TUOYI

Toripalimab 240 mg/6 ml (40 mg/ml)

Concentrate for Solution for Infusion

1. DOSAGE FORMS AND STRENGTHS

Concentrate for solution for infusion: 240 mg/6 mL (40 mg/mL) clear to slightly opalescent, colorless to slightly yellow solution in a single-dose vial.

2. DESCRIPTION AND COMPOSITION

TUOYI (toripalimab) concentrate for solution for infusion is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution for intravenous use supplied in a single-dose vial.

Each vial contains 240 mg of TUOYI in 6 mL of solution. Each mL of solution contains 40 mg toripalimab.

3. INDICATIONS AND USAGE

3.1 First-line Treatment of Metastatic or Recurrent, Locally Advanced NPC with Cisplatin and Gemcitabine

TUOYI is indicated, in combination with cisplatin and gemcitabine, for the first-line treatment of adults with metastatic or with recurrent, locally advanced nasopharyngeal carcinoma (NPC).

4. DOSAGE AND ADMINISTRATION

4.1 Recommended Dosage

The recommended dosages of TUOYI are provided in Table 1. Administer as recommended *[see Dosage and Administration (4.3)]*.

Table 1: Recommended Dosage

Indication	Recommended Dosage of TUOYI	Duration of Treatment
First-line NPC	240 mg every three weeks	Until disease progression, unacceptable toxicity, or up to 24 months.

4.2 Dosage Modifications

No dose reductions of TUOYI are recommended. In general, withhold TUOYI for severe (Grade 3) immune-mediated adverse reactions. Permanently discontinue TUOYI for life-threatening (Grade 4) immune-mediated adverse reactions, recurrent severe (Grade 3) immune-mediated reactions that require systemic immunosuppressive treatment, or an inability to

reduce prednisone to 10 mg per day or less (or equivalent) within 12 weeks of initiating steroids.

Dosage modifications for TUOYI for adverse reactions that require management different from these general guidelines are summarized in Table 2.

Table 2: Recommended Dosage Modifications for Adverse Reactions

Adverse Reaction	**Severity**[1]	**Dose Modification**
Immune-Related Adverse Reactions *[see Warnings and Precautions (6.1)]*		
Pneumonitis	Grade 2	Withhold[2]
	Grades 3 or 4	Permanently discontinue
Colitis	Grade 2 or 3	Withhold[2]
	Grade 4	Permanently discontinue
Hepatitis with no tumor involvement of the liver	AST/ALT increases to more than 3 and up to 8 times ULN or Total bilirubin increases to more than 1.5 and up to 3 times ULN	Withhold[2]
	AST or ALT increases to more than 8 times ULN or Total bilirubin increases to more than 3 times ULN	Permanently discontinue
Hepatitis with tumor involvement of the liver[3]	Baseline AST or ALT is more than 1 and up to 3 times ULN and increases to more than 5 and up to 10 times ULN or Baseline AST or ALT is more than 3 and up to 5 times ULN and increases to more than 8 and up to 10 times ULN	Withhold[2]
	Baseline AST or ALT is above the ULN and increases to more than 10 times ULN or Total bilirubin increases to more than 3 times ULN	Permanently discontinue
Endocrinopathies	Grades 3 or 4	Withhold until clinically stable or permanently discontinue depending on severity[2]
Nephritis with Renal Dysfunction	Grade 2 or 3 increased blood creatinine	Withhold[2]
	Grade 4 increased blood creatinine	Permanently discontinue
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold[2]
	Confirmed SJS, TEN, or DRESS	Permanently discontinue
Myocarditis	Grades 2, 3, or 4	Permanently discontinue
Neurological toxicities	Grade 2	Withhold[2]
	Grade 3-4	Permanently discontinue
Other Adverse Reactions		
Infusion-related reactions *[see Warnings and Precautions (6.2)]*	Grade 1 or 2	Interrupt or slow the rate of infusion
	Grade 3 or 4	Stop infusion Permanently discontinue

[1] Based on National Cancer Institute (NCI) Common Terminology for Adverse Events (CTCAE) version 5.0

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

[3] If AST and ALT are less than or equal to ULN at baseline in patients with liver involvement, withhold or permanently discontinue TUOYI based on recommendations for hepatitis with no liver involvement.

ALT=alanine aminotransferase, AST=aspartate aminotransferase, DRESS=drug rash with eosinophilia and systemic symptoms, SJS=Stevens Johnson syndrome, TEN=toxic epidermal necrolysis, ULN=upper limit of normal

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4.3 Preparation and Administration

Preparation for Intravenous Infusion

- Visually inspect the solution for particulate matter and discoloration. The solution is clear to slightly opalescent, colorless to slightly yellow. Discard the vial if visible particles are observed.
- Withdraw the required volume of TUOYI and inject slowly into a 100 mL or 250 mL infusion bag containing 0.9% Sodium Chloride Injection, USP. **Mix diluted solution by gentle inversion.** Do not shake. The final concentration of the diluted solution should be between 1 mg/mL to 3 mg/mL.
- Discard any unused portion left in the vial.

Storage of Diluted Solution for Infusion

TUOYI does not contain a preservative.

If the diluted solution is not administered immediately, store either:

- At room temperature, 20°C to 25°C (68°F to 77°F), for no more than 8 hours from the time of dilution to the completion of the infusion. Discard diluted solution stored at room temperature after 8 hours.

  Or
- Refrigerated at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of dilution to the completion of the infusion. If refrigerated, allow the diluted solution to come to room temperature prior to administration. Discard the refrigerated diluted solution after 24 hours.

Do not freeze.

Administration

- Administer diluted solution intravenously via an infusion pump using an in-line aseptic filter (0.2 or 0.22 micron).
- First Infusion: Infuse over at least 60 minutes.
- Subsequent infusions: If no infusion-related reactions occurred during the first infusion, subsequent infusions may be administered over 30 minutes *[see Dose Modifications (4.2)]*.
- Do not co-administer other drugs through the same intravenous line.
- When administered on the same day as chemotherapy, TUOYI should be administered prior to chemotherapy.
- Refer to the Prescribing Information for cisplatin and gemcitabine for recommended dosing information.

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5. CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.

6. WARNINGS AND PRECAUTIONS

6.1 Severe and Fatal Immune-Mediated Adverse Reactions

TUOYI is a monoclonal antibody that belongs to a class of drugs that bind to either the programmed death receptor-1 (PD-1) or PD-ligand 1 (PD-L1), blocking the PD-1/PD-L1 pathway, thereby removing inhibition of the immune response, potentially breaking peripheral tolerance and inducing immune-mediated adverse reactions. Important immune-mediated adverse reactions listed under WARNINGS AND PRECAUTIONS may not include all possible severe and fatal immune-mediated reactions.

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue and can affect more than one body system simultaneously. Immune-mediated adverse reactions can occur at any time after starting PD-1/PD-L1 blocking antibody. While immune mediated adverse reactions usually manifest during treatment with PD-1/PD-L1 blocking antibodies, immune-mediated adverse reactions can also manifest after discontinuation of PD-1/PD-L1 blocking antibodies.

Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Monitor closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue TUOYI depending on severity *[see Dosage and Administration (4.2)]*. In general, if TUOYI requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy.

Toxicity management guidelines for adverse reactions that do not necessarily require systemic steroids (e.g., endocrinopathies and dermatologic reactions) are discussed below.

Immune-Mediated Pneumonitis

TUOYI in Combination with Cisplatin and Gemcitabine

TUOYI in combination with cisplatin and gemcitabine can cause immune-mediated pneumonitis. In patients treated with other PD-1/PD-L1 blocking antibodies, the incidence of pneumonitis is higher in patients who have received prior thoracic radiation. Immune-mediated pneumonitis occurred in 2.1% (3/146) of patients receiving TUOYI, including Grade 2 (1.4%) adverse reactions. Pneumonitis resolved in 67% (2/3) of these patients.

TUOYI as a Single-Agent

TUOYI can cause immune-mediated pneumonitis. In patients treated with other PD-1/PD-L1 blocking antibodies, the incidence of pneumonitis is higher in patients who have received prior thoracic radiation. Immune-mediated pneumonitis occurred in 2.6% (22/851) of patients receiving TUOYI, including fatal (0.2%), Grade 3 (0.7%), and Grade 2 (1.1%) adverse reactions. Systemic corticosteroids were required in 82% (18/22) of patients with pneumonitis. Pneumonitis led to permanent discontinuation of TUOYI in 1.2% (10/851) of patients. Pneumonitis resolved in 23% (5/22) of these patients.

Immune-Mediated Colitis

TUOYI can cause immune-mediated colitis, which may present with diarrhea. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies.

TUOYI as a Single-Agent

Immune-mediated colitis occurred in 0.4% (3/851) of patients receiving TUOYI, including Grade 3 (0.2%) and Grade 2 (0.1%) adverse reactions. Colitis resolved in all 3 patients.

Hepatotoxicity and Immune-Mediated Hepatitis

TUOYI in Combination with Cisplatin and Gemcitabine

TUOYI in combination with cisplatin and gemcitabine can cause immune-mediated hepatitis. Immune-mediated hepatitis occurred in 0.7% (1/146) of patients receiving TUOYI in combination with cisplatin and gemcitabine, which was a Grade 3 (0.7%) adverse reaction. The patient with immune-mediated hepatitis required systemic corticosteroids.

TUOYI as a Single-Agent

TUOYI can cause immune-mediated hepatitis. Immune-mediated hepatitis occurred in 3.3% (28/851) of patients receiving TUOYI, including Grade 4 (0.8%), Grade 3 (2.1%), and Grade 2 (0.4%) adverse reactions. Hepatitis led to permanent discontinuation of TUOYI in 1.1% of

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patients and withholding of TUOYI in 0.8% of patients. Hepatitis resolved in 54% (15/28) of these patients.

Immune-Mediated Endocrinopathies

Adrenal Insufficiency

TUOYI can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold or permanently discontinue TUOYI depending on severity *[see Dosage and Administration (4.2)]*.

TUOYI as a Single-Agent

Adrenal insufficiency occurred in 0.5% (4/851) of the patients receiving TUOYI, including Grade 2 (0.4%) and Grade 1 (0.1%) adverse reactions. Systemic corticosteroids were required in 75% (3/4) of the patients with adrenal insufficiency. Adrenal insufficiency led to withholding of TUOYI in 0.1% (1/851) of patients. In the one patient in whom TUOYI was withheld, TUOYI was reinitiated after symptom improvement.

Hypophysitis

TUOYI can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effects such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism. Initiate hormone replacement as indicated. Withhold or permanently discontinue TUOYI depending on severity *[see Dosage and Administration (4.2)]*.

TUOYI as a Single-Agent

Hypophysitis occurred in 0.4% (3/851) of patients receiving TUOYI, including Grade 3 (0.2%) and Grade 2 (0.1%) adverse reactions. All three patients received systemic corticosteroids. Hypophysitis led to permanent discontinuation of TUOYI in 0.1% (1/851) of patients and withholding of TUOYI in 0.1% (1/851) of patients. The one patient in whom TUOYI was withheld reinitiated TUOYI.

Thyroid Disorders

TUOYI can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement for hypothyroidism or institute medical management of hyperthyroidism as clinically indicated. Withhold or permanently discontinue TUOYI depending on severity *[see Dosage and Administration (4.2)]*.

TUOYI in Combination with Cisplatin and Gemcitabine

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Thyroiditis occurred in 2.1% (3/146) of patients receiving TUOYI in combination with cisplatin and gemcitabine, including Grade 2 (1.4%). Three patients required thyroid hormone replacement therapy. Thyroiditis resolved in one of the 3 patients.

Hyperthyroidism occurred in 1.4% (2/146) of patients receiving TUOYI in combination with cisplatin and gemcitabine. Hyperthyroidism resolved in these 2 patients.

Hypothyroidism occurred in 30% (44/146) of patients receiving TUOYI in combination with cisplatin and gemcitabine, including Grade 2 (24%) and Grade 1 (6%). Eighty percent of the 44 patients required thyroid hormone replacement therapy. TUOYI was withheld in 2.1% (3/146) of the patients. Of the 3 patients in whom TUOYI was withheld, 2 patients reinitiated TUOYI.

TUOYI as a Single-Agent

Thyroiditis occurred in 0.6% (5/851) of patients receiving TUOYI, including Grade 2 (0.1%). Two of these 5 patients received systemic corticosteroids and 2 required thyroid hormone replacement therapy. Thyroiditis resolved in 2 of the 5 patients.

Hyperthyroidism occurred in 7% (55/851) of patients receiving TUOYI, including Grade 2 (1.9%). Hyperthyroidism resolved in 85% (47/55) of the patients.

Hypothyroidism occurred in 15% (128/851) of patients receiving TUOYI, including Grade 2 (8%). Sixty three percent of the 128 patients required thyroid hormone replacement therapy. TUOYI was withheld in 0.5% of patients. Of the 4 patients in whom TUOYI was withheld, 3 patients reinitiated TUOYI.

Type 1 Diabetes Mellitus, which can present with Diabetic Ketoacidosis

Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold or permanently discontinue TUOYI depending on severity *[see Dosage and Administration (4.2)]*.

TUOYI as a Single-Agent

Diabetes mellitus occurred in 0.9% (8/851) of patients receiving TUOYI, including Grade 4 (0.1%), Grade 3 (0.7%), and Grade 2 (0.1%). Diabetes mellitus led to permanent discontinuation in 0.4% of patients. Six of the 8 (75%) patients with diabetes mellitus required long-term insulin therapy.

Immune-Mediated Nephritis with Renal Dysfunction

TUOYI in Combination with Cisplatin and Gemcitabine

TUOYI in combination with cisplatin and gemcitabine can cause immune-mediated nephritis. Immune-mediated nephritis occurred in 0.7% (1/146) of patients receiving TUOYI. The one

patient with immune-mediated nephritis (Grade 4) required systemic corticosteroids and nephritis led to discontinuation of TUOYI. Nephritis resolved in this patient.

TUOYI as a Single-Agent

TUOYI can cause immune-mediated nephritis. Immune-mediated nephritis occurred in 0.5% (4/851) of patients receiving TUOYI, including Grade 3 (0.5%) adverse reactions. Nephritis resolved in 75% (3/4) of these patients.

Immune-Mediated Dermatologic Adverse Reactions

TUOYI can cause immune-mediated rash or dermatitis. Exfoliative dermatitis, including Stevens-Johnson Syndrome (SJS), drug rash with eosinophilia and systemic symptoms (DRESS), and toxic epidermal necrolysis (TEN), has occurred with PD-1/PD-L1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes. Withhold or permanently discontinue TUOYI depending on severity *[see Dosage and Administration (4.2)]*.

TUOYI in Combination with Cisplatin and Gemcitabine

Immune-mediated dermatologic adverse reactions occurred in 8% (12/146) of patients receiving TUOYI, including Grade 3 (3.4%) and Grade 2 (1.4%) adverse reactions. Systemic corticosteroids were required in 25% (3/12) of the patients with immune-mediated dermatologic adverse reactions. Immune-mediated dermatologic adverse reactions led to permanent discontinuation of TUOYI in 2.1% (3) of patients. Immune-mediated dermatologic adverse reactions resolved in 92% (11/12) of these patients.

TUOYI as a Single-Agent

Immune-mediated dermatologic adverse reactions occurred in 4% (34/851) of patients receiving TUOYI, including Grade 3 (0.4%) and Grade 2 (1.4%) adverse reactions. Immune-mediated dermatologic adverse reactions led to withholding of TUOYI in 0.4% (3) of the patients. Systemic corticosteroids were required in 12% (4/34) of the patients with immune-mediated dermatologic adverse reactions. Immune-mediated dermatologic adverse reactions resolved in 71% (24/34) of these patients.

Other Immune-Mediated Adverse Reactions

The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% (unless otherwise noted) in patients who received TUOYI or were reported with the use of other PD1/PD-L1 blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions.

Cardiac/Vascular: Myocarditis, pericarditis, vasculitis, pericardial effusion

Nervous System: Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy

Ocular: Uveitis, iritis and other ocular inflammatory toxicities can occur. Some cases can be associated with retinal detachment. Various grades of visual impairment, including blindness, can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada-like syndrome, as this may require treatment with systemic steroids to reduce the risk of permanent vision loss.

Gastrointestinal: Pancreatitis, to include increases in serum amylase and lipase levels, gastritis, duodenitis

Musculoskeletal and Connective Tissue: Myositis/polymyositis, rhabdomyolysis (and associated sequelae, including renal failure), arthritis, polymyalgia rheumatica, dermatomyositis

Endocrine: Hypoparathyroidism

Hematologic/Immune: Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection, other transplant (including corneal graft) rejection.

6.2 Infusion-Related Reactions

TUOYI can cause severe or life-threatening infusion-related reactions including hypersensitivity and anaphylaxis.

TUOYI in Combination with Cisplatin and Gemcitabine

Infusion-related reactions have been reported in 4.1% of patients receiving TUOYI in combination with cisplatin and gemcitabine, including Grade 2 (0.7%) reactions.

TUOYI as a Single-Agent

Infusion-related reactions occurred in 2% of 851 patients receiving TUOYI as single agent, including Grade 3 (0.1%) and Grade 2 (0.6%). TUOYI was withheld for one Grade 3 infusion related reaction.

Monitor patients for signs and symptoms of infusion-related reactions including rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever. Interrupt or slow the rate of infusion for mild (Grade 1) or moderate (Grade 2) infusion-related reactions. For severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions, stop infusion and permanently discontinue TUOYI *[see Dosage and Administration (4.2)]*.

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6.3 Complications of Allogeneic HSCT

Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with a PD-1/PD-L1 blocking antibody. Transplant-related complications include hyperacute graft-versus-host-disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease (VOD) after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between PD-1/PD-L1 blockade and allogeneic HSCT.

Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with a PD-1/PD-L1 blocking antibody prior to or after an allogeneic HSCT.

6.4 Embryo-Fetal Toxicity

Based on its mechanism of action, TUOYI can cause fetal harm when administered to a pregnant woman. Animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus resulting in fetal death. Advise women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TUOYI and for 4 months after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

7. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

No formal interaction studies have been performed. Since toripalimab is cleared from the circulation through catabolism, no metabolic drug-drug interactions are expected. Toripalimab is not a substrate for cytochrome P450 or active substance transporters. Toripalimab is not a cytokine and is unlikely to be a cytokine modulator. Additionally, pharmacokinetic (PK) interaction of toripalimab with small molecule active substances is not expected. There is no evidence of interaction mediated by non-specific clearance of lysosome degradation for antibodies.

The use of systemic corticosteroids or immunosuppressants before starting toripalimab should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of toripalimab. However, systemic corticosteroids or other immunosuppressants can be used after starting toripalimab to treat immune-related adverse reactions *[see Warnings and Precautions (6.1)]*. Corticosteroids can also be used as premedication, when toripalimab is used

in combination with chemotherapy, as antiemetic prophylaxis and/or to alleviate chemotherapy-related adverse reactions.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, TUOYI can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. There are no available data on the use of TUOYI in pregnant women. Animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus and result in fetal death *(see Data)*. Human IgG4 immunoglobulins (IgG4) are known to cross the placenta; therefore, TUOYI can potentially be transmitted from the mother to the developing fetus. Advise women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

Animal reproduction studies have not been conducted with TUOYI to evaluate its effect on reproduction and fetal development. A central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the fetus. In murine models of pregnancy, blockade of PD-L1 signaling has been shown to disrupt tolerance to the fetus and to result in an increase in fetal loss; therefore, potential risks of administering TUOYI during pregnancy could include increased rates of abortion or stillbirth. As reported in the literature, there were no malformations related to the blockade of PD-1/PD-L1 signaling in the offspring of these animals; however, immune-mediated disorders occurred in PD-1 and PD-L1 knockout mice. Based on its mechanism of action, fetal exposure to toripalimab may increase the risk of developing immune-mediated disorders or altering the normal immune response.

8.2 Lactation

Risk Summary

There are no data on the presence of toripalimab in human milk or its effects on the breastfed child or on milk production. Maternal IgG is known to be present in human milk. The effects of local gastrointestinal exposure and limited systemic exposure in the breastfed child to toripalimab are unknown. Because of the potential for serious adverse reactions in breastfed

children, advise lactating women not to breastfeed during treatment with TUOYI and for 4 months after the last dose.

8.3 Females and Males of Reproductive Potential

TUOYI can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating TUOYI *[see Use in Specific Populations (8.1)]*.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with TUOYI and for 4 months after the last dose.

8.4 Pediatric Use

The safety and effectiveness of TUOYI have not been established in pediatric patients *[see Indications and Usage (3)]*.

8.5 Geriatric Use

Of the 146 patients with NPC who were treated with TUOYI in combination with cisplatin and gemcitabine 7 (4.8%) were 65 years or older; there were no patients 75 years and older. Clinical studies of TUOYI in combination with cisplatin and gemcitabine did not include a sufficient number of patients aged 65 years and over with NPC to determine whether they respond differently from younger patients.

Of the 851 patients with tumor types including nasopharyngeal carcinoma or other types of tumors from the safety pool treated with TUOYI as a single agent, 171 (20%) patients were 65 years or older and 13 (1.5%) patients were 75 years and older. No overall differences in safety were observed between elderly patients and younger patients *[see Adverse Reactions (10.1)]*.

Of the 190 patients with NPC treated with TUOYI as single agent, 10 (5%) patients were 65 years or older; there were no patients 75 years and older. Clinical studies of TUOYI did not include sufficient numbers of patients aged 65 years and over with NPC to determine whether they respond differently from younger patients.

9. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Toripalimab has minor influence on the ability to drive and use machines. In some patients, dizziness and fatigue have been reported following administration of toripalimab.

10. ADVERSE REACTIONS

10.1 Summary of the Safety Profile

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described in the WARNINGS AND PRECAUTIONS section reflect exposure to TUOYI at a dose of 240 mg every 3 weeks in combination with up to 6 cycles of cisplatin and gemcitabine, followed by TUOYI 240 mg IV every 3 weeks, in 146 patients with NPC enrolled in a randomized, double-blind, placebo-controlled trial (JUPITER-02). Among the 146 patients, 73% were exposed to TUOYI for 6 months or more and 54% were exposed for 12 months or more. The most common adverse reactions (≥ 20%) were: nausea (71%), vomiting (68%), decreased appetite (55%), constipation (39%), hypothyroidism (38%), rash (36%), pyrexia (32%), diarrhea (31%), peripheral neuropathy (30%), cough (26%), musculoskeletal pain (25%), upper respiratory infection (23%), insomnia (23%), dizziness (21%), and malaise (21%). The most common Grade 3 or 4 laboratory abnormalities (≥2%) were: decreased neutrophils (58%), decreased lymphocytes (57%), decreased hemoglobin (50%) decreased platelets (33%), decreased potassium (10%), decreased sodium (9%), increased alanine aminotransferase (6%) increased or decreased magnesium (4.2% each), decreased calcium (3.5%), increased aspartate aminotransferase (2.7%), and bilirubin increased (2.1%).

The data described in the WARNINGS AND PRECAUTIONS section also reflects exposure to TUOYI as a single agent at a dose of 3 mg/kg IV every 2 weeks in 851 patients enrolled in 12 trials: one randomized, active-controlled trial and 11 open-label, non-randomized trials. The tumor types included nasopharyngeal carcinoma (n=193) or other types of tumors (n=658). Among the 851 patients treated with TUOYI as a single agent, 35% were exposed for 6 months or more and 20% were exposed for 12 months or more. In this pooled safety population, the most common (≥20%) adverse reactions were: fatigue (22%), hypothyroidism (20%), and musculoskeletal pain (20%). The most common Grade 3 or 4 laboratory abnormalities (≥2%), were decreased sodium (9%), decreased lymphocytes (8%), decreased hemoglobin (7%), decreased fibrinogen (4.5%), increased lipase (4.0%), increased amylase (2.9%), decreased phosphate (2.8%), increased aspartate aminotransferase (2.6%), increased glucose (2.5%), and increased triglycerides (2.1%).

<u>First-line Treatment of Metastatic or Recurrent, Locally Advanced Nasopharyngeal Carcinoma (NPC)</u>

The safety of TUOYI in combination with cisplatin and gemcitabine was evaluated in JUPITER-02 *[see Clinical Studies (14)]*. Key eligibility criteria were recurrent locally advanced or metastatic nasopharyngeal carcinoma (NPC) not previously treated with systemic chemotherapy for recurrent or metastatic disease. Patients with recurrent NPC after treatment with curative intent were required to have an interval of at least 6 months between the last dose of radiotherapy or chemotherapy and recurrence. Patients received TUOYI 240 mg (n=146) or placebo intravenously (IV) every 3 weeks (n=143), in combination with cisplatin 80 mg/m^2 IV every 3 weeks and gemcitabine 1000 mg/m^2 IV days 1 and 8 for up to 6 cycles followed by TUOYI 240 mg or placebo IV every 3 weeks until disease progression, unacceptable toxicity, or completion of 2 years of treatment. Among patients who received TUOYI, 73% were exposed for 6 months or longer and 54% were exposed for greater than one year.

The median age of patients who received TUOYI was 48 years (range: 19 to 72), 83% male, 100% Asian, 60% had recurrent disease, and 40% presented with metastatic disease. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) was 0 (57%) or 1 (43%). Approximately 59% of patients had received at least one prior systemic therapy for locally advanced disease and 60% had received prior radiation therapy.

Serious adverse reactions occurred in 43% of patients receiving TUOYI in combination with cisplatin and gemcitabine. Serious adverse drug reactions in ≥ 2% were thrombocytopenia (14%), neutrophil count decreased (10%), pneumonia (10%), anemia (9%), abnormal hepatic function (2.7%), and rash (2.1%). Of the patients who received TUOYI in combination with cisplatin and gemcitabine, there were three fatal adverse reactions (2.1%) one due to epistaxis; one due to intracranial hemorrhage associated with immune-related thrombocytopenia and coagulopathy; and one due to pneumonia.

Permanent discontinuation of TUOYI, when given in combination with cisplatin and gemcitabine, due to an adverse reaction occurred in 12% of patients. Adverse reactions resulting in permanent discontinuation of TUOYI in ≥1% were pneumonia (2.1%), pulmonary tuberculosis (1.4%), rash (1.4%), and vomiting (1.4%).

Dosage interruptions of TUOYI due to an adverse reaction occurred in 50% of patients. Adverse reactions which required dosage interruption in ≥2% were anemia (17%), decreased neutrophils (12%), thrombocytopenia (12%), acute kidney injury (4.1%), pneumonia (6%), fatigue (2.7%), upper respiratory infection (2.7%), and hypothyroidism (2.1%).

10.2 Tabulated List of Adverse Reactions

Table 3 summarizes the adverse reactions in JUPITER-02.

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Table 3: Adverse Reactions (≥ 10%) in Patients with Recurrent, Locally Advanced or Metastatic NPC Who Received TUOYI in Combination with Cisplatin and Gemcitabine in JUPITER-02

Adverse Reaction[1]	TUOYI Cisplatin/Gemcitabine N = 146		Placebo Cisplatin/Gemcitabine N = 143	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal Disorders				
Nausea	71	1.4	84	2.8
Vomiting	68	2.1	66	2.1
Constipation	39	0	46	0
Diarrhea	31	1.4	23	0
Stomatitis[2]	12	0	8	0.7
Metabolism and Nutrition Disorders				
Decreased appetite	55	0.7	63	0
Endocrine Disorders				
Hypothyroidism[3]	38	0.7	17	0
Skin Disorders				
Rash[4]	36	3.4	28	2.8
Pruritus	17	0	8	0
General Disorders				
Pyrexia	32	1.4	24	0.7
Malaise	21	0.7	20	0
Fatigue[5]	19	0.7	22	2.1
Nervous System Disorders				
Peripheral neuropathy[6]	30	0	31	0.7
Dizziness	21	0	22	0.7
Headache	18	0	23	0.7
Respiratory, Thoracic and Mediastinal Disorders				
Cough[7]	26	0	27	0
Musculoskeletal Disorders				
Musculoskeletal pain[8]	25	0	25	0.7
Infections				
Upper respiratory infection[9]	23	3.4	13	2.8
Pneumonia[10]	18	11	7	3.5
Psychiatric Disorders				
Insomnia	23	0	17	0
Vascular Disorders				
Epistaxis	10	1.3	13	2.8
Hypertension[11]	10	6	6	4.2

[1]NCI CTCAE v5.0.
[2]Includes mouth ulceration, stomatitis, and radiation stomatitis.
[3]Includes hypothyroidism, tri-iodothyronine decreased, tri-iodothyronine free decreased, and thyroiditis.
[4]Includes acneiform dermatitis, allergic dermatitis, catheter-site rash, dermatitis, drug eruption, eczema, erythema, macule, maculopapular rash, palmar-plantar erythrodysesthesia syndrome, papule, pruritic rash, rash, and urticaria.
[5]Includes asthenia and fatigue.
[6]Includes hypoesthesia, neuralgia, neuropathy peripheral, paresthesia, peripheral sensory neuropathy.
[7]Includes cough and productive cough.
[8]Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, pain in extremity, pain in jaw.
[9]Includes acute sinusitis, bronchitis, laryngitis, nasopharyngitis, pharyngitis, respiratory tract infection, rhinitis, sinusitis, and upper respiratory tract infection.
[10]Includes aspiration pneumonia and pneumonia
[11]Includes blood pressure increased, blood pressure systolic increased, hypertension, and hypertensive crisis.

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Table 4 summarizes the laboratory abnormalities in JUPITER-02.

Table 4: Select Laboratory Abnormalities (≥20%) That Worsened from Baseline in Patients with Recurrent, Locally Advanced or Metastatic NPC Who Received TUOYI in Combination with Cisplatin and Gemcitabine in JUPITER-02

Laboratory Abnormalities*	TUOYI Cisplatin/Gemcitabine		Placebo Cisplatin/Gemcitabine	
	All Grades† (%)	Grade 3 or 4 (%)	All Grades (%)	Grades 3 or 4 (%)
Hematology				
Decreased hemoglobin	94	50	97	38
Decreased neutrophils	91	58	95	63
Decreased lymphocytes	88	57	88	49
Decreased platelets	71	33	66	31
Chemistry				
Decreased magnesium	78	4.2	77	8
Decreased sodium	63	9	62	6
Increased alanine aminotransferase	58	6	50	3.5
Increased aspartate aminotransferase	58	2.7	53	4.9
Decreased albumin	49	0	48	0
Decreased calcium	45	3.5	46	4.2
Increased lactate dehydrogenase	42	0	35	0
Increased calcium	39	0	35	0.7
Decreased potassium	40	10	39	8
Increased creatinine	39	0.7	41	0
Increased alkaline phosphatase	27	0	27	0
Decreased glucose	23	1.4	16	0

*Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: TUOYI/chemotherapy (range: 139 to 146 patients) and placebo/chemotherapy (range: 136 to 143 patients). † Graded per NCI CTCAE v5.0; AKP=alkaline phosphatase. ALT=alanine aminotransferase. AST=aspartate aminotransferase.

10.3 Description of Selected Adverse Reactions

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Severe and fatal immune-mediated adverse reactions *[see Warnings and Precautions (6.1)]*
- Infusion-related reactions *[see Warnings and Precautions (6.2)]*
- Complications of Allogeneic HSCT *[see Warnings and Precautions (6.3)]*

10.4 Reporting of Suspected Adverse Reactions

Reporting suspected adverse reactions after authorisation 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 via:

Pharmaceutical Industry Reporting Contacts

PT. Anvita Pharma Indonesia

Karawang New Industry City Blok B No. 8, Jl. Trans Heksa Km. 7, Desa Wanajaya, Kec. Telukjambe Barat, Kab. Karawang, Provinsi Jawa Barat 41361

e-mail: pv@anvitapharma.com

Pusat Farmakovigilans/MESO Nasional

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

Badan Pengawas Obat dan Makanan

Jl. Percetakan Negara No. 23, Jakarta Pusat, 10560

Email: pv-center@pom.go.id

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

11. OVERDOSE

In case of overdose, patients should be closely monitored for signs or symptoms of adverse reactions and appropriate symptomatic treatment instituted.

12. CLINICAL PHARMACOLOGY

Toripalimab is a programmed death receptor-1 (PD-1) blocking antibody. Toripalimab is a humanized immunoglobulin G4 (IgG4) kappa immunoglobulin that has a predicted molecular weight of approximately 150 kDa. It is expressed in a recombinant Chinese Hamster Ovary (CHO) mammalian cell expression system.

12.1 Mechanism of Action

Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Toripalimab is a humanized IgG4 monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth.

12.2 Pharmacodynamics

Pharmacotherapeutic group: Antineoplastic agents, ATC code: L01FF13

The toripalimab exposure-response relationships and time course of pharmacodynamic response are not fully characterized.

12.3 Pharmacokinetics

Toripalimab pharmacokinetic parameters are presented as geometric mean (coefficient of variation [CV]%) unless otherwise noted. Toripalimab concentrations increased in non-linearly over the dose range of 0.3 to 10 mg/kg every two weeks (0.1 to 3.3 times the approved recommended 3 mg/kg dosage in a 64 kg patient). Steady state was reached by Week 7. The

mean accumulation ratio was approximately 1.4 for maximum concentration (C_{max}) and 1.9 for area under the serum concentration curve (AUC) following multiple doses at the approved recommended dosages of 240 mg Q3W in combination with cisplatin and gemcitabine and 3 mg/kg Q2W as monotherapy.

Distribution

The mean volume of distribution at steady state (V_{ss}) of toripalimab was 3.7 L (27%).

Elimination

The mean clearance (CL) was 14.9 mL/h (31%) after the first dose and 9.5 mL/h (36%) at steady state. The mean terminal half-life ($t_{1/2}$) (± standard deviation) was 10 ± 1.5 days after the first dose and 18 ± 9.4 days at steady state.

Metabolism

Toripalimab is expected to be metabolized into small peptides by catabolic pathways.

Specific Populations

No clinically significant differences in the pharmacokinetics were observed based on age (21 to 85 years), body weight (32 to 164 kg), sex, race (White and Asian), concomitant chemotherapy, mild renal impairment (creatinine clearance [CLcr] 60 to 89 mL/min), mild hepatic impairment (total bilirubin > 1 to 1.5 times ULN with any AST or total bilirubin ≤ ULN with AST > ULN), tumor burden and primary cancer.

The effect of moderate (total bilirubin >1.5 to 3 times ULN and any AST) or severe (total bilirubin > 3 times ULN and any AST) hepatic impairment or of moderate (CLcr 30 to 59 mL/min) or severe (CLcr 15 to 29 mL/min**)** renal impairment on the pharmacokinetics of toripalimab has not been studied.

12.4 Immunogenicity

The observed incidence of anti-drug antibodies (ADA) is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of ADA in the studies described below with the incidence of ADA in other studies, including those of TUOYI or of other toripalimab products.

Of the 146 evaluable patients in JUPITER-02 with nasopharyngeal cancer who received TUOYI 240 mg every 3 weeks for a median duration of 15.1 months, in combination with gemcitabine and cisplatin, 3.4% tested positive for treatment-emergent ADA. Of the 190 evaluable patients in study POLARIS-02 with nasopharyngeal cancer who received TUOYI 3 mg/kg every 2 weeks for a median duration of 3.3 months, 3.7% of patients developed treatment-emergent ADA. Neutralizing antibodies have not been tested.

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Due to the low incidence of ADA, the effect of these antibodies on the pharmacokinetics, pharmacodynamics, safety, or effectiveness of TUOYI is unknown.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been performed to test the potential of toripalimab for carcinogenicity or genotoxicity.

Fertility studies have not been conducted with toripalimab. In 4-week and 26-week repeat-dose toxicology studies in sexually mature cynomolgus monkeys, there were no adverse or notable effects in the male and female reproductive organs.

13.2 Animal Toxicology and/or Pharmacology

In animal models, inhibition of PD-1/PD-L1 signaling increased the severity of some infections and enhanced inflammatory responses. *Mycobacterium tuberculosis*-infected PD-1 knockout mice exhibit markedly decreased survival compared with wild-type controls, which correlated with increased bacterial proliferation and inflammatory responses in these animals. PD-1 blockade using a primate anti-PD1 antibody was also shown to exacerbate *M. tuberculosis* infection in rhesus macaques. PD-1 and PD-L1 knockout mice and mice receiving PD-L1 blocking antibody have also shown decreased survival following infection with lymphocytic choriomeningitis virus.

14. CLINICAL STUDIES

14.1 First-line Treatment of Metastatic or Recurrent, Locally Advanced NPC with Cisplatin and Gemcitabine

The efficacy of TUOYI in combination with cisplatin and gemcitabine was investigated in JUPITER-02 (NCT03581786), a randomized, multicenter, single region, double-blind, placebo-controlled trial in 289 patients with metastatic or recurrent, locally advanced NPC who had not received previous systemic chemotherapy for recurrent or metastatic disease. Patients with recurrent NPC after treatment with curative intent were required to have an interval of at least 6 months between the last dose of radiotherapy or chemotherapy and recurrence. Patients with autoimmune disease, other than stable hypothyroidism or Type I diabetes, and patients who required systemic immunosuppression were ineligible.

Randomization was stratified according to Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) (0 versus 1) and disease stage (recurrent versus metastatic). Patients were randomized (1:1) to receive one of the following treatments:

- TUOYI 240 mg intravenously every 3 weeks in combination with cisplatin 80 mg/m^2 on Day 1 every 3 weeks gemcitabine 1000 mg/m^2 on Days 1 and 8 for up to 6 cycles, followed by TUOYI 240 mg once every 3 weeks, or
- Placebo intravenously every 3 weeks in combination with cisplatin 80 mg/m^2 on Day 1 every 3 weeks and gemcitabine 1000 mg/m^2 on Days 1 and 8 for up to 6 cycles, followed by placebo once every 3 weeks.

Treatment with TUOYI or placebo continued until disease progression per RECIST v1.1, unacceptable toxicity, or a maximum of 2 years. Administration of TUOYI was permitted beyond radiographic progression if the patient was deriving benefit as assessed by the investigator. Tumor assessments were performed every 6 weeks for the first 12 months and every 9 weeks thereafter. The main efficacy outcome measure was Blinded Independent Review Committee (BIRC)-assessed progression-free survival (PFS) according to RECIST v1.1. Additional efficacy outcome measures include BIRC-assessed overall response rate (ORR) and overall survival (OS).

The study population characteristics were: median age of 48 years (range: 19 to 72), 4.8% age 65 or older, 83% male, 100% Asian, and 57% had ECOG PS of 0. Eighty-six percent of patients had metastatic disease at study entry. Histological subtypes of NPC included 98% non-keratinizing, 1% keratinizing squamous cell carcinoma, and 1% did not have the subtype identified.

Efficacy results of the pre-specified interim analysis of PFS and final analysis of OS are summarized in Table 5 and Figure 1 below. The trial demonstrated statistically significant improvements in BIRC-assessed PFS, ORR and OS for patients randomized to TUOYI in combination with cisplatin/gemcitabine compared to cisplatin and gemcitabine with placebo.

Table 5: Efficacy Results in JUPITER-02

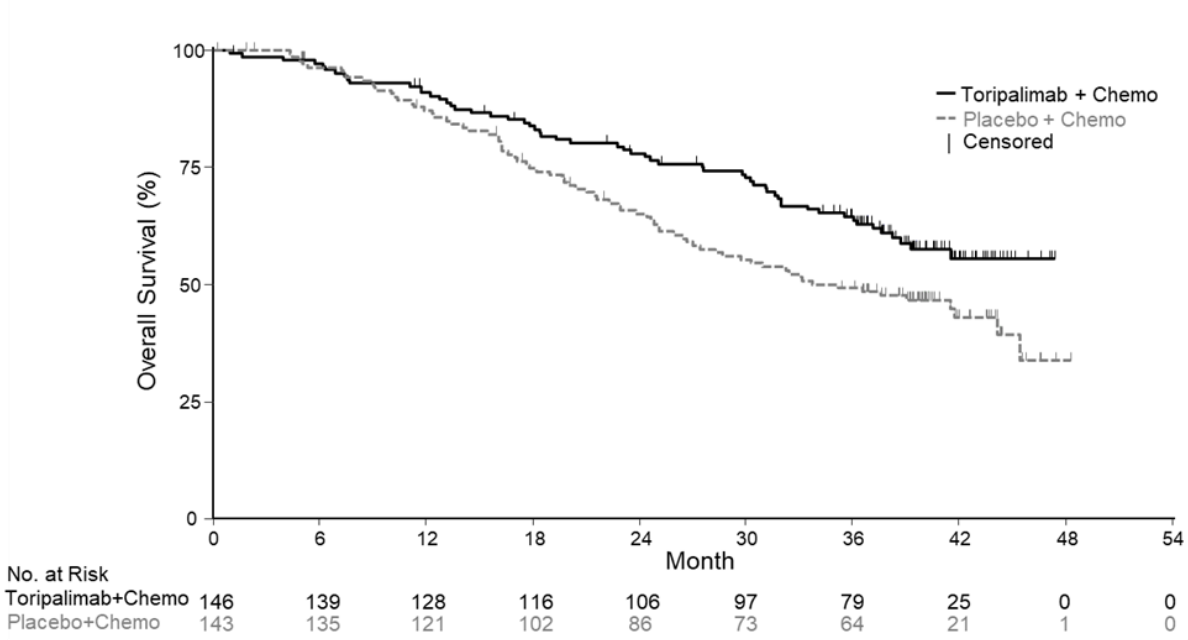
Endpoints	TUOYI Cisplatin/Gemcitabine N =146	Placebo Cisplatin/Gemcitabine N =143
BIRC-Assessed Progression-free Survival[1]		
Number of Events, n (%)	49 (34)	79 (55)
Median, months (95% CI)	11.7 (11.0, NE)	8.0 (7.0, 9.5)
Hazard Ratio (95% CI)[3]	0.52 (0.36, 0.74)	
p-value[4]	0.0003	
BIRC-Assessed Overall Response Rate[1]		
ORR, % (95% CI)	77 (70, 84)	66 (58, 74)
Complete Response Rate (%)	19	11
Partial Response Rate (%)	58	55
p-value [5]	0.0353	

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BIRC-Assessed Duration of Response		
Median, months (95% CI)	10.0 (8.8, NE)	5.7 (5.4, 6.8)
Overall Survival[2]		
Number of Deaths, n (%)	57 (39)	76 (53)
Median, months (95% CI)	NR (38.7, NE)	33.7 (27.0, 44.2)
Hazard Ratio (95% CI)[3]	0.63 (0.45, 0.89)	
p-value[6]	0.0083	

[1]PFS and ORR results are based on the pre-specified interim analysis with data cutoff of May 30, 2020.
[2]OS results are based on the final analysis with a data cutoff of November 18, 2022.
[3]Based on the stratified Cox proportional-hazards model using the stratification factors at randomization, ECOG performance status and disease stage.
[4]Two-sided p-value, based on the stratified log-rank test, as compared with an alpha boundary of 0.010.
[5]Two-sided p-value, based upon Cochran-Mantel-Haenszel test.
[6]Two-sided p-value, based on the stratified log-rank test, as compared with an alpha boundary of 0.049995.
BIRC=blinded independent review committee; CI= confidence interval; NR=Not Reached; NE=Not estimable.

Figure 1: Kaplan-Meier Curves of Overall Survival for JUPITER-02



15. HOW SUPPLIED/STORAGE AND HANDLING

TUOYI (toripalimab), concentrate for solution for infusion is a clear to slightly opalescent, colorless to slightly yellow solution supplied in a carton containing one 240 mg/6 mL (40 mg/mL) single-dose vial (NDC 70114-340-01).

Store in a refrigerator (2°C to 8°C) in the original carton to protect from light. Do not freeze or shake.

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16. PATIENT COUNSELING INFORMATION

Advise the patient to read the Patient Information Leaflet (Informasi Produk Untuk Pasien).

Immune-Mediated Adverse Reactions

Inform patients of the risk of immune-mediated adverse reactions that may be severe or fatal, may occur after discontinuation of treatment, and may require corticosteroid treatment and interruption or discontinuation of TUOYI. These reactions may include:

- Pneumonitis: Advise patients to contact their healthcare provider immediately for new or worsening cough, chest pain, or shortness of breath *[see Warnings and Precautions (6.1)]*.
- Colitis: Advise patients to contact their healthcare provider immediately for diarrhea or severe abdominal pain *[see Warnings and Precautions (6.1)]*.
- Hepatitis: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, or easy bruising or bleeding *[see Warnings and Precautions (6.1)]*.
- Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of adrenal insufficiency, hypophysitis, hypothyroidism, hyperthyroidism, or Type 1 diabetes mellitus *[see Warnings and Precautions (6.1)]*.
- Nephritis: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis *[see Warnings and Precautions (6.1)]*.
- Severe skin reactions: Advise patients to contact their healthcare provider immediately for any signs or symptoms of severe skin reactions, SJS or TEN *[see Warnings and Precautions (6.1)]*.
- Other immune-mediated adverse reactions:
  - Advise patients that other immune-mediated adverse reactions can occur and may involve any organ system. Advise patients to contact their healthcare provider immediately for any new or worsening signs or symptoms *[see Warnings and Precautions (6.1)]*.
  - Advise patients of the risk of solid organ transplant rejection and to contact their healthcare provider immediately for signs or symptoms of organ transplant rejection *[see Warnings and Precautions (6.1)]*.

Infusion-Related Reactions

Advise patients to contact their healthcare provider immediately for signs or symptoms of infusion related reactions *[see Warnings and Precautions (6.2)]*.

Complications of Allogeneic HSCT

Advise patients of the risk of post-allogeneic hematopoietic stem cell transplantation complications *[see Warnings and Precautions (6.3)]*.

Embryo-Fetal Toxicity

- Advise females of reproductive potential that TUOYI can cause harm to a fetus and to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (6.4), Use in Specific Populations (8.1, 8.3)]*.
- Advise females of reproductive potential to use effective contraception during treatment with TUOYI and for 4 months after the last dose *[see Warnings and Precautions (6.4), Use in Specific Populations (8.1, 8.3)]*.

Lactation

Advise women not to breastfeed during treatment with TUOYI and for 4 months after the last dose *[see Use in Specific Populations (8.2)]*.

Laboratory Tests

Advise patients of the importance of keeping scheduled appointments for blood work or other laboratory tests *[see Warnings and Precautions (6.1)]*.

17. PHARMACEUTICAL PARTICULARS

17.1 List of excipients

Each mL of solution contains citric acid monohydrate (0.51 mg), mannitol (25 mg), polysorbate 80 (0.20 mg), sodium chloride (2.92 mg), sodium citrate (4.65 mg), and Water for Injection, USP, at pH 6.0.

17.2 Packaging and Registration Number

Box, 1 vial @ 240 mg/6 ml (40 mg/ml)

Reg. No.

HARUS DENGAN RESEP DOKTER

Manufactured by

Suzhou Union Biopharm Co., Ltd.

No. 999, Longqiao Road, Wujiang Economic and Technological Development Zone

Suzhou, Jiangsu, 215200, China

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Imported by

PT. Anvita Pharma Indonesia

Karawang New Industry City, Blok B No. 8, Jl. Trans Heksa Km.7

Karawang, Jawa Barat, 41361, Indonesia

Date of first authorisation: dd/mm/yyyy

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INFORMASI PRODUK UNTUK PASIEN

TUOYI

Toripalimab 240 mg/6 ml (40 mg/ml)

Larutan Konsentrat untuk Infus

1. Apa itu TUOYI?

TUOYI merupakan larutan bening hingga sedikit buram, tidak berwarna hingga sedikit kuning, pada dasarnya bebas dari partikel yang terlihat.

TUOYI adalah obat resep yang digunakan untuk mengobati orang dewasa yang menderita kanker yang disebut karsinoma nasofaring (NPC).

TUOYI dapat digunakan dalam kombinasi dengan obat kemoterapi cisplatin dan gemcitabine, sebagai pengobatan pertama Anda ketika NPC Anda telah menyebar ke bagian lain dari tubuh Anda (metastatik) atau telah kembali (berulang) di jaringan terdekat (lanjut secara lokal).

Tidak diketahui apakah TUOYI aman dan efektif pada anak-anak.

2. Bagaimana saya menerima TUOYI?

- Dosis yang dianjurkan adalah 240 mg setiap 3 minggu.
- Fasilitas kesehatan Anda akan memberikan TUOYI ke pembuluh darah Anda melalui jalur intravena (IV) selama 30 atau 60 menit.
- TUOYI biasanya diberikan setiap dua atau tiga minggu sebagai infus intravena (IV).
- Fasilitas kesehatan Anda akan memutuskan berapa banyak pengobatan yang Anda perlukan.
- Fasilitas kesehatan Anda akan menguji darah Anda untuk memeriksa efek samping tertentu.
- Jika Anda melewatkan janji temu, hubungi fasilitas kesehatan Anda sesegera mungkin untuk menjadwalkan ulang.

3. Apa yang perlu Anda ketahui sebelum menggunakan TUOYI?

Anda tidak boleh diberikan TUOYI jika Anda alergi terhadap toripalimab atau bahan lain obat ini (tercantum dalam bagian 6).

Sebelum menerima TUOYI, beri tahu fasilitas kesehatan Anda tentang semua kondisi medis Anda, termasuk jika Anda:

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- memiliki masalah sistem kekebalan tubuh seperti penyakit Crohn, kolitis ulserativa, atau lupus
- telah menerima transplantasi organ
- telah menerima atau berencana menerima transplantasi sel induk yang menggunakan sel induk donor (alogenik)
- telah menerima pengobatan radiasi pada area dada Anda
- pernah mengalami kondisi yang memengaruhi sistem saraf, seperti miastenia gravis atau sindrom Guillain-Barré
- sedang hamil atau berencana untuk hamil. TUOYI dapat membahayakan bayi Anda yang belum lahir.

  Wanita usia subur:
  - Fasilitas kesehatan Anda harus melakukan tes kehamilan sebelum Anda memulai pengobatan dengan TUOYI.
  - Anda harus menggunakan metode kontrasepsi yang efektif selama perawatan Anda dan selama 4 bulan setelah dosis terakhir TUOYI. Konsultasikan dengan fasilitas kesehatan Anda tentang metode pengendalian kelahiran yang dapat Anda gunakan selama ini.
  - Beritahu fasilitas kesehatan Anda segera jika Anda merasa hamil atau jika Anda hamil selama pengobatan dengan TUOYI.
- sedang menyusui atau berencana untuk menyusui. Tidak diketahui apakah TUOYI masuk ke dalam Air Susu Ibu (ASI) Anda. Jangan menyusui selama pengobatan dan selama 4 bulan setelah dosis terakhir TUOYI.

Beritahu fasilitas kesehatan Anda tentang semua obat yang Anda minum, termasuk obat resep dan obat bebas, vitamin, dan suplemen herbal.

Obat lain dan TUOYI

Beri tahu dokter atau perawat Anda

- Jika Anda sedang mengonsumsi obat yang menekan sistem imun Anda, seperti kortikosteroid (seperti prednison). Obat-obatan ini dapat mengganggu efek TUOYI.

  Namun, setelah Anda diobati dengan TUOYI, dokter Anda mungkin akan memberikan kortikosteroid untuk mengurangi efek samping yang mungkin Anda alami akibat TUOYI. Kortikosteroid juga dapat diberikan kepada Anda sebelum menerima TUOYI dalam kombinasi dengan kemoterapi untuk mencegah dan/atau mengobati mual, muntah, dan efek samping lain yang disebabkan oleh kemoterapi.

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- Jika Anda sedang mengonsumsi, baru saja mengonsumsi, atau mungkin akan mengonsumsi obat lain. Jangan mengonsumsi obat lain selama pengobatan tanpa berkonsultasi dengan dokter Anda terlebih dahulu.

Mengemudi dan menggunakan mesin

TUOYI dapat sedikit memengaruhi kemampuan Anda untuk mengemudi atau menggunakan mesin, karena pusing atau lelah merupakan efek samping yang mungkin terjadi. Jangan mengemudi atau menggunakan mesin kecuali Anda yakin bahwa Anda merasa sehat.

Apa informasi paling penting yang harus saya ketahui tentang TUOYI?

TUOYI adalah obat yang dapat mengobati kanker nasofaring dengan bekerja sama dengan sistem kekebalan tubuh Anda. TUOYI dapat menyebabkan sistem kekebalan tubuh Anda menyerang organ dan jaringan normal di area mana pun dari tubuh Anda dan dapat memengaruhi cara kerjanya. Masalah-masalah ini kadang-kadang bisa menjadi parah atau mengancam jiwa dan bisa menyebabkan kematian. Anda dapat mengalami lebih dari satu masalah ini pada saat bersamaan. Masalah ini dapat terjadi kapan saja selama pengobatan atau bahkan setelah pengobatan berakhir.

Hubungi atau temui fasilitas kesehatan Anda segera jika Anda mengalami tanda atau gejala baru atau lebih buruk, termasuk:

Masalah paru-paru

- batuk
- sesak napas
- nyeri dada

Masalah usus

- diare (buang air besar) atau buang air besar lebih sering dari biasanya
- tinja berwarna hitam pekat seperti aspal, lengket, atau mengandung darah atau lendir
- nyeri atau nyeri tekan yang parah di area perut (abdomen).

Masalah hati

- menguningnya kulit atau bagian putih mata

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- mual atau muntah parah
- nyeri di area perut sebelah kanan (abdomen)
- urin berwarna gelap (berwarna teh)
- lebih mudah berdarah atau memar dibandingkan biasanya

Masalah kelenjar hormon

- sakit kepala yang tidak kunjung hilang atau sakit kepala yang tidak biasa
- sensitivitas mata terhadap cahaya
- masalah mata
- detak jantung cepat
- peningkatan keringat
- kelelahan ekstrem
- penambahan atau penurunan berat badan
- merasa lebih lapar atau haus dari biasanya
- buang air kecil lebih sering dari biasanya
- rambut rontok
- merasa kedinginan
- sembelit
- suara Anda menjadi lebih dalam
- pusing atau pingsan
- perubahan suasana hati atau perilaku, seperti penurunan gairah seks, mudah tersinggung, atau lupa

Masalah ginjal

- penurunan jumlah urin
- darah dalam urin Anda
- pembengkakan pada pergelangan kaki
- kehilangan nafsu makan

Masalah kulit

- ruam
- gatal
- kulit melepuh atau mengelupas

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- luka atau bisul yang menyakitkan di mulut, hidung, tenggorokan, atau area genital
- demam atau gejala mirip flu
- pembengkakan kelenjar getah bening

Masalah juga bisa terjadi pada organ dan jaringan lain. Ini belum semua tanda dan gejala masalah sistem kekebalan tubuh yang dapat terjadi akibat TUOYI. Hubungi atau temui fasilitas kesehatan Anda segera untuk mengetahui tanda atau gejala baru atau yang memburuk, yang mungkin termasuk:

- nyeri dada, detak jantung tidak teratur, sesak napas, pembengkakan pada pergelangan kaki
- kebingungan, mengantuk, masalah ingatan, perubahan suasana hati atau perilaku, leher kaku, masalah keseimbangan, kesemutan atau mati rasa pada lengan atau kaki
- Penglihatan ganda, pandangan kabur, sensitif terhadap cahaya, nyeri mata, perubahan penglihatan
- nyeri atau kelemahan otot yang menetap atau parah, kram otot
- sel darah merah rendah, memar

Reaksi infus yang terkadang parah atau mengancam jiwa. Tanda atau gejala reaksi infus dapat meliputi:

- menggigil atau gemetar
- gatal atau ruam
- kemerahan
- sesak napas atau mengi.
- pusing
- terasa ingin pingsan
- demam
- nyeri punggung

Penolakan terhadap organ yang ditransplantasikan. Fasilitas kesehatan Anda harus memberi tahu Anda tanda dan gejala apa yang harus Anda laporkan dan pantau, tergantung pada jenis transplantasi organ yang Anda jalani.

Komplikasi, termasuk penyakit *graft-versus-host* (GVHD), pada orang yang telah menerima transplantasi sumsum tulang (sel induk) yang menggunakan sel induk donor

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(alogenik). Komplikasi ini bisa serius dan bisa berujung pada kematian. Komplikasi ini mungkin terjadi jika Anda menjalani transplantasi sebelum atau sesudah dirawat dengan TUOYI. Fasilitas kesehatan Anda akan memantau Anda untuk komplikasi ini.

Mendapatkan perawatan medis segera dapat membantu mencegah masalah ini menjadi lebih serius.

Fasilitas kesehatan Anda akan memeriksa masalah ini selama perawatan dengan TUOYI. Fasilitas kesehatan Anda mungkin merawat Anda dengan obat kortikosteroid atau pengganti hormon. Fasilitas kesehatan Anda mungkin juga perlu menunda atau menghentikan pengobatan dengan TUOYI jika Anda mengalami efek samping yang parah.

4. Apa kemungkinan efek samping dari TUOYI?

TUOYI dapat menyebabkan efek samping yang serius. Lihat "Apa informasi paling penting yang harus saya ketahui tentang TUOYI?"

Efek samping yang umum dari TUOYI bila digunakan dengan cisplatin dan gemcitabine meliputi:

- mual
- muntah
- nafsu makan berkurang
- sembelit
- rendahnya kadar hormon tiroid
- ruam
- demam
- diare
- rasa terbakar atau kesemutan di kaki dan jari kaki
- batuk
- nyeri otot dan tulang
- infeksi saluran pernapasan atas
- masalah tidur
- pusing
- merasa tidak enak badan secara umum

Ini bukan semua efek samping yang mungkin terjadi akibat penggunaan TUOYI.

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Hubungi dokter Anda untuk saran medis tentang efek samping. Anda dapat melaporkan efek samping ke dokter Anda.

Kontak Pelaporan Efek Samping Industri Farmasi

PT. Anvita Pharma Indonesia

Karawang New Industry City Blok B No. 8, Jl. Trans Heksa Km. 7, Desa Wanajaya, Kec. Telukjambe Barat, Kab. Karawang, Provinsi Jawa Barat 41361

e-mail: pv@anvitapharma.com

Overdosis

Jika terjadi overdosis, Anda harus diawasi secara ketat untuk mengetahui tanda atau gejala reaksi yang merugikan dan pengobatan simtomatik yang tepat harus segera diberikan.

5. Bagaimana cara menyimpan TUOYI?

Simpan di lemari pendingin (2°C - 8°C) dalam kemasan aslinya untuk melindungi dari cahaya. Jangan dibekukan atau dikocok.

Jika larutan yang telah diencerkan tidak segera digunakan, simpan dengan salah satu cara berikut:

- Pada suhu ruang (20°C–25°C) selama tidak lebih dari 8 jam sejak larutan diencerkan hingga infus selesai diberikan. Buang larutan yang telah diencerkan jika telah disimpan pada suhu ruang lebih dari 8 jam.

  Atau
- Di dalam lemari pendingin (2°C–8°C) selama tidak lebih dari 24 jam sejak larutan diencerkan hingga infus selesai diberikan. Jika disimpan di dalam lemari pendingin, biarkan larutan mencapai suhu ruang sebelum digunakan. Buang larutan yang telah diencerkan jika telah disimpan di dalam lemari pendingin lebih dari 24 jam.

6. Kemasan dan informasi lainnya

Informasi umum tentang penggunaan TUOYI yang aman dan efektif.

Obat-obatan terkadang diresepkan untuk tujuan selain yang tercantum dalam Informasi Produk Untuk Pasien. Anda dapat bertanya kepada apoteker atau fasilitas kesehatan Anda untuk informasi tentang TUOYI yang ditulis untuk tenaga kesehatan.

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Apa bahan-bahan dalam TUOYI?

Bahan aktif: toripalimab

Bahan tidak aktif: asam sitrat monohidrat, manitol, polisorbat 80, natrium klorida, natrium sitrat, dan Air untuk Injeksi.

Kemasan dan Nomor Registrasi

Box, 1 vial @ 240 mg/6 ml (40 mg/ml)

No. Reg.

HARUS DENGAN RESEP DOKTER

Diproduksi oleh

Suzhou Union Biopharm Co., Ltd.

No. 999, Longqiao Road, Wujiang Economic and Technological Development Zone

Suzhou, Jiangsu, 215200, China

Diimpor oleh

PT. Anvita Pharma Indonesia

Karawang New Industry City, Blok B No. 8, Jl. Trans Heksa Km.7

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Tanggal persetujuan pertama kali: dd/mm/yyyy

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