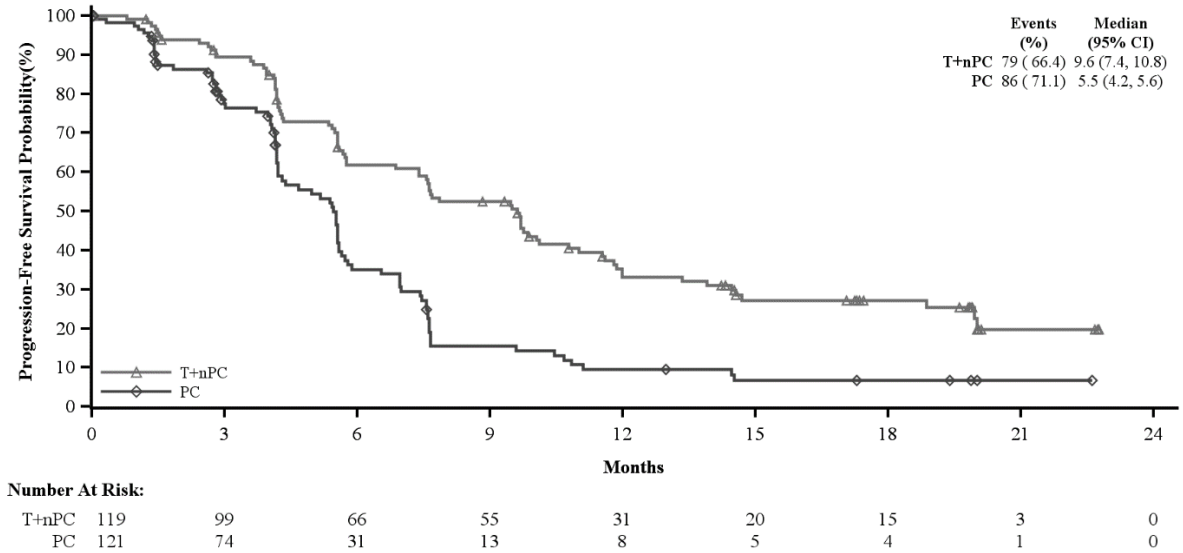
Figure 3 Kaplan-Meier plot of PFS in RATIONALE-307 by IRC



Hazard ratio based on stratified analysis
Abbreviations: CI = Confidence Interval; T+PC = Tislelizumab + Paclitaxel + Carboplatin; PC = Paclitaxel + Carboplatin.

Figure 4 Kaplan-Meier plot of PFS in RATIONALE 307 by IRC

T+nPC arm vs. PC arm



Hazard ratio based on stratified analysis
Abbreviations: CI = Confidence Interval; T+nPC = Tislelizumab + nab-Paclitaxel + Carboplatin; PC = Paclitaxel + Carboplatin.

Subgroup analyses demonstrated a homogeneous and generally consistent PFS treatment effect across major demographic and prognostic subgroups, including PD-L1 expression, and disease stages IIIB and IV:

- for T+PC, with PFS HR of 0.38 (95% CI, HR = 0.22, 0.67) for stage IIIB and 0.51 (95% CI, 0.35, 0.75) for stage IV.

- for T+nPC, with PFS HR of 0.40 (95% CI, HR = 0.24, 0.67) for stage IIIB and 0.50 (95% CI, 0.33, 0.74) for stage IV.

Efficacy results of PFS by tumour PD-L1 expression in pre-specified subgroup analyses are shown in Table 13.

Table 13 Efficacy results of PFS by tumour PD-L1 expression in study BGB-A317-307

	tislelizumab + Paclitaxel + Carboplatin arm (N = 120)	**Paclitaxel + Carboplatin arm (N = 121)**	**tislelizumab + Paclitaxel + Carboplatin arm (N = 119)**	**Paclitaxel + Carboplatin arm (N = 121)**
PD-L1 expression in tumour cell <1%, n	**47**	**45**	**46**	**45**
Events, n (%)	31 (66.0)	31 (68.9)	35 (76.1)	31 (68.9)
Median PFS (months), (95% CI)	7.6 (5.5, 14.5)	5.5 (4.2, 7.0)	7.6 (5.4, 9.9)	5.5 (4.2, 7.0)
Hazard ratio (95% CI)	0.57 (0.34, 0.94)		0.65 (0.39, 1.05)	
PD-L1 expression in tumour cell 1% to 49%, n	**30**	**31**	**30**	**31**
Events, n (%)	18 (60.0)	24 (77.4)	20 (66.7)	24 (77.4)
Median PFS (months)	10.4 (5.5, 20.0)	5.0 (2.8, 6.5)	10.1 (7.4,12.0)	5.0 (2.8, 6.5)
Hazard ratio (95% CI)	0.40 (0.21, 0.76)		0.40 (0.21, 0.74)	
PD-L1 expression in tumour cell ≥50%, n	**42**	**41**	**42**	**41**
Events, n (%)	31 (73.8)	29 (70.7)	23 (54.8)	29 (70.7)
Median PFS (months)	7.7 (5.9, 9.8)	5.5 (4.1, 7.0)	9.7 (5.6, NE)	5.5 (4.1, 7.0)
Hazard ratio[a] (95% CI)	0.44 (0.26, 0.75)		0.33 (0.18, 0.59)	

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

PROs were collected using the EORTC-QLQ-C30 questionnaire. Completion rates among all treatment arms were >99% at baseline and remained 97% through cycle 5.

The baseline EORTC QLQ-C30 global health status/QoL scores were similar for the 3 treatment arms. Patients in T+PC and T+nPC arms had similar HRQoL outcomes to those in PC arm as measured by the QLQ-C30 global health status/QoL and by lung cancer-specific symptoms of cough, chest pain and dyspnea.

The median TTD for QLQ-C30 global health status/QoL was not reached in all treatment arms; the median TTD for the composite of cough, chest pain, and dyspnea scores was reached in P+PC arm and was 5.7 months (95% CI: 3.06, NE).

Previously Treated Non-Small Cell Lung Cancer

RATIONALE-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-containing regimen.

The study excluded patients with known EGFR mutation or ALK rearrangement, 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 randomized (2:1) ratio to receive tislelizumab 200 mg intravenously every 3 weeks (N = 535) or docetaxel 75 mg/m2 intravenously every 3 weeks (N = 270).

Randomization 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 VentanaPD-L1 (SP263) assay that identified PD-L1 staining on tumour cells. Tumour assessments were conducted every 9 weeks for 52 weeks after randomization 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 years), 32.4% with 65 years of age or older, 3.2% with 75 years of age 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 34.0% with unknown EGFR status; 46.1% with wild-type and 53.9% with unknown ALK status; 7.1% with brain metastases.

57.0% of the patients had aPD-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, and 15.3% had received two prior therapies. The co-primary efficacy endpoints were OS in the ITT and PD-L1 TC score ≥25% analysis sets. Additional endpoints included investigator assessed PFS, ORR, and DoR.

RATIONALE-303 met both its co-primary endpoints of OS in the ITT analysis set and PD-L1 TC ≥25% analysis set. At the prespecified interim analysis (data cut-off 10-Aug-2020 with a median duration of study follow-up time of 11.7 months), a statistically significant and clinically meaningful improvement in OS was observed in the ITT population. Results favored treatment with tislelizumab, with a 36% relative risk reduction relative to docetaxel (HR = 0.64; 95% CI: 0.53, 0.78; p <0.0001). Median OS was prolonged by 5.3 months, from 11.9 months for patients receiving docetaxel to 17.2 months for tislelizumab-treated patients.

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

At the final analysis, a statistically significant and clinically meaningful improvement in OS of tislelizumab compared with docetaxel was observed in the PD-L1 TC ≥25% analysis set, with a one-sided stratified p <0.0001. Results favored treatment with tislelizumab, with a 47% relative risk reduction in death relative to docetaxel (HR = 0.53; 95% CI: 0.41, 0.70) in the PD-L1 TC ≥25% population, and a clinically meaningful improvement for median OS from 11.5 months (95% CI: 8.15, 13.54 months) in the docetaxel arm to 19.3 months (95% CI: 16.49, 22.60 months) in the tislelizumab arm.

Efficacy results for the interim and final analysis are shown in Table 14 (ITT analysis set) and Table 15 (PD-L1 TC ≥25% analysis set), Figures 5 and 6 (ITT analysis set) and Figure 7 (PD-L1 TC ≥25% analysis set).

Table 14 Efficacy results in RATIONALE 303 (ITT analysis set)

Endpoint	tislelizumab (N = 535)	Docetaxel (N = 270)
Interim analysis (data cut-off date of 10 Aug 2020)		
OS		
Deaths n (%)	275 (51.4)	166 (61.5)
Median OS (months) (95% CI)	17.2 (15.28, 20.04)	11.9 (10.18, 13.93)

Endpoint	tislelizumab (N = 535)	Docetaxel (N = 270)
Hazard ratio (95% CI) [b]	0.64 (0.53, 0.78)	
P-value (stratified log-rank) [a]	<0.0001	
OS event-free rate, (%) (95% CI)		
12 months	61.9 (57.5, 66.0)	49.8 (43.4, 55.9)
18 months	48.4 (43.7, 53.0)	31.9 (25.5, 38.6)
24 months	39.4 (34.1, 44.6)	25.0 (18.4, 32.2)
PFS		
Events, n (%）	418 (78.1)	200 (74.1)
Median PFS in months (95% CI）	4.1 (3.75, 5.03)	2.6 (2.17, 3.78)
Hazard Ratio [b]（95% CI）	0.64 (0.53, 0.76)	
ORR (%) (95% CI) [c]	20.0 (16.69, 23.64)	3.7 (1.79, 6.71)
Best overall response [c]		
CR（%）	1.3	0.4
PR（%）	18.7	3.3
SD (%)	32.0	37.0
DoR [d]		
Median（months) (95% CI)	14.5 (10.18, NE)	6.7 (4.11, NE)
Event-free rate (%), (95% CI) [d]		
6-months	83.7 (74.73, 89.67)	87.5 (38.70, 98.14)
12-months	56.3 (44.93, 66.27)	25.0 (3.71, 55.81)
Final Analysis (data cut-off date of 15 Jul 2021)		
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)	
OS event-free rate, (%) (95% CI)		
12 months	62.1 (57.86, 66.13)	49.7 (43.45, 55.71)
18 months	47.5 (43.12, 51.67)	32.6 (26.94, 38.45)
24 months	36.8 (32.62, 41.01)	23.7 (18.57, 29.17)
36 months	24.7 (20.29, 29.43)	13.8 (8.87, 19.69)
PFS		
Events, n (%）	451 (84.3)	208 (77.0)
Median PFS in months (95% CI）	4.2 (3.88, 5.52)	2.6 (2.17, 3.78)
Hazard Ratio [a b]（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
SD (%)	31.0	37.0
DoR		
Median（months) (95% CI)	14.7 (10.55, 21.78)	6.2 (4.11, 8.31)
Event-free rate (%), (95% CI)		
6-months	84.5 (76.21, 90.05)	80.0 (40.87, 94.59)
12-months	56.5 (46.45, 65.35)	20.0 (3.09, 47.47)

Abbreviations: 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; NE=Not estimable.

Endpoint	tislelizumab (N = 535)	Docetaxel (N = 270)

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

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

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

[c] Confirmed response by investigator

[d] Event free rates were estimated by Kaplan-Meier method with 95% CI evaluated using Greenwood's formula.

Table 15 Efficacy results in BGB-A317-303 (PD-L1 TC ≥25% analysis set) (data cut-off date of 15-Jul-2021)

Endpoint	TEVIMBRA (N = 227)	Docetaxel (N = 115)
OS		
Deaths n (%)	141 (62.1)	86 (74.8)
Median OS (months) (95% CI)	19.3 (16.49, 22.60)	11.5 (8.15, 13.54)
Hazard ratio (95% CI) [a]	0.53 (0.41, 0.70)	
OS event-free rate, (%) (95% CI)		
12 months	67.4 (60.83, 73.11)	48.3 (38.51, 57.38)
18 months	52.8 (45.98, 59.10)	30.0 (21.49, 38.87)
24 months	42.3 (35.62, 48.82)	22.6 (14.98, 31.10)

Median follow-up time was estimated by the reverse Kaplan-Meier method.

Medians and other quartiles were estimated by Kaplan-Meier method with 95% Cis estimated using the method of Brookmeyer and Crowley.

Event free rates were estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula.

Docetaxel arm was the reference group for hazard ratio.

[a] Stratified by stratification factors: histology (squamous versus non-squamous), lines of therapy (second versus third).

Figure 5 Kaplan-Meier plot of OS in RATIONALE-303 (ITT analysis Set) (data cut-off date of 10-Aug-2020)

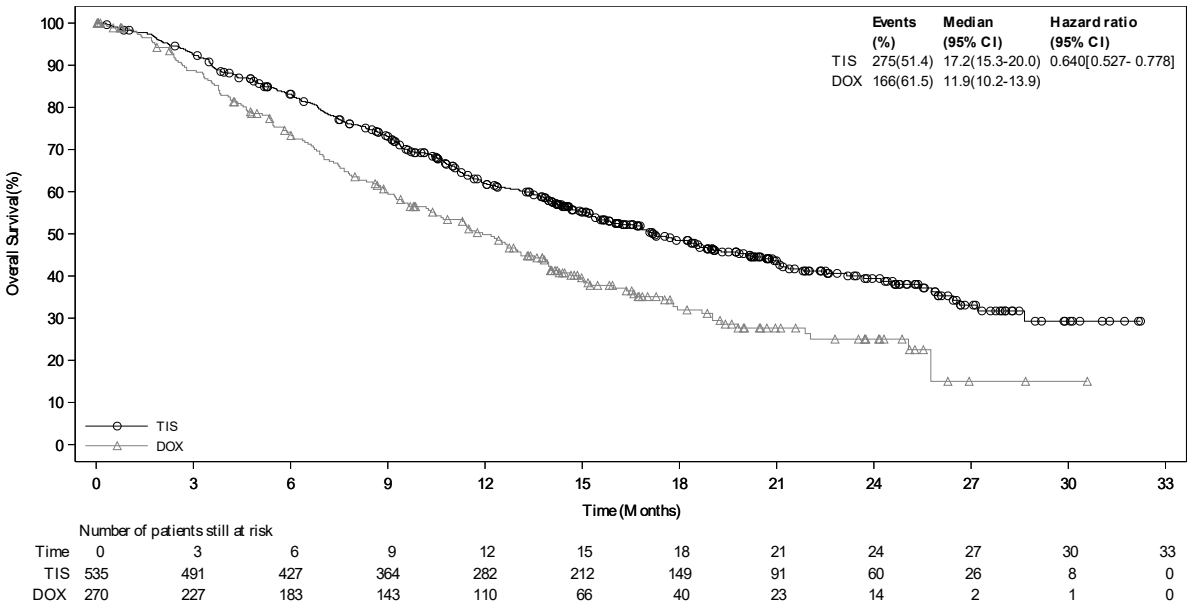


Figure 6 Kaplan-Meier plot of OS in BGB-A317-303 (PD-L1 TC ≥25% analysis set) (data cut-off date of 15-Jul-2021)

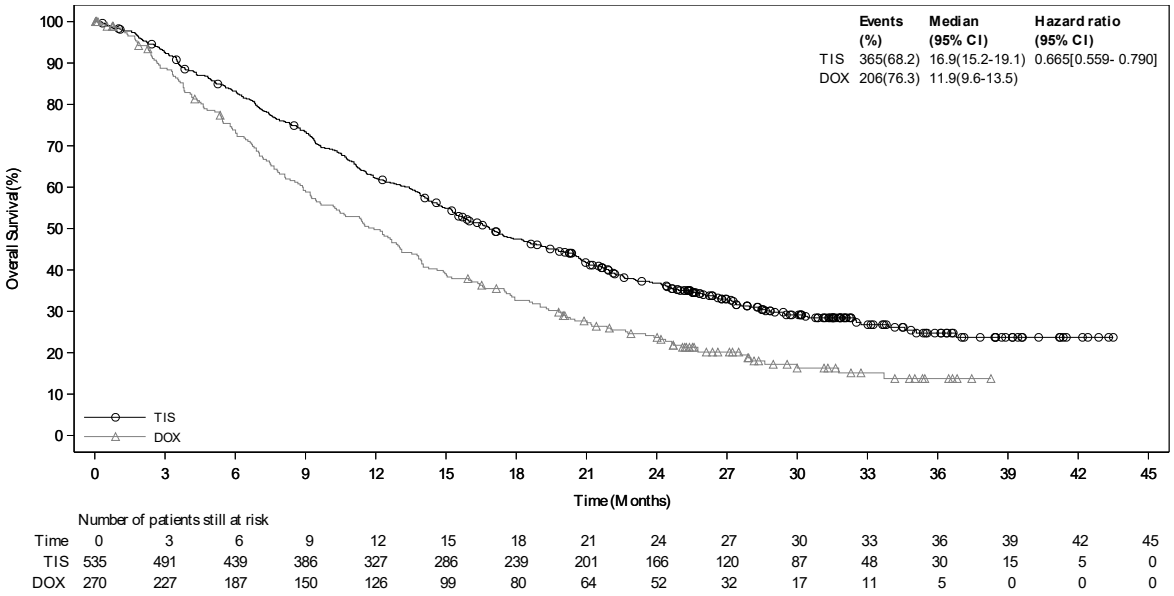
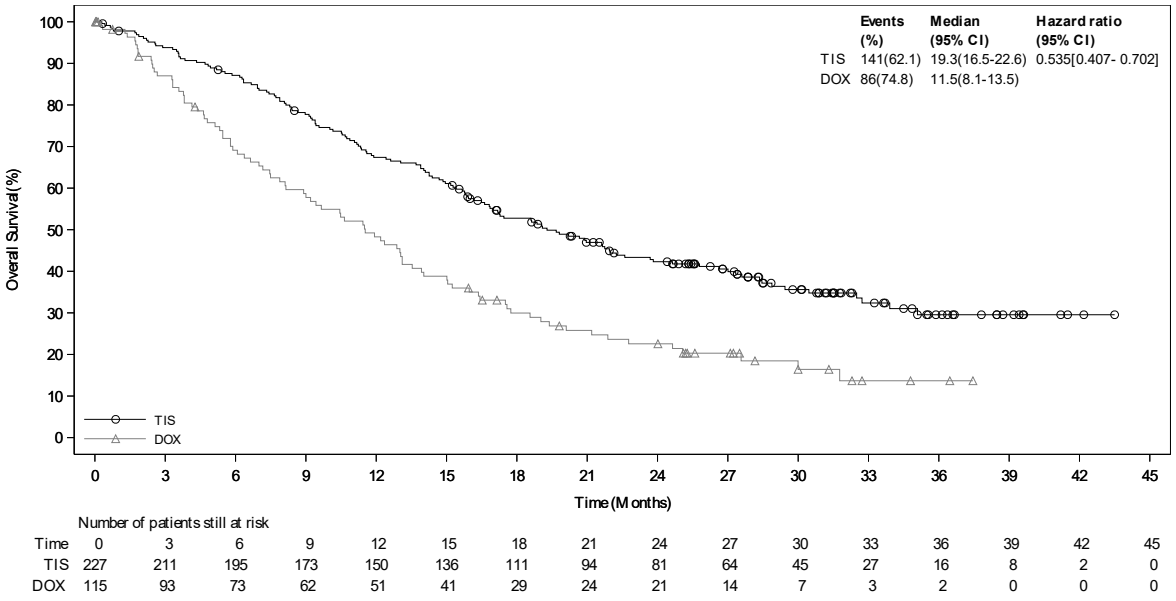


Figure 7 Kaplan-Meier plot of OS in BGB-A317-303 (PD-L1 TC ≥25% analysis set) (data cut-off date of 15-Jul-2021)



At the interim and final analyses, prespecified subgroup analyses demonstrated a consistent OS treatment effect in favour of tislelizumab across major demographic and prognostic subgroups, including race, PD-L1 expression, histology and line of therapy.

At the interim analysis, consistent treatment benefit was observed in both race types, with OS HR of 0.62 (95% CI, HR = 0.51, 0.77) for Asian and OS HR of 0.61 (95% CI, HR = 0.34, 1.08) for White patients. OS benefits were observed in both histological types, with OS HR of 0.58 (95% CI: 0.44, 0.76) for squamous NSCLC and OS HR of 0.71 (95% CI: 0.54, 0.93) for non-squamous NSCLC.

The final analysis confirmed consistent treatment benefit in both race types with OS HR of 0.66 (95% CI, HR = 0.54, 0.79) for Asian vs. 0.63 (95% CI, HR = 0.41, 0.98) for White patients. Consistent OS benefits were observed in both histological types as well, with OS HR of 0.60 (95% CI: 0.47, 0.77) for squamous NSCLC vs. 0.72 (95% CI: 0.56, 0.91) for non-squamous NSCLC.

Figure 8, Figure 9. Figure 10 and Figure 11 summarise efficacy results of OS by tumour PD-L1 expression in prespecified subgroup analyses.

Figure 8 Efficacy results of OS by tumour PD-L1 expression in BGB-A317-303 (data cut-off date 10-Aug-2020)

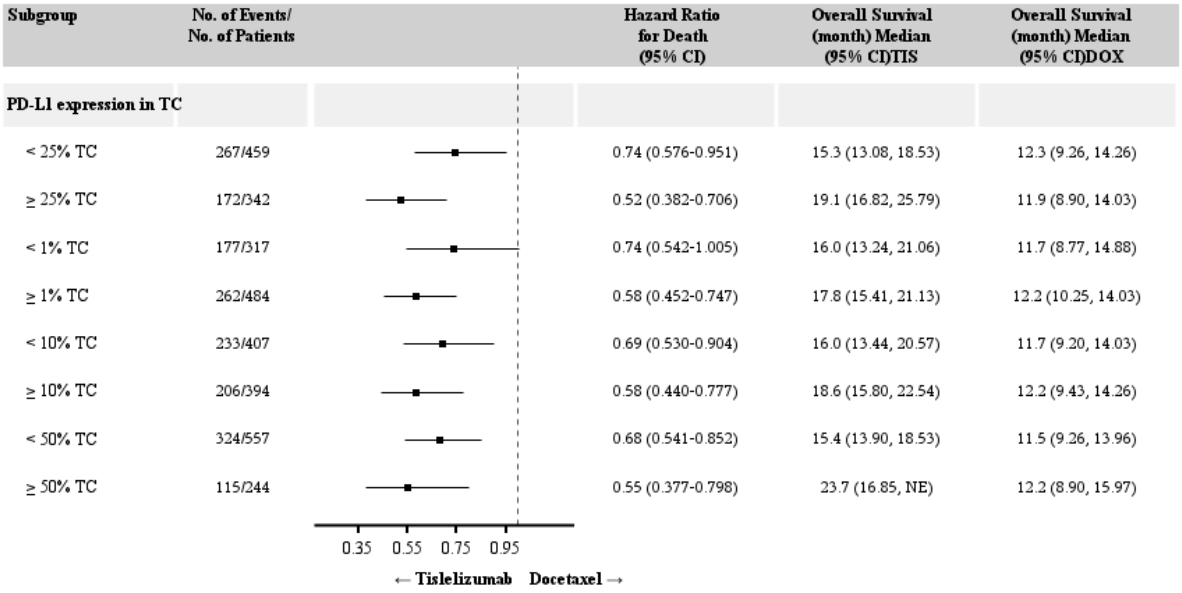


Figure 9 Efficacy results of OS by tumour PD-L1 expression in study BGB-A317-303 (data cut-off date of 15-Jul-2021)

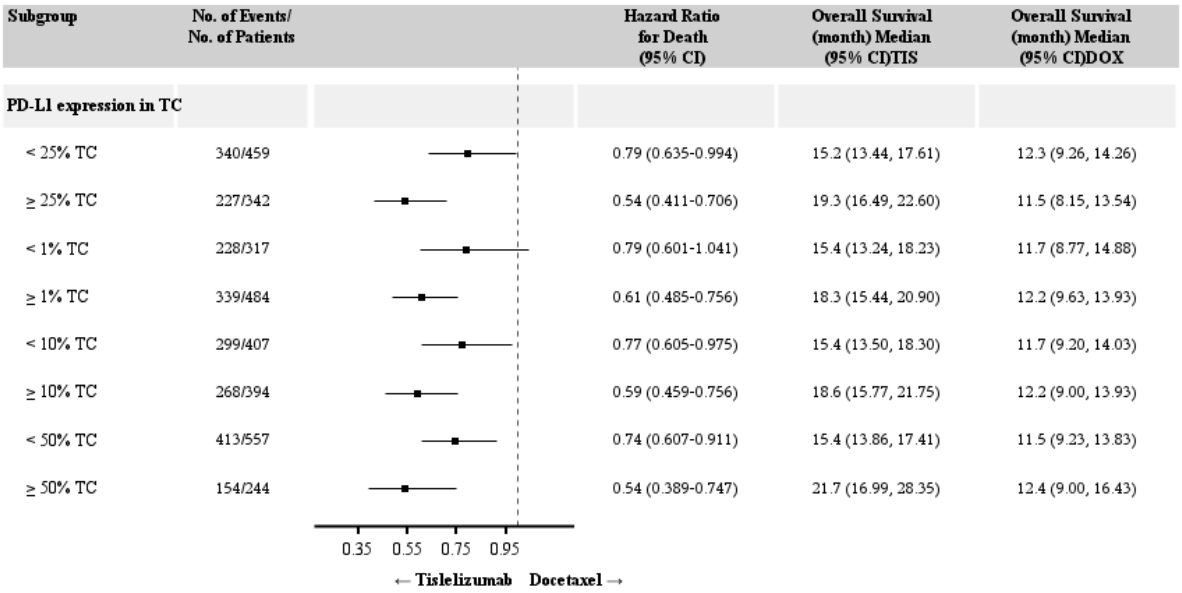
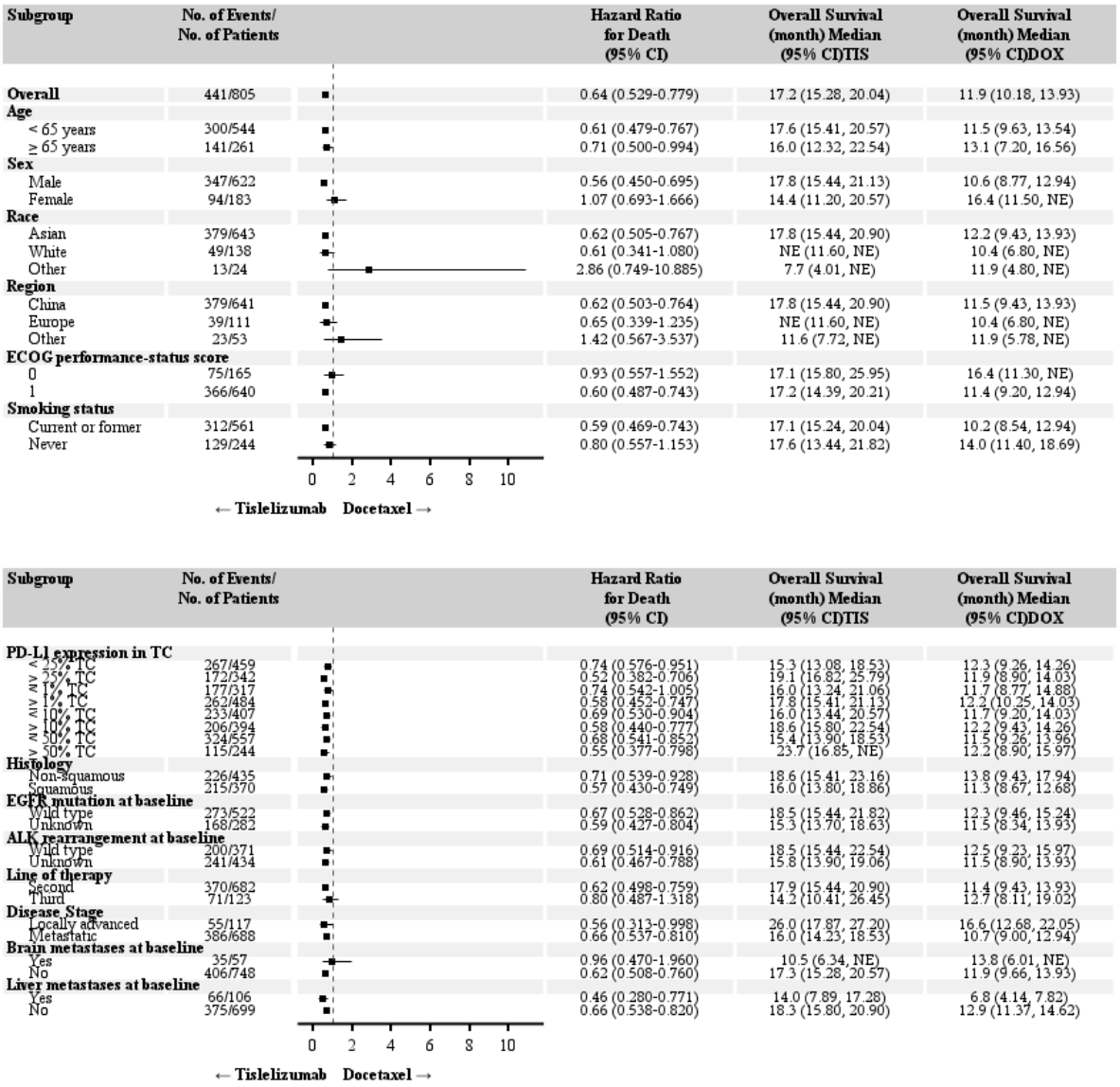


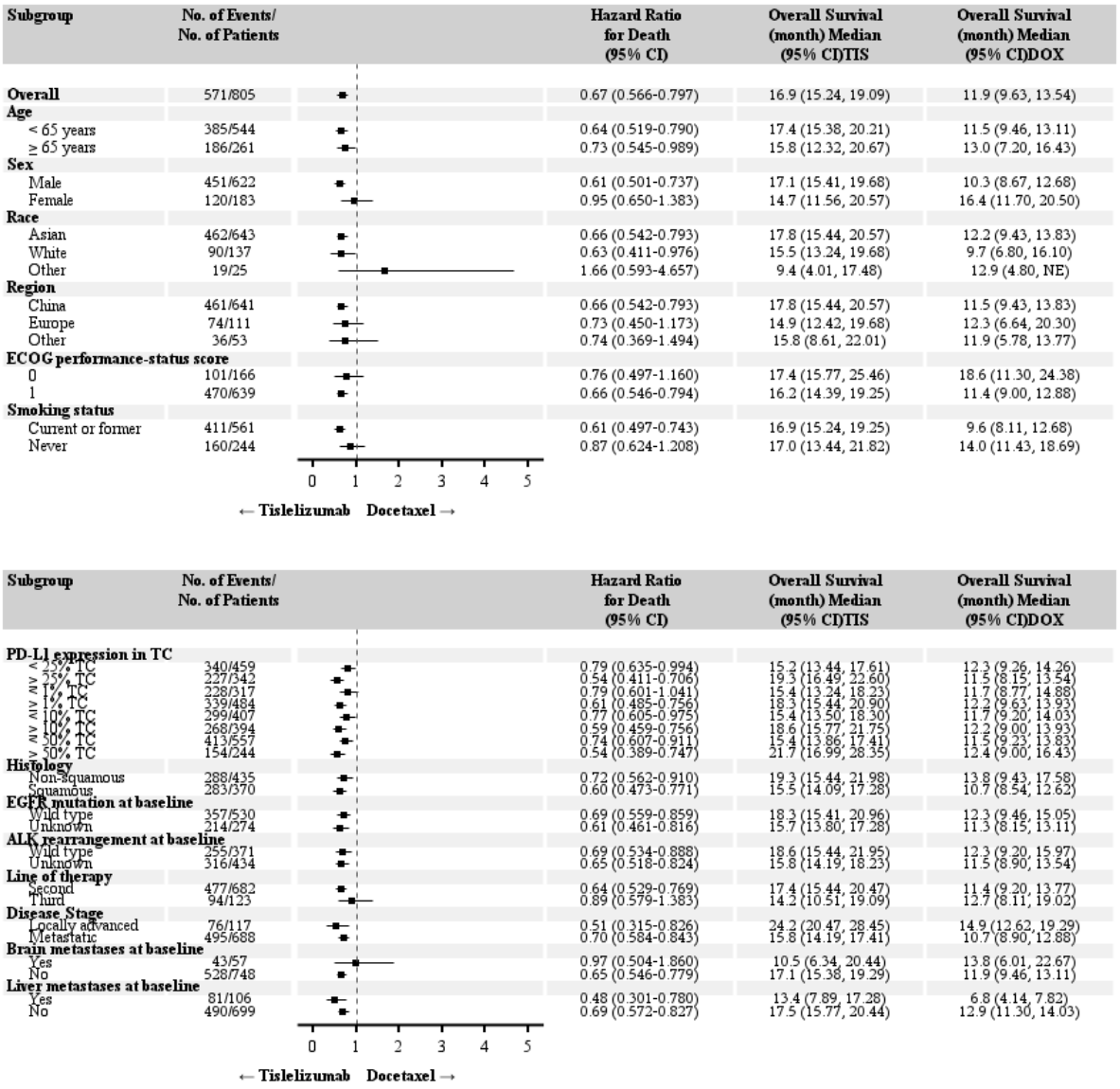
Figure 10 Forest plot of OS by subgroups in BGB-A317-303 (ITT analysis set) (data cut-off date of 10-Aug-2020)



Subgroup	No. of Events/ No. of Patients	Hazard Ratio for Death (95% CI)	Overall Survival (month) Median (95% CI)TIS	Overall Survival (month) Median (95% CI)DOX
Overall	441/805	0.64 (0.529-0.779)	17.2 (15.28, 20.04)	11.9 (10.18, 13.93)
Age				
< 65 years	300/544	0.61 (0.479-0.767)	17.6 (15.41, 20.57)	11.5 (9.63, 13.54)
≥ 65 years	141/261	0.71 (0.500-0.994)	16.0 (12.32, 22.54)	13.1 (7.20, 16.56)
Sex				
Male	347/622	0.56 (0.450-0.695)	17.8 (15.44, 21.13)	10.6 (8.77, 12.94)
Female	94/183	1.07 (0.693-1.666)	14.4 (11.20, 20.57)	16.4 (11.50, NE)
Race				
Asian	379/643	0.62 (0.505-0.767)	17.8 (15.44, 20.90)	12.2 (9.43, 13.93)
White	49/138	0.61 (0.341-1.080)	NE (11.60, NE)	10.4 (6.80, NE)
Other	13/24	2.86 (0.749-10.885)	7.7 (4.01, NE)	11.9 (4.80, NE)
Region				
China	379/641	0.62 (0.503-0.764)	17.8 (15.44, 20.90)	11.5 (9.43, 13.93)
Europe	39/111	0.65 (0.339-1.235)	NE (11.60, NE)	10.4 (6.80, NE)
Other	23/53	1.42 (0.567-3.537)	11.6 (7.72, NE)	11.9 (5.78, NE)
ECOG performance-status score				
0	75/165	0.93 (0.557-1.552)	17.1 (15.80, 25.95)	16.4 (11.30, NE)
1	366/640	0.60 (0.487-0.743)	17.2 (14.39, 20.21)	11.4 (9.20, 12.94)
Smoking status				
Current or former	312/561	0.59 (0.469-0.743)	17.1 (15.24, 20.04)	10.2 (8.54, 12.94)
Never	129/244	0.80 (0.557-1.153)	17.6 (13.44, 21.82)	14.0 (11.40, 18.69)

Subgroup	No. of Events/ No. of Patients	Hazard Ratio for Death (95% CI)	Overall Survival (month) Median (95% CI)TIS	Overall Survival (month) Median (95% CI)DOX
PD-L1 expression in TC				
< 25% TC	267/459	0.74 (0.576-0.951)	15.3 (13.08, 18.53)	12.3 (9.26, 14.26)
≥ 25% TC	172/342	0.52 (0.382-0.706)	19.1 (16.82, 25.79)	11.9 (8.90, 14.03)
< 1% TC	177/317	0.74 (0.542-1.005)	16.0 (13.24, 21.06)	11.7 (8.77, 14.88)
≥ 1% TC	262/484	0.58 (0.452-0.747)	17.8 (15.41, 21.13)	12.2 (10.25, 14.03)
< 10% TC	233/407	0.69 (0.530-0.904)	16.0 (13.44, 20.57)	11.7 (9.20, 14.03)
≥ 10% TC	206/394	0.58 (0.440-0.777)	18.6 (15.80, 22.54)	12.2 (9.43, 14.26)
< 50% TC	324/557	0.68 (0.541-0.852)	15.4 (13.90, 18.53)	11.5 (9.26, 13.96)
≥ 50% TC	115/244	0.55 (0.377-0.798)	23.7 (16.85, NE)	12.2 (8.90, 15.97)
Histology				
Non-squamous	226/435	0.71 (0.539-0.928)	18.6 (15.41, 23.16)	13.8 (9.43, 17.94)
Squamous	215/370	0.57 (0.430-0.749)	16.0 (13.80, 18.86)	11.3 (8.67, 12.68)
EGFR mutation at baseline				
Wild type	273/522	0.67 (0.528-0.862)	18.5 (15.44, 21.82)	12.3 (9.46, 15.24)
Unknown	168/282	0.59 (0.427-0.804)	15.3 (13.70, 18.63)	11.5 (8.34, 13.93)
ALK rearrangement at baseline				
Wild type	200/371	0.69 (0.514-0.916)	18.5 (15.44, 22.54)	12.5 (9.23, 15.97)
Unknown	241/434	0.61 (0.467-0.788)	15.8 (13.90, 19.06)	11.5 (8.90, 13.93)
Line of therapy				
Second	370/682	0.62 (0.498-0.759)	17.9 (15.44, 20.90)	11.4 (9.43, 13.93)
Third	71/123	0.80 (0.487-1.318)	14.2 (10.41, 26.45)	12.7 (8.11, 19.02)
Disease Stage				
Locally advanced	55/117	0.56 (0.313-0.998)	26.0 (17.87, 27.20)	16.6 (12.68, 22.05)
Metastatic	386/688	0.66 (0.537-0.810)	16.0 (14.23, 18.53)	10.7 (9.00, 12.94)
Brain metastases at baseline				
Yes	35/57	0.96 (0.470-1.960)	10.5 (6.34, NE)	13.8 (6.01, NE)
No	406/748	0.62 (0.508-0.760)	17.3 (15.28, 20.57)	11.9 (9.66, 13.93)
Liver metastases at baseline				
Yes	66/106	0.46 (0.280-0.771)	14.0 (7.89, 17.28)	6.8 (4.14, 7.82)
No	375/699	0.66 (0.538-0.820)	18.3 (15.80, 20.90)	12.9 (11.37, 14.62)

Figure 11 Forest plot of OS by subgroups in BGB-A317-303 (ITT analysis set) (data cut-off date of 15-Jul-2021)



PROs were collected using EORTC-QLQ-C30, QLQ-LC13 and EQ-5D-5L questionnaires. At the interim analysis, completion rates for all the 3 questionnaires were similar in both treatment arms, with compliance rates of >98% to 100% for QLQ-C30 and QLQ-LC13 and 78% to 100% for EQ-5D-5L.

Tislelizumab trended towards improvements in HRQoL compared to docetaxel in patients with NSCLC who had progressed on a prior platinum-containing regimen.

The tislelizumab arm showed improvements over time in QLQ-C30 GHS/QoL, as well as physical function, fatigue in QLQ-C30. Additionally, in the tislelizumab arm, there was a trend towards improvement in coughing, dyspnea and pain symptoms of the QLQ-C13 compared to docetaxel arm.

The change from baseline scores of EQ-5D-5L in the descriptive domain's total score as well as the visual analogue scale showed better outcomes in the tislelizumab Arm.

The median time to deterioration (TTD) for QLQ-C30 GHS/QoL and for the index score of the QLQ-LC13 was not reached in either treatment arm.

At the final analysis, compliance rates for all 3 questionnaires were similar in both treatment arms, with compliance rates of >96% to 100% for QLQ-C30 and QLQ-LC13 and >75% for EQ-5D-5L. Compliance rates of QoL assessments remained above 75% at baseline and during cycles 4 and 6.

The TEVIMBRA arm trended towards improvement from baseline in GHS/QoL as well as fatigue and coughing compared with the docetaxel arm. Improvements were observed in fatigue and QLQ-LC13 index score assessing overall lung cancer symptoms, while physical functioning was maintained compared to patients in the docetaxel arm who experienced worsening.

A arm were observed to be at lower risk of experiencing a deterioration event compared with those in the docetaxel arm, as indicated by stratified hazard ratio of 0.77 (95% [CI:0.57, 1.03]) in GHS/QoL and 0.24 (95% [CI:0.16,0.36]) in index score of QLQ-LC13.

The change from baseline scores of EQ-5D-5Lvisual analogue scale (VAS) showed similar outcomes in both arms.

Safety and efficacy in elderly patients

No overall differences in safety and efficacy were observed between patients aged <65 years, patients aged between 65 and 75 years and patients aged >75 years receiving tislelizumab as monotherapy or in combination treatment.

5.2 PHARMACOKINETICS PROPERTIES

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

The PK of tislelizumab was characterized 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.

Tislelizumab exhibited linear PK in the dose range tested (0.5 mg/kg to 10 mg/kg, including 200 mg flat dose). The time to reach 90% steady-state level is approximately 84 days (12 weeks) after 200 mg once every 3 weeks (Q3W) doses, and the steady-state accumulation ratio of tislelizumab PK exposure is approximately 2-fold.

Absorption

Tislelizumab is administered via the intravenous route 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%. Time-varying clearance was not observed in tislelizumab PK.

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), PK of tislelizumab were observed to be linear and dose proportional, suggesting saturation of the target-mediated pathway.

Special populations

The effects of various covariates on the PK of tislelizumab 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 (CLCr) ≥30 mL/min), mild to moderate hepatic impairment (total bilirubin ≤3 times ULN and any AST), and tumour burden.

Elderly patients

Of 2,596 patients who received tislelizumab as monotherapy or combination therapies, 1,750 patients (67.4%) were <65 years and 846 (32.6%) patients were ≥65 years of age, 737 (28.4%) patients between 65 and 75 years, and 109 (4.2%) patients >75 years).

Based on population PK and exposure- response analysis, no clinically relevant differences in PK or safety or efficacy of tislelizumab were observed between patient's aged <65 years, patients aged between 65 and 75 years and patients aged >75 years (see section 4 Dosage regimen and administration).

Patients with 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) or severe renal impairment (CL_{Cr} 15 to 29 mL/min, n=5) and patients with normal renal function (CL_{Cr} ≥90 mL/min, n=1223). Mild and moderate renal impairment had no effect on the exposure of tislelizumab (see section 4 Dosage regimen and administration).

Patients with hepatic impairment

No dedicated studies of tislelizumab have been conducted in patients with hepatic impairment. In the population PK analyses of tislelizumab, no clinically important 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 × ULN and any AST, n=396), moderate hepatic impairment (bilirubin >1.5 to 3 × 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 Dose and method of administration). Based on the limited number of patients with severe hepatic impairment (n=2), the effect of severe hepatic impairment on the pharmacokinetics of tislelizumab is unknown.

Hepatic impairment was defined by the National Cancer Institute-Organ Dysfunction Working Group (NCI-ODWG) criteria of hepatic dysfunction.

5.3 PRECLINICAL SAFETY DATA

Tislelizumab was evaluated in single- and repeated-dose toxicity studies including safety pharmacology endpoints.

In a repeat-dose toxicology study in cynomolgus monkeys, following intravenous infusion at 3, 10, or 30 mg/kg (once every 2 weeks (Q2W), 7 doses) for 13 weeks, no apparent treatment-related toxicity or histopathological changes were observed in any tissues or organs, including the reproductive system of male and females. However, many of the monkeys in these studies were not sexually mature and thus no explicit conclusions regarding effects on reproductive organs can be made. No specific concerns were identified regarding vital functions, including cardiovascular system, central nervous system, and respiratory system.

Reproductive toxicity/Fertility

No developmental and reproductive toxicity studies or animal fertility studies have been conducted with tislelizumab. Literature based data are reported in section 9.1 Pregnancy and section 9.3 Females and males of reproductive potential.

Animal toxicology and/or Pharmacology

In animal models, inhibition of PD-1 signaling resulted in an increased severity of some infections and enhanced inflammatory responses. PD-1 knockout mice infected with certain bacterial (e.g., mycobacterium tuberculosis) and viral pathogens (e.g., lymphocytic choriomeningitis) exhibited an increased severity of infection and enhanced inflammatory responses.

Carcinogenicity and mutagenicity or genotoxicity

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, histidine hydrochloride monohydrate, histidine, trehalose dihydrate, polysorbate-20, and water for injection (WFI).

6.2 INCOMPATIBILITIES

This product must not be mixed with products except sodium chloride, which is used to prepare diluted solution.

6.3 SHELF LIFE

Unopened vial

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

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 infusion

The dilution can be stored at 2°C to 8°C for up to 24 hours. The 24 hours include storage of the diluted solution under refrigeration (2 to 8°C) for no more than 20 hours, and time required for returning to room temperature (25°C and below) as well as completing the infusion within 4 hours.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store in a refrigerator at 2 to 8°C. Do not freeze. Store in the original carton box to protect from light.

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

6.5 NATURE AND CONTENTS OF CONTAINER

10mL of TEVIMBRA concentrate is provided in a 20 mL clear Type 1 glass vial, with a grey chlorobutyl stopper with FluroTec coating and seal cap with a flip-off button.

Each carton contains one vial.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Instructions for use and handling

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

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

Preparation of solution for infusion

1. Two TEVIMBRA vials are required for each dose. Remove the vials from the refrigerator, taking care not to shake them.
2. Inspect each vial visually for particulate matter and discoloration prior to administration. The concentrate is a clear to slightly opalescent, colorless to slightly yellowish solution. Do not use a vial if the solution is cloudy or if visible particles or discoloration are observed.
3. Invert the vials gently, without shaking. Withdraw the solution from the two vials (a total of 200 mg in 20 mL) and transfer into an intravenous (I.V.) infusion bag containing sodium chloride 9 mg/mL (0.9%) to prepare a diluted solution with a final concentration ranging from 1 to 5 mg/mL. Mix diluted solution by gentle inversion to avoid foaming or excessive shearing of the solution.

Administration

1. Administer the diluted tislelizumab solution by I.V. 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.
2. The first infusion should be delivered over 60 minutes. If well tolerated, subsequent infusions may be administered over 30 minutes.
3. Other drugs should not be co-administered through the same infusion line.
4. Tislelizumab must not be administered as an intravenous push or single bolus injection.
5. TEVIMBRA does not contain any preservatives. It is recommended to prepare the solution immediately after taking it out of the refrigerator. From a microbiological point of view, once infusion is prepared, it is recommended to use the solution immediately after dilution. The diluted solution can be stored at 2°C to 8°C (36°F to 46°F) for up to 24 hours. The 24 hours include storage of the diluted solution under refrigeration (2 to ~8°C) for no more than 20 hours, and time required for returning to room temperature (25°C and below) as well as completing the infusion within 4 hours.
6. The diluted solution must not be frozen.
7. TEVIMBRA vials are for single use only. Discard any unused portion left in the vial.

8. The intravenous line must be flushed at the end of the infusion.

Disposal

TEVIMBRA is for single use only. Any unused product or waste material should be disposed of in accordance with local requirements.

6.7 PHYSIOCHEMICAL PROPERTIES

Chemical structure

TEVIMBRA (tislelizumab) is a humanized monoclonal antibody that binds with high affinity to the human programmed cell death protein 1 (PD-1). Tislelizumab is an immunoglobulin subclass 4 (IgG4) variant produced by recombinant DNA technology in Chinese hamster ovary cells, with an approximate molecular weight of 144 kDa.

CAS number

1858168-59-8

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription only medicine

8 SPONSOR

BeiGene NZ Unlimited
c/o Quigg Partners
Level 7, The Bayleys Building
36 Brandon Street
Wellington 6011
New Zealand

9 DATE OF FIRST APPROVAL

5 December 2024

10 DATE OF REVISION

Not applicable

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
NA	New Data Sheet