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

AUSTRALIAN PRODUCT INFORMATION – ZYTORVI™ (toripalimab)

1. NAME OF THE MEDICINE

Toripalimab

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single dose vial of concentrate contains 240 mg/6 mL (equivalent to 40 mg/mL) of toripalimab as the active ingredient.

Toripalimab is an immunoglobulin G4 (IgG4) humanised monoclonal antibody (mAb), produced in Chinese hamster ovary cells by recombinant DNA technology.

For the full list of excipients, see section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Concentrated injection for intravenous (IV) infusion.

Clear to slightly opalescent, colourless to slightly yellow solution essentially free from visible particles. The concentrate for solution has a pH of 5.5–6.5 and an osmolality of 240-340 mOsmol/kg.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

ZYTORVI is indicated, as a single agent, for the treatment of adults with recurrent unresectable or metastatic nasopharyngeal carcinoma (NPC) with disease progression on or after a platinum-containing chemotherapy.

4.2 DOSE AND METHOD OF ADMINISTRATION

The recommended dosages of ZYTORVI are provided in Table 1.

Table 1: Recommended dosage

Indication	**Recommended dosage of ZYTORVI**	**Duration of treatment**
First-line NPC	240 mg every three weeks	Until disease progression, unacceptable toxicity, or up to 24 months.
Recurrent NPC	3 mg/kg every two weeks	Until disease progression, unacceptable toxicity, or up to 24 months.

Dosage modifications

No dose reductions of ZYTORVI are recommended. In general, withhold ZYTORVI for severe (Grade 3) immune-mediated adverse reactions. Permanently discontinue ZYTORVI 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 ZYTORVI for adverse reactions that require management different from these general guidelines are summarized in Table 2.

Table 2: Recommended dosage

Adverse Reaction	Severity[1]	Dose modification
Immune-related adverse reactions		
Pneumonitis	Grade 2	Withhold[2]
	Grades 3 or 4	Permanently discontinue
Diarrhoea/colitis	Grade 2 or 3	Withhold[2]
	Grade 4	Permanently discontinue
Hepatitis	Aspartate aminotransferase (AST)/ alanine aminotransferase (ALT) increases to more than 3 and up to 5 times the upper limit of normal (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 5 times ULN or Total bilirubin increases to more than 3 times ULN	Permanently discontinue
Endocrinopathies	Grade 2-4 adrenal insufficiency or hypophysitis	Withhold if not clinically stable on hormone replacement therapy[2]
	Grades 3 or 4 hyperthyroidism or thyroiditis	Withhold until clinically stable on appropriate medical management
	Grade 3-4 diabetes mellitus	Withhold until clinically stable on antihyperglycemic (insulin) therapy
	Grade 1-4 hypothyroidism	Manage with hormone replacement therapy without toripalimab interruption
Nephritis with Renal Dysfunction	Grade 2 -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

Adverse Reaction	Severity[1]	Dose modification
Myocarditis	Grades 2, 3, or 4	Permanently discontinue
Neurological toxicities	Grade 2	Withhold[2]
	Grade 3-4	Permanently discontinue
Other immune related adverse reactions	Grade 2-3	Withhold or permanently discontinue based on severity and type of reaction[2]
	Grade 4, recurrent Grade 3 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	Permanently discontinue
Other Adverse Reactions		
Infusion-related reactions	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 toripalimab 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, or for endocrinopathies cannot be clinically stabilised on hormone replacement therapy.

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

Administration

Administer diluted solution intravenously via an infusion pump using an in-line aseptic filter (0.2 micron or 0.22 micron pore size).

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 Dosage modifications)

Do not co-administer other medicines through the same intravenous line.

When administered on the same day as chemotherapy, ZYTORVI should be administered prior to chemotherapy.

Refer to the Product Information for cisplatin and gemcitabine for recommended dosing information.

Preparation for intravenous infusion

Visually inspect the solution for particulate matter and discoloration. The solution is clear to slightly opalescent, colourless to slightly yellow. Discard the vial if visible particles are observed.

Withdraw the required volume of ZYTORVI and inject slowly into a 100 mL or 250 mL infusion bag containing sodium chloride 9 mg/mL (0.9%) solution for injection for infusion using aseptic technique. 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.

ZYTORVI is compatible with polypropylene infusion bags and infusion sets with 0.2 or 0.22 micron in-line filter.

Each vial is for use in one patient on one occasion only. Discard any unused portion left in the vial.

Refer to Section 6.4 Special precautions for storage, if the diluted solution is not administered immediately.

Special populations

Elderly

No dose adjustment is recommended for patients who are aged 65 years or over (see section 5.2 Pharmacokinetic properties).

Renal impairment

No dose adjustment is needed for patients with mild or moderate renal impairment. There are insufficient data in patients with severe renal impairment for dosing recommendations (see section 5.2 Pharmacokinetic properties).

Hepatic impairment

No dose adjustment is recommended for patients with mild hepatic impairment. There are insufficient data in patients with moderate or severe hepatic impairment for dosing recommendations (see section 5.2 Pharmacokinetic properties).

Paediatric population

The safety and efficacy of toripalimab in children and adolescents aged under 18 years have not been established. No data are available.

4.3 CONTRAINDICATIONS

Severe hypersensitivity to the active ingredient or to any excipients listed in section 6.1 List of excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Immune-related adverse reactions

Immune-related adverse reactions, which may be severe or fatal, can occur in patients treated with antibodies blocking the programmed cell death protein-1 / programmed death-ligand 1 (PD-1/PD-L1) pathway, including toripalimab. Immune-related 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-related adverse reactions can occur at any time after starting PD-1/PD-L1 blocking antibody. While immune-related adverse reactions usually manifest during treatment with PD-1/PD-L1 blocking antibodies, immune-related adverse reactions can also manifest after discontinuation of PD-1/PD-L1 blocking antibodies. Important immune-related adverse reactions listed under this section are not inclusive of all possible severe and fatal immune-related reactions.

Early identification and management of immune-related 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-related adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected immune-related adverse reactions, initiate appropriate workup to exclude alternative aetiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue toripalimab depending on severity of the immune-related adverse reaction (see section 4.2 Dose and method of administration). In general, if treatment with toripalimab requires interruption or discontinuation for an adverse reaction, 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-related adverse reactions are not controlled with corticosteroid therapy. Hormone replacement therapy for endocrinopathies should be instituted as warranted.

Treatment with toripalimab may be restarted within 12 weeks after last dose of toripalimab if the adverse reaction recovers to Grade ≤1 and the corticosteroid dose has been reduced to ≤10 mg prednisone or equivalent per day.

Immune-related pneumonitis

Toripalimab can cause immune-related pneumonitis (see section 4.8 Adverse effects (Undesirable effects)). Patients should be monitored for signs and symptoms of pneumonitis. Suspected pneumonitis should be confirmed with radiographic imaging and other causes excluded. Patients should be managed with toripalimab treatment modifications and corticosteroids, as clinically indicated (see section 4.2 Dose and method of administration and directions for corticosteroid treatment in section 4.4 Special warnings and precautions for use, Immune-related adverse reactions above).

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-related colitis

Toripalimab can cause immune-related colitis, which may present with diarrhoea (see section 4.8 Adverse effects (Undesirable effects)). Patients should be monitored for signs and symptoms of colitis and managed with toripalimab treatment modifications, anti-diarrhoeal agents and corticosteroids, as clinically indicated (see section 4.2 Dose and method of administration and directions for corticosteroid treatment in section 4.4 Special warnings and precautions for use, Immune-related adverse reactions above). In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative aetiologies. Cytomegalovirus (CMV) infection/reactivation has been reported in patients receiving other PD-1/PD-L1 blocking antibodies with corticosteroid-refractory immune-related colitis.

Hepatotoxicity and immune-related hepatitis

Toripalimab can cause immune-related hepatitis (see section 4.8 Adverse effects (Undesirable effects)). Patients should be monitored for changes in liver function periodically and as indicated, based on clinical evaluation. Patients should be managed with toripalimab treatment modifications (see section 4.2 Dose and method of administration) and corticosteroids, as clinically indicated (see directions for corticosteroid treatment in section 4.4 Special warnings and precautions for use, Immune-related adverse reactions above).

Immune-related endocrinopathies

Adrenal insufficiency

Toripalimab can cause primary or secondary adrenal insufficiency (see section 4.8 Adverse effects (Undesirable effects)). Patients should be monitored for clinical signs and symptoms of adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. For Grade 2-4 adrenal insufficiency, toripalimab should be withheld until patient is clinically stable on physiologic hormone replacement therapy (see section 4.2 Dose and method of administration).

Hypophysitis

Toripalimab can cause immune-related hypophysitis (see section 4.8 Adverse effects (Undesirable effects)). Hypophysitis can present with acute symptoms associated with mass effects such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism. Patients should be monitored for signs and symptoms of hypophysitis. Initiate hormone replacement as indicated. For Grade 2-4 hypophysitis, toripalimab should be withheld until patient is clinically stable on physiologic hormone replacement therapy (see section 4.2 Dose and method of administration).

Thyroid disorders

Toripalimab can cause immune-related thyroid disorders (see section 4.8 Adverse effects (Undesirable effects)). Patients should be monitored for signs and symptoms of thyroid disorders prior to and periodically during treatment, and as indicated based on clinical evaluation.

Hypothyroidism may be managed with replacement therapy without toripalimab interruption and without corticosteroids (see section 4.2 Dose and method of administration). Thyroiditis can present with or without concomitant thyroid dysfunction. Thyroiditis and hyperthyroidism may be managed symptomatically which may include thyroid suppression and/or corticosteroid therapy for acute thyroiditis. Toripalimab should be withheld for Grade ≥ 3 thyroiditis or hyperthyroidism until controlled with medical management and patient is clinically stable. Patients should be monitored for hypothyroidism that may follow hyperthyroidism or thyroiditis. Thyroid function and hormone levels should be monitored to ensure appropriate hormone replacement.

Type 1 diabetes mellitus, which can present with diabetic ketoacidosis

Toripalimab can cause immune-related type I diabetes mellitus. Monitor patients for hyperglycaemia and other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withold toripalimab for Grade ≥ 3 hyperglycaemia (see section 4.2 Dose and method of administration). Treatment with toripalimab may be resumed when diabetes is controlled with medical management including insulin therapy and the patient is clinically stable.

Immune-related nephritis with renal dysfunction

Toripalimab can cause immune-related nephritis. Patients should be monitored for changes in renal function and other causes of renal dysfunction excluded. Patients should be managed with toripalimab treatment modifications (see section 4.2 Dose and method of administration) and corticosteroids, as clinically indicated (see directions for corticosteroid treatment in

section 4.4 Special warnings and precautions for use, Immune-related adverse reactions above).

Immune-related dermatologic adverse reactions

Toripalimab can cause immune-related 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 toripalimab depending on the severity (see section 4.2 Dose and method of administration).

Immune-related myocarditis

Toripalimab can cause immune-related myocarditis. Patients should be monitored for signs and symptoms of myocarditis. If myocarditis is suspected, high-dose steroids should be promptly initiated with cardiology consultation and diagnostic workup according to current clinical guidelines. Patients should be managed with toripalimab treatment modifications (see section 4.2 Dose and method of administration) and corticosteroids, as clinically indicated (see instructions for corticosteroid treatment in section 4.4 Special warnings and precautions for use Immune-related adverse reactions above). Consider the addition of immunosuppressants if the event does not improve within 48 hours after start of corticosteroid therapy.

Immune-related myositis

Toripalimab can cause immune-related myositis. Patients should be monitored for signs and symptoms of myositis. For suspected myositis, monitor serial aldolase and creatine kinase and consider diagnostic workup according to current clinical guidelines. Patients should be managed with toripalimab treatment modifications (see section 4.2 Dose and method of administration, Other immune related adverse reactions) and corticosteroids, as clinically indicated (see instructions for corticosteroid treatment in section 4.4 Special warnings and precautions for use, Immune-related adverse reactions above).

Other immune-related adverse reactions

Given the mechanism of action of toripalimab, other potential immune-related adverse reactions may occur. Clinically significant immune-related adverse reactions, including some that were severe or fatal, have been reported in less than 1 % of patients treated with toripalimab in clinical studies include myocarditis, myositis, pancreatitis, encephalitis, immune-related thrombocytopenia, iritis, uveitis, immune-related inflammatory arthritis, and immune-related cystitis. Cases of myasthenia gravis (including exacerbation), Guillain-Barré syndrome, rhabdomyolysis and aseptic meningitis have been reported in post-marketing use.

Patients should be monitored for signs and symptoms of immune-related adverse reactions and managed with toripalimab treatment modifications (see section 4.2 Dose and method of administration and corticosteroids, as clinically indicated (see instructions for corticosteroid treatment in section 4.4 Special warnings and precautions for use, Immune-related adverse reactions above).

Infusion-related reactions

Toripalimab can cause severe or life-threatening infusion-related reactions (see section 4.8 Adverse effects (Undesirable effects)). Patients should be managed with toripalimab treatment modifications and supportive care, as clinically indicated (see section 4.2 Dose and method of administration). 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 ZYTORVI [see Dosage and Administration (4.2)].

For patients with infusion-related reactions, pre-medications with antipyretics and antihistamines to mitigate the risk of subsequent infusion reactions may be considered.

Transplant-related adverse reactions

Solid organ or tissue (including corneal graft) transplant rejection has been reported in the post-marketing setting in patients treated with PD-1 inhibitors, including ZYTORVI. Treatment with toripalimab may increase the risk of rejection in solid organ transplant recipients. The benefit of treatment with toripalimab versus the risk of possible organ rejection should be considered in these patients.

Fatal and other serious complications can occur in patients who received an allogeneic haematopoietic 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 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 the allogeneic HSCT. Follow patients closely for evidence of transplant-related complications and intervene promptly. The benefits of treatment with toripalimab versus the risks listed above should be considered in patients who have received or who may receive an allogeneic HSCT.

Patient Alert Card

All prescribers of ZYTORVI should inform patients about the Patient Alert Card, explaining what to do should they experience any symptoms of an immune-related adverse reaction. The physician will provide the Patient Alert Card to each patient.

Use in hepatic impairment

Based on a population pharmacokinetic analysis, no dose adjustment is required for patients with mild hepatic impairment (see sections 4.2 Dose and method of administration and 5.2 Pharmacokinetic properties). There are limited data in patients with moderate or severe hepatic impairment.

Use in renal impairment

Based on a population pharmacokinetic analysis, no dose adjustment is required in patients with mild renal impairment (see sections 4.2 Dose and method of administration and 5.2 Pharmacokinetic properties). There are limited data in patients with moderate or severe renal impairment.

Use in the elderly

No overall differences in safety were reported between elderly patients (65 years and over) and younger patients (less than 65 years). No dose adjustment is necessary in this population. Clinical studies of ZYTORVI did not include sufficient numbers of patients aged 65 years and over with NPC to determine whether they respond differently from younger patients.

Paediatric use

No data available.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No drug-drug interaction studies have been conducted with toripalimab. Monoclonal antibodies such as toripalimab are not substrates for cytochrome P450 or drug transporters. Based on population PK analyses, there is no evidence of an effect of toripalimab on concomitant chemotherapy.

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 section 4.4 Special warnings and precautions for use). 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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Studies to evaluate the effect of toripalimab on fertility have not been performed. No effects on the male and female reproductive organs were observed in 4-week and 26-week repeat dose toxicology studies in cynomolgus monkeys.

Use in pregnancy (Category D)

There are no data on the use of toripalimab in pregnant women. Animal studies have not been conducted with toripalimab; however, animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-related rejection of the developing fetus and result in fetal death. Human immunoglobulin G4 (IgG4) is known to cross the placental barrier; therefore, toripalimab can potentially be transmitted from the mother to the developing fetus.

Toripalimab should not be used during pregnancy or in women of childbearing potential not using effective contraception unless the clinical benefit outweighs the potential risk.

Women of childbearing potential should use effective contraception during treatment with toripalimab and for at least 4 months after the last dose of toripalimab.

Use in lactation

It is unknown whether toripalimab is secreted in human milk. It is known that antibodies (including IgG4) are secreted in human milk; thus, a risk to the breast-feeding newborn/infant cannot be excluded.

If a woman who is breastfeeding is treated with toripalimab, she should be instructed not to breast-feed while receiving toripalimab and for at least 4 months after the last dose of toripalimab.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Toripalimab may have a minor effect on your ability to drive or use machines, as feeling dizzy or tired are possible side effects. No studies on the effects on the ability to drive and use machines have been performed. Based on its pharmacodynamic properties, ZYTORVI is unlikely to affect this ability. Because of potential adverse reactions such as fatigue (see Section 4.8 Adverse effects), patients should be advised to use caution when driving or operating machinery until they are certain that ZYTORVI does not adversely affect them..

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

First-line treatment of metastatic or recurrent, locally advanced nasopharyngeal carcinoma (NPC)

The data below reflect exposure to toripalimab at a dose of 240 mg intravenously every 3 weeks in combination with up to 6 cycles of cisplatin and gemcitabine followed by toripalimab monotherapy for up to 2 years in 146 patients with NPC enrolled in a randomized, double-blind, placebo-controlled trial (JUPITER-02). Among the 146 patients, 73% were exposed to ZYTORVI for 6 months or more and 54% were exposed for 12 months or more.

Serious adverse reactions occurred in 43% of patients receiving toripalimab in JUPITER-02. Serious adverse drug reactions occurring in ≥ 2% of patients were thrombocytopenia (14%), neutrophil count decreased (10%), pneumonia (10%), anaemia (9%), abnormal hepatic function (2.7%), and rash (2.1%).

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 haemoglobin (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%).

Adverse reactions and laboratory abnormalities in JUPITER-02 are summarised in Table 3 and Table 4 respectively.

Table 3: Adverse reactions (≥ 10%) in patients with recurrent, locally advanced or metastatic NPC who received toripalimab in combination with cisplatin and gemcitabine in JUPITER-02

Adverse Reaction[1]	Toripalimab + 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
Diarrhoea	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, triiodothyronine 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, paraesthesia, 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.

Table 4: Select laboratory abnormalities (≥20%) that worsened from baseline in patients with recurrent, locally advanced or metastatic NPC who received toripalimab in combination with cisplatin and gemcitabine in JUPITER-02

Laboratory abnormalities*	Toripalimab + Cisplatin/Gemcitabine		Placebo + Cisplatin/Gemcitabine	
	All Grades† (%)	Grade 3 or 4 (%)	All Grades (%)	Grades 3 or 4 (%)
Hematology				
Decreased haemoglobin	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: Toripalimab/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.

Previously treated, unresectable or metastatic nasopharyngeal carcinoma (NPC)

The data below reflect exposure to toripalimab at a dose of 3 mg/kg intravenously every 2 weeks in 190 patients with NPC enrolled in a single-arm trial (POLARIS-02). Among the 190 patients, 33% were exposed for 6 months or longer and 21% were exposed for greater than one year. Serious adverse reactions occurred in 24% of patients who received toripalimab. Serious adverse drug reactions occurring in ≥2% of patients were pneumonia (4.7%), hepatic function abnormal (2.6%), and hyperbilirubinemia (2.1%).

Adverse reactions and laboratory abnormalities in POLARIS-02 are summarised in Table 5 and Table 6 respectively.

Table 5: Adverse reactions (≥10%) in patients with previously treated, unresectable or metastatic NPC who received toripalimab in POLARIS-02

Adverse reaction*	**Toripalimab N=190**	
	All Grades (%)	**Grade 3 or 4 (%)**
Endocrine disorders		
Hypothyroidism[1]	27	0
General disorders		
Fatigue[2]	22	2.6
Pyrexia	16	0
Respiratory disorders		
Cough[3]	20	0
Musculoskeletal disorders		
Musculoskeletal Pain[4]	18	1.1
Metabolism and nutrition		
Decreased Appetite	13	1.1
Gastrointestinal disorders		
Constipation	11	0
Skin and subcutaneous disorders		
Pruritus	11	0
Rash[5]	11	0
Investigations		
Weight Decreased	11	0

* Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03.

[1] Includes hypothyroidism, thyroiditis, triiodothyronine decreased, and tri-iodothyronine free decreased

[2] Includes fatigue and asthenia.

[3] Includes cough and productive cough.

[4] Includes musculoskeletal pain and myalgia.

[5] Includes dermatitis allergic, eczema, and rash.

Table 6: Select Laboratory Abnormalities (≥20%) That Worsened from Baseline in Patients with Previously Treated, Unresectable or Metastatic NPC Who Received Toripalimab in POLARIS-02

	Toripalimab	
	All Grades (%)[1]	**Grade 3 or 4 (%)[1]**
Chemistry		
Decreased albumin	38	0.5
Decreased sodium	35	11
Increased aspartate aminotransferase	30	3.8
Decreased calcium	29	0.5
Increased alkaline phosphatase	28	2.2
Increased triglyceride	26	1.1
Increased glucose	24	1.1
Increased alanine aminotransferase	23	1.6
Hematology		
Decreased lymphocytes	52	9
Decreased haemoglobin	43	6

[1] Toxicity graded per NCI CTCAE v4.03. The denominator used to calculate the rate varied from 141 to 186 based on the number of patients with a baseline value and at least one post-treatment value.

Description of selected adverse reactions

Immune-related adverse reactions

The selected adverse reactions described below are based on exposure to toripalimab at a dose of 240 mg every 3 weeks in combination with up to 6 cycles of cisplatin and gemcitabine followed by toripalimab monotherapy for up to 2 years of in 146 patients with NPC in JUPITER-02) (see section 5.1) and the exposure to toripalimab as a single agent at a dose of 3 mg/kg every 2 weeks in 851 patients enrolled in 12 trials: one randomized, active-controlled trial and 11 open-label, non-randomized trials. The tumour types included nasopharyngeal carcinoma (n=193) or other types of tumours (n=658).

Immune-related pneumonitis

Immune-related pneumonitis occurred in 2.1% (3/146) of patients receiving toripalimab in combination with cisplatin and gemcitabine, including Grade 2 (1.4%) adverse reactions. Pneumonitis resolved in 67% (2/3) of these patients.

Immune-related pneumonitis occurred in 2.6% (22/851) of patients receiving toripalimab as single agent, 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 toripalimab in 1.2% (10/851) of patients. Pneumonitis resolved in 23% (5/22) of these patients.

Immune-related colitis

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

Hepatotoxicity and immune-related hepatitis

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

Immune-related hepatitis occurred in 3.3% (28/851) of patients receiving toripalimab as single agent, including Grade 4 (0.8%), Grade 3 (2.1%), and Grade 2 (0.4%) adverse reactions. Hepatitis led to permanent discontinuation of toripalimab in 1.1% of patients and withholding of toripalimab in 0.8% of patients. Hepatitis resolved in 54% (15/28) of these patients.

Adrenal insufficiency

Adrenal insufficiency occurred in 0.5% (4/851) of the patients receiving toripalimab as single agent, 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 toripalimab in 0.1% (1/851) of patients. In the one patient in whom toripalimab was withheld, toripalimab was reinitiated after symptom improvement.

Hypophysitis

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

Thyroid disorders

Hypothyroidism occurred in 30% (44/146) of patients receiving toripalimab 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. Toripalimab was withheld in 2.1% (3/146) of the patients. Of the 3 patients in whom toripalimab was withheld, 2 patients reinitiated toripalimab.

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

Thyroiditis occurred in 2.1% (3/146) of patients receiving toripalimab 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.

Thyroiditis occurred in 0.6% (5/851) of patients receiving toripalimab as single agent, 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 1.4% (2/146) of patients receiving toripalimab in combination with cisplatin and gemcitabine. Hyperthyroidism resolved in these 2 patients.

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

Type 1 diabetes mellitus

Diabetes mellitus occurred in 0.9% (8/851) of patients receiving toripalimab as single agent, 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-related nephritis with renal dysfunction

Immune-related nephritis occurred in 0.7% (1/146) of patients receiving toripalimab in combination with cisplatin and gemcitabine. This patient with Grade 4 immune-related nephritis required systemic corticosteroids and nephritis led to discontinuation of toripalimab. Nephritis resolved in this patient.

Immune-related nephritis occurred in 0.5% (4/851) of patients receiving toripalimab as single agent, including Grade 3 (0.5%) adverse reactions. Nephritis resolved in 75% (3/4) of these patients.

Immune-related dermatologic adverse reactions

Immune-related dermatologic adverse reactions occurred in 8% (12/146) of patients receiving toripalimab in combination with cisplatin and gemcitabine, 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-related dermatologic adverse reactions. Immune-related dermatologic adverse reactions led to permanent discontinuation of toripalimab in 2.1% (3) of patients. Immune-related dermatologic adverse reactions resolved in 92% (11/12) of these patients.

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

Infusion-related reactions

Infusion-related reactions occurred in 4.1% (6/146) of patients receiving toripalimab in combination with cisplatin and gemcitabine, including Grade 2 reactions in 0.7% (1/146) of patients.

Infusion-related reactions occurred in 2% (17/851) of patients receiving toripalimab as single agent, including Grade 3 (0.1%) and Grade 2 in 0.6% (5/851) adverse reactions. Toripalimab was withheld for Grade 3 infusion related reactions in 0.1% of patients.

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 toripalimab or of other toripalimab products.

Of the 146 evaluable patients in JUPITER-02 with nasopharyngeal cancer who received toripalimab 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 POLARIS-02 with nasopharyngeal cancer who received toripalimab 3 mg/kg every 2 weeks for a median duration of 3.3 months, 3.7% of patients developed treatment-emergent ADA. Neutralising antibodies have not been tested.

Because of the low incidence of anti-drug antibodies, the effect of these antibodies on the pharmacokinetics, pharmacodynamics, safety, or effectiveness of toripalimab is unknown.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumours and signalling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumours. Toripalimab is a humanised 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-tumour immune response. In syngeneic mouse tumour models, blocking PD-1 activity resulted in decreased tumour growth.

Clinical trials

First-line treatment of metastatic or recurrent, locally advanced NPC with cisplatin and gemcitabine

The efficacy of toripalimab in combination with cisplatin and gemcitabine was investigated in JUPITER-02, a randomised, multi-centre, 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.

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

- Toripalimab 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 toripalimab 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 toripalimab or placebo continued until disease progression per RECIST v1.1, unacceptable toxicity, or a maximum of 2 years. Administration of toripalimab was permitted beyond radiographic progression if the patient was deriving benefit as assessed by the investigator. Tumour 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, of whom 41% presented with metastatic disease at diagnosis and 45% had distant metastatic disease at the time of recurrence. The remaining 14% of patients had loco-regional recurrence at study entry. Histological subtypes of NPC included 98% non-keratinising, 1% keratinising squamous cell carcinoma, and 1% did not have the subtype identified.

Efficacy results of the pre-specified final analysis of BIRC-determined PFS and final analysis of OS are summarised in Table 7, Figure 1 and Figure 2 below. The trial demonstrated statistically significant improvements in BIRC-assessed PFS, ORR and OS for patients randomised to toripalimab in combination with cisplatin/gemcitabine compared to cisplatin and gemcitabine with placebo.

Efficacy results for JUPITER-02 are summarised in Table 7, Figure 1 and Figure 2.

Table 7: Efficacy Results in JUPITER-02

Endpoints	**Toripalimab + cisplatin/gemcitabine N =146**	**Placebo + cisplatin/gemcitabine N =143**
BIRC-assessed progression-free survival (PFS)		
Number of PFS events, n (%)	63 (43.2)	87 (60.8)
Median PFS, months (95% CI)	21.4 (11.7, NE)	8.2 (7.0, 9.8)
Hazard ratio (95% CI)[2]	0.52 (0.37, 0.73)	
Nominal[3] p-value[4]	<0.0001	
BIRC-assessed objective response rate (ORR)		
Overall response rate, % (95% CI)	78.8% (71.2, 85.1)	67.1% (58.8, 74.8)
Complete response rate (%)	26.7%	13.3%
Partial response rate (%)	52.1%	53.8%
Nominal[3] p-value[6]	0.0221	
BIRC-assessed duration of response (DoR)		
Median DoR, months (95% CI)	18.0 (10.5, NE)	6.0 (5.6, 8.2)
Overall survival (OS)		
Number of Deaths, n (%)	57 (39.0)	76 (53.1)
Median OS, months (95% CI)	NE (38.7, NE)	33.7 (27.0, 44.2)
Hazard ratio (95% CI)[2]	0.63 (0.45, 0.89)	
p-Value[4]	0.0083	

[1] PFS, ORR and DoR were based on the data with cut-off date of 08 Jun 2021. OS was based on the data with cut-off date of 18 Nov 2022.

[2] The hazard ratio and its confidence interval were computed using a stratified Cox proportional-hazards model.

[3] At the earlier pre-specified interim analysis of PFS (data cut-off on 30 May 2020), statistically significant superiority was achieved for PFS and ORR comparing toripalimab with placebo plus cisplatin/gemcitabine.

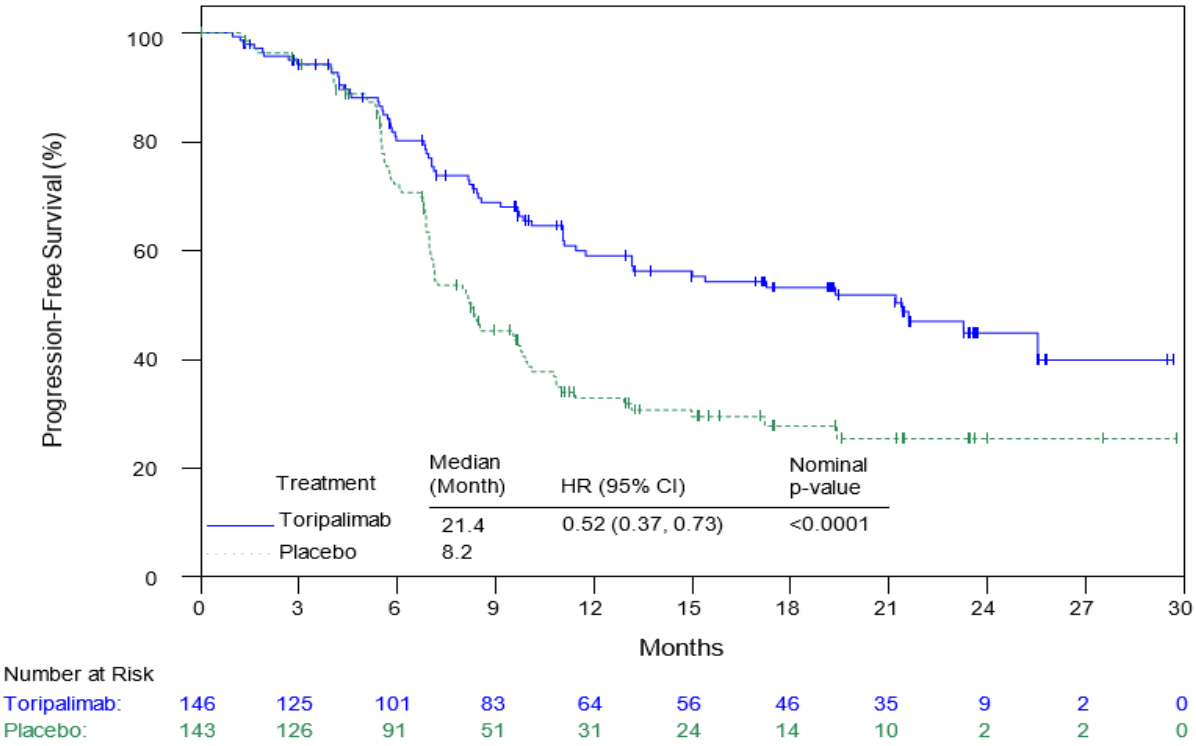
[4] Two-sided p-value, based on the stratified log-rank test.

[5] The confidence interval for ORR for each group was computed using the Clopper-Pearson method.

[6] Two-sided p-value, based on the Cochran-Mantel-Haenszel test.

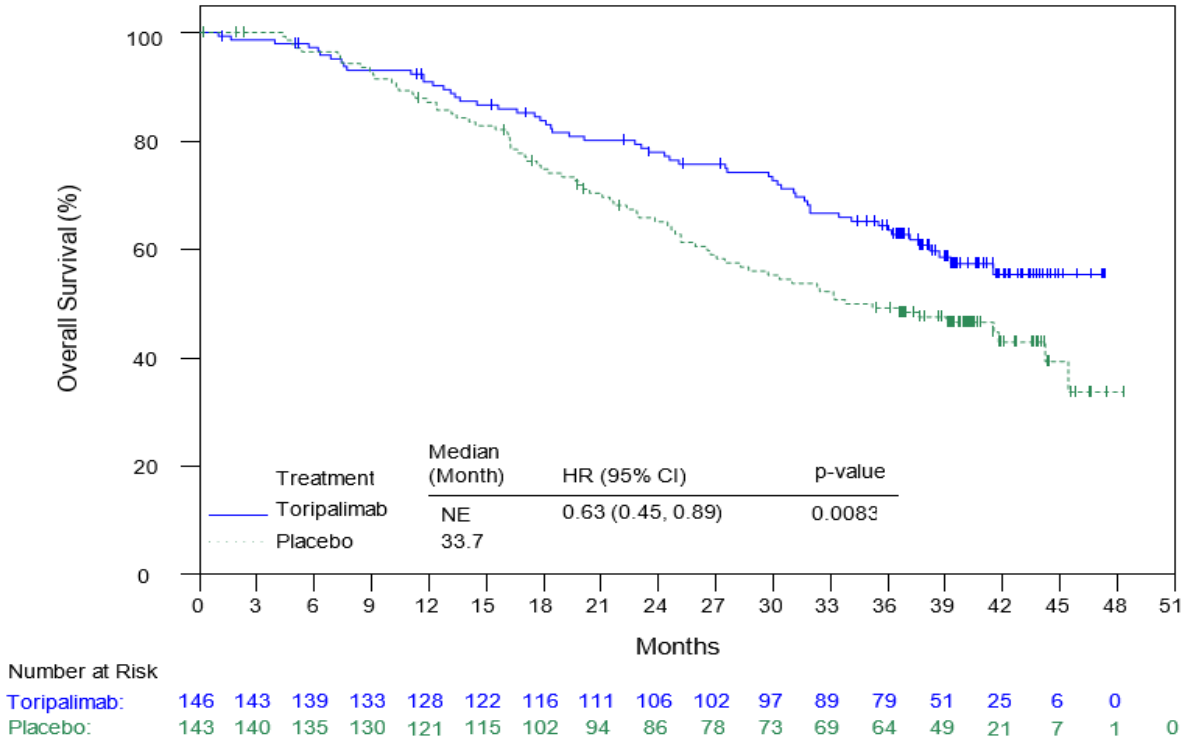
BIRC=blinded independent review committee; CI= confidence interval; NE=Not estimable

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



Data cut-off date: 08 June 2021

Figure 2: Kaplan-Meier Curves of Overall Survival for JUPITER-02



Data cut-off date: 18 November 2022

Previously treated, unresectable or metastatic NPC

The efficacy of toripalimab was investigated in POLARIS-02, an open-label, multi-centre, multicohort trial conducted in a single country. The trial included a total of 172 patients with unresectable or metastatic NPC who had received prior platinum-based chemotherapy for treatment of recurrent or metastatic NPC or had disease progression within 6 months of completion of platinum-based chemotherapy administered as neoadjuvant, adjuvant, or definitive chemoradiation treatment for locally advanced disease. Key exclusion criteria included active autoimmune disease or other medical conditions requiring immunosuppressive therapy. Patients received toripalimab 3 mg/kg intravenously every 2 weeks until disease progression per RECIST v1.1 or unacceptable toxicity. Tumour response assessments were performed every 8 weeks for the first year and every 12 weeks thereafter. The major efficacy outcome measures were confirmed ORR and duration of response (DOR) as assessed by a Blinded Independent Review Committee (BIRC) using RECIST v1.1.

The median age was 45 years (range: 22 to 68), 4.1% age 65 or older, 83% male, 100% Asian, and ECOGPS of 0 (37%). Patients had received a median of 2 prior systemic therapies for recurrent/metastatic disease (range: 1-13). Ninety-nine percent of patients had metastatic disease, 95% had non-keratinising NPC, 2.9% had keratinising squamous cell carcinoma and 1.7% did not have the subtype identified.

Efficacy results are summarised in Table 8 below.

Table 8: Efficacy Results for (POLARIS-02)

Endpoint	toripalimab (N=172)
BIRC-Assessed Overall Response Rate[1]	
Overall Response Rate, % (95% CI)	21 (15, 28)
Complete Response Rate, %	2.3
Partial Response Rate, %	19
BIRC-Assessed Duration of Response (DOR)	(N = 36)
Median, months (95% CI)	14.9 (10.3, NE)
Patients with DOR> 6 months[2], n (%)	30 (83%)
Patients with DOR > 12 months[2], n (%)	14 (39%)

CI=confidence interval. n=number. NE=not estimable.
[1] Confirmed overall response rate assessed by BIRC
[2] Based on observed duration of response BIRC=blinded independent review committee

5.2 PHARMACOKINETIC PROPERTIES

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

Toripalimab is primarily distributed in the plasma with a geometric mean volume of distribution at steady state of approximately 3.7 L (CV=27%).

Metabolism

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

Excretion

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 ($t_{½}$) (± standard deviation) was 10 ± 1.5 days after the first dose and 18 ± 9.4 days at steady state.

Special populations

In the population PK analysis, no clinically significant differences in the pharmacokinetics of toripalimab 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 (x) the upper limit of normal (ULN) and/or AST/ALT >1.0 to 3.0 x ULN), tumour burden or primary cancer.

The effect of moderate (total bilirubin >1.5 to 3 x ULN and/or AST/ALT >3 to 5.0 x ULN) or severe (total bilirubin > 3 x ULN and/or AST/ALT > 5.0 x ULN) hepatic impairment or of

moderate (CLcr 30 to 59 mL/min) or severe (CLcr ≤ 29 mL/min) renal impairment on the pharmacokinetics of toripalimab has not been studied.

Hepatic impairment

The effects of baseline hepatic impairment using the US National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) grading system for hepatic dysfunction on the clearance and volume of distribution of toripalimab were evaluated using population pharmacokinetic analyses. No differences in clearance or volume of distribution were found between patients with mild (Grade 1, n=142) hepatic impairment compared to patients with normal liver function (n=871). There was a limited number of patients with moderate (Grade 2, n=1) hepatic impairment and no patients with severe (Grade 3 or 4) hepatic impairment enrolled in clinical studies of toripalimab.

Renal impairment

The effect of baseline renal impairment based on the estimated creatinine clearance on the clearance and volume of distribution of toripalimab were evaluated using population pharmacokinetic analyses. No differences in clearance or volume of distribution were found between patients with mild (n=447) renal impairment and patients with normal renal function (n=567). The effect of moderate or severe renal impairment on the pharmacokinetics of toripalimab has not been studied.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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

Carcinogenicity

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

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Citric acid monohydrate, sodium citrate dihydrate, sodium chloride, mannitol, polysorbate 80 and water for injections.

6.2 INCOMPATIBILITIES

This medicine must not be mixed with other medicines except those mentioned in section 4.2 Dose and method of administration.

6.3 SHELF LIFE

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

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at 2°C to 8°C (Refrigerate. Do not freeze). Keep the vial in its carton in order to protect from light. Do not shake.

Diluted solutions: Chemical and physical in-use stability has been demonstrated for up to 8 hours at room temperature (20°C - 25°C) and for up to 24 hours refrigerated (2°C - 8°C).

ZYTORVI does not contain a preservative. From a microbiological safety point of view, ZYTORVI should be used immediately. To reduce microbiological hazard, use as soon as possible after dilution. If storage is necessary, hold at 2-8°C for not more than 24 hours.

Discard diluted solution stored at room temperature after 8 hours.

Discard the refrigerated diluted solution after 24 hours.

6.5 NATURE AND CONTENTS OF CONTAINER

Clear Type I glass vial with chlorobutyl rubber stopper and an aluminium plastic flip-off seal.

Pack-size of 1 vial.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSIOCHEMICAL PROPERTIES

Chemical structure

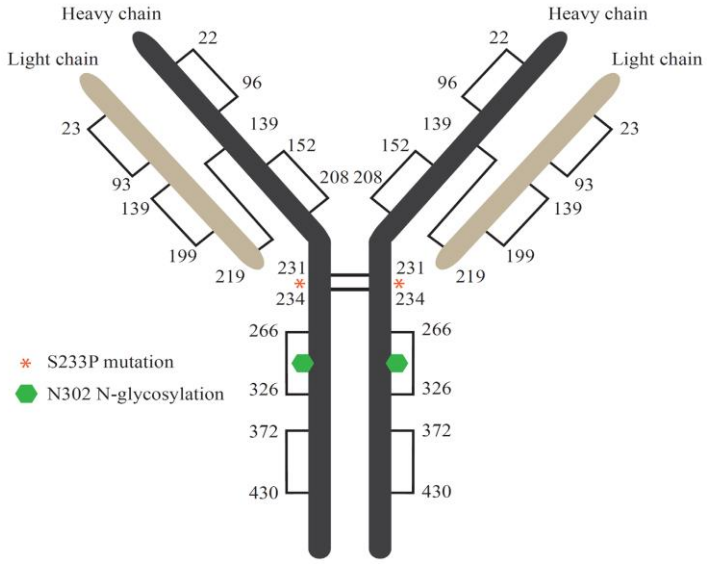


Figure 2: Schematic – Molecular structure of toripalimab

CAS number:

1924598-82-2

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8. SPONSOR

Dr Reddy's Laboratories (Australia) Pty Ltd

Suite 3.03, Level 3, 390 St Kilda Road

Melbourne, VIC, 3004, Australia

Telephone: 1800 733 397

9. DATE OF FIRST APPROVAL

21 January 2025

10. DATE OF REVISION

4 April 2025

Summary table of changes

Section changed	Summary of new information
All	Changed trade name to Zytorvi
8	Changed sponsor details