Summary of Product Characteristic

ETAPIDI
Tislelizumab

1 PRODUCT NAME

Generic name : Tislelizumab

Trade name : ETAPIDI

2 PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate)

Clear to slightly opalescent, colorless to slightly yellow liquid.

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

3 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

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

Excipient with known effect

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

For the full list of excipients, see section 18. EXCIPIENTS.

4 INDICATION

a. Non-Small Cell Lung Cancer (NSCLC)

Tislelizumab in combination with Paclitaxel plus Carboplatin or Paclitaxel for Injection (Albumin Bound) plus Carboplatin as first-line treatment in adult patients with unresectable, locally advanced or metastatic squamous NSCLC.

Tislelizumab in combination with pemetrexed and platinum chemotherapy as the first-line treatment in adult patients with unresectable, locally advanced or metastatic non-squamous NSCLC whose tumors have PD-L1 expression on ≥50% of tumor cells, with EGFR genomic tumor aberrations negative and ALK genomic tumor negative.

Tislelizumab as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic non-small-cell lung cancer (NSCLC) of either squamous or non-squamous histology with EGFR genomic tumor aberrations negative and ALK genomic tumor negative, that has progressed after prior platinum-based chemotherapy.

b. Esophageal Squamous Cell Carcinoma (ESCC)

Tislelizumab is indicated for the treatment of adult patients with unresectable locally advanced or metastatic esophageal squamous cell carcinoma who have disease progression following to first-line standard chemotherapy.

c. Gastric or Gastroesophageal Junction (G/GEJ) Adenocarcinoma

Tislelizumab in combination with platinum and fluoropyrimidine-based chemotherapy, is indicated for the first-line treatment of adult patients with HER-2 negative locally advanced unresectable or metastatic gastric or gastro-esophageal junction (G/GEJ) adenocarcinoma with a PD-L1 expression ≥ 1%.

5 DOSAGE AND ADMINISTRATION

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

Posology

Tislelizumab monotherapy

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

Tislelizumab combination therapy

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

When Tislelizumab and chemotherapy are administered on the same day, Tislelizumab should be administered before chemotherapy. The Summary of Product Characteristics (SmPC) for the chemotherapy product should be referred to for dosing as well as for recommendations on corticosteroid use as pre-medication for the prevention of chemotherapy-related adverse reactions.

Duration of treatment

Patients should be treated with Tislelizumab until disease progression or unacceptable toxicity.

Patient selection

Prior to the use of tislelizumab for the treatment of first-line non-squamous NSCLC or first-line G/GEJ adenocarcinoma, tumour PD-L1 status must be established. Testing used in clinical practice should be adequately comparable to the testing used in pivotal trials (Ventana PD-L1 (SP263) assay)

Dose delay or discontinuation (see also section 7. WARNINGS AND PRECAUTIONS)

No dose reductions of Tislelizumab as monotherapy or in combination therapy are recommended. Tislelizumab should be withheld or discontinued based on safety and tolerability as described in Table 1.

Detailed guidelines for the management of immune-related- adverse reactions are described in section 7. WARNINGS AND PRECAUTION.

Table 1: Recommended treatment modification for Tislelizumab

Immune-related adverse reaction	Severity[1]	Treatment modification
Pneumonitis	Grade 2	Withhold[2,3]
	Recurrent grade 2; grade 3 or 4	Permanently discontinue[3]
Hepatitis	ALT or AST >3 to 8 x ULN or total bilirubin >1.5 to 3 x ULN	Withhold[2,3]
	ALT or AST >8 x ULN or total bilirubin >3 x ULN	Permanently discontinue[3]
Rash	Grade 3	Withhold[2,3]
	Grade 4	Permanently discontinue[3]
Severe cutaneous adverse reactions (SCARs)	Suspected SCARs, including SJS or TEN	Withhold[2,3] For suspected SJS or TEN, do not resume unless SJS/TEN has been ruled out in consultation with appropriate specialist(s).
	Confirmed SCARs, including SJS or TEN	Permanently discontinue
Colitis	Grade 2 or 3	Withold[2,3]
	Recurrent grade 3; grade 4	Permanently discontinue[3]
Myositis/rhabdomyolysis	Grade 2 or 3	Withhold[2,3]
	Recurrent grade 3; grade 4	Permanently discontinue[3]
Hypothyroidism	Grade 2, 3 or 4	Hypothyroidism may be managed with replacement therapy without treatment interruption.
Hyperthyroidism	Grade 3 or 4	Withhold[2] For grade 3 or 4 that has improved

		to grade ≤2 and is controlled with anti-thyroid therapy, if indicated continuation of Tislelizumab may be considered after corticosteroid taper. Otherwise, treatment should be discontinued.
Adrenal insufficiency	Grade 2	Consider withholding treatment until controlled by HRT.
	Grade 3 or 4	Withhold[3] For grade 3 or 4 that has improved to grade ≤2 and is controlled with HRT, if indicated continuation of Tislelizumab may be considered after corticosteroid taper. Otherwise, treatment should be discontinued.[3]
Hypophysitis	Grade 2	Consider withholding treatment until controlled by HRT.
	Grade 3 or 4	Withhold[2,3] For grade 3 or 4 that has improved to grade ≤2 and is controlled with HRT, if indicated continuation of Tislelizumab may be considered after corticosteroid taper. Otherwise, treatment should be discontinued.[3]
Type 1 diabetes mellitus	Type 1 diabetes mellitus associated with grade ≥3 hyperglycaemia (glucose >250 mg/dl or >13.9 mmol/l) or associated with ketoacidosis	Withhold For grade 3 or 4 that has improved to grade ≤2 with insulin therapy, if indicated continuation of Tislelizumab may be considered once metabolic control is achieved. Otherwise, treatment should be discontinued.
Nephritis with renal dysfunction	Grade 2 (creatinine >1.5 to 3 x baseline or >1.5 to 3 x ULN)	Withhold[2,3]
	Grade 3 (creatinine >3 x baseline or >3 to 6 x ULN) or grade 4 (creatinine >6 x ULN)	Permanently discontinue[3]
Myocarditis	Grade 2, 3 or 4	Permanently discontinue[3]
Neurological toxicities	Grade 2	Withhold[2,3]
	Grade 3 or 4	Permanently discontinue[3]

Pancreatitis	Grade 3 pancreatitis or grade 3 or 4 serum amylase or lipase levels increased (>2 x ULN)	Withhold[2,3]
	Grade 4	Permanently discontinue[3]
Other immune-related adverse reactions	Grade 3	Withhold[2,3]
	Recurrent grade 3; grade 4	Permanently discontinue[3]
Other adverse drug reactions		
Infusion-related reactions	Grade 1	Consider pre-medication for prophylaxis of subsequent infusion reactions. Slow the rate of infusion by 50%.
	Grade 2	Interrupt infusion. Resume infusion if resolved or decreased to grade 1, and slow rate of infusion by 50%.
	Grade 3 or 4	Permanently discontinue

ALT = alanine aminotransferase, AST = aspartate aminotransferase, HRT= hormone replacement therapy, SJS = Stevens Johnson syndrome, TEN = Toxic epidermal necrolysis, ULN = upper limit of normal

[1] Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI-CTCAE v4.0). Hypophysitis grade is in accordance with NCI-CTCAE v5.0.

[2] Resume in patients with complete or partial resolution (grade 0 to 1) after corticosteroid taper over at least 1 month. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating corticosteroids or inability to reduce prednisone to ≤10 mg/day (or equivalent) within 12 weeks of initiating corticosteroids.

[3] Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper to ≤10 mg/day (or equivalent) over at least 1 month is recommended, except for pneumonitis, where initial dose of 2 to 4 mg/kg/day is recommended.

Special Populations

a. Pediatric population

The safety and efficacy of Tislelizumab in patients aged below 18 years have not been established. No data are available.

b. Elderly

No dose adjustment is needed for patients aged ≥65 years (see section 11. ADVERSE REACTIONS).

c. Renal impairment

No dose adjustment is needed for patients with mild or moderate renal impairment. Data from patients with severe renal impairment are too limited to make dosing recommendations for this population (see section 15. PHARMACOKINETICS).

d. Hepatic impairment

No dose adjustment is needed for patients with mild or moderate hepatic impairment. Data from patients with severe hepatic impairment are too limited to make dosing

recommendations for this population (see section 15. PHARMACOKINETICS).

Method of Administration

Tislelizumab is for intravenous use only. It is to be administered as an infusion and must not be administered as an intravenous push or single bolus injection.

The first infusion should be administered over a period of 60 minutes. If this is well tolerated, the subsequent infusions may be administered over a period of 30 minutes. The infusion should be given via an intravenous line containing a sterile, non-pyrogenic, low protein binding 0.2 or 0.22 micron in-line or add-on filter.

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

Preparation of solution for infusion

- Two Tislelizumab vials are required for each dose.
- Remove the vials from the refrigerator, taking care not to shake them.
- Inspect each vial visually for particulate matter and 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.
- Invert the vials gently without shaking. Withdraw the solution from the two vials (a total of 200 mg in 20 ml) into a syringe and transfer into an intravenous infusion bag containing sodium chloride 9 mg/ml (0.9%) solution for injection, to prepare a diluted solution with a final concentration ranging from 2 to 5 mg/ml. Mix diluted solution by gentle inversion to avoid foaming or excessive shearing of the solution.

Administration

- Administer the diluted Tislelizumab solution by infusion through an intravenous administration line with a sterile, non-pyrogenic, low-protein-binding 0.2 micron or 0.22 micron in-line or add-on filter with a surface area of approximately 10 cm^2.
- The first infusion should be delivered over 60 minutes. If well tolerated, subsequent infusions may be administered over 30 minutes.
- Other medicinal products should not be co-administered through the same infusion line.
- Tislelizumab must not be administered as an intravenous push or single bolus injection.
- The intravenous line must be flushed at the end of the infusion.
- Discard any unused portion left in the vial.
- Tislelizumab vials are for single use only

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

6 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in section 18. EXCIPIENTS.

7 WARNINGS AND PRECAUTIONS

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Immune-related adverse reactions

Immune-related adverse reactions have been reported, including fatal cases, during treatment with Tislelizumab (see section 11. ADVERSE REACTIONS). The majority of these events improved with interruption of Tislelizumab, administration of corticosteroids and/or supportive care. Immune-related adverse reactions have also been reported after the last dose of Tislelizumab. Immune-related adverse reactions affecting more than one body system can occur simultaneously.

For suspected immune-related adverse reactions, adequate evaluation to confirm etiology or exclude alternative etiologies, including infection, should be ensured. Based on the severity of the adverse reaction, Tislelizumab should be withheld and corticosteroids administered (see section 5. DOSAGE AND ADMINISTRATION). Based on limited data from clinical studies, administration of other systemic immunosuppressants can be considered in patients whose immune-related adverse reactions are not controlled with corticosteroid use (see sections 5. DOSAGE AND ADMINISTRATION and 11. ADVERSE REACTIONS). Upon improvement to grade ≤1, corticosteroid taper should be initiated and continued over at least 1 month.

Immune-related pneumonitis

Immune-related pneumonitis, including fatal cases, has been reported in patients receiving Tislelizumab. Patients should be monitored for signs and symptoms of pneumonitis. Patients with suspected pneumonitis should be evaluated with radiographic imaging and infectious or disease-related etiologies should be ruled out.

Patients with immune-related pneumonitis should be managed according to the treatment modifications as recommended in Table 1 (see section 5. DOSAGE AND ADMINISTRATION).

Immune-related hepatitis

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

Patients with immune-related hepatitis should be managed according to the treatment modifications as recommended in Table 1 (see section 5. DOSAGE AND ADMINISTRATION).

Immune-related skin reactions

Immune-related skin rash or dermatitis have been reported in patients receiving Tislelizumab. Patients should be monitored for suspected skin reactions and other causes should be excluded. Based on the severity of the skin adverse reactions, Tislelizumab should be withheld or permanently discontinued as recommended in Table 1 (see section 5. DOSAGE AND ADMINISTRATION).

Cases of severe cutaneous adverse reactions (SCARs) including erythema multiforme (EM), Stevens-Johnson Syndrome (SJS) and Toxic epidermal necrolysis (TEN), some of them with fatal outcome, have been reported in patients receiving Tislelizumab (see section 11. ADVERSE REACTIONS). Patients should be monitored for signs or symptoms of SCARs (e.g. a prodrome of fever, flu-like symptoms, mucosal lesions or progressive skin rash) and other causes should be excluded. For suspected SCAR, Tislelizumab should be withheld and the patient should be referred to specialized care for assessment and treatment. If SCAR is confirmed, Tislelizumab should be permanently discontinued (see section 5. DOSAGE AND ADMINISTRATION).

Immune-related colitis

Immune-related colitis, frequently associated with diarrhea, has been reported in patients treated with Tislelizumab. Patients should be monitored for signs and symptoms of colitis. Infectious and disease-related etiologies should be ruled out.

Patients with immune-related colitis should be managed according to the treatment modifications as recommended in Table 1 (see section 5. DOSAGE AND ADMINISTRATION).

Immune-related endocrinopathies

Immune-related endocrinopathies, including thyroid disorders, adrenal insufficiency, hypophysitis and type 1 diabetes mellitus, have been reported in patients treated with Tislelizumab. These may require supportive treatment depending on the specific endocrine disorder. Long-term hormone replacement therapy (HRT) may be necessary in cases of immune-related endocrinopathies.

Patients with immune-related endocrinopathies should be managed according to the treatment modifications as recommended in Table 1 (see section 5. DOSAGE AND ADMINISTRATION).

Thyroid disorders

Thyroid disorders, including thyroiditis, hypothyroidism and hyperthyroidism, have been reported in patients treated with Tislelizumab. Patients should be monitored (at the start of treatment, periodically during treatment and as indicated based on clinical evaluation) for changes in thyroid function and clinical signs and symptoms of thyroid disorders. Hypothyroidism may be managed with HRT without treatment interruption and without corticosteroids. Hyperthyroidism may be managed symptomatically (see section 5. DOSAGE AND ADMINISTRATION).

Adrenal insufficiency

Adrenal insufficiency has been reported in patients treated with Tislelizumab. Patients should be monitored for signs and symptoms of adrenal insufficiency. Monitoring of adrenal function and hormone levels should be considered. Corticosteroids and HRT should be administered as clinically indicated (see section 5. DOSAGE AND ADMINISTRATION).

Hypophysitis

Hypophysitis has been reported in patients treated with Tislelizumab. Patients should be monitored for signs and symptoms of hypophysitis/hypopituitarism. Monitoring of pituitary function and hormone levels should be considered. Corticosteroids and HRT should be administered as clinically indicated (see section 5. DOSAGE AND ADMINISTRATION).

Type 1 diabetes mellitus

Type 1 diabetes mellitus, including diabetic ketoacidosis, has been reported in patients treated with Tislelizumab. Patients should be monitored for hyperglycemia and other signs and symptoms of diabetes. Insulin should be administered for type 1 diabetes. In patients with severe hyperglycemia or ketoacidosis (grade ≥3), Tislelizumab should be withheld and anti-hyperglycemic treatment should be administered (see section 5. DOSAGE AND ADMINISTRATION). Treatment with Tislelizumab may be resumed when metabolic control is achieved.

Immune-related nephritis with renal dysfunction

Immune-related nephritis with renal dysfunction has been reported in patients treated with Tislelizumab. Patients should be monitored for changes in renal function (elevated serum creatinine), and other causes of renal dysfunction should be excluded.

Patients with immune-related nephritis with renal dysfunction should be managed according to the treatment modifications as recommended in Table 1 (see section 5. DOSAGE AND ADMINISTRATION).

Other immune-related adverse reactions

Other clinically important immune-related adverse reactions were reported with Tislelizumab: myositis, myocarditis, arthritis, polymyalgia rheumatica, pericarditis, immune thrombocytopenia, encephalitis, myasthenia gravis, Sjögren's syndrome and Guillain-Barré syndrome (see section 11. ADVERSE REACTIONS).

Patients with other immune-related adverse reactions should be managed according to the treatment modifications as recommended in Table 1 (see section 5. DOSAGE AND ADMINISTRATION).

Solid organ transplant rejection

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

Infusion-related reactions

Severe infusion-related reactions (grade 3 or higher) have been reported in patients receiving Tislelizumab (see section 11. ADVERSE REACTIONS). 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 5. DOSAGE AND ADMINISTRATION).

Patients excluded from clinical studies

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

Patients on controlled sodium diet

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

8 DRUG INTERACTION

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

The use of systemic corticosteroids and other immunosuppressants at baseline, before starting Tislelizumab, except for low doses of systemic corticosteroid (10 mg/day prednisone or equivalent), should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of Tislelizumab. However, systemic corticosteroids and other immunosuppressants can be used after starting Tislelizumab to treat immune-related adverse reactions (see section 7. WARNINGS AND PRECAUTIONS). Corticosteroids can also be used as pre-medication when Tislelizumab is used in combination with chemotherapy, as antiemetic prophylaxis and/or to alleviate chemotherapy-related adverse reactions.

9 USE IN PREGNANT AND LACTATING WOMEN

Women of childbearing potential/Contraception

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

Pregnancy

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

Animal reproduction studies have not been conducted with Tislelizumab. However, in murine models of pregnancy, blockade of PD-1/PD-L1 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. Women should be advised of the potential risk to a fetus.

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

Breast-feeding

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

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

Fertility

No clinical data are available on the possible effects of Tislelizumab on fertility. No reproductive and development toxicity studies have been conducted with Tislelizumab. Based on a 3-month repeat-dose toxicity study, there were no notable effects in the male and female reproductive organs in cynomolgus monkeys when Tislelizumab was given at doses of 3, 10 or 30 mg/kg every 2 weeks for 13 weeks (7 dose administrations) (see section 16. PRECLINICAL SAFETY DATA).

10 EFFECTS ON ABILITY TO DRIVE AND OPERATE MACHINERY

Tislelizumab has minor influence on the ability to drive and use machines. In some patients, fatigue has been reported following administration of Tislelizumab (see section 11. ADVERSE REACTIONS).

11 ADVERSE REACTIONS

Summary of the safety profile

The safety of Tislelizumab as monotherapy is based on pooled data in 1 534 patients across multiple tumor types who received 200 mg Tislelizumab every 3 weeks. The most common adverse reactions were anemia (29.2%), fatigue (22.9%) and aspartate aminotransferase (20.9%) increased. The most common grade 3/4 adverse reactions were anemia (5.0%), pneumonia (4.2%), hyponatremia (2.7%), aspartate aminotransferase increased (2.6%), blood bilirubin increased (2.0%), pneumonitis (2.0%) and fatigue (2.0%). 1.2% of patients experienced adverse reactions leading to death. The adverse reactions leading to death were pneumonia (0.78%), hepatitis (0.13%), pneumonitis (0.07%), dyspnea (0.07%), decreased appetite (0.07%) and thrombocytopenia (0.07%). Among the 1 534 patients, 40.1% were exposed to Tislelizumab for longer than 6 months, and 22.2% were exposed for longer than 12 months.

The safety of Tislelizumab given in combination with chemotherapy is based on data in 995 patients with G/GEJ adenocarcinoma or NSCLC. The most common adverse reactions were neutropenia (66.8%), anemia (64.5%), thrombocytopenia (56.0%), nausea (45.9%), fatigue (42.3%), decreased appetite (40.9%), aspartate aminotransferase increased (36.8%), alanine aminotransferase increased (35.3%), rash (21.3%) and diarrhea (21.0%). The most common grade 3/4 adverse reactions were neutropenia (38.5%), thrombocytopenia (16.3%), anemia (12.0%), fatigue (3.7%), pneumonia (3.4%), hypokalemia (3.0%), alanine aminotransferase increased (2.7%), decreased appetite (2.6%), aspartate aminotransferase increased (2.5%), lymphopenia (2.3%), pneumonitis (2.1%), hepatitis (2.1%) and rash (2.1%). 1.1% of patients experienced adverse reactions leading to death. The adverse reactions leading to death were pneumonia (0.3%), pneumonitis (0.3%), dyspnea (0.2%), myocarditis (0.2%), colitis (0.1%), hypokalemia (0.1%) and myositis (0.1%). Among the 995 patients, 58.3%

were exposed to Tislelizumab for longer than 6 months, and 31.6% were exposed for longer than 12 months.

Tabulated list of adverse reactions

Adverse reactions reported in the pooled dataset for patients treated with Tislelizumab monotherapy (N= 1 534) and in combination with chemotherapy (N = 995) are presented in Table 2. Adverse reactions are listed according to system organ class in MedDRA. Within each system organ class, the adverse reactions are presented in decreasing frequency. The corresponding frequency category for each adverse reaction is defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1 000 to <1/100); rare (≥1/10 000 to <1/1 000); very rare (<1/10 000); not known (cannot be estimated from available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2 Adverse reactions with Tislelizumab as monotherapy (N = 1 534) and in combination with chemotherapy (N = 995)

	Tislelizumab monotherapy N = 1 534	**Tislelizumab plus chemotherapy N =995**
Adverse reactions	**Frequency category (All grades)**	**Frequency category (All grades)**
Infections and infestations		
Pneumonia[1]	Very common*	Very common*
Blood and lymphatic system disorders		
Anaemia[2]	Very common	Very common
Thrombocytopenia[3]	Common*	Very common
Neutropenia[4]	Common	Very common
Lymphopenia[5]	Common	Very common
Immune system disorders		
Sjogren's syndrome	-	Uncommon
Endocrine disorders		
Hypothyroidism[6]	Very common	Very common
Hyperthyroidism[7]	Common	Common
Thyroiditis[8]	Common	Uncommon
Adrenal insufficiency[9]	Uncommon	Uncommon
Hypophysitis[10]	Rare	Uncommon
Metabolism and nutrition disorders		
Hyperglycaemia[11]	Common	Common
Hyponatraemia[12]	Common	Very common
Hypokalaemia[13]	Common	Very common*
Diabetes mellitus[14]	Uncommon	Common
Nervous system disorders		
Encephalitis[15]	-	Uncommon

Guillain-Barré syndrome	-	Uncommon
Myasthenia gravis	-	Uncommon
Eye disorders		
Uveitis[16]	Uncommon	Uncommon
Cardiac disorders		
Myocarditis[17]	Uncommon	Common*
Pericarditis	Rare	Uncommon
Vascular disorders		
Hypertension[18]	Common	Common
Respiratory, thoracic and mediastinal disorders		
Cough	Very common	Common
Dyspnoea	Common*	Common*
Pneumonitis[19]	Common*	Common*
Gastrointestinal disorders		
Nausea	Very common	Very common
Diarrhoea[20]	Common	Very common
Stomatitis[21]	Common	Common
Pancreatitis[22]	Common	Uncommon
Colitis[23]	Uncommon	Common*
Coeliac disease	Rare	-
Hepatobiliary disorders		
Hepatitis[24]	Common*	Common
Skin and subcutaneous tissue disorders		
Rash[25]	Very common	Very common
Pruritus	Very common	Common
Vitiligo[26]	Uncommon	Uncommon
Severe skin reactions[27]	Uncommon	-
Stevens-Johnson Syndrome[28]	Not known	Not known
Toxic epidermal necrolysis[28]	Not known*	Not known*
Musculoskeletal and connective tissue disorders		
Arthralgia	Common	Very common
Myalgia	Common	Common
Myositis[29]	Uncommon	Uncommon*
Arthritis[30]	Uncommon	Common
Renal and urinary disorders		
Nephritis[31]	Uncommon	Uncommon
General disorders and administration site conditions		
Fatigue[32]	Very common	Very common
Pyrexia[33]	Very common	Very common
Decreased appetite	Very common*	Very common

Investigations		
Aspartate aminotransferase increased	Very common	Very common
Alanine aminotransferase increased	Very common	Very common
Blood bilirubin increased[34]	Very common	Very common
Blood alkaline phosphatase increased	Common	Common
Blood creatinine increased	Common	Common
Injury, poisoning and procedural complications		
Infusion-related reaction[35]	Common	Common

[1] Pneumonia includes preferred terms (PTs) of pneumonia, lower respiratory tract infection, lower respiratory tract infection bacterial, pneumonia bacterial, pneumonia fungal, pneumonia viral and pneumocystis jirovecii pneumonia.
[2] Anaemia includes PTs of anemia and hemoglobin decreased.
[3] Thrombocytopenia includes PTs of thrombocytopenia, immune thrombocytopenia and platelet count decreased.
[4] Neutropenia includes PTs of neutropenia and neutrophil count decreased.
[5] Lymphopenia includes PTs of lymphopenia, lymphocyte count decreased and lymphocyte percentage decreased.
[6] Hypothyroidism includes preferred terms (PTs) of hypothyroidism, thyroxine free decreased, tri-iodothyronine free decreased, tri-iodothyronine decreased, primary hypothyroidism, central hypothyroidism and thyroxine decreased.
[7] Hyperthyroidism includes PTs of hyperthyroidism, blood thyroid stimulating hormone decreased, tri-iodothyronine free increased, thyroxine free increased, thyroxine increased and tri-iodothyronine increased.
[8] Thyroiditis includes PTs of thyroiditis, autoimmune thyroiditis and thyroiditis subacute.
[9] Adrenal insufficiency includes PTs of adrenal insufficiency, glucocorticoid deficiency, immune-mediated adrenal insufficiency and secondary adrenocortical insufficiency.
[10] Hypophysitis includes PTs of hypopituitarism.
[11] Hyperglycaemia includes PTs of hyperglycaemia and blood glucose increased.
[12] Hyponatraemia includes PTs of hyponatraemia and blood sodium decreased.
[13] Hypokalaemia includes PTs of hypokalaemia and blood potassium decreased.
[14] Diabetes mellitus includes PTs of diabetes mellitus, type 1 diabetes mellitus, diabetic ketoacidosis and latent autoimmune diabetes in adults.
[15] Encephalitis includes the PT of immune-mediated encephalitis.
[16] Uveitis includes PTs of uveitis and iritis.
[17] Myocarditis includes PTs of myocarditis, immune-mediated myocarditis and autoimmune myocarditis.
[18] Hypertension includes PTs of hypertension, blood pressure increased and essential hypertension.
[19] Pneumonitis includes PTs of pneumonitis, immune-mediated lung disease, interstitial lung disease and organizing pneumonia.
[20] Diarrhoea includes PTs of diarrhea and frequent bowel movements.
[21] Stomatitis includes PTs of stomatitis, mouth ulceration, aphthous ulcer and oral mucosa erosion.
[22] Pancreatitis includes PTs of amylase increased, lipase increased, pancreatitis and pancreatitis acute.
[23] Colitis includes PTs of colitis and immune-mediated enterocolitis.
[24] Hepatitis includes PTs of hepatitis, hepatic function abnormal, immune-mediated hepatitis. liver injury, drug-induced liver injury, hepatotoxicity and autoimmune hepatitis.

[25] Rash includes PTs of rash, rash maculo-papular, eczema, rash erythematous, dermatitis, dermatitis allergic, rash papular, urticaria, erythema, skin exfoliation, drug eruption, rash macular, psoriasis, rash pustular, dermatitis acneiform, rash pruritic, lichenoid keratosis, hand dermatitis, immune-mediated dermatitis, rash follicular, acute febrile neutrophilic dermatosis, erythema nodosum and pemphigoid.
[26] Vitiligo includes PTs of vitiligo, skin hypopigmentation, skin depigmentation and leukoderma.
[27] Severe skin reaction includes erythema multiforme.
[28] Post-marketing experience.
[29] Myositis includes PTs of myositis, rhabdomyolysis and immune-mediated myositis.
[30] Arthritis includes PTs of arthritis and immune-mediated arthritis.
[31] Nephritis includes PTs of nephritis, focal segmental glomerulosclerosis, immune-mediated nephritis and tubulointerstitial nephritis.
[32] Fatigue includes PTs of fatigue, asthenia, malaise and lethargy.
[33] Pyrexia includes the PTs of pyrexia and body temperature increased.
[34] Blood bilirubin increased includes PTs of blood bilirubin increased, bilirubin conjugated increased, blood bilirubin unconjugated increased and hyperbilirubinemia.
[35] Infusion-related reaction includes PTs of rash, chills, infusion-related reaction, rhinitis allergic, urticaria, drug hypersensitivity, laryngeal oedema, rash erythematous, rash pruritic, swelling face, anaphylactic reaction, corneal oedema, dermatitis allergic, drug eruption, face oedema, gingival swelling, and pruritus allergic. Cases of anaphylaxis, including anaphylactic reaction and anaphylactic shock, have been reported in the post-marketing setting.
*including fatal outcomes

Description of selected adverse reactions

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

Immune-related pneumonitis

In patients treated with Tislelizumab as monotherapy, immune-related pneumonitis occurred in 4.3% of patients, including grade 1 (0.3%), grade 2 (2.0%), 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 3.2 months (range: 1.0 day to 16.5 months), and the median duration from onset to resolution was 6.1 months (range: 1.0+ day to 22.8+ months). + denotes a censored observation, with ongoing events at the time of the analysis. Tislelizumab was permanently discontinued in 1.8% of patients and Tislelizumab treatment was interrupted in 1.8% of patients. Pneumonitis resolved in 45.5% of patients.

In patients treated with Tislelizumab as monotherapy, pneumonitis occurred more frequently in patients with a history of prior thoracic radiation (6.3%) than in patients who did not receive prior thoracic radiation (2.8%).

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

Immune-related hepatitis

In patients treated with Tislelizumab as monotherapy, immune-related hepatitis occurred in 1.7% of patients, including grade 1 (0.1%), grade 2 (0.5%), grade 3 (0.9%), grade 4 (0.1%) and grade 5 (0.1%) events.

The median time from first dose to onset of the event was 31.0 days (range: 8.0 days to 13.1 months), and the median duration from onset to resolution was 2.0 months (range: 1.0+ day to 37.9+ months). + denotes a censored observation, with ongoing events at the time of the analysis. Tislelizumab was permanently discontinued in 0.4% of patients and Tislelizumab treatment was interrupted in 1.0% of patients for immune related hepatitis. Hepatitis resolved in 50.0% of patients.

Immune-related skin adverse reactions

In patients treated with Tislelizumab as monotherapy, immune-related skin adverse reactions occurred in 1.8% of patients, including grade 1 (0.4%), grade 2 (0.8%), grade 3 (0.3%) and grade 4 (0.3%) events.

The median time from first dose to onset of the event was 2.5 months (range: 7.0 days to 11.6 months). The median duration from onset to resolution was 11.2 months (range: 4.0 days to 34.0+ months). + denotes a censored observation, with ongoing events at the time of the analysis. Tislelizumab was permanently discontinued in 0.3% of patients, and Tislelizumab treatment was interrupted in 0.5% of patients. Skin adverse reactions resolved in 51.9% of patients.

Cases of SJS and TEN have been reported from post-marketing experience, some with fatal outcome (see section 5. DOSAGE AND ADMINISTRATION and 7. WARNINGS AND PRECAUTIONS).

Immune-related colitis

In patients treated with Tislelizumab as monotherapy, immune-related colitis occurred in 0.7% of patients, including grade 2 (0.6%) and grade 3 (0.1%) events.

The median time from first dose to onset of the event was 6.0 months (range: 12.0 days to 14.4 months), and the median duration from onset to resolution was 28.0 days (range: 9.0 days to 3.6 months). Tislelizumab was not permanently discontinued in any patient and Tislelizumab treatment was interrupted in 0.6% of patients. Colitis resolved in 81.8% of patients.

Immune-related myositis/rhabdomyolysis

In patients treated with Tislelizumab as monotherapy, immune-related myositis/rhabdomyolysis occurred in 0.9% 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 0.7% of patients. Myositis/rhabdomyolysis resolved in 57.1% of patients.

Immune-related endocrinopathies

Thyroid disorders

Hypothyroidism:

In patients treated with Tislelizumab as monotherapy, hypothyroidism occurred in 7.6% of patients, including grade 1 (1.4%), grade 2 (6.1%) and grade 4 (0.1%) events.

The median time from first dose to onset of the event was 3.7 months (range: 0 days to 16.6 months). The median duration from onset to resolution was 15.2 months (range: 12.0 days to 28.6+ 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 0.4% of patients. Hypothyroidism resolved in 31.9% of patients.

Hyperthyroidism:

In patients treated with Tislelizumab as monotherapy, hyperthyroidism occurred in 0.3% of patients, including grade 1 (0.1%) and grade 2 (0.3%) events.

The median time from first dose to onset of the event was 31.0 days (range: 19.0 days to 14.5 months). The median duration from onset to resolution was 1.4 months (range: 22.0 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 not interrupted in any patient. Hyperthyroidism resolved in 80.0% of patients.

Thyroiditis:

In patients treated with Tislelizumab as monotherapy, thyroiditis occurred in 0.8% of patients, including grade 1 (0.2%) and grade 2 (0.6%) events.

The median time from first dose to onset of the event was 2.0 months (range: 20.0 days to 20.6 months). The median duration from onset to resolution was not evaluable based on currently available data (range: 22.0 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. Thyroiditis resolved in 16.7% of patients.

Adrenal insufficiency

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

The median time from first dose to onset of the event was 3.1 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: 1.0 month to 6.5+ 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 0.2% of patients. Adrenal insufficiency resolved in 25.0% of 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 0.4% of patients, including grade 1 (0.1%) and grade 3 (0.3%) events.

The median time from first dose to onset of the event was 2.5 months (range: 33.0 days to 13.8 months). The median duration from onset to resolution was not evaluable based on currently available data (range: 4.0 days to 19.9+ months). + denotes a censored observation, with ongoing events at the time of the analysis. Tislelizumab was permanently discontinued in 0.1% of patients and Tislelizumab treatment was interrupted in 0.1% of patients. Type 1 diabetes mellitus resolved in 16.7% of patients.

Immune-related nephritis and renal dysfunction

In patients treated with Tislelizumab as monotherapy, immune-related nephritis and renal dysfunction occurred in 0.7% of patients, including grade 2 (0.3%), grade 3 (0.2%), grade 4 (0.1%) and grade 5 (0.1%) events.

The median time from first dose to onset of the event was 1.2 months (range: 3.0 days to 5.7 months). The median duration from onset to resolution was 1.9 months (range: 3.0+ days to 16.2+ months). + denotes a censored observation, with ongoing events at the time of the analysis. Tislelizumab was permanently discontinued in 0.3% of patients and Tislelizumab treatment was interrupted in 0.3% of patients. Immune-related nephritis and renal dysfunction resolved in 50.0% of patients.

Immune-related myocarditis

In patients treated with Tislelizumab as monotherapy, immune-related myocarditis occurred in 0.5% of patients, including grade 1 (0.1%), grade 2 (0.1%), grade 3 (0.2%) and grade 4 (0.1%) events.

The median time from first dose to onset of the event was 1.6 months (range: 14.0 days to 6.1 months), and the median duration from onset to resolution was 5.1 months (range: 4.0 days to 7.6 months). Tislelizumab was permanently discontinued in 0.3% of patients and Tislelizumab treatment was interrupted in 0.2% of patients. Myocarditis resolved in 57.1% of patients.

Myocarditis occurred in 1.3% of patients treated with Tislelizumab in combination with chemotherapy, including grade 5 (0.2%).

Immune checkpoint inhibitor class effects

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

Infusion-related reactions

In patients treated with Tislelizumab as monotherapy, infusion-related reactions occurred in 3.5% of patients, including grade 3 (0.3%) events. Tislelizumab was permanently discontinued in 0.1% of patients and Tislelizumab treatment was interrupted in 0.5% of patients.

Laboratory abnormalities

In patients treated with Tislelizumab monotherapy, the proportion of patients who experienced a shift from baseline to a grade 3 or 4 laboratory abnormality was as follows: 0.1% for increased hemoglobin, 4.4% for decreased hemoglobin, 0.9% for decreased leukocytes, 8.5% for decreased lymphocytes, 0.07% for increased lymphocytes, 1.7% for decreased neutrophils, 1.1% for decreased platelets, 2.0% for increased alanine aminotransferase, 0.4% for decreased albumin, 2.3% for increased alkaline phosphatase, 3.2% for increased aspartate aminotransferase, 2.2% for increased bilirubin, 2.0% for increased creatine kinase, 0.9% for increased creatinine, 0.9% for increased potassium, 2.2% for decreased potassium, 0.1% for increased sodium, 5.7% for decreased sodium.

In patients treated with Tislelizumab in combination with chemotherapy, the proportion of patients who experienced a shift from baseline to a grade 3 or 4 laboratory abnormality was as follows: 12.4% for decreased hemoglobin, 19.3% for decreased leukocytes, 13.2% for decreased lymphocytes, 39.4% for decreased neutrophils, 16.0% for decreased platelets, 4.9% for increased alanine aminotransferase, 0.7% for albumin decreased, 0.9% for increased alkaline phosphatase, 4.1% for increased aspartate aminotransferase, 2.5% for increased bilirubin, 2.2% for increased creatine kinase, 2.4% for increased creatinine, 0.2% for decreased glucose, 1.5% for increased potassium, 8.1% for decreased potassium, 0.3% for increased sodium, 9.3% for decreased sodium.

Immunogenicity

Of 2386 antidrug antibodies (ADA)-evaluable patients treated at the recommended dose of 200 mg once every 3 weeks with tislelizumab as monotherapy or in combination with chemotherapies, 19.2% of patients tested positive for treatment-emergent ADA, and neutralizing antibodies (NAbs) were detected in 1.0% of patients. Population pharmacokinetic analysis showed that ADA status was a statistically significant covariate on clearance; however, the presence of treatment-emergent ADA against Tislelizumab appears to have no clinically relevant impact on pharmacokinetics or efficacy.

Among 470 ADA-evaluable patients in the first-line treatment of G/GEJ adenocarcinoma phase III study BGB-A317-305, the following rates of adverse events (AEs) have been observed for the treatment-emergent ADA-positive compared to the ADA-negative groups , respectively: grade ≥3 AEs 70.1% vs. 68.0%, serious adverse events (SAEs) 38.3% vs. 41.0%, and AEs leading to treatment discontinuation 16.8% vs. 13.8%.Patients who developed treatment-emergent ADAs tended to have overall poorer health and disease characteristics at baseline which can confound the interpretation of the safety analysis. Available data do not allow firm conclusions to be drawn on possible patterns of adverse drug reactions.

Elderly

No overall differences in safety were observed with Tislelizumab as monotherapy or in combination with chemotherapy between patients aged <65 years and patients aged between 65 and 74 years. Data for patients aged 75 years and above are too limited to draw conclusions.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to the pharmaceutical industry.

Pharmaceutical Industry Reporting Contact

PT ETANA BIOTECHNOLOGIES INDONESIA

Kawasan Industri Pulogadung, Jl. Rawa Gelam V, Blok. L, Kav.11-13, Jakarta

Email: pv@id.etanabiotech.com

Web-site: https://ebi-pharmacovigilance.azurewebsites.net/

Pusat Farmakovigilans/MESO Nasional

Badan Pengawas Obat dan Makanan Deputi Bidang Pengawasan Obat, Narkotika, Psikotropika, Prekursor dan Zat Adiktif

Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika, Psikotropika, Prekursor dan Zat Adiktif

Jl. Percetakan Negara 23 Jakarta Pusat, 10560

No. Telp: (021) 4244691 ext. 1079

Email: pv-center@pom.go.id dan Indonesia-MESO-BadanPOM@hotmail.com

Website: https://e-meso.pom.go.id/ADR

12 OVERDOSE

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

13 CLINICAL PHARMACOLOGY

Mechanism of action

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

14 PHARMACODYNAMICS

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies and antibody drug conjugates, ATC code: L01FF09.

15 PHARMACOKINETICS

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

The PK of Tislelizumab were 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 body weight every 3 weeks, and 200 mg every 3 weeks.

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

Absorption

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

Distribution

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

Biotransformation

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

Elimination

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

Linearity/non-linearity

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

Special populations

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

Renal impairment

No dedicated studies of Tislelizumab have been conducted in patients with renal impairment. In the population PK analyses of Tislelizumab, no clinically relevant differences in the clearance of Tislelizumab were found between patients with mild renal impairment (CrCl 60 to 89 ml/min, N = 1 046) or moderate renal impairment (CrCl 30 to 59 ml/min, n = 320) and patients with normal renal function (CrCl ≥90 ml/min, n = 1 223). Mild and moderate renal impairment had no effect on the exposure of Tislelizumab (see section 5. DOSAGE AND 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.

Hepatic impairment

No dedicated studies of Tislelizumab have been conducted in patients with hepatic impairment. In the population PK analyses of Tislelizumab, no clinically relevant differences in the clearance of Tislelizumab were found between patients with mild hepatic impairment (bilirubin ≤ ULN and AST >ULN or bilirubin >1.0 to 1.5 x ULN and any AST, n = 396) or moderate hepatic impairment (bilirubin >1.5 to 3 x ULN and any AST; n = 12), compared to patients with normal hepatic function (bilirubin ≤ ULN and AST = ULN, n = 2 182) (see section 5. DOSAGE AND ADMINISTRATION). Based on the limited number of patients with severe hepatic impairment (bilirubin >3 x ULN and any AST, n = 2), the effect of severe hepatic impairment on the pharmacokinetics of Tislelizumab is unknown.

16 PRECLINICAL SAFETY DATA

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

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

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

17 CLINICAL TRIAL

Clinical efficacy and safety

Non-small cell lung cancer

First-line treatment of non-squamous NSCLC: BGB-A317-304

BGB-A317-304 was a randomized, open-label, multicenter phase III study to investigate the efficacy and safety of Tislelizumab in combination with platinum-pemetrexed versus platinum-pemetrexed alone as first-line treatment for chemotherapy-naïve patients with locally advanced non-squamous NSCLC who were not candidates for surgical resection or platinum-based chemoradiation, or metastatic non-squamous NSCLC.

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

A total of 334 patients were 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 the T+PP arm received Tislelizumab 200 mg combined with pemetrexed 500 mg/m^2 on a 3-week cycle until disease progression or unacceptable toxicity; patients in the PP arm received pemetrexed 500 mg/m^2 alone until disease progression or unacceptable toxicity, and those with disease progression confirmed by Independent Review Committee (IRC) were given the option to cross over to receive Tislelizumab monotherapy on a 3-week cycle.

Randomization was stratified by PD-L1 expression in tumor cells (TC) (<1% versus 1% to 49% versus ≥50%) and disease stage (IIIB versus IV), as classified according to American Joint Committee on Cancer (AJCC), 7th edition of Cancer Staging Manual. PD-L1 expression was evaluated at a central laboratory using the Ventana PD-L1 (SP263) assay that identified PD-L1 staining on tumor cells. Tumor assessments were conducted every 6 weeks

for the first 6 months, then every 9 weeks for the second 6 months, then every 12 weeks.

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

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

The study met its primary endpoint at the interim analysis (data cut-off date of 23-Jan-2020), showing a statistically significant improvement in PFS with T+PP compared with PP. The stratified hazard ratio was 0.65 (95% CI: 0.47, 0.91; p = 0.0054) with a median PFS of 9.7 months with T+PP and 7.6 months with PP. The median OS follow-up times by reverse Kaplan-Meier methodology were 9.9 months in the T+PP arm and 9.7 months in the PP arm.

The efficacy results of the final analysis (data cut-off date of 26-Oct-2020) and study closure (data cut-off date of 26-Apr-2023) were consistent with those of the interim analysis. At the final analysis, the median OS follow-up times by reverse Kaplan-Meier methodology were 18.4 months in the T+PP arm and 18.0 months in the PP arm. At the study closure, the median OS follow-up times by reverse Kaplan-Meier methodology were 45.5 months in the T+PP arm and 42.6 months in the PP arm.

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

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

Endpoint	Tislelizumab + Pemetrexed + Platinum (N = 74)	Pemetrexed + Platinum (N = 36)
PFS		
Events, n (%)	33 (44.6)	22 (61.1)
Median PFS (months) (95% CI)	14.6 (11.5, NE)	4.6 (3.5, 9.7)
Stratified hazard ratio[a] (95% CI)	0.31 (0.18, 0.55)	
OS		
Deaths, n (%)	24 (32.4)	20 (55.6)
Median OS (months) (95% CI)	NE (NE, NE)	13.1 (5.6, NE)
Stratified hazard ratio[a] (95% CI)	0.39 (0.22, 0.71)	
Best overall response, n (%)[b]		
ORR[b], n (%)	52 (70.3)	11 (30.6)

95% CI[c]	(58.5, 80.3)	(16.3, 48.1)
DoR[b]		
Median DoR (months) (95% CI)	NE (13.2, NE)	8.5 (3.3 NE)

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

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

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

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

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

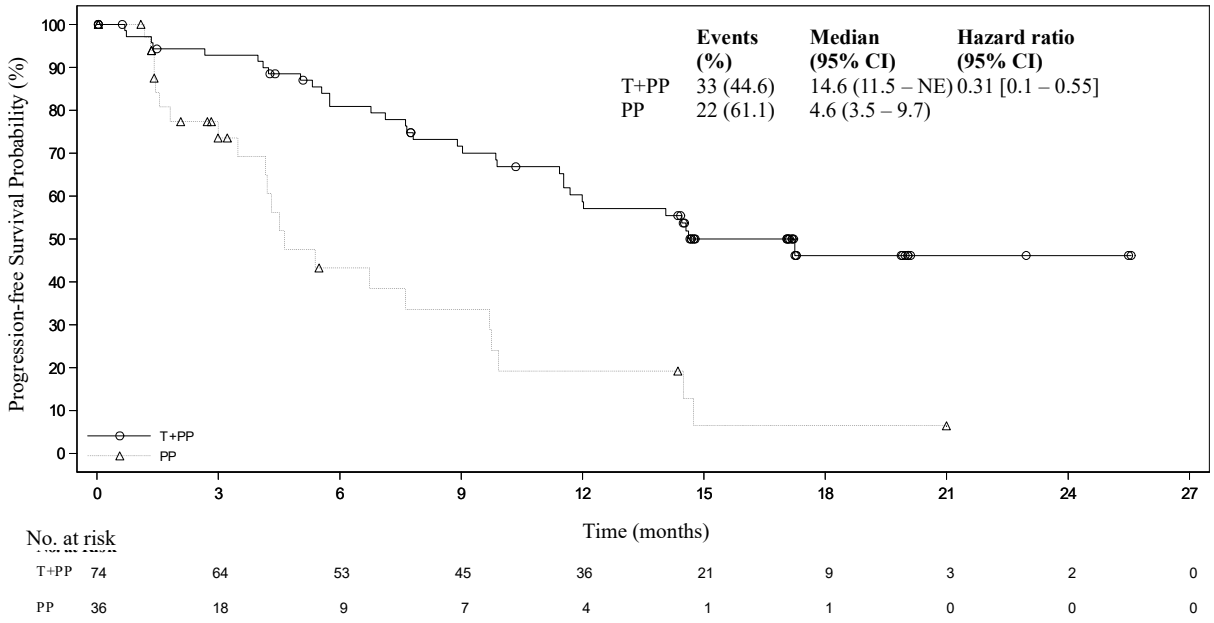
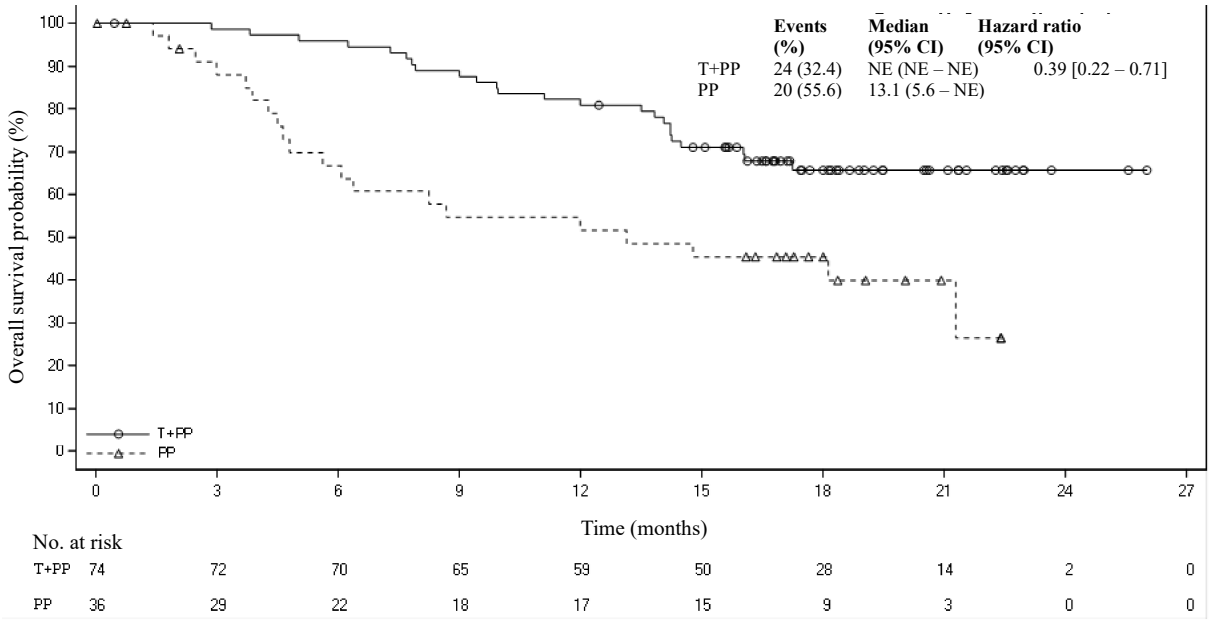


Figure 2 Kaplan-Meier plot of OS in BGB-A317-304 in patients with PD-L1 ≥50%



As of data cut-off date of 26-Apr-2023, in patients with PD-L1 expression ≥50%, the median PFS was 17.2 months (95% CI: 11.5, 31.4) for the T+PP arm and 4.6 months (95% CI: 3.5, 9.7) for the PP arm, with HR of 0.27 (95% CI: 0.16, 0.46); while the median OS was 41.9 months (95% CI: 24.1, NE) for the T+PP arm and 13.1 months (95% CI: 5.6 – 19.4) for the PP arm, with HR of 0.38 (95% CI: 0.24-0.63).

First-line treatment of squamous NSCLC: BGB-A317-307

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

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

A total of 360 patients were 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).

The treatment was administered on a 3-week cycle, until the patient completed administration of 4 to 6 cycles of chemotherapy or Tislelizumab combined with chemotherapy at the investigator's

discretion. Patients in the T+nPC and T+PC arms received Tislelizumab until disease progression or unacceptable toxicity. Patients in the PC arm with disease progression were given the option to cross over to receive Tislelizumab monotherapy on a 3-week cycle.

Randomization was stratified by PD-L1 expression in tumor cells (TC) (<1% versus 1% to 49% versus ≥50%) and tumor 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. Tumor assessments were conducted every 6 weeks for the first 6 months, then every 9 weeks for the remainder of the first year, then every 12 weeks until disease progression.

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

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

The study met its primary endpoint at the interim analysis (data cut-off date of 06-Dec-2019), showing statistically significant improvements in PFS with Tislelizumab in combination with paclitaxel and carboplatin (T+PC arm) and Tislelizumab in combination with nab-paclitaxel and carboplatin (T+nPC arm) compared with paclitaxel and carboplatin alone (PC arm). The stratified HR (T+PC arm versus PC arm) was 0.48 (95% CI: 0.34, 0.69; p <0.0001). The stratified HR (T+nPC arm versus PC arm) was 0.45 (95% CI: 0.32, 0.64; p <0.0001). Median PFS was 7.6 months in the T+PC arm, 7.6 months in the T+nPC arm and 5.4 months in the PC arm. The median OS follow-up times by reverse Kaplan-Meier methodology were 8.8 months in the T+PC arm, 8.8 months in the T+nPC arm, and 8 months in the PC arm.

The final analysis (data cut-off date of 30-Sep-2020) and study closure (data cut-off date of 28-Apr-2023) showed consistent results with those of the interim analysis. At the final analysis, the median OS follow-up times by reverse Kaplan-Meier methodology were 18.8 months in the T+PC arm, 18.9 months in the T+nPC arm, and 18.1 months in the PC arm. At the study closure, the median OS follow-up times by reverse Kaplan-Meier methodology were 44.3 months in the T+PC arm, 47.0 months in the T+nPC arm, and 44.7 months in the PC arm.

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

Table 4 Efficacy results in BGB-A317-307

Endpoint	Tislelizumab + Paclitaxel + Carboplatin (N = 120)	Tislelizumab + nab-Paclitaxel + Carboplatin (N = 119)	Paclitaxel + Carboplatin (N = 121)
PFS			
Events, n (%)	80 (66.7)	79 (66.4)	86 (71.1)
Median PFS (months) (95% CI)	7.7 (6.7, 10.4)	9.6 (7.4, 10.8)	5.5 (4.2, 5.6)
Stratified hazard ratio[a] (95% CI)	0.45 (0.33, 0.62)	0.43 (0.31, 0.60)	-
OS			
Deaths, n (%)	48 (40.0)	47 (39.5)	52 (43.0)
Median OS (months) (95% CI)	22.8 (19.1, NE)	NE (18.6, NE)	20.2 (16.0, NE)
Stratified hazard ratio (95% CI)	0.68 (0.45, 1.01)	0.752 (0.50, 1.12)	-
ORR[b]			
ORR, n (%)	74 (61.7)	74 (62.2)	45 (37.2)
95% CI	(52.4, 70.4)	(52.8, 70.9)	(28.6, 46.4)
DoR[b]			
Median DoR (months) (95% CI)	13.2 (7.85, 18.79)	10.4 (8.34, 17.15)	4.8 (4.04, 5.72)

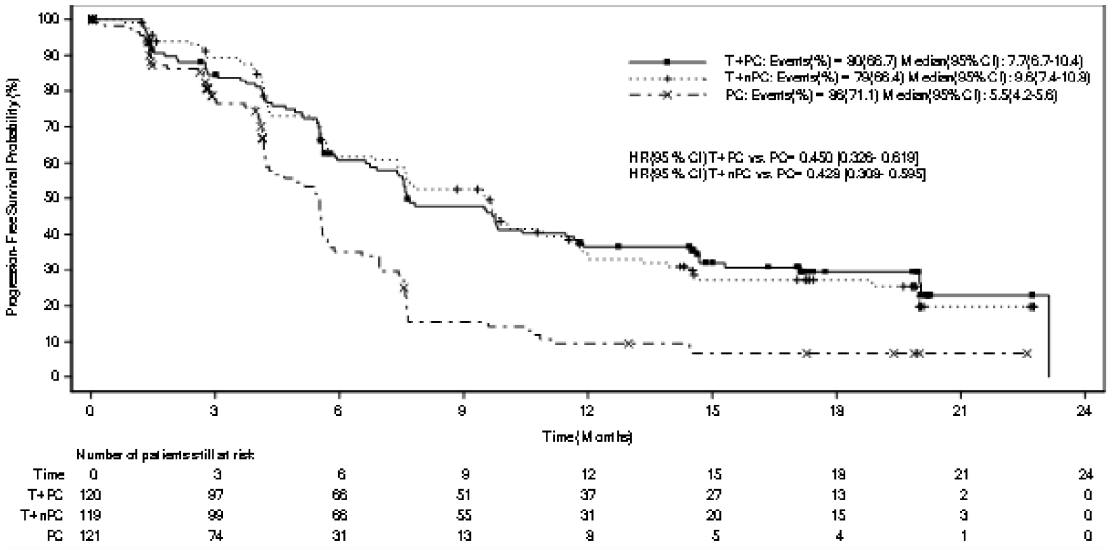
PFS = progression-free survival; CI = confidence interval; OS = overall survival; ORR = objective response rate; DoR = duration of response; NE = not estimable.

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

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

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

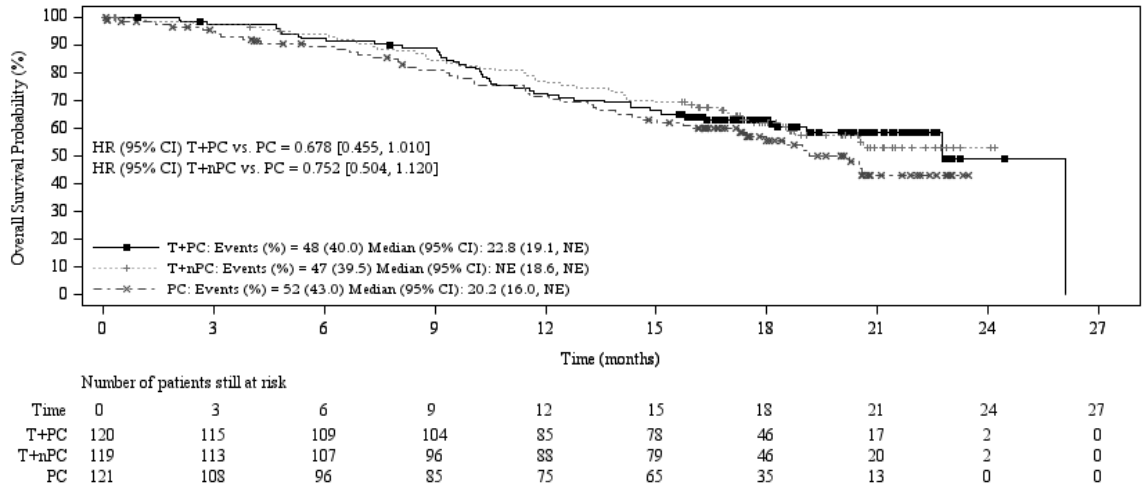
T+PC arm versus T+nPC arm versus PC arm



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

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

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



CI = Confidence interval; T+PC = Tislelizumab+paclitaxel+carboplatin; T+nPC = Tislelizumab+nab paclitaxel+carboplatin; PC = paclitaxel+carboplatin; NE = not estimable

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

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

As of data cut-off date of 28-Apr-2023,

- The stratified HR for PFS Arm T+PC versus Arm PC and Arm T+nPC versus Arm PC were 0.45 (95% CI, 0.33, 0.62), with median PFS of 7.7 months for Arm T+PC and 9.5 months for Arm T+nPC, compared with 5.5 months in Arm PC. The trend of PFS benefit in Arm T+PC and T+nPC was observed in all subgroups including PD-L1 expression <1%, >1% to <49%, and >50%
- The stratified HR for OS Arm T+PC versus Arm PC was 0.67 (95% CI, 0.49, 0.92), 0.82 (95% CI, 0.60, 1.11) for Arm T+nPC versus Arm PC, with a median OS of 26.1 months for Arm T+PC, 23.3 months for Arm T+nPC, compared with 19.4 months in Arm PC.

Second-line treatment of NSCLC: BGB-A317-303

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

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

A total of 805 patients were 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 tumor cells (TC) (≥25% versus <25%). Administration of docetaxel and Tislelizumab continued until disease progression, as assessed by investigator per RECIST v1.1, or unacceptable toxicity. PD-L1 expression was evaluated at a central laboratory using the Ventana PD-L1 (SP263) assay that identified PD-L1 staining on tumor cells. Tumor 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), 32.4% age 65 years or older, 3.2% age 75 years or older; 77.3% male; 17.0% White and 79.9% Asian; 20.6% with ECOG PS of 0 and 79.4% with ECOG PS of 1; 85.5% with metastatic disease; 30.3% never-smokers; 46.0% with squamous and 54.0% non-squamous histology; 65.8% with wild-type and 34% with unknown EGFR status; 46.1% with wild-type and 53.9% with unknown ALK status; 7.1% with previously treated brain metastases.

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

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

BGB-A317-303 met both dual-primary endpoints of OS in the ITT analysis and PD-L1 ≥25% analysis sets. At the prespecified interim analysis (data cut-off date 10-Aug-2020), a statistically significant improvement in OS was observed in the ITT population. Results favored the Tislelizumab arm (HR = 0.64; 95% CI: 0.53, 0.78; $p < 0.0001$). Median OS was 17.2 months for the Tislelizumab arm and 11.9 months for the docetaxel arm. The median follow-up times by reverse Kaplan-Meier methodology were 19.5 months in the Tislelizumab arm and 17.0 months in the docetaxel arm. At the final analysis (data cutoff date 15-Jul-2021), a statistically significant improvement in OS was observed in the PD-L1 ≥25% analysis set favoring the Tislelizumab arm (stratified HR = 0.53; 95% CI: 0.41, 0.70; $p < 0.0001$) with median OS being 19.3 months for the Tislelizumab arm and 11.5 months for the docetaxel arm. The median follow-up time by reverse Kaplan-Meier methodology at the final analysis were 31.1 months in the Tislelizumab arm and 27.9 months in the docetaxel arm.

The final analysis (data cut-off date 15-Jul-2021) and study closure (data cut-off date 18-Jan-2024) showed consistent efficacy results in the ITT population compared to the interim analysis. At the study closure, the median OS follow-up times by reverse Kaplan-Meier methodology were 46.5 months in the tislelizumab arm and 41.0 months in the docetaxel arm.

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

Table 5 Efficacy results in BGB-A317-303

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

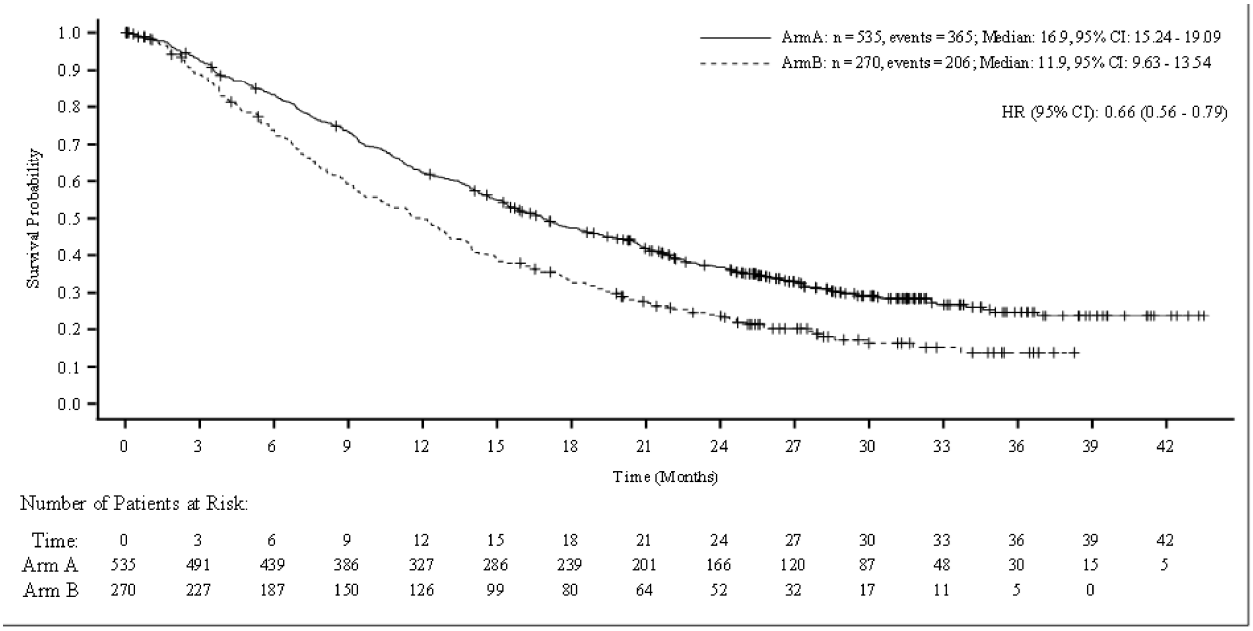
OS = overall survival; CI = confidence interval; PFS = progression-free survival; ORR = objective response rate; DoR = duration of response.
Medians were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley.

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

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

[c] Confirmed by investigator.

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



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

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

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

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

As of data cut-off date of 18-Jan-2024, median OS in the ITT population was 16.9 (95% CI: 15.24, 19.09) months for tislelizumab, compared with 11.9 (95% CI: 9.63, 13.54) months for docetaxel with HR of 0.67 (95% CI: 0.57, 0.80).

Gastric or gastroesophageal junction (G/GEJ) adenocarcinoma

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

BGB-A317-305 is a randomised, multicentre, double-blind, placebo-controlled phase III trial in patients with previously untreated locally advanced unresectable or metastatic gastric or gastroesophageal junction (G/GEJ) adenocarcinoma.

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

The study included only patients with histologically confirmed adenocarcinoma. The trial excluded patients who had squamous cell or undifferentiated or other histological type of G/GEJ cancer; patients diagnosed with G/GEJ adenocarcinoma with known human epidermal growth factor receptor 2 (HER2) positive tumours; patients who had active leptomeningeal disease or uncontrolled brain metastasis; patients with active autoimmune disease or history of autoimmune diseases, that may relapse.

Tislelizumab plus platinum and fluoropyrimidine based chemotherapy (T+PtF) or placebo plus platinum and fluoropyrimidine based chemotherapy (P+PtF) were administered on a 21-day cycle. Tislelizumab was administered until disease progression or unacceptable toxicity.

The administration of chemotherapy agents consisted of:

- Oxaliplatin 130 mg/m² IV on Day 1, and capecitabine 1000 mg/m² orally twice daily for 14 consecutive days, repeated every 3 weeks. Oxaliplatin was administered for up to 6 cycles and capecitabine was administered as maintenance therapy at investigator's discretion until disease progression or unacceptable toxicity.

Or

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

Cross-over between treatment arms was not allowed.

Randomisation was stratified by region (China (including Taiwan), vs. Japan and South Korea vs. rest of the world (ROW), including US and Europe); PD-L1 expression (PD-L1 TAP score ≥5% vs. PD-L1 TAP score <5%); presence of peritoneal metastasis (yes vs. no) and ICC option (oxaliplatin plus capecitabine vs. cisplatin plus 5-FU). Additional analyses of efficacy outcome measures were also conducted based on PD-L1 TAP score ≥1%.

The primary efficacy endpoints were overall survival (OS) that was tested hierarchically in the PD-L1 TAP score ≥5% population and in the Intent-to-Treat (ITT) population. Secondary outcome measures included progression- free survival (PFS), objective response rate (ORR), and duration of response (DoR) as assessed by the investigator per RECIST v1.1. Tumour assessments were performed every 6 weeks for the first 48 weeks and thereafter approximately every 9 weeks.

A total of 997 patients were randomized to receive either tislelizumab plus platinum and fluoropyrimidine based chemotherapy (T+PtF Arm, N = 501), or placebo plus platinum and fluoropyrimidine based chemotherapy (P+PtF Arm, N = 496). Of the 997 patients, 885 (88.8%) had PD-L1 TAP score ≥1% (T+PtF Arm, N = 432; P+PtF Arm, N = 453).

The demographics and baseline characteristics of PD-L1 TAP ≥1% population were generally balanced in T+PtF and P+PTF arms. 34.5% patients in T+PtF Arm and 37.1% patients in P+PtF Arm were aged 65 years or older. 65.5% patients in T+PtF Arm and 68.0% patients in P+ PtF Arm had ECOG performance status score of 1 at baseline. 24.8% patients in T+PtF Arm and 25.4% patients in P+PtF Arm were enrolled from US/Europe. Most patients had metastatic disease at baseline (98.6% in T+PtF Arm and 99.1% in P+PtF Arm), while 44.0% patients in T+PtF Arm and 43.3% patients in P+PtF Arm had peritoneal metastasis.

At final analysis (DCO: 28 February 2023), with a minimum follow-up time of 24.6 months, the trial met the primary endpoint of OS in the ITT analysis set, demonstrating a statistically significant and clinically meaningful improvement for the ITT population. In the PD-L1 TAP ≥1% population, the OS HR was 0.78 (95% CI: 0.67, 0.90), with a median OS of 15.0 months (95% CI: 13.3, 16.7) for the T+C arm vs. 12.8 months (95% CI: 12.1, 14.1) for the P+C arm, showing clinical meaningful survival benefit favouring T+C arm.

The median PFS was 6.9 months in T+PtF arm and 5.9 months in P+PtF arm, with HR of 0.78 (95% HR 0.67, 0.91). The ORR was 47.7% in T+PtF arm and 41.1% in P+PtF arm, with Odds Ratio of 1.31 (95%CI: 1.00, 1.72). For patients with response, the median DoR was 8.6 months T+PtF arm and 7.2 months in P+PtF arm. Analysis of these efficacy endpoints also demonstrated better disease control in T+PtF arm in this population.

Final analysis efficacy results of PD-L1 TAP ≥1% population are shown in Table 7, and Figure 6

and 7.

Table 7 Efficacy Results in PD-L1 TAP ≥ 1% population of BGB-A317-305 (final analysis)

Endpoint	**T+PtF (N = 432)**	**P+PtF (N = 453)**
OS		
Deaths, n (%)	318 (73.6)	370 (81.7)
Median (months) (95% CI)	15.0 (13.3, 16.7)	12.8 (12.1, 14.1)
Unstratified Hazard ratio (95% CI) [a]	0.78 (0.67, 0.90)	
PFS		
Disease progression or death, n (%)	316 (73.1)	364 (80.4)
Median (months) (95% CI)	6.9 (5.7, 7.2)	5.9 (5.6, 6.9)
Unstratified Hazard ratio (95% CI) [a]	0.78 (0.67, 0.91)	
ORR		
ORR, n	206	186
ORR, %	47.7	41.1
95% CI (%)	(42.9, 52.5)	(36.5, 45.7)
Unstratified Odds Ratio for ORR, (95% CI) [b]	1.31 (1.00, 1.71)	
DoR		
Median (months) (95% CI)	8.6 (7.8, 10.4)	7.2 (5.8, 8.3)

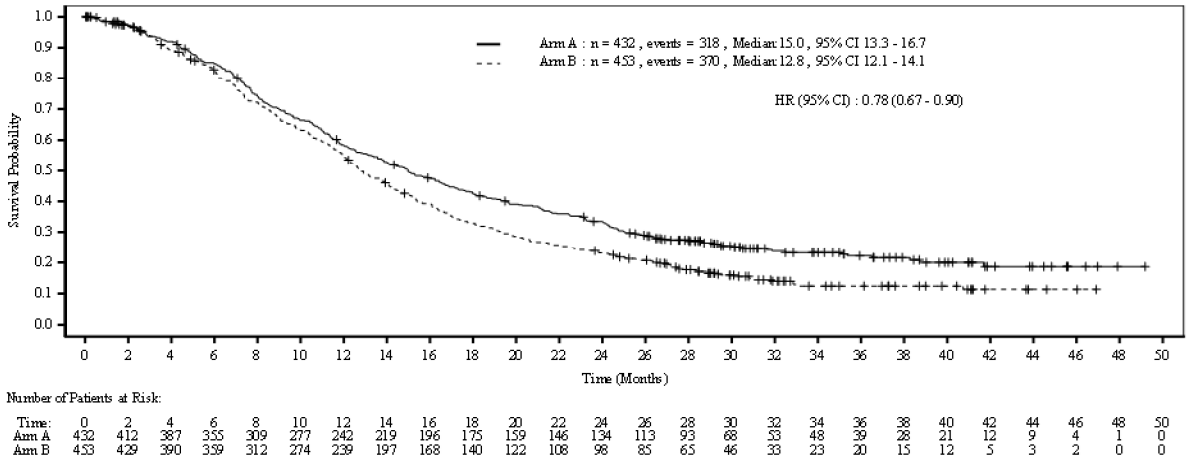
Data cutoff: 28FEB2023

CI = confidence interval; : T+PtF = Tislelizumab + Platinum fluoropyrimidine based chemotherapy; P+PtF = Placebo + Platinum fluoropyrimidine based chemotherapy; PD-L1 = programmed cell death protein ligand-1; DoR = Duration of response; ORR = objective response rate; OS = overall survival; PFS = progression-free survival.

[a] Unstratified OS: Hazard ratio was estimated from Cox model with P+PtF arm as the reference group.

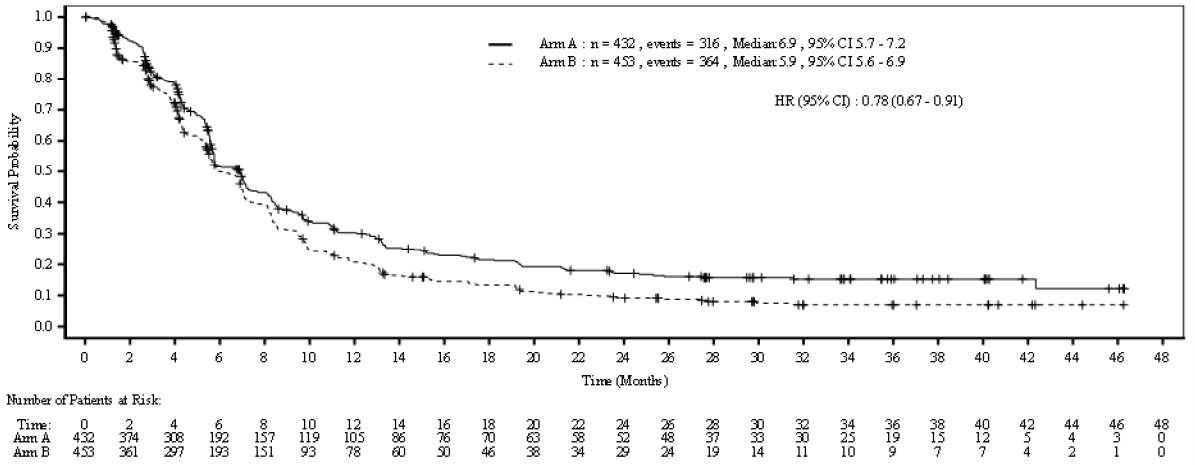
[b] Unstratified odds ratios between arms were calculated using the unstratified Cochran-Mantel-Haenszel method.

Figure 6: Kaplan-Meier Curve for Overall Survival in PD-L1 TAP ≥ 1% population of BGB-A317-305 (final analysis)



Data cutoff: 28FEB2023.
Arm A = Tislelizumab + Platinum fluoropyrimidine based chemotherapy, Arm B = Placebo + Platinum fluoropyrimidine based chemotherapy; PD-L1 = programmed cell death protein ligand-1.
Hazard ratio was based on unstratified Cox regression model.
'+' = censored.

Figure 7: Kaplan-Meier Curve for Progression-Free Survival in PD-L1 TAP ≥ 1% population of BGB-A317-305(final analysis)



Data cutoff: 28FEB2023.
Arm A = Tislelizumab + Platinum fluoropyrimidine based chemotherapy, Arm B = Placebo + Platinum fluoropyrimidine based chemotherapy; PD-L1 = programmed cell death protein ligand-1.
Hazard ratio was based on unstratified Cox regression model.
'+' = censored.

Esophageal squamous cell carcinoma (ESCC)

Second-line treatment of ESCC: BGB-A317-302

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

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

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

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 countryspecific guidelines for standard of care), or
- docetaxel 75 mg/m^2 on day 1, given every 3 weeks, or
- irinotecan 125 mg/m^2 on days 1 and 8, given every 3 weeks.

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

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

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

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

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

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

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

Efficacy results of the updated analysis are shown in Table 8 and Figure 8.

Table 8 Efficacy results in BGB-A317-302 – Updated analysis

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

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

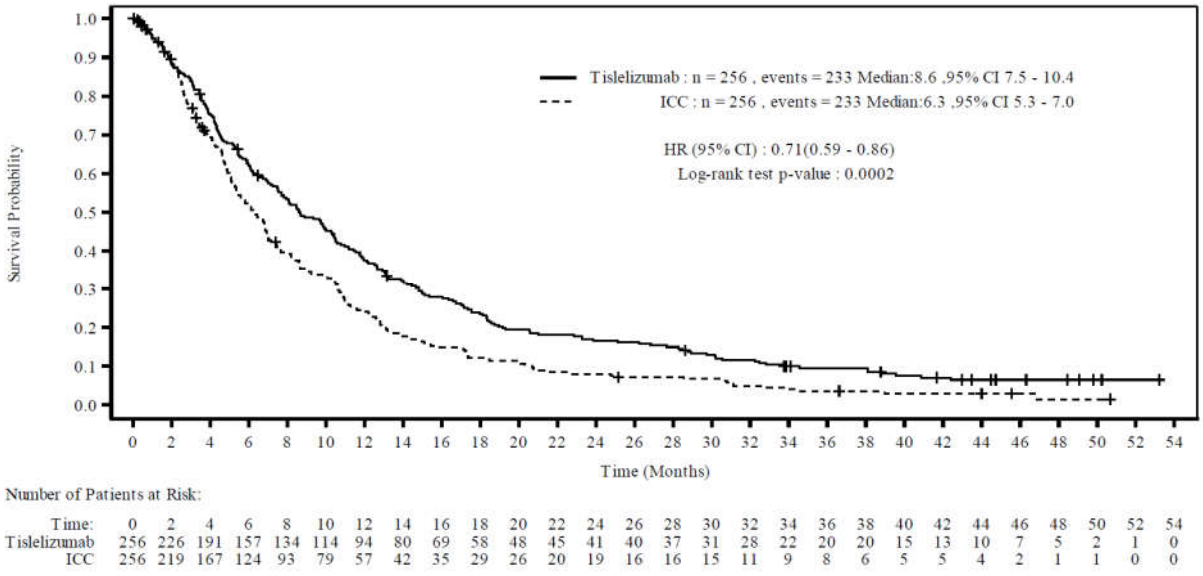
[a] Estimated using Kaplan-Meier method.

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

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

[d] Based on ad hoc analysis.

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



Nominal one-sided p-value is based on a log-rank test stratified by ECOG performance status and

investigator's choice of chemotherapy.

Efficacy and PD-L1 subgroups (Updated analysis):

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

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

18 EXCIPIENTS

Trisodium citrate dihydrate, Citric acid monohydrate, L-histidine hydrochloride monohydrate, L-histidine, Trehalose dihydrate, polysorbate-20 (E432), and Water for injections.

Incompatibility

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except those mentioned in section 5. DOSAGE AND ADMINISTRATION.

19 STORAGE

Store in a refrigerator (2 °C – 8 °C).

Do not freeze.

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

For storage conditions after dilution of the medicinal product, see section 20. SHELF LIFE.

20 SHELF LIFE

Unopened vial

Please use before the time printed on the label or box.

After opening

Once opened, the medicinal product should be diluted and infused immediately (see section 5. DOSAGE AND ADMINISTRATION for instructions on dilution of the medicinal product before administration).

After preparation of solution for infusion

Tislelizumab does not contain a preservative. Chemical and physical in-use stability has been demonstrated for 24 hours at 2 °C to 8 °C. The 24 hours include storage of the diluted solution

under refrigeration (2 °C to 8 °C) for no more than 20 hours, time required for returning to room temperature (25 °C or below) and time to complete the infusion within 4 hours.

From a microbiological point of view, once diluted, the product should be used immediately.

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

21 PACKAGING

1 vial/carton. 1 vial contains Tislelizumab 100 mg/10 mL.

22 MARKETING AUTHORIZATION NUMBER

DKI2468600149A1

23 APPLICANT

Name : PT Etana Biotechnologies Indonesia

Address : Rawa Gelam V St. Block L, Lots 11-13, Jakarta Industrial Estate Pulo Gadung, East Jakarta

24 MANUFACTURER

Name : BeiGene Guangzhou Biologics Manufacturing Co., Ltd

Address : No.83 Kangyao South Road, Huangpu District, Guangzhou City, Guangdong Province, China.

25 DRUG CATEGORY

26 SPECIAL PRECAUTION

HARUS DENGAN RESEP DOKTER

First approval date: 26/11/2024

Informasi Produk untuk Pasien
ETAPIDI
Tislelizumab

A. Nama Obat
Nama generik : Tislelizumab
Nama dagang : ETAPIDI

B. Bentuk Sediaan
Larutan konsentrat untuk infus (konsentrat steril)
Larutan memiliki pH sekitar 6.5 dan osmolalitas sekitar 270 sampai 330 mOsm/kg.

C. Komposisi Zat Aktif/Apa yang terkandung dalam obat?
Setiap ml larutan konsentrat untuk infus mengandung 10 mg Tislelizumab.

D. Kekuatan Obat/Berapa kekuatan obat ini?
Setiap vial 10 ml mengandung 100 mg Tislelizumab (100mg/10ml).

E. Pemerian Obat/Bagaimana penampakan obat ini?
Larutan jernih sampai agak keruh, tidak berwarna sampai agak kuning.

F. Indikasi/Untuk apa obat digunakan?
ETAPIDI merupakan obat kanker yang mengandung zat aktif tislelizumab. Ini adalah antibodi monoklonal, yaitu sejenis protein yang dirancang untuk mengenali dan menempel pada target tertentu dalam tubuh yang disebut *programmed death-1 receptor (PD-1)* yang ditemukan pada permukaan sel T dan B (jenis sel darah putih yang merupakan bagian dari sistem kekebalan tubuh, pertahanaalami tubuh). Ketika PD-1 diaktifkan oleh sel kanker, ia dapat mematikan aktivitas sel T. Dengan memblokir PD-1, ETAPIDI mencegah sel kanker mematikan sel T yang membantu sistem kekebalan tubuh melawan kanker.

ETAPIDI digunakan pada orang dewasa untuk mengobati:
- Kanker paru-paru non-sel kecil yang telah menyebar ke bagian tubuh lain, belum diobati dengan kemoterapi dan tidak dapat diangkat melalui pembedahan. Ketika digunakan untuk mengobati kanker jenis ini, ETAPIDI diberikan dalam kombinasi dengan kemoterapi.
- Kanker paru-paru non-sel kecil yang telah menyebar ke bagian tubuh lain dan telah diobati dengan kemoterapi. Ketika digunakan untuk mengobati kanker jenis ini, ETAPIDI diberikan sendiri.
- Kanker lambung stadium lanjut atau adenokarsinoma pada sambungan gastroesofageal (kanker perut) yang telah menyebar ke bagian tubuh lain, belum pernah diobati dengan terapi anti-kanker, dan tidak dapat diangkat melalui pembedahan. Dalam pengaobatan jenis kanker ini, ETAPIDI diberikan dalam kombinasi dengan kemoterapi.
- Jenis kanker esofagus yang disebut karsinoma sel skuamosa esofagus yang telah menyebar ke bagian tubuh lain, telah diobati dengan terapi antikanker dan tidak dapat diangkat melalui pembedahan

Jika Anda memiliki pertanyaan tentang cara kerja ETAPIDI atau mengapa obat ini diresepkan untuk Anda, tanyakan langsung kepada dokter Anda.

ETAPIDI dapat diberikan dalam kombinasi dengan obat antikanker lainnya. Penting bagi Anda juga untuk membaca brosur kemasan obat-obatan lain tersebut. Jika Anda memiliki pertanyaan tentang obat-obatan ini, tanyakan langsung kepada dokter Anda.

G. Posologi dan Cara Pemberian/Berapa banyak dan seberapa sering obat ini boleh digunakan? Apa yang harus dilakukan bila lupa menggunakan obat ini?
ETAPIDI akan diberikan kepada Anda di rumah sakit atau klinik di bawah pengawasan dokter yang berpengalaman.

- Dosis lazim ETAPIDI adalah 200 mg yang diberikan melalui infus intravena (diteteskan ke pembuluh darah vena) setiap 3 minggu.
- ETAPIDI dosis pertama akan diberikan melalui infus selama 60 menit. Jika Anda menoleransi dosis pertama dengan baik, maka infus berikutnya dapat diberikan selama 30 menit.
- Apabila ETAPIDI diberikan bersamaan dengan kemoterapi, Anda akan diberikan ETAPIDI terlebih dahulu baru kemudian kemoterapi.
- Silakan merujuk pada brosur kemasan obat anti kanker lainnya untuk memahami penggunaan obat-obatan tersebut. Jika Anda memiliki pertanyaan, tanyakan kepada dokter Anda.
- Dokter Anda akan menentukan berapa banyak pengobatan yang Anda perlukan.

Jika Anda melewatkan satu dosis ETAPIDI
- Segera hubungi dokter Anda untuk menjadwal ulang janji temu Anda.
- Sangat penting agar Anda tidak melewatkan satu dosis obat ini.

Jika Anda menghentikan pengobatan ETAPIDI
Menghentikan pengobatan Anda dapat menghentikan efek obatnya. Jangan menghentikan pengobatan dengan ETAPIDI kecuali Anda telah membicarakan hal ini dengan dokter Anda.

Jika Anda memiliki pertanyaan lebih lanjut mengenai pengobatan atau penggunaan obat ini, tanyakan kepada dokter Anda.

H. Kontraindikasi/Pada keadaan apa Anda tidak diperbolehkan menggunakan obat ini?
Anda tidak boleh diberikan ETAPIDI:
- jika Anda alergi terhadap tislelizumab atau bahan lain dari obat ini (tercantum di bagian Q. Informasi Lain). Bicarakan langsung dengan dokter Anda jika Anda merasa tidak yakin.

I. Peringatan dan Perhatian/Apa yang perlu diperhatikan bila menggunakan obat ini?
Beri tahu dokter Anda sebelum Anda diberikan ETAPIDI jika Anda memiliki atau pernah memiliki:
- penyakit autoimun (kondisi dimana sistem pertahanan tubuh menyerang sel normal)
- radang hati (hepatitis) atau masalah hati lainnya
- radang ginjal (nefritis)
- pneumonia atau radang paru-paru (pneumonitis)
- radang usus besar (kolitis)
- ruam serius
- masalah dengan kelenjar penghasil hormon (termasuk kelenjar adrenal, hipofisis, dan tiroid)
- diabetes melitus tipe 1
- transplantasi organ
- reaksi terkait infus

Jika salah satu gejala di atas berlaku pada Anda, atau Anda merasa tidak yakin, bicarakan dengan dokter Anda sebelum diberikan ETAPIDI.

Waspadai efek samping yang serius
ETAPIDI dapat menyebabkan efek samping yang serius, yang terkadang dapat mengancam jiwa dan menyebabkan kematian.

Beritahu dokter Anda segera jika Anda mengalami salah satu dari efek samping serius berikut selama pengobatan dengan ETAPIDI:
- radang hati (hepatitis) atau masalah hati lainnya
- radang ginjal (nefritis)
- radang paru-paru (pneumonitis)
- radang usus besar (kolitis)

- reaksi kulit yang parah (termasuk sindrom Stevens-Johnson (SJS) atau Toxic epidermal necrolysis (TEN): gejala mungkin termasuk demam, gejala mirip flu, ruam, gatal, kulit melepuh atau luka di mulut atau pada permukaan lembab lainnya
- masalah dengan kelenjar penghasil hormon (terutama kelenjar adrenal, hipofisis atau tiroid): gejala mungkin termasuk detak jantung cepat, kelelahan ekstrem, penambahan atau penurunan berat badan, pusing atau pingsan, rambut rontok, rasa dingin, sembelit, sakit kepala yang tidak kunjung hilang atau sakit kepala yang tidak biasa
- diabetes melitus tipe 1
- reaksi terkait infus
- radang otot (miositis)
- radang otot jantung (miokarditis)
- radang selaput jantung (perikarditis)
- radang sendi (artritis)
- kelainan inflamasi yang menyebabkan nyeri dan kekakuan otot, terutama pada bahu dan pinggul (polymyalgia rheumatica): gejalanya mungkin berupa nyeri pada bahu, leher, lengan atas, bokong, pinggul atau paha, kekakuan pada area yang terkena, nyeri atau kaku pada pergelangan tangan, siku atau lutut
- radang saraf: gejala mungkin termasuk nyeri, kelemahan dan kelumpuhan pada ekstremitas (sindrom Guillain-Barré)

Untuk informasi lebih lanjut mengenai gejala-gejala di atas, baca bagian M. Efek Samping. Bicaralah dengan dokter Anda jika Anda memiliki pertanyaan atau kekhawatiran.

Anak-anak dan remaja
ETAPIDI tidak boleh digunakan pada anak-anak dan remaja di bawah usia 18 tahun.

Pemantauan selama perawatan Anda dengan ETAPIDI
Dokter Anda akan melakukan tes rutin (tes fungsi hati, tes fungsi ginjal, tes pencitraan radiografi) sebelum dan selama pengobatan.

Dokter Anda juga akan melakukan tes darah secara rutin sebelum dan selama pengobatan dengan ETAPIDI untuk memantau kadar gula darah dan hormon dalam tubuh Anda. Hal ini karena kadar gula darah dan hormon dapat dipengaruhi oleh ETAPIDI.

J. **Interaksi Obat/Obat dan makanan apa yang harus dihindari jika menggunakan obat ini?**
Beritahu dokter Anda jika Anda sedang mengonsumsi, baru saja mengonsumsi, atau mungkin mengonsumsi obat lain. Ini termasuk obat-obatan herbal dan obat-obatan yang diperoleh tanpa resep dokter.

Secara khusus, beri tahu dokter Anda jika Anda sedang mengonsumsi obat apa pun yang menekan sistem kekebalan tubuh Anda, termasuk kortikosteroid (seperti prednison), karena obat ini dapat mengganggu efek ETAPIDI. Namun, setelah Anda memulai pengobatan dengan ETAPIDI, dokter Anda mungkin memberi Anda kortikosteroid untuk mengurangi efek samping yang mungkin Anda alami.

K. Kehamilan dan Menyusui/Apakah obat boleh digunakan pada wanita hamil dan menyusui?
Jika Anda sedang hamil atau menyusui, mengira Anda sedang hamil atau berencana untuk memiliki bayi, mintalah nasihat dokter Anda sebelum Anda diberikan obat ini.

Anda tidak boleh diberikan ETAPIDI jika Anda sedang hamil kecuali jika dokter Anda meresepkannya secara khusus untuk Anda. Efek ETAPIDI pada ibu hamil belum diketahui, namun ada kemungkinan zat aktifnya, tislelizumab, dapat membahayakan bayi yang belum lahir.
- Jika Anda seorang wanita yang mungkin hamil, Anda harus menggunakan kontrasepsi yang efektif selama Anda menjalani pengobatan ETAPIDI dan setidaknya selama 4 bulan setelah dosis terakhir ETAPIDI.

- Jika Anda sedang hamil, mengira sedang hamil atau berencana untuk memiliki bayi, beri tahu dokter Anda.

Tidak diketahui apakah ETAPIDI dapat dikeluarkan melalui ASI. Risiko terhadap bayi yang diberi ASI tidak dapat dikesampingkan. Jika Anda sedang menyusui, beri tahu dokter Anda. Anda tidak boleh menyusui selama pengobatan dengan ETAPIDI dan setidaknya 4 bulan setelah dosis terakhir ETAPIDI.

L. Efek pada Pengemudi dan Pengoperasian Mesin/Apakah aman mengemudi dan mengoperasikan mesin selama menggunakan obat ini?

ETAPIDI memiliki pengaruh kecil pada kemampuan Anda untuk mengemudi atau menggunakan mesin.

Merasa lelah atau lemah merupakan efek samping yang mungkin terjadi akibat penggunaan ETAPIDI. Jangan mengemudi atau menggunakan mesin setelah Anda diberikan ETAPIDI kecuali Anda yakin Anda merasa sehat.

M. Efek Samping/Apa efek yang tidak diinginkan yang mungkin terjadi jika menggunakan obat ini?

Seperti obat-obatan lainnya, obat ini dapat menimbulkan efek samping, meski tidak semua orang mengalaminya.

Efek samping berikut telah dilaporkan pada penggunaan ETAPIDI sebagai obat tunggal:

Sangat umum (dapat mempengaruhi lebih dari 1 dari 10 orang)
- Radang paru-paru
- Kelenjar tiroid yang kurang aktif, yang dapat menyebabkan kelelahan, penambahan berat badan, perubahan pada kulit dan rambut (hipotiroidisme)
- Batuk
- Mual
- Ruam
- Gatal (pruritus)
- Kelelahan
- Nafsu makan menurun
- Demam
- Kelemahan, detak jantung cepat, sesak napas (anemia)
- Kadar bilirubin dalam darah meningkat, produk pemecahan sel darah merah, yang dapat menyebabkan kulit dan mata menguning, menandakan adanya masalah hati
- Peningkatan kadar enzim hati aspartat aminotransferase dalam darah
- Peningkatan kadar enzim hati alanine aminotransferase dalam darah

Umum (dapat mempengaruhi hingga 1 dari setiap 10 orang)
- Diare
- Perdarahan atau memar spontan (trombositopenia)
- Sering infeksi, demam, menggigil, sakit tenggorokan atau sariawan akibat infeksi (neutropenia atau limfopenia)
- Merasa mual (mual), muntah, kehilangan nafsu makan, nyeri pada perut sebelah kanan, kulit atau bagian putih mata menguning, mengantuk, urine berwarna gelap, lebih mudah berdarah atau memar dari biasanya – gejala yang mungkin terjadi pada masalah hati (hepatitis)
- Nyeri sendi (artralgia)
- Nyeri otot (mialgia)
- Sesak napas, batuk atau nyeri dada - kemungkinan gejala masalah paru-paru (pneumonitis)
- Kelelahan, bengkak di bawah leher, nyeri di depan tenggorokan – kemungkinan gejala masalah kelenjar tiroid (tiroiditis)
- Peningkatan kadar gula darah, rasa haus, mulut kering, buang air kecil lebih sering, kelelahan, nafsu makan meningkat disertai penurunan berat badan, kebingungan, mual,

muntah, napas berbau buah, kesulitan bernapas, dan kulit kering atau memerah – kemungkinan gejala hiperglikemia
- Kelelahan, kebingungan, otot berkedut, kejang (hiponatremia)
- Kelemahan otot, kejang otot, irama jantung tidak normal (hipokalemia)
- Kelenjar tiroid yang terlalu aktif, dapat menyebabkan hiperaktif, berkeringat, penurunan berat badan dan rasa haus (hipertiroidisme)
- Kesulitan bernapas (dispnea)
- Peningkatan tekanan darah (hipertensi)
- Luka pada mulut atau sariawan disertai radang gusi (stomatitis)
- Nyeri hebat pada perut bagian atas, mual, muntah, demam, nyeri tekan di perut – kemungkinan gejala masalah pankreas (pankreatitis)
- Menggigil atau gemetar, gatal atau ruam, kulit memerah, sesak napas atau mengi, pusing atau demam yang mungkin terjadi selama infus atau hingga 24 jam setelah infus – kemungkinan gejala reaksi terkait infus
- Peningkatan kadar enzim hati alkaline fosfatase dalam darah
- Kadar enzim kreatin dalam darah meningkat
- Kadar hemoglobin dalam darah rendah
- Rendahnya kadar sel darah berikut: limfosit, neutrofil, dan trombosit
- Tingginya kadar enzim berikut: alanin aminotransferase, alkalin aminotransferase, aspartat aminotransferase, dan kreatinin kinase
- Kadar bilirubin dalam darah tinggi
- Kadar kalium dan natrium dalam darah rendah

Tidak umum (dapat mempengaruhi hingga 1 dari setiap 100 orang)
- Perubahan jumlah atau warna urin, nyeri saat buang air kecil, nyeri di area ginjal – kemungkinan gejala masalah ginjal (nefritis)
- Diare atau buang air besar lebih sering dari biasanya, tinja berwarna hitam seperti ter, lengket, darah atau lendir pada tinja, nyeri hebat atau nyeri tekan pada perut – kemungkinan gejala masalah usus (kolitis)
- Gula darah tinggi, merasa lebih lapar atau haus dari biasanya, buang air kecil lebih sering dari biasanya – kemungkinan gejala diabetes melitus
- Nyeri otot, kaku, lemah, nyeri dada atau kelelahan parah – kemungkinan gejala masalah otot (miositis)
- Nyeri dada, detak jantung cepat atau tidak normal, sesak napas saat istirahat atau selama beraktivitas, penumpukan cairan disertai pembengkakan pada tungkai, pergelangan kaki dan kaki, kelelahan – kemungkinan gejala masalah otot jantung (miokarditis)
- Nyeri sendi, kaku, bengkak atau kemerahan, penurunan rentang gerak sendi – kemungkinan gejala masalah sendi (radang sendi)
- Mata merah, sakit dan bengkak – kemungkinan gejala masalah yang melibatkan uvea, lapisan di bawah bagian putih bola mata (uveitis)
- Insufisiensi adrenal (kelainan di mana kelenjar adrenal tidak menghasilkan cukup hormon tertentu)
- Perubahan warna kulit (vitiligo)
- Kulit gatal atau mengelupas, luka pada kulit, kemungkinan gejala reaksi kulit yang parah
- Kadar hemoglobin darah tinggi
- Kadar leukosit darah rendah
- Kadar albumin darah rendah
- Kadar kreatinin darah tinggi
- Kadar kalium darah tinggi

Jarang (dapat mempengaruhi hingga 1 dari setiap 1.000 orang)
- Nyeri dada, demam, batuk, jantung berdebar kemungkinan gejala masalah yang mempengaruhi selaput di sekitar jantung (perikarditis)
- Sering sakit kepala, perubahan penglihatan (baik penglihatan kabur atau ganda), kelelahan dan/atau kelemahan, kebingungan, penurunan tekanan darah, pusing – kemungkinan gejala masalah kelenjar pituitari (hipofisis)

- Penyakit celiac (ditandai dengan gejala seperti sakit perut, diare, dan kembung setelah mengonsumsi makanan yang mengandung gluten)
- Kadar limfosit darah tinggi
- Kadar natrium darah tinggi

Efek samping lain yang telah dilaporkan (frekuensi tidak diketahui):
Kurangnya atau berkurangnya enzim pencernaan yang dibuat oleh pankreas (insufisiensi eksokrin pankreas).

Efek samping berikut telah dilaporkan dengan ETAPIDI ketika ETAPIDI diberikan bersama dengan obat anti kanker lainnya.

Perlu diingat bahwa penting bagi Anda untuk juga membaca brosur kemasan obat antikanker lain yang Anda terima karena obat tersebut juga dapat menyebabkan efek samping.

Sangat umum (dapat mempengaruhi lebih dari 1 dari 10 orang)
- Radang paru-paru
- Kelemahan, detak jantung cepat, sesak napas (anemia)
- Perdarahan atau memar spontan (trombositopenia)
- Sering infeksi, demam, menggigil, sakit tenggorokan atau sariawan akibat infeksi (neutropenia atau limfopenia)
- Kelenjar tiroid kurang aktif yang dapat menyebabkan kelelahan, penambahan berat badan, perubahan kulit dan rambut (hipotiroidisme)
- Kelelahan, kebingungan, otot berkedut, kejang (hiponatremia)
- Kelemahan otot, kejang otot, irama jantung tidak normal (hipokalemia)
- Mual
- Diare
- Ruam
- Nyeri sendi (artralgia)
- Kelelahan (kelelahan)
- Demam
- Penurunan nafsu makan
- Peningkatan kadar enzim hati aspartat aminotransferase dalam darah
- Peningkatan kadar enzim hati alanine aminotransferase dalam darah
- Peningkatan kadar bilirubin dalam darah, produk pemecahan sel darah merah yang dapat menyebabkan kulit dan mata menguning, menandakan adanya masalah hati
- Rendahnya kadar hemoglobin
- Rendahnya kadar sel darah berikut: leukosit, limfosit, neutrofil, trombosit

Umum (dapat mempengaruhi hingga 1 dari setiap 10 orang)
- Kelenjar tiroid yang terlalu aktif, yang dapat menyebabkan hiperaktif, berkeringat, penurunan berat badan dan rasa haus (hipertiroidisme)
- Peningkatan kadar gula darah, rasa haus, mulut kering, buang air kecil lebih sering, kelelahan, nafsu makan meningkat disertai penurunan berat badan, kebingungan, mual, muntah, napas berbau buah, kesulitan bernapas, dan kulit kering atau memerah – kemungkinan gejala hiperglikemia
- Gula darah tinggi, merasa lebih lapar atau haus dari biasanya, buang air kecil lebih sering dari biasanya – kemungkinan gejala diabetes melitus
- Nyeri dada, detak jantung cepat atau tidak normal, sesak napas saat istirahat atau selama beraktivitas, penumpukan cairan disertai pembengkakan pada tungkai, pergelangan kaki dan kaki, kelelahan – kemungkinan gejala masalah otot jantung (miokarditis)
- Tekanan darah meningkat (hipertensi)
- Batuk
- Kesulitan bernapas (dispnea)
- Sesak napas, batuk atau nyeri dada - kemungkinan gejala masalah paru-paru (pneumonitis)
- Luka pada mulut atau sariawan disertai radang gusi (stomatitis)

- Merasa mual, muntah, kehilangan nafsu makan, nyeri pada perut sebelah kanan, kulit atau bagian putih mata menguning, mengantuk, urine berwarna gelap, lebih mudah berdarah atau memar dari biasanya – gejala yang mungkin terjadi masalah hati (hepatitis)
- Diare atau buang air besar lebih banyak dari biasanya, kotoran berwarna hitam seperti ter, tinja lengket, darah atau lendir pada tinja, nyeri hebat atau nyeri tekan pada perut – kemungkinan gejala masalah usus (kolitis)
- Gatal (pruritus)
- Nyeri otot (mialgia)
- Nyeri sendi, kaku, bengkak atau kemerahan, penurunan rentang gerak sendi – kemungkinan gejala masalah sendi (radang sendi)
- Peningkatan kadar enzim hati alkaline fosfatase dalam darah
- Peningkatan kreatinin dalam darah, zat yang secara normal dikeluarkan oleh ginjal melalui urin. Hal ini dapat berarti ginjal Anda tidak berfungsi dengan normal.
- Menggigil atau gemetar, gatal atau ruam, kulit memerah, sesak napas atau mengi, pusing atau demam yang mungkin terjadi selama infus atau hingga 24 jam setelah infus – kemungkinan gejala reaksi terkait infus
- Kadar enzim berikut tinggi dalam darah: alanine aminotransferase dan aspartat aminotransferase
- Kadar bilirubin dalam darah tinggi
- Kadar kreatinin kinase dan kreatinin dalam darah tinggi
- Kadar kalium yang tinggi
- Kadar kalium dan natrium darah rendah

Tidak umum (dapat mempengaruhi hingga 1 dari setiap 100 orang)
- Penyakit di mana sistem kekebalan tubuh menyerang kelenjar yang menghasilkan kelembapan bagi tubuh, seperti air mata dan air liur (sindrom Sjögren)
- Kelelahan, bengkak di dasar leher, nyeri di depan tenggorokan – kemungkinan gejala masalah kelenjar tiroid (tiroiditis)
- Insufisiensi adrenal (kelainan di mana kelenjar adrenal tidak menghasilkan cukup hormon tertentu)
- Sering sakit kepala, perubahan penglihatan (baik penglihatan kabur atau penglihatan ganda), kelelahan dan/atau kelemahan, kebingungan, penurunan tekanan darah, pusing – kemungkinan gejala masalah kelenjar pituitari (hipofisitis)
- Inflamasi pada otak, yang mungkin dapat menyebabkan kebingungan, demam, masalah ingatan atau kejang (radang otak)
- Masalah serius pada saraf, yang dapat menyebabkan kesulitan bernapas, sensasi tertusuk-tusuk atau kesemutan di jari tangan, kaki, pergelangan kaki atau pergelangan tangan, kelemahan pada kaki yang menjalar ke tubuh bagian atas, gangguan berjalan atau ketidakmampuan berjalan atau menaiki tangga, kesulitan dengan gerakan wajah termasuk berbicara, mengunyah atau menelan, penglihatan ganda atau ketidakmampuan menggerakkan mata, kesulitan mengontrol kandung kemih atau fungsi usus, detak jantung cepat dan kelumpuhan – kemungkinan gejala sindrom Guillain-Barré
- Kelemahan otot dan kelelahan (miastenia gravis)
- Mata merah, sakit mata dan bengkak – kemungkinan gejala masalah yang mempengaruhi uvea, lapisan di bawah bagian putih bola mata (uveitis)
- Nyeri dada, demam, batuk, jantung berdebar kemungkinan gejala masalah yang mempengaruhi selaput di sekitar jantung (perikarditis)
- Perubahan jumlah atau warna urin, nyeri saat buang air kecil, nyeri di area ginjal – kemungkinan gejala masalah ginjal (nefritis)
- Sakit perut bagian atas yang parah, mual, muntah, demam, nyeri tekan di perut – kemungkinan gejala masalah pankreas (pankreatitis)
- Nyeri otot, kaku, lemah, nyeri dada, atau kelelahan parah – kemungkinan gejala masalah otot (miositis)
- Kulit memutih tidak merata (vitiligo)
- Kadar albumin dalam darah yang rendah
- Kadar alkaline fosfatase dalam darah yang tinggi
- Kadar gula dalam darah yang rendah

- Kadar natrium dalam darah yang tinggi

Beritahu dokter Anda segera jika Anda mengalami salah satu efek samping serius yang tercantum di atas.

Penggunaan ETAPIDI harus dihentikan dan perhatian medis harus segera dicari jika Anda melihat salah satu gejala berikut:

Frekuensi tidak diketahui (tidak dapat diperkirakan dari data yang tersedia)

- Bercak kemerahan yang datar, berbentuk seperti target, atau melingkar pada batang tubuh, seringkali disertai lepuh di bagian tengah, pengelupasan kulit, sariawan pada mulut, tenggorokan, hidung, alat kelamin dan mata. Ruam kulit yang serius ini bisa saja terjadi didahului oleh demam dan gejala mirip flu (SJS atau TEN).

Pelaporan efek samping

Jika Anda mendapatkan efek samping apa pun, bicarakan dengan dokter Anda. Ini termasuk kemungkinan efek samping yang tidak tercantum dalam brosur ini. Dengan melaporkan efek samping, Anda dapat membantu memberikan informasi lebih lanjut mengenai keamanan obat ini.

Kontak untuk Pelaporan ke Industri Farmasi

PT ETANA BIOTECHNOLOGIES INDONESIA
Kawasan Industri Pulogadung, Jl. Rawa Gelam V, Blok. L, Kav.11-13, Jakarta
Email: pv@id.etanabiotech.com
Web-site: https://ebi-pharmacovigilance.azurewebsites.net/

N. Overdosis dan Penanganannya/Apa tanda dan gejala kelebihan dosis? Apa yang harus dilakukan bila menggunakan obat ini melebihi dosis yang dianjurkan?

Tidak ada informasi mengenai overdosis Tislelizumab. Jika terjadi overdosis, Anda harus dipantau secara ketat untuk mengetahui tanda atau gejala reaksi obat yang merugikan, dan pengobatan simtomatik yang tepat harus segera diberikan.

O. Cara Penyimpanan/Bagaimana cara menyimpan obat ini?

Dokter, apoteker atau perawat Anda bertanggung jawab untuk menyimpan obat ini dan membuang produk yang tidak terpakai dengan benar. Informasi berikut ini ditujukan untuk para profesional kesehatan.

Jauhkan obat ini dari pandangan dan jangkauan anak-anak.

Simpan di lemari es (2 °C - 8 °C). Jangan dibekukan. Simpan botol di dalam kemasan luar untuk melindungi dari cahaya.

P. **Batas Penggunaan Setelah Direkonstitusi atau Setelah Wadah Dibuka/Berapa lama obat ini dapat digunakan setelah kemasan dibuka?**

Jangan menggunakan obat ini setelah tanggal kadaluwarsa yang tertera pada karton dan label vial setelah EXP. Tanggal kedaluwarsa mengacu pada hari terakhir bulan itu.

ETAPIDI tidak mengandung bahan pengawet. Stabilitas penggunaan kimia dan fisik telah dibuktikan selama 24 jam pada suhu 2 °C hingga 8 °C. Waktu 24 jam termasuk penyimpanan larutan yang telah diencerkan dalam lemari es (2 °C hingga 8 °C) selama tidak lebih dari 20 jam, waktu yang diperlukan untuk kembali ke suhu ruang (25 °C atau lebih rendah) dan waktu untuk menyelesaikan infus dalam waktu 4 jam.

Jika tidak segera digunakan, waktu dan kondisi penyimpanan selama digunakan menjadi tanggung jawab pengguna. Larutan yang telah diencerkan tidak boleh dibekukan.

Jangan menyimpan bagian larutan infus yang tidak terpakai untuk digunakan kembali. Obat-obatan atau bahan limbah yang tidak terpakai harus dibuang sesuai dengan prosedur setempat.

Q. Informasi Lain/Informasi apa yang harus diketahui dari obat ini?

Apa isi ETAPIDI

- Zat aktif ETAPIDI adalah tislelizumab. Setiap ml konsentrat larutan infus mengandung 10 mg tislelizumab.
- Tiap vial mengandung 100 mg tislelizumab dalam 10 ml konsentrat.

Bahan lainnya adalah natrium sitrat dihidrat, asam sitrat monohidrat, L-histidin hidroklorida monohidrat, L-histidin, trehalosa dihidrat, polisorbat 20 dan air untuk injeksi.

ETAPIDI mengandung natrium

Beritahu dokter Anda jika Anda sedang menjalani diet rendah sodium (rendah garam) sebelum diberikan ETAPIDI. Obat ini mengandung 1,6 mg natrium (komponen utama garam masak/garam meja) dalam setiap ml konsentrat. Infus tunggal ETAPIDI mengandung 32 mg natrium dalam dua botol 10 ml. Jumlah ini setara dengan 1,6% dari asupan natrium harian maksimum yang direkomendasikan untuk orang dewasa.

Seperti apa ETAPIDI dan isi paketnya

Konsentrat ETAPIDI untuk larutan infus (konsentrat steril) berbentuk larutan bening sampai agak opalescent, tidak berwarna sampai agak kekuningan.

ETAPIDI tersedia dalam kemasan berisi 1 vial.

***R.* Nomor Izin Edar**

DKI2468600149A1

S. Nama dan Alamat Pendaftar

PT Etana Biotechnologies Indonesia
Rawa Gelam V St. Block L, Lots 11-13, Jakarta Industrial Estate Pulo Gadung, East Jakarta

T. Nama dan Alamat Produsen

BeiGene Guangzhou Biologics Manufacturing Co., Ltd
No.83 Kangyao South Road, Huangpu District, Guangzhou City, Guangdong Province, China.

U. Peringatan Khusus

HARUS DENGAN RESEP DOKTER

Tanggal persetujuan pertama kali: 26/11/2024