▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at https://www.tga.gov.au/reporting-problems.

# AUSTRALIAN PRODUCT INFORMATION
# TEVIMBRA (tislelizumab (rch))

## 1 NAME OF THE MEDICINE

tislelizumab

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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 to 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 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 anti-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, 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.

Patients should be treated with TEVIMBRA 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 1.

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

**Table 1 Recommended treatment modifications for TEVIMBRA**

| **Immune-related adverse drug reaction** | **Severity[1]** | **TEVIMBRA treatment modification** |
|---|---|---|
| Pneumonitis | Grade 2 | Withhold[2] |
| | Recurrent Grade 2;<br>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) total bilirubin >3 times ULN | Permanently discontinue |
| Rash | Grade 3 | Withhold[2] |
| | Grade 4 | Permanently discontinue |
| Severe cutaneous adverse reactions (SCARs) | Suspected SCARs, including SJS or TEN | Withhold[2]<br>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;<br>Grade 4 | Permanently discontinue |
| Myositis/Rhabdomyolysis | Grade 2 or 3 | Withhold[2] |
| | Recurrent Grade 3; Grade 4 | Permanently discontinue |
| Hypothyroidism | Grade 2, 3 or 4 | Hypothyroidism may be managed with replacement therapy without treatment interruption. |
| Hyperthyroidism | Grade 3 or 4 | Withhold[2]<br>For grade 3 or 4 that has improved to grade ≤2 and is controlled with anti-thyroid therapy, if indicated continuation of TEVIMBRA may be considered after corticosteroid taper. Otherwise, treatment should be discontinued. |
| Adrenal insufficiency | Grade 2 | Consider withholding treatment until controlled by HRT. |
| | Grade 3 or 4 | Withhold[3]<br>For grade 3 or 4 that has improved to grade ≤2 and is controlled with HRT, if indicated continuation of TEVIMBRA may be considered after corticosteroid taper. Otherwise, treatment should be discontinued.[3] |
| Hypophysitis | Grade 2 | Consider withholding treatment until controlled by HRT. |
| | Grade 3 or 4 | Withhold[2,3]<br>For grade 3 or 4 that has improved to grade ≤2 and is controlled with HRT, if indicated continuation of Tevimbra may be considered after corticosteroid taper. Otherwise, treatment should be discontinued.[3] |
| Type 1 diabetes mellitus | Type 1 diabetes mellitus associated with grade ≥3 hyperglycaemia (glucose >250 mg/dl or >13.9 mmol/l) or associated with ketoacidosis | Withhold<br>For grade 3 or 4 that has improved to grade ≤2 with insulin therapy, if indicated continuation of Tevimbra may be considered once metabolic control is achieved. Otherwise, treatment should be discontinued. |
| Nephritis with renal dysfunction | Grade 2 (creatinine >1.5 to 3 times baseline or >1.5 to 3 times ULN) | Withhold[2] |

| | | |
|---|---|---|
| | Grade 3 (creatinine >3 times baseline or >3 to 6 times ULN)<br>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 |
| Pancreatitis | Grade 3 pancreatitis or<br>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 pre-medication for prophylaxis of subsequent infusion reactions.<br>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%. Consider pre-medication for prophylaxis of subsequent infusion-related reactions.*

## 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 5.2 Pharmacokinetic properties).

## Method of administration

TEVIMBRA is for intravenous infusion use only.

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 Australian Prescribing Information for the chemotherapy administered in combination with TEVIMBRA.

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

## 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

### Patient Alert Card and Patient/Caregiver Guide

Patients treated with TEVIMBRA must be given the Patient/Caregiver Guide and Patient Alert Card to be informed about the risks of immune-related adverse reactions during tislelizumab therapy.

Prescribers must discuss the risks of immune-related adverse reactions during tislelizumab therapy with the patient.

### Immune-related adverse drug reactions

Severe, including fatal, cases of pneumonitis and hepatitis have been reported. 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 TEVIMBRA. 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 1 (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 TEVIMBRA, 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 1 (see section 4.2 Dose and method of administration) as well as applicable current local treatment guidelines.

*Immune-related skin reactions*

Cases of severe cutaneous adverse reactions (SCARs) including erythema multiforme (EM), Stevens-Johnson-Syndrome (SJS)and toxic epidermal necrolysis (TEN), some with fatal outcome, have been

reported in patients receiving TEVIMBRA. 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, TEVIMBRA should be withheld, and the patient should be referred to specialized care for assessment and treatment. If SCARs is confirmed, TEVIMBRA should be permanently discontinued (see section 4.2 Dose and method of administration).

Immune-related skin rash or dermatitis have been reported in patients receiving TEVIMBRA. 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, TEVIMBRA should be withheld or permanently discontinued as recommended in Table 1 (see section 4.2 Dose and method of administration) as well as per applicable current local treatment guidelines.

*Immune-related colitis*

Immune-related colitis, frequently associated with diarrhea, has been reported in patients treated with TEVIMBRA. 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 1 (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, hypophysitis and type 1 diabetes mellitus, have been reported in patients treated with TEVIMBRA, which may require supportive treatment depending on the specific endocrine disorder. Long-term hormone replacement therapy (HRT) may be necessary in cases of immune-related endocrinopathies.

Patients with immune-related endocrinopathies should be managed according to treatment modifications as recommended in Table 1 (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 TEVIMBRA. Thyroiditis can present with or without other forms of 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 TEVIMBRA. 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 TEVIMBRA. 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.

*Type 1 Diabetes mellitus*

Type 1 diabetes mellitus, including diabetic ketoacidosis has been reported in patients treated with TEVIMBRA. Patients should be monitored for hyperglycaemia or other signs and symptoms of diabetes. Insulin should be administered as clinically indicated for type 1 diabetes. In patients with severe hyperglycaemia or ketoacidosis (Grade ≥3), TEVIMBRA should be withheld and anti-hyperglycaemic treatment should be administered (see section 4.2 Dose and method of administration). Treatment with TEVIMBRA 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 TEVIMBRA. 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 1 (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 TEVIMBRA: myositis, myocarditis, arthritis, polymyalgia rheumatica, pericarditis, immune thrombocytopenia 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 1 (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 TEVIMBRA may increase the risk of rejection in solid organ transplant recipients. The benefit of treatment with TEVIMBRA 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 TEVIMBRA as a single agent (see 4.8 Adverse effects (Undesirable effects)). Cases of anaphylaxis, including anaphylactic reaction and anaphylactic shock, have been reported in the post-marketing setting. Patients should be monitored for signs and symptoms of infusion-related reactions.

Infusion-related reactions should be managed as recommended in Table 1 (see section 4.2 Dose and method of administration).

**Embryo-fetal toxicity**

There are no available data on the use of TEVIMBRA in pregnant women. Based on its mechanism of action, TEVIMBRA 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. TEVIMBRA 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 TEVIMBRA.

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 TEVIMBRA and for at least 4 months after the last dose of TEVIMBRA (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

**Effects on 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.

**Use in pregnancy (Category D)**

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 fetal harm.

Animal reproduction studies have not been conducted with tislelizumab. However, in murine models of pregnancy, blockade of PD1/PDL1 signaling has been shown to disrupt tolerance to the fetus and to result in increased fetal 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 fetus. Tislelizumab is not recommended during pregnancy unless the clinical benefit is expected to outweigh the potential risk to the fetus. Tislelizumab should not be used during pregnancy and in women of childbearing potential not using effective contraception. 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.

**Use in lactation**

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.

## 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 tislelizumab as monotherapy is based on pooled data in 1,972 patients across multiple tumour types. The most common adverse drug reaction (ADR) (reported at a frequency >20%, with tislelizumab as monotherapy) was fatigue. The most common Grade 3/4 ADRs (reported at a frequency >2%, with tislelizumab as monotherapy) were increased aspartate aminotransferase and fatigue.

ADRs leading to death were reported in 0.3% of patients. The ADRs leading to death were pneumonitis (0.1%), hepatitis (0.1%) and dyspnoea (0.05%).

*Tislelizumab as combination therapy*

The safety of tislelizumab given in combination with chemotherapy is based on data in 497 patients with NSCLC. Tislelizumab 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 tislelizumab in combination with chemotherapy) were rash, fatigue, increased aspartate aminotransferase, increased alanine aminotransferase. The most common Grade 3/4 ADRs (reported at a frequency >2%, with tislelizumab in combination with chemotherapy) were pneumonitis, rash, fatigue and increased alanine aminotransferase.

ADRs leading to death were reported in 1.2% of patients. The ADRs leading to death were pneumonitis (0.6%), dyspnoea (0.4%) and myocarditis (0.4%).

**Tabulated list of adverse reactions**

Table 2 lists the incidence of adverse reactions in the monotherapy safety dataset and in patients treated with tislelizumab 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. The corresponding frequency category for each ADR is defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from available data). Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness.

**Table 2 Adverse drug reactions with tislelizumab as monotherapy (N = 1,972) and in combination with chemotherapy (N = 497)**

| | **Tislelizumab monotherapy N = 1972** | **Tislelizumab combination therapy N = 497** |
|---|---|---|
| **Adverse drug reactions** | **All Grades n (%)** | **All Grades n (%)** |
| **Endocrine disorders** | | |
| Hypothyroidism[1] | 233 (11.8) | 77 (15.5) |
| Hyperthyroidism[2] | 104 (5.3) | 54 (10.9) |
| Thyroiditis[3] | 23 (1.2) | 3 (0.6) |
| Adrenal insufficiency[4] | 9 (0.5) | - |
| Hypophysitis[5] | 2 (0.1) | - |
| **Metabolism and nutrition disorders** | | |
| Hyperglycaemia[6] | 148 (7.5) | 81 (16.3) |
| Diabetes mellitus[7] | 13 (0.7) | 6 (1.2) |
| **Nervous system disorders** | | |
| Guillain-Barré syndrome | - | 1 (0.2) |
| **Eye disorders** | | |
| Uveitis[8] | 5 (0.3) | - |
| **Cardiac disorders** | | |
| Myocarditis[9] | 12 (0.6) | 9 (1.8)* |
| Pericarditis | 1 (0.05) | - |
| **Respiratory, thoracic and mediastinal disorders** | | |
| Cough | 298 (15.1) | 76 (15.3) |
| Dyspnoea | 157 (8.0)* | 60 (12.1)* |
| Pneumonitis[10] | 93 (4.7)* | 60 (12.1)* |
| **Gastrointestinal disorders** | | |
| Diarrhoea[11] | 221 (11.2) | 73 (14.7) |
| Stomatitis[12] | 56 (2.8) | 29 (5.8) |
| Pancreatitis[13] | 16 (0.8) | 1 (0.2) |
| Colitis[14] | 13 (0.7) | 6 (1.2) |
| **Hepatobiliary disorders** | | |
| Hepatitis[15] | 47 (2.4)* | 21 (4.2) |
| **Skin and subcutaneous tissue disorders** | | |
| Rash[16] | 322 (16.3) | 131 (26.4) |
| Pruritus | 209 (10.6) | 34 (6.8) |
| Severe skin reactions[17] | 2 (0.1) | - |

| | | |
|---|---|---|
| **Musculoskeletal and connective tissue disorders** | | |
| Arthralgia | 181 (9.2) | 78 (15.7) |
| Myalgia | 37 (1.9) | 19 (3.8) |
| Myositis[18] | 16 (0.8) | 1 (0.2) |
| Arthritis[19] | 13 (0.7) | 5 (1.0) |
| **Renal and urinary disorders** | | |
| Nephritis[20] | 4 (0.2) | 2 (0.4) |
| **General disorders and administration site conditions** | | |
| Fatigue[21] | 485 (24.6) | 214 (43.1) |
| **Investigations** | | |
| Aspartate aminotransferase increased | 341 (17.3) | 210 (42.3) |
| Alanine aminotransferase increased | 318 (16.1) | 229 (46.1) |
| Blood bilirubin increased[22] | 192 (9.7) | 90 (18.1) |
| Blood alkaline phosphatase increased | 121 (6.1) | 55 (11.1) |
| **Injury, poisoning and procedural complications** | | |
| Infusion-related reaction[23] | 29 (1.5) | 12 (2.4) |

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

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

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

[4] Adrenal insufficiency includes PTs of adrenal insufficiency and secondary adrenocortical insufficiency.

[5] Hypophysitis includes PTs of hypopituitarism and lymphocytic hypophysitis.

[6] Hyperglycaemia includes PTs of hyperglycaemia and blood glucose increased.

[7] Diabetes mellitus includes PTs of diabetes mellitus, type 1 diabetes mellitus, diabetic ketoacidosis and latent autoimmune diabetes in adults.

[8] Uveitis includes PTs of uveitis and iritis.

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

[10] Pneumonitis includes PTs of pneumonitis, immune-mediated lung disease, interstitial lung disease and organising pneumonia.

[11] Diarrhoea includes PTs of diarrhoea and frequent bowel movements.

[12] Stomatitis includes PTs of stomatitis, mouth ulceration and aphthous ulcer.

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

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

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

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

[17] Severe skin reaction includes erythema multiforme.

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

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

[20] Nephritis includes PTs of nephritis, focal segmental glomerulosclerosis and immune-mediated nephritis.

[21] Fatigue includes PTs of fatigue, asthenia, malaise and lethargy.

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

[23] Infusion-related reaction includes PTs of rash, infusion-related reaction, chills, rash erythematous, rhinitis allergic, urticaria, drug hypersensitivity, laryngeal oedema, rash macular, rash pruritic, swelling face, anaphylactic reaction, corneal oedema, dermatitis allergic, drug eruption, face oedema, gingival swelling, lip oedema, lip swelling, mouth swelling, pruritus allergic, tongue oedema and type I hypersensitivity. Cases of anaphylaxis, including anaphylactic reaction and anaphylactic shock have been reported in the post-marketing setting.

[*] Including fatal outcomes.

**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 3adverse 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 3.

**Table 3 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) |
| 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/m$^2$ and carboplatin AUC 5 mg/mL/min or cisplatin 75 mg/m$^2$ (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 4.

**Table 4 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) |

| | T+PP (N = 222) | | PP (N = 110) | |
|---|---|---|---|---|
| **System Organ Class Preferred Term** | **All Grades n (%)** | **≥Grade 3 n (%)** | **All Grades n (%)** | **≥Grade 3 n (%)** |
| 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) |
| 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 5.

**Table 5 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) |

| | 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 (%)** |
| 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 conditions | 77 (64.2) | 5 (4.2) | 70 (59.3) | 3 (2.5) | 62 (53.0) | 5 (4.3) |
| 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 6.

**Table 6 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 7 pooled studies of tislelizumab as monotherapy and the 3 pooled studies of tislelizumab in combination with chemotherapy are presented in Table 7.

**Table 7 Laboratory abnormalities worsening from baseline with tislelizumab as monotherapy (N = 1,972) and in combination with chemotherapy (N = 497)**

| | **Tislelizumab monotherapy N = 1972** | **Tislelizumab combination therapy N = 497** |
|---|---|---|
| **Laboratory abnormality parameter*** | **All Grades n/m (%)** | **All Grades n/m (%)** |
| **Hematological parameters** | | |
| Haemoglobin increased | 61/1911 (3.2) | 7/495 (1.4) |
| Haemoglobin decreased | 716/1911 (37.5) | 459/495 (92.7) |
| Leukocytes decreased | 267/1909 (14.0) | 439/495 (88.7) |
| Lymphocytes increased | 27/1891 (1.4) | - |
| Lymphocytes decreased | 728/1891 (38.5) | - |
| Neutrophils decreased | 194/1892 (10.3) | 445/494 (90.1) |
| Platelets decreased | 248/1910 (13.0) | 364/495 (73.5) |
| **Biochemical parameters** | | |
| Alanine aminotransferase increased | 547/1909 (28.7) | 274/495 (55.4) |
| Albumin decreased | 625/1908 (32.8) | - |
| Alkaline phosphatase increased | 586/1907 (30.7) | 161/494 (32.6) |
| Aspartate aminotransferase increased | 601/1907 (31.5) | 262/495 (52.9) |
| Bilirubin increased | 330/1902 (17.4) | 141/495 (28.5) |
| Creatine kinase increased | 165/894 (18.5) | 97/457 (21.2) |
| Creatinine increased | 260/1908 (13.6) | 92/495 (18.6) |
| Potassium increased | 188/1903 (9.9) | 53/495 (10.7) |
| Potassium decreased | 262/1903 (13.8) | 142/495 (28.7) |
| Sodium increased | 110/1904 (5.8) | 39/495 (7.9) |
| Sodium decreased | 595/1904 (31.3) | 287/495 (58.0) |

**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: 1,891 to 1,911 patients), combination therapy (range: 457 to 495 patients).*
*n is the number of patients with worsen toxicity grade compared with baseline. m is the number of patients with both baseline and post-baseline laboratory test assessments.*

## ADRs from spontaneous reports and literature cases (frequency not known)

The following ADRs are derived from post-marketing experience with tislelizumab via spontaneous case reports and literature cases. As these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known.

| System Organ Class | Adverse drug reaction |
|---|---|
| Skin and subcutaneous tissue disorders | Stevens-Johnson-Syndrome, Toxic Epidermal Necrolysis[1] (see section 6 Warnings and precautions). |

[1]*Fatal outcomes reported.*

## 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 TEVIMBRA when given in combination are presented if clinically relevant differences were noted in comparison to TEVIMBRA monotherapy.

*Immune-related pneumonitis*

In patients treated with TEVIMBRA as monotherapy, immune-related pneumonitis occurred in 3.9% of patients, including Grade 1 (0.3%), Grade 2 (1.7%), Grade 3 (1.5%), Grade 4 (0.3%) and Grade 5 (0.2%) events.

The median time from first dose to onset of the event was 3.1 months (range: 1.0 day to 16.5 months), and the median duration from onset to resolution was 5.8 months (range: 1+ day to 22.8+ 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 1.5% of patients. All 77 patients received systemic corticosteroids. + denotes a censored observation. 70 (90.9%) of the 77 patients received high-dose (defined as a dose ≥40 mg/day of prednisone or equivalent) systemic corticosteroids. One (1.3%) of 77 patients received immunosuppressive treatment. Pneumonitis resolved in 37 (48.1%) of the 77 patients.

*Immune-related hepatitis*

In patients treated with tislelizumab as monotherapy, immune--related hepatitis occurred in 36 (1.8%) of 1,972 patients, including Grade 1 (1 patient, 0.1%), Grade 2 (12 patients, 0.6%), Grade 3 (20 patients, 1.0%), Grade 4 (1 patient, 0.1%) and Grade 5 (2 patients, 0.1%) events.

The median time from first dose to onset of the event was 1.3 months (range: 8.0 days to 34.8 months), and the median duration from onset to resolution was 1.2 months (range: 1 day to 37.9+ months). + denotes a censored observation, with ongoing events at the time of the analysis. tislelizumab was permanently discontinued in 0.5% of patients and tislelizumab treatment was interrupted in 21 (1.1%) of patients for immune-related hepatitis. Thirty-five (97.2%) out of 36 patients received systemic corticosteroids. Thirty (83.3%) of the 36 patients received high-dose systemic corticosteroids. One (2.8%) of the 36 patients received other immunosuppressive treatment. Hepatitis resolved in 20 (55.6%) of the 36 patients.

*Immune-related skin adverse reactions*

In patients treated with tislelizumab as monotherapy, immune-related skin adverse reactions occurred in 1.6% of patients, including Grade 1 (0.4%), Grade 2 (0.6%), Grade 3 (0.4%) and Grade 4 (0.2%) events.

The median time from first dose to onset of the event was 1.9 months (range: 2.0 days to 19.8 months). The median duration from onset to resolution was 6.7 months (range: 4.0 days to 34.0+ months). + denotes a censored observation, with ongoing events at the time of the analysis. TEVIMBRA was permanently discontinued in 0.3% of patients, and tislelizumab treatment was

interrupted in 0.6% of patients. Thirty-one (96.9%) of the 32 patients received systemic corticosteroids. + denotes a censored observation. Fifteen (46.9%) of the 32 patients received high-dose systemic corticosteroids. Two out of 32 patients (6.3%) received immunosuppressive treatment. Skin adverse reactions resolved in 17 (53.1%) of the 32 patients.

*Immune-related colitis*

In patients treated with tislelizumab as monotherapy, immune-related colitis occurred in 1.0% of patients, including Grade 2 (0.6%) and Grade 3 (0.4%) events.

The median time from first dose to onset of the event was 3.1 months (range: 12 days to 14.4 months), and the median duration from onset to resolution was 21.0 days (range: 1.0 day to 15.6+ months). + denotes a censored observation, with ongoing events at the time of the analysis. Tislelizumab was permanently discontinued in 0.2% of patients and tislelizumab treatment was interrupted in 0.6% of patients.

All 19 patients received systemic corticosteroids. + denotes a censored observation. Fourteen (73.7%) of the 19 patients were treated with high-dose systemic corticosteroids. Two (10.5%) of the 19 patients received immunosuppressive treatment. Colitis resolved in 15 (78.9%) 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 (0.2%), Grade 2 (0.3%), Grade 3 (0.3%) and Grade 4 (0.1%) events.

The median time from first dose to onset of the event was 1.8 months (range: 15.0 days to 17.6 months), and the median duration from onset to resolution was 2.1 months (range: 5.0 days to 11.2+ months). + denotes a censored observation, with ongoing events at the time of the analysis. Tislelizumab was permanently discontinued in 0.2% of patients and tislelizumab treatment was interrupted in 0.5% of patients.

All 14 patients received systemic corticosteroids. + denotes a censored observation. Ten (71.4%) of the 14 patients were treated with high-dose systemic corticosteroids. No patients received immunosuppressive treatment. Myositis/rhabdomyolysis resolved in 8 (57.1%) of the 14 patients.

*Immune-related endocrinopathies*

*Thyroid disorders*

Hypothyroidism

In patients treated with tislelizumab as monotherapy, hypothyroidism occurred in 6.7% of patients, including Grade 1 (1.3%), Grade 2 (5.4%) and Grade 4 (0.1%) events.

The median time from first dose to onset of the event was 3.6 months (range: 0 days to 16.6 months). The median duration from onset to resolution was not evaluable based on currently available data (range: 12.0 days to 46.1+ months). + denotes a censored observation, with ongoing events at the time of the analysis. Tislelizumab was not permanently discontinued in any patient and tislelizumab treatment was interrupted in 0.3% of patients. Two (1.5%) of the 133 patients received systemic corticosteroids. No patient received high-dose systemic corticosteroids. All 133 patients received hormone replacement therapy. Hypothyroidism resolved in 37 (27.8%) of the 133 patients.

Hyperthyroidism

In patients treated with tislelizumab as monotherapy, hyperthyroidism occurred in 0.6% of patients, including Grade 1 (0.1%), Grade 2 (0.5%) and Grade 3 (0.1%) events.

The median time from first dose to onset of the event was 1.3 months (range: 19.0 days to 14.5 months). The median duration from onset to resolution was 1.6 months (range: 22 days to 4.0+ months). + denotes a censored observation, with ongoing events at the time of the analysis. Tislelizumab was permanently discontinued in 0.1% of patients and tislelizumab treatment was interrupted in 0.1% of patients. One (8.3%) of the 12 patients received systemic corticosteroids. No patient received high-dose systemic corticosteroids. All 12 patients received hormone replacement therapy. Hyperthyroidism resolved in 11 (91.7%) of the 12 patients.

Thyroiditis

In patients treated with tislelizumab as monotherapy, thyroiditis occurred in 0.7% of patients, including Grade 1 (0.2%) and Grade 2 (0.5%) events.

The median time from first dose to onset of the event was 2.0 months (range: 20 days to 20.6 months). The median duration from onset to resolution was not evaluable (range: 22 days to 23.1+ months). + denotes a censored observation, with ongoing events at the time of the analysis. Tislelizumab was not permanently discontinued in any patient and tislelizumab treatment was interrupted in 0.1% of patients. One (7.7%) of the 13 patients received systemic corticosteroids. Twelve (92.3%) of the 13 patients received hormone replacement therapy. One (7.7%) of 13 patients received high-dose systemic corticosteroids. Thyroiditis resolved in 3 (23.1%) of the 13 patients.

*Adrenal insufficiency*

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

The median time from first dose to onset of the event was 3.4 months (range: 1.3 months to 11.6 months). The median duration from onset to resolution was not evaluable based on currently available data (range: 1 month to 27.9+ months). + denotes a censored observation, with ongoing events at the time of the analysis. Tislelizumab was not permanently discontinued in any patient and tislelizumab treatment was interrupted in 0.3% of patients. All 6 patients received systemic corticosteroids. Two (33.3%) of the 6 patients received high-dose systemic corticosteroids. Adrenal insufficiency resolved in 1 (16.7%) of the 6 patients.

*Hypophysitis*

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

*Type 1 diabetes mellitus*

In patients treated with tislelizumab as monotherapy, type 1 diabetes mellitus occurred in 8 (0.4%) patients, including Grade 1 (1 patient, 0.1%), Grade 3 (6 patients, 0.3%) and Grade 4 (1 patient, 0.1%) events.

The median time from first dose to onset of the event was 2.5 months (range: 29 days to 13.8 months). The median duration from onset to resolution was not evaluable (range: 2 days to 20.2+ months). + denotes a censored observation, with ongoing events at the time of the analysis. Tislelizumab was permanently discontinued in 0.2% of patients and tislelizumab treatment was interrupted in 0.1% of patients. Type 1 diabetes mellitus resolved in one (12.5%) of 8 patients. The median duration for all

resolved events was not evaluable (range: 2 days to 20.2+ months). All patients received hormone therapy for Type 1 diabetes mellitus.

*Immune-related nephritis and renal dysfunction*

In patients treated with tislelizumab as monotherapy, type 1 diabetes mellitus occurred in 10 (0.5%) of 1,972 patients, including Grade 2 (4 patients, 0.2%), Grade 3 (3 patients, 0.2%), Grade 4 (2 patients, 0.1%) and Grade 5 (1 patient, 0.1%) events.

The median time from first dose to onset of the event was 1.2 months (range: 3 days to 5.8 months). The median duration from onset to resolution was 1.9 months (range: 3+ days to 16.2+ months). + denotes a censored observation, with ongoing events at the time of the analysis. Tislelizumab was permanently discontinued in 4 (0.2%) of patients and tislelizumab treatment was interrupted in 4 (0.2%) of patients. 9 (90%) out of 10 patients received systemic corticosteroids. + denotes a censored observation. Seven (70%) of the 10 patients received high-dose systemic corticosteroids. One (10%) of the 10 patients received immunosuppressive treatment.

Immune-related nephritis and renal dysfunction resolved in 5 (50%) of the 10 patients.

*Immune-related myocarditis*

In patients treated with tislelizumab as monotherapy, immune-related myocarditis occurred in 7 (0.4%) of 1,972 patients, including Grade 1 (1 patient, 0.1%), Grade 2 (2 patients, 0.1%), Grade 3 (3 patients, 0.2%) and Grade 4 (1 patient, 0.1%) events.

The median time from first dose to onset of the event was 1.6 months (range: 14 days to 6.1 months), and the median duration from onset to resolution was 5.1 months (range: 4.0 days to 7.6+ months). + denotes a censored observation. Tislelizumab was permanently discontinued in 5 (0.3%) of patients and tislelizumab treatment was interrupted in 3 (0.2%) of patients. All 7 patients received systemic corticosteroids, with a median initial dose of 80 mg/day (range: 20.0 to 200.0 mg/day) for a median duration of 15 days (range: 1.0 day to 2.4+ months). All 7 patients received high-dose corticosteroids. One (14.3%) of the 7 patients received immunosuppressive treatment. Myocarditis resolved in 4 (57.1%) of the 7 patients.

*Infusion related reactions*

In patients treated with tislelizumab as monotherapy, infusion-related reactions occurred in 83 (4.2%) of 1,972 patients, including Grade 3 (5 patients, 0.3%) and Grade 4 (1 patient, 0.1%) events. Twenty-six (31.3%) of the 83 patients received treatment with corticosteroids. Tislelizumab was permanently discontinued in 5 (0.3%) of patients and tislelizumab treatment was interrupted in 21 (1.1%) of patients. Cases of anaphylaxis, including anaphylactic reaction and anaphylactic shock, have been reported in the post-marketing setting.

*Immunogenicity*

Of 1,916 antidrug antibodies (ADA)-evaluable patients treated at the recommended dose of 200 mg once every 3 weeks, 350 (18.3%) of patients tested positive for treatment-emergent ADA, and neutralising antibodies (NAbs) were detected in 18 (0.9%) of patients. Population pharmacokinetic analysis showed that ADA status was a statistically significant covariate on clearance; however, the presence of treatment-emergent ADA against tislelizumab appears to have no clinically relevant impact on pharmacokinetics, efficacy or safety.

*Elderly*

No overall differences in safety were observed with tiselizumab 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 registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reportingproblems.

## 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 Poisons Information Centre on 131126 (Australia).

# 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 ($K_D$ = 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. In *in vitro* studies, tislelizumab did not bind to Fc gamma receptors (FcγRs) and *C1q*, and therefore did not induce antibody-dependent cellular cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC); it is not expected to induce antibody-dependent cellular phagocytosis (ADCP). 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), those who had received a prior immune checkpoint inhibitor, 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. The key secondary efficacy outcome measure was OS in PD-L1 Positive Analysis Set (PD-L1 score of visually-estimated Combined Positive Score, now known as Tumour Area Positivity [TAP][PD-L1 score]≥10%).

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 512 patients were: median age of 63 years (range: 35 to 86 years), 39.5% with 65 years of age or older; 84.4% male; 18.9% White and 79.7% Asian; 24.8% with an

eastern cooperative oncology group performance status (ECOG PS) of 0 and 75.2% with an ECOG PS of 1. 95.1% of the study population had metastatic disease at study entry. All patients had received at least one prior anti-cancer chemotherapy, which was a platinum-based combination chemotherapy for 97% of patients.

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 of OS by reverse Kaplan-Meier methodology were 20.8 months in the tislelizumab arm and 21.1 months in the ICC arm. Efficacy results are shown in Table 8 and Figure 1.

**Table 8 Efficacy results in RATIONALE-302 (ITT analysis set)**

| **Endpoint** | **TEVIMBRA (N = 256)** | **Chemotherapy (N = 256)** |
|---|---|---|
| **OS** | | |
| Deaths n (%) | 197 (77.0) | 213 (83.2) |
| Median (months) (95% CI) [a] | 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) | 1180 (70.3) |
| Median (months) (95% CI) [a] | 1.6 (1.4, 2.7) | 2.1 (1.5, 2.7) |
| Hazard ratio (95% CI) [b] | 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*. * Not alpha controlled.*

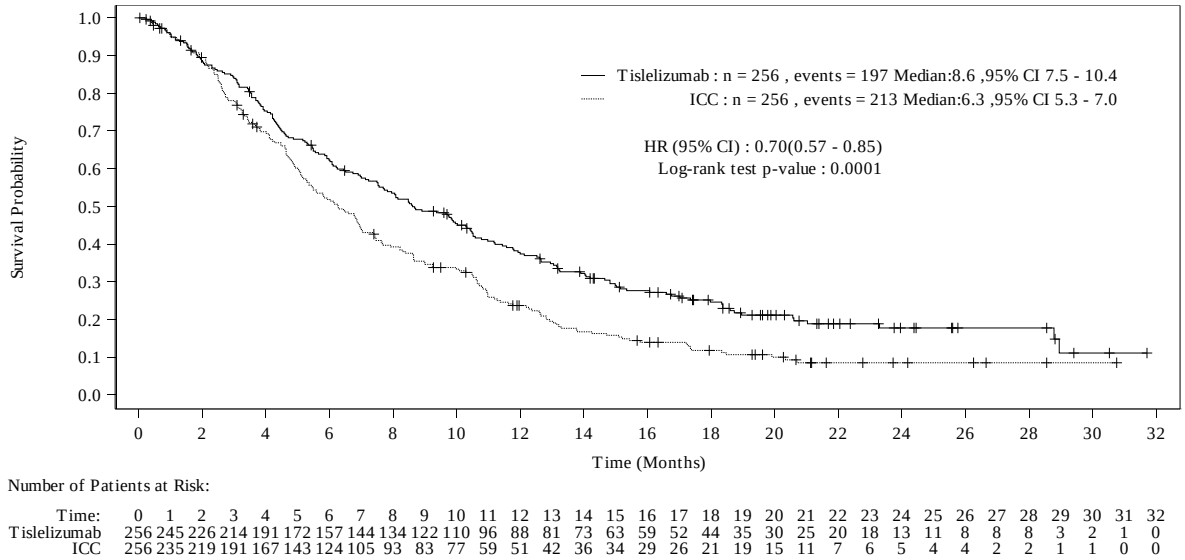
*Data cutoff: 01DEC2020.*

[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] *One-sided p-value was estimated from log rank test stratified by ECOG performance status and ICC option, for descriptive purpose only.*

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




**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 TEVIMBRA 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, conducted in China, 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/m$^2$ and carboplatin AUC 5 mg/mL/min or cisplatin 75 mg/m$^2$ (T+PP arm, N = 223), or pemetrexed 500 mg/m$^2$ and carboplatin AUC 5 mg/mL/min or cisplatin 75 mg/m$^2$ (PP arm, N = 111). The choice of platinum (cisplatin or carboplatin) was at the investigator's discretion.

The treatment was administered on a 3-week cycle. After the administration of 4, 5, or 6 cycles of chemotherapy or tislelizumab combined with chemotherapy at the investigator's discretion, patients in arm T+PP received tislelizumab 200 mg combined with pemetrexed 500 mg/m$^2$ 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/m$^2$ 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 TEVIMBRA 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, 41.6% 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 generally 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 TEVIMBRA 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 TEVIMBRA in combination with PP and 7.6 months with PP.

The final analysis (data cutoff date of 26-Oct-2020 and a median duration of study follow-up of 16.1 months) were consistent with the results from the interim analysis. Efficacy results for the final analysis are shown in Table 9 and Figure 2.

**Table 9 Efficacy results in RATIONALE-304**

| 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 (8.9, 11.7) | 7.6 (5.6, 8.0) |
| 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, 21.2) |
| **OS** | | |
| Deaths n (%) | 96 (43.0) | 46 (41.4) |
| Median OS (months) (95% CI) | 21.4 (17.7, NE) | 21.3 (15.6, 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; OS = overall survival*, ORR = objective response rate*; CR = complete response; PR = partial response; DoR = duration of response*, NE = not estimable.* = not alpha controlled.*

*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.*

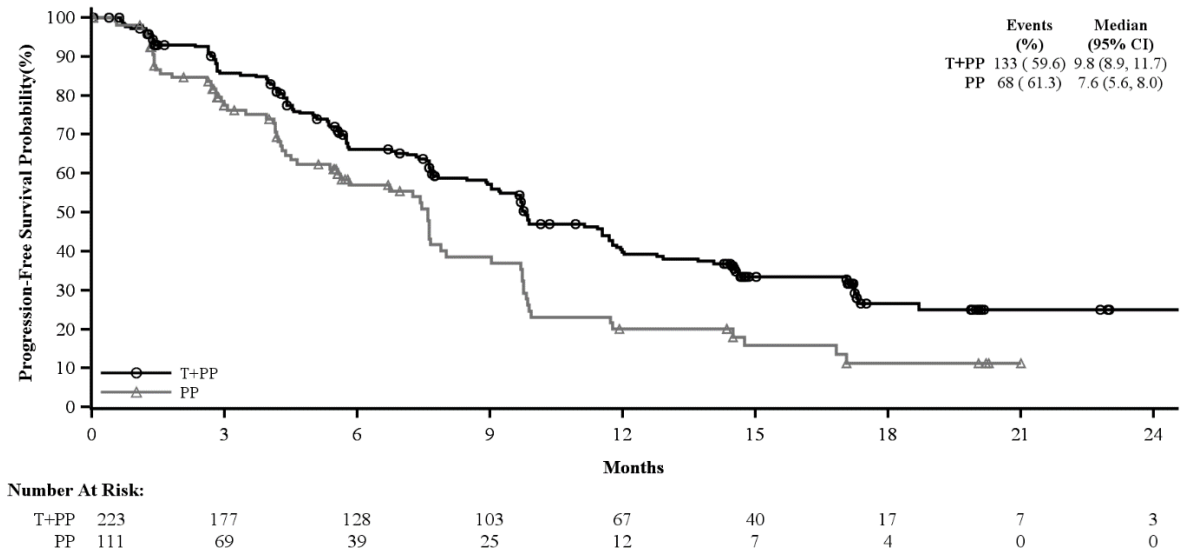
*[c] The median time from randomization to crossover was 35.1 weeks and from end of study treatment to crossover is 2.6 weeks.*

*[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.*

PD-L1 expression in tumor cell<1%, 1%-49%, ≥50% of PFS were pre-specified PFS subgroup analyses, which were not alpha controlled; the results of PFS by tumor PD-L1 expression in the final analysis are shown in Table 10.

**Table 10 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 |
| 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[a] (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[a] (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[a] (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*

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, conducted in China, comparing the efficacy and safety of tislelizumab combined with carboplatin and paclitaxel or *nab*-paclitaxel versus carboplatin and

paclitaxel alone as first-line treatment of 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/m$^2$ and carboplatin AUC 5 mg/ml/min (T+PC arm, N = 120), or tislelizumab 200 mg combined with nab-paclitaxel 100 mg/m$^2$ and carboplatin AUC 5 mg/mL/min (T+nPC arm, N = 119), or paclitaxel 175 mg/m$^2$ and carboplatin AUC 5 mg/mL/min (PC arm, N = 121 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 Ventana PD-L1 (SP263) assay that identified PD-L1 staining on tumor 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 generally 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), showing statistically 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) showed consistent results with the interim analysis. Efficacy results for the final analysis are shown in Table 11, Figure 3 and Figure 4.

**Table 11 Efficacy results in RATIONALE-307**

| **Endpoint** | **Tislelizumab+ Paclitaxel + Carboplatin (N = 120)** | **Tislelizumab+ nab-Paclitaxel + Carboplatin (N = 119)** | **Paclitaxel + Carboplatin (N = 121)** |
|---|---|---|---|
| **PFS** | | | |
| Events, n (%) | 80 (66.7) | 79 (66.4) | 86 (71.1) |
| Median PFS (months) (95% CI) | 7.7 (6.7, 10.4) | 9.6 (7.4, 10.8) | 5.5 (4.2, 5.6) |
| Stratified hazard ratio[a] (95% CI) | 0.45 (0.33, 0.62) | 0.43 (0.31, 0.60) | - |
| 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** | | | |
| 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, 1.01) | 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. * not alpha controlled.*

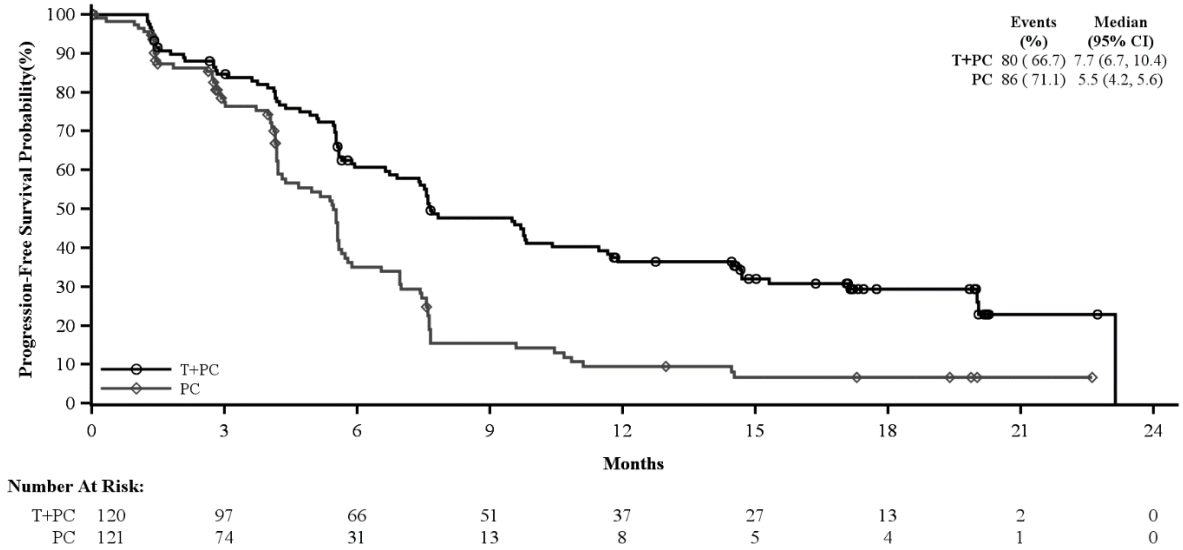
*[a] Stratified by stratification factors: disease stage (IIIB versus IV) and PD-L1 score in tumour cell (≥ 50% versus 1%-49% versus < 1%).*

*[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 KaplanMeier plot of PFS in RATIONALE-307 by IRC**

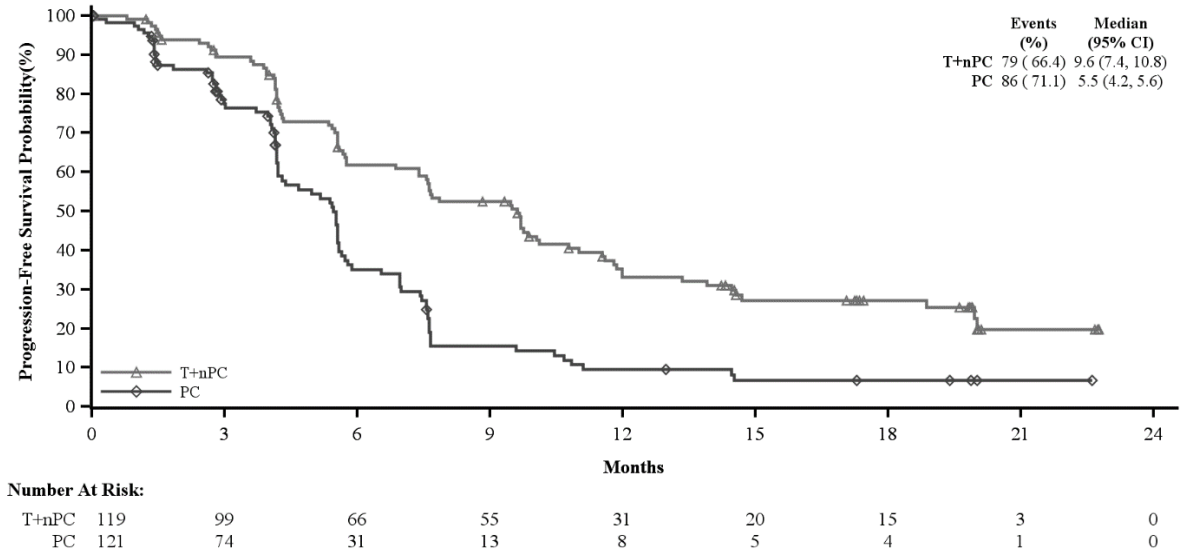
T+PC arm vs. PC arm




[a] *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




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

Efficacy results of PFS by tumour PD-L1 expression in pre-specified subgroup analyses for final analysis are shown in Table 12.

**Table 12 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 tumor 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 tumor 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 tumor 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 (6.0, 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*

Previously Treated Non-Small Cell Lung Cancer

The efficacy of tislelizumab was evaluated in RATIONALE-303 (NCT03358875), a multicenter, randomized, open-label, phase 3 study in patients with locally advanced or metastatic NSCLC (squamous or non-squamous), who had experienced disease progression on or after a prior platinum-based regimen. The study excluded patients with known EGFR mutation or ALK rearrangement, those who had received prior PD-1/PD-L1 antibody treatment, active autoimmune disease, or any condition requiring systemic treatment with either corticosteroids (>10 mg daily of prednisone or equivalent) or other immunosuppressive treatments.

A total of 805 patients were randomized (2:1) ratio to receive tislelizumab 200 mg intravenously every 3 weeks (N = 535) or docetaxel 75 mg/m$^2$ intravenously every 3 weeks (N = 270). 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 TEVIMBRA continued until disease progression, as assessed by investigator per RECIST v1.1, or unacceptable toxicity. PD-L1 expression was evaluated at a central laboratory using the Ventana PD-L1 (SP263) assay that identified PD-L1 staining on tumour cells. Tumour assessments were conducted every 9 weeks for 52 weeks after 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 a PD-L1 TC score ≤25%, and 42.5% had a PD-L1 TC score ≥25%. All patients had received prior therapy with a platinum-doublet regimen, 84.7% patients received one prior therapy, and 15.3% had received two prior therapies. The dual-primary efficacy endpoints were OS in the ITT and PD-L1 TC score ≥25% analysis sets. Additional endpoints included investigator assessed PFS, ORR, and DoR.

RATIONALE-303 met both its dual-primary endpoints of OS in the ITT and PD-L1 TC ≥25% analysis sets. 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.

At the final analysis (data cut-off date of 15-Jul-2021 and a median duration of study follow up of 14.2 months) 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 TEVIMBRA, with a 47% relative risk reduction in death relative to docetaxel (stratified HR= 0.53; 95% CI: 0.41, 0.70) in the PD-L1 TC ≥25% population, with median OS being 19.3 months for the tislelizumab arm and 11.5 months for the docetaxel arm. Efficacy results for the final analysis are shown in Table 13 (ITT analysis set) and Table 14 (PD-L1 TC ≥25% analysis set), Figure 5 (ITT analysis set) and Figure 6 (PD-L1 TC ≥25% analysis set).

**Table 13 Efficacy results in RATIONALE 303 (ITT analysis set)**

| **Endpoint** | **Tislelizumab (N = 535)** | **Docetaxel (N = 270)** |
|---|---|---|
| **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 (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 |
| **DoR** [c] | | |
| Median DOR (months) (95% CI) | 14.7 (10.55, 21.78) | 6.2 (4.11, 8.31) |
| DoR event-free rate (%), (95% CI) | | |

| Endpoint | Tislelizumab (N = 535) | Docetaxel (N = 270) |
|---|---|---|
| 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. 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 tumor cell (≥25% versus <25%).*

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

| Endpoint | Tislelizumab (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 BGB-A317-303 (ITT analysis set) (data cut-off date of 15-Jul-2021)**

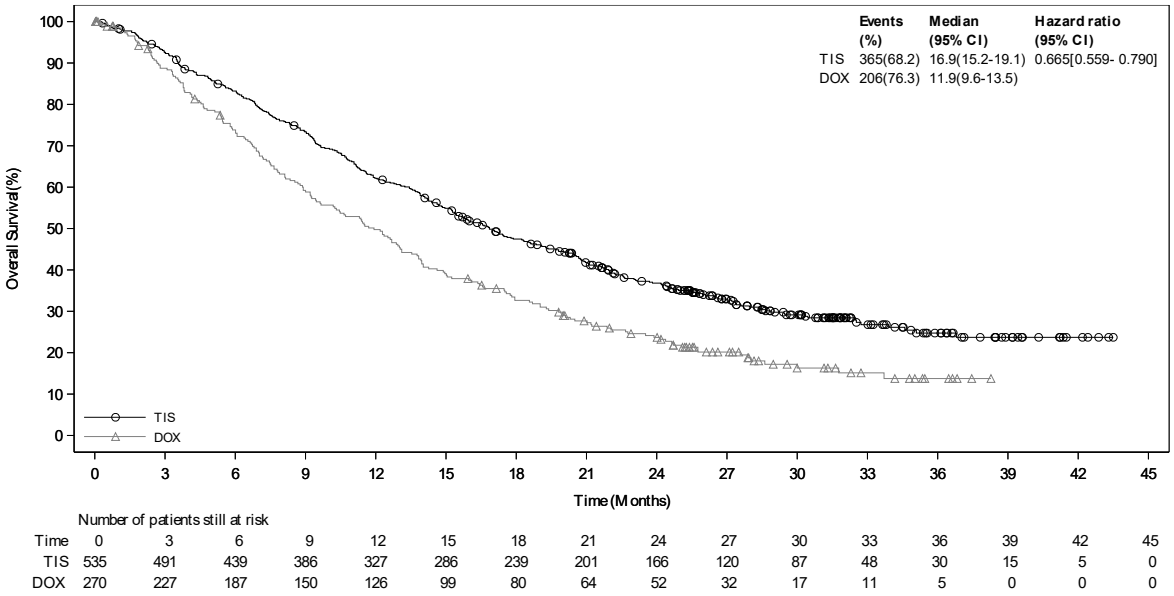



**Figure 6 Kaplan-Meier plot of OS in BGB-A317-303 (PD-L1 TC ≥25% analysis set) (data cut-off date of 15-Jul-2021)**

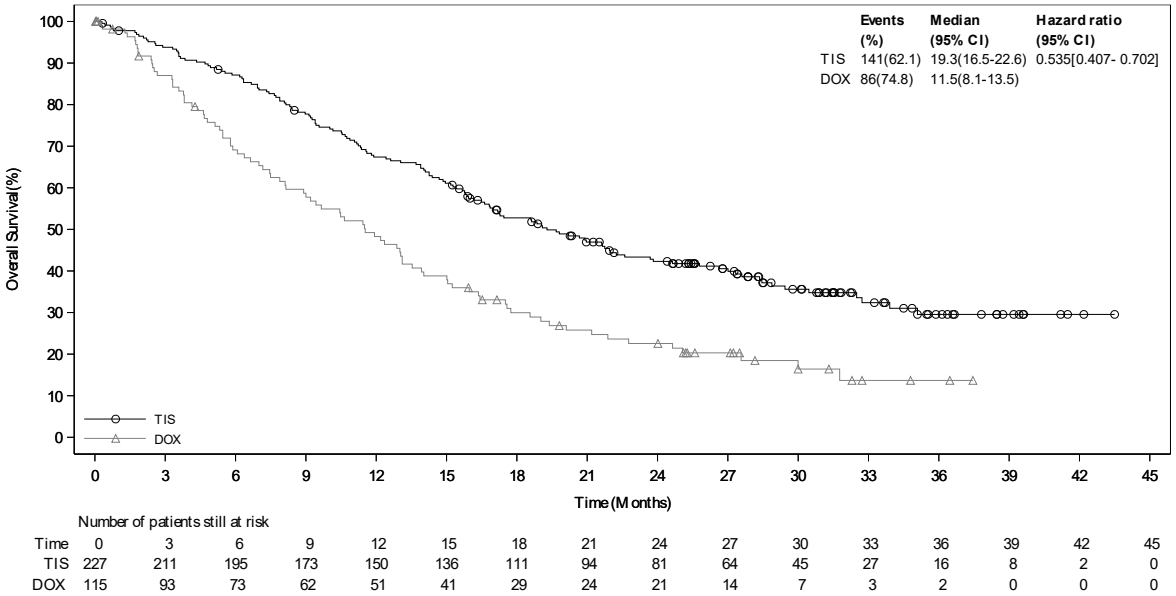
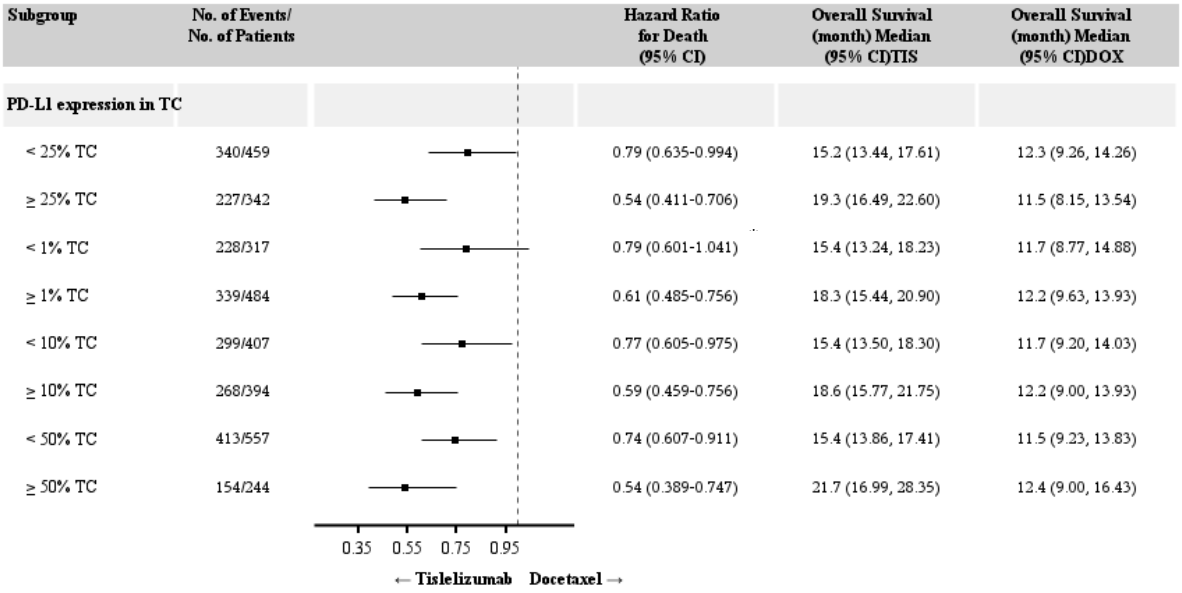



**Figure 7** summarises efficacy results of OS by tumour PD-L1 expression in prespecified subgroup analyses at the final analysis.

**Figure 7 Efficacy results of OS by tumour PD-L1 expression in study BGB-A317-303 (data cut-off date of 15-Jul-2021)**




## 5.2 PHARMACOKINETIC 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.

*Metabolism*

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

*Excretion*

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 patients between 65 and 75 years, and 109 (4.2%) patients >75 years).

Of the 256 patients with ESCC who were treated with tislelizumab in the clinical study, 99 (38.7%) were aged 65 years and over.

Of the 983 patients with NSCLC who were treated with tislelizumab in the clinical studies, 310 (31.5%) were aged 65 years and over.

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 (CLCr) 60 to 89 mL/min, n=1,046) or moderate renal impairment (CLCr 30 to 59 mL/min, n=320) and patients with normal renal function (CLCr ≥90 mL/min, n=1223). Mild and moderate renal impairment had no effect on the exposure of tislelizumab (see section 4.2 Dose and method of administration). Based on the limited number of patients with severe renal impairment (n=5), the effect of severe renal impairment on the pharmacokinetics of tislelizumab is not conclusive.

*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

*Genotoxicity and carcinogenicity*

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 sterile 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

*Disposal*

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

### 6.7 PHYSICOCHEMICAL PROPERTIES

#### 6.7.1 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.

#### 6.7.2 CAS number

1858168-59-8

## 7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription only medicine (Schedule 4)

## 8 SPONSOR

BeiGene AUS Pty Ltd
Suite 11.01, Level 11
66 Goulburn St
Sydney NSW 2000
Australia

## 9 DATE OF FIRST APPROVAL

30 May 2024

## 10 DATE OF REVISION

Not applicable

### 10.1 SUMMARY TABLE OF CHANGES

| Section Changed | Summary of new information |
|---|---|
| NA | New PI |