NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Jemperli 500 mg/10 mL concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of concentrate for solution for infusion contains 50 mg of dostarlimab.

One vial of 10 mL concentrate for solution for infusion contains 500 mg of dostarlimab (50 mg/mL).

Dostarlimab is produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology.

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

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

Dostarlimab is a clear to slightly opalescent colourless to yellow solution, free from visible particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Jemperli is indicated in combination with platinum-containing chemotherapy for the treatment of adult patients with primary advanced or recurrent endometrial cancer (EC).

Jemperli is indicated as monotherapy for the treatment of adult patients with recurrent or advanced mismatch repair deficient (dMMR) endometrial cancer (EC) that has progressed on or following prior treatment with a platinum-containing regimen.

4.2 Dose and method of administration

Dostarlimab in combination with chemotherapy

When dostarlimab is administered in combination with chemotherapy, refer to the full Data Sheet for the combination products (see also section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical efficacy and safety).

The recommended dose as combination therapy is 500 mg dostarlimab administered as an intravenous infusion over 30 minutes every 3 weeks for 6 doses, followed by 1000 mg every 6 weeks for all cycles thereafter.

The dosage regimen in combination with chemotherapy is presented in Table 1.

Table 1. Dosage regimen for dostarlimab in combination with chemotherapy

500 mg once every 3 weeks in combination with chemotherapy[a] (1 Cycle = 3 weeks)							**1000 mg once every 6 weeks until disease progression or unacceptable toxicity (1 Cycle = 6 weeks)**			
Cycle	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Cycle 8	Cycle 9	Continue dosing
Week	1	4	7	10	13	16	19	25	31	Q6W

3 weeks between Cycle 6 and Cycle 7

[a] Administer dostarlimab prior to chemotherapy on the same day.

Administration of dostarlimab should continue according to the recommended dose and schedule until disease progression or unacceptable toxicity.

Dostarlimab monotherapy

The recommended dose as monotherapy is 500 mg dostarlimab administered as an intravenous infusion over 30 minutes every 3 weeks for 4 cycles followed by 1,000 mg every 6 weeks for all cycles thereafter.

The dosage regimen as monotherapy is presented in Table 2.

Table 2. Dosage regimen for dostarlimab as monotherapy

500 mg once every 3 weeks (1 Cycle = 3 weeks)					**1,000 mg once every 6 weeks until disease progression or unacceptable toxicity (1 Cycle = 6 weeks)**			
Cycle	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Continue dosing
Week	1	4	7	10	13	19	25	Q6W

3 weeks between Cycle 4 and Cycle 5

Administration of dostarlimab should continue according to the recommended dose and schedule until disease progression or unacceptable toxicity.

Dose modifications

Dose reduction is not recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability. Recommended modifications to manage adverse reactions are provided in Table 3. Detailed guidelines for the management of immune-

related adverse reactions and infusion-related reactions are described in Section 4.4 Special Warnings and Precautions for use.

Table 3. Recommended dose modifications for dostarlimab		
Immune-related adverse reactions	**Severity grade[a]**	**Dose modification**
Colitis	2 or 3	Withhold dose. Restart dosing when toxicity resolves to Grade 0 or 1.
	4	Permanently discontinue.
Hepatitis	Grade 2 (AST[b] or ALT[c] > 3 and up to 5 × ULN[d] or total bilirubin > 1.5 and up to 3 × ULN)	Withhold dose. Restart dosing when toxicity resolves to Grade 0 or 1.
	Grade ≥3 (AST or ALT > 5 × ULN or total bilirubin > 3 × ULN)	Permanently discontinue (see exception below)[e]
Type 1 diabetes mellitus (T1DM)	3 or 4 (hyperglycaemia)	Withhold dose. Restart dosing in appropriately managed, clinically and metabolically stable patients.
Hypophysitis or adrenal insufficiency	2, 3 or 4	Withhold dose. Restart dosing when toxicity resolves to Grade 0 or 1. Permanently discontinue for recurrence or worsening while on adequate hormonal therapy.
Hypothyroidism or hyperthyroidism	3 or 4	Withhold dose. Restart dosing when toxicity resolves to Grade 0 or 1.
Pneumonitis	2	Withhold dose. Restart dosing when toxicity resolves to Grade 0 or 1. If Grade 2 recurs, permanently discontinue.
	3 or 4	Permanently discontinue.
Nephritis	2	Withhold dose. Restart dosing when toxicity resolves to Grade 0 or 1.
	3 or 4	Permanently discontinue.

Table 3. Recommended dose modifications for dostarlimab		
Immune-related adverse reactions	**Severity grade[a]**	**Dose modification**
Exfoliative dermatologic conditions (e.g. SJS, TEN, DRESS)	Suspected	Withhold dose for any grade. Restart dosing if not confirmed and when toxicity resolves to Grade 0 or 1.
	Confirmed	Permanently discontinue.
Myocarditis	2, 3 or 4	Permanently discontinue.
Severe neurological toxicities (myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome, encephalitis, transverse myelitis)	2, 3 or 4	Permanently discontinue.
Other immune-related adverse reactions involving a major organ	3	Withhold dose. Restart dosing when toxicity resolves to Grade 0 or 1.
	4	Permanently discontinue.
Recurrence of immune-related adverse reactions after resolution to ≤ Grade 1 (except for pneumonitis, see above)	3 or 4	Permanently discontinue.
Other adverse reactions	**Severity grade[a]**	**Dose modification**
Infusion-related reactions	2	Withhold dose. If resolved within 1 hour of stopping, may be restarted at 50% of the original infusion rate, or restart when symptoms resolve with pre-medication. If Grade 2 recurs with adequate premedication, permanently discontinue.
	3 or 4	Permanently discontinue.

[a] Toxicity graded per National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

[b] AST = aspartate aminotransferase

[c] ALT = alanine aminotransferase

[d] ULN = upper limit of normal

[e] For patients with liver metastases who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by ≥50% relative to baseline and lasts for at least 1 week, then treatment should be discontinued.

Special Populations

Elderly

No dose adjustment is recommended for patients who are 65 years of age or over. There are limited clinical data with dostarlimab in patients 75 years of age or over (see section 5.1 PHARMACODYNAMIC PROPERTIES).

Renal impairment

No dose adjustment is recommended for patients with mild or moderate renal impairment. There are limited data in patients with severe renal impairment or end-stage renal disease undergoing dialysis (see Section 5.2 PHARMACOKINETIC PROPERTIES).

Hepatic impairment

No dose adjustment is recommended for patients with mild hepatic impairment. There are limited data in patients with moderate or severe hepatic impairment (see Section 5.2 PHARMACOKINETIC PROPERTIES).

Paediatric Population

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

Method of administration

Preparation

Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration. Dostarlimab is a slightly opalescent colourless to yellow solution. Discard the vial if visible particles are observed.

Dilution

For instructions on dilution of the medicine before administration, see section 6.6.

Administration

Dostarlimab is for intravenous infusion only. Dostarlimab should be administered by intravenous infusion using an intravenous infusion pump over 30 minutes by a health care practitioner.

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

Dostarlimab is compatible with an IV bag made of polyvinyl chloride (PVC) with or without di(2-ethylhexyl) phthalate (DEHP), ethylene vinyl acetate, polyethylene (PE), polypropylene (PP) or polyolefin blend (PP+PE), and a syringe made from PP. Infusion tubing should be made of PVC, platinum cured silicon or PP; fittings made from PVC or polycarbonate and needles made from stainless steel. A 0.2 or 0.22 micron in-line polyethersulfone (PES) filter must be used during administration of dostarlimab.

4.3 Contraindications

None

4.4 Special warnings and precautions for use

Traceability

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

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 dostarlimab. While immune-related adverse reactions usually occur during treatment with PD-1/PD-L1 blocking antibodies, symptoms can also manifest after discontinuation of treatment. Immune-related adverse reactions may occur in any organ or tissue and may affect more than one body system simultaneously. Important immune-related adverse reactions listed in 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 for symptoms and signs of immune-related adverse reactions. Evaluate haematological and clinical chemistries, including liver, kidney and thyroid function tests, at baseline and periodically during treatment. For suspected immune-related adverse reactions, adequate evaluation including specialty consultation should be ensured.

Based on the severity of the adverse reaction, dostarlimab should be withheld or permanently discontinued and corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) or other appropriate therapy administered (see below and section 4.2 DOSING AND ADMINISTRATION, Dose modification). Upon improvement to Grade 0 or 1, corticosteroid taper should be initiated and continued for 1 month or longer. Based on limited data from clinical studies in patients whose immune-related adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants can be considered. Institute hormone replacement therapy for endocrinopathies as warranted.

Dostarlimab should be permanently discontinued for any Grade 3 immune-related adverse reaction that recurs and for any Grade 4 immune-related adverse reaction toxicity, except for endocrinopathies that are controlled with replacement hormones and unless otherwise specified in Table 3.

Immune-related pneumonitis

Pneumonitis has been reported in patients receiving dostarlimab (see Section 4.8 ADVERSE 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 dostarlimab treatment modifications and corticosteroids (see Section 4.2 DOSING AND ADMINISTRATION).

Immune-related colitis

Dostarlimab can cause immune-related colitis (see Section 4.8 ADVERSE EFFECTS). Monitor patients for signs and symptoms of colitis and manage with dostarlimab treatment

modifications, anti-diarrhoeal agents and corticosteroids (see Section 4.2 DOSING AND ADMINISTRATION).

Immune-related hepatitis

Dostarlimab can cause immune-related hepatitis. Monitor patients for changes in liver function periodically as indicated based on clinical evaluation and manage with dostarlimab treatment modifications and corticosteroids (see Section 4.2 DOSING AND ADMINISTRATION).

Immune-related endocrinopathies

Immune-related endocrinopathies, including hypothyroidism, hyperthyroidism, thyroiditis, hypophysitis, type 1 diabetes mellitus, diabetic ketoacidosis and adrenal insufficiency, have been reported in patients receiving dostarlimab (see Section 4.8 ADVERSE EFFECTS).

Hypothyroidism and hyperthyroidism

Immune-related hypothyroidism and hyperthyroidism (including thyroiditis) occurred in patients receiving dostarlimab, and hypothyroidism may follow hyperthyroidism. Patients should be monitored for abnormal thyroid function tests prior to and periodically during treatment and as indicated based on clinical evaluation. Immune-related hypothyroidism and hyperthyroidism (including thyroiditis) should be managed as recommended in Section 4.2 DOSING AND ADMINISTRATION.

Adrenal insufficiency

Immune-related adrenal insufficiency occurred in patients receiving dostarlimab. Patients should be monitored for clinical signs and symptoms of adrenal insufficiency. For symptomatic adrenal insufficiency, patients should be managed as recommended in Section 4.2 DOSING AND ADMINISTRATION.

Immune-related nephritis

Dostarlimab can cause immune-related nephritis (see Section 4.8 ADVERSE EFFECTS). Monitor patients for changes in renal function and manage with dostarlimab treatment modifications and corticosteroids (see Section 4.2 DOSING AND ADMINISTRATION).

Immune-related rash

Immune-related rash has been reported in patients receiving dostarlimab, including pemphigoid (see Section 4.8 ADVERSE EFFECTS). Patients should be monitored for signs and symptoms of rash. Exfoliative dermatologic conditions should be managed as recommended (see 4.2 DOSING AND ADMINISTRATION). Events of Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN) or drug rash with eosinophilia and systemic symptoms (DRESS) have been reported in patients treated with PD-1 inhibitors.

Caution should be used when considering the use of dostarlimab in a patient who has previously experienced a severe or life-threatening skin adverse reaction on prior treatment with other immune-stimulatory anticancer agents.

Other immune-related adverse reactions

Given the mechanism of action of dostarlimab other potential immune-related adverse reactions may occur. Clinically significant immune-related adverse reactions reported in less than 1% of patients treated with dostarlimab as monotherapy in clinical trials include encephalitis, autoimmune haemolytic anaemia, uveitis, and iridocyclitis. Patients should be monitored for signs and symptoms of immune-related adverse reactions and managed as described in Section 4.2 DOSING AND ADMINISTRATION.

Transplant-related adverse reactions

Solid organ transplant rejection

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

Complications of allogeneic Haematopoietic Stem Cell Transplant (HSCT)

Fatal and other serious complications can occur in patients who receive 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 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.

Infusion-related reactions

Dostarlimab can cause infusion-related reactions, which can be severe (see Section 4.8 ADVERSE EFFECTS). For severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions, stop infusion and permanently discontinue Dostarlimab (see Section 4.2 DOSING AND ADMINISTRATION).

4.5 Interaction with other medicines and other forms of interaction

No drug-drug interaction studies have been conducted with dostarlimab. Monoclonal antibodies (mAbs) such as dostarlimab are not substrates for cytochrome P450 or drug transporters. Additionally, pharmacokinetic (PK) drug-drug interaction of dostarlimab with small molecule drugs is not expected.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no available data on the use of dostarlimab in pregnant women. Animal reproduction studies have not been conducted with dostarlimab to evaluate its effect on reproduction and fetal development. Based on its mechanism of action, dostarlimab can cause fetal harm when administered to a pregnant woman. Animal models link the PD-1/PD-

L1 signalling pathway with maintenance of pregnancy through induction of maternal immune tolerance to fetal tissue. Human IgG4 immunoglobulins (IgG4) are known to cross the placental barrier; therefore, dostarlimab has the potential to be transmitted from the mother to the developing fetus. Advise women of the potential risk to a fetus.

Dostarlimab is not recommended during pregnancy. Women of childbearing potential should use highly effective contraception during treatment with dostarlimab and for 4 months after the last dose.

Breast-feeding

There is no information regarding the presence of dostarlimab in human milk, or its effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment and for 4 months after the last dose of dostarlimab.

Fertility

Fertility studies have not been conducted with dostarlimab. No effects on male and female reproductive organs were observed in a 3-month repeat dose toxicity study in cynomolgus monkeys at ≤100 mg/kg/week IV, resulting in exposures (AUC) at least 28 times that expected in patients; however, these results may not be predictive of clinical risk because of the immaturity of the reproductive system of animals used in the study.

4.7 Effects on ability to drive and use machines

Dostarlimab has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The safety of dostarlimab as monotherapy has been evaluated in 605 patients with recurrent or advanced solid tumours, including 314 patients with endometrial cancer and 291 patients with other advanced solid tumours, in the GARNET study. Patients received doses of dostarlimab 500 mg every 3 weeks for 4 cycles, followed by 1000 mg every 6 weeks for all cycles thereafter.

The safety of dostarlimab in combination with chemotherapy has been evaluated in 241 patients with primary advanced or recurrent endometrial cancer in the RUBY study. Patients received doses of dostarlimab 500 mg every 3 weeks for 6 cycles, followed by 1000 mg every 6 weeks for all cycles thereafter.

Adverse reactions observed in patients who received dostarlimab monotherapy in the GARNET study are listed in Table 4. Adverse reactions observed in patients who received dostarlimab in combination with chemotherapy in the RUBY study, as well as additional adverse reactions identified from other clinical trials in patients with solid tumors receiving dostarlimab in combination with various types of anticancer therapies are shown in Table 5.

Adverse reactions known to occur with dostarlimab or with combination therapy components when given alone may occur during treatment with these medicinal products in combination, even if these reactions were not reported in clinical studies with combination therapy.

When dostarlimab is administered in combination, refer to the local label for the respective combination therapy component prior to initiation of treatment.

Tabulated list of adverse reactions

Adverse reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); and not known (cannot be estimated from the available data).

Table 4. Adverse reactions in patients with solid tumours treated with dostarlimab monotherapy

System Organ Class/Adverse Reaction	Dostarlimab monotherapy	All Grades n (%)	Grades 3-4 n (%)
Blood and lymphatic system disorders			
Anaemia	Very common	173 (28.6)	59 (9.8)
Autoimmune haemolytic anaemia	Uncommon	1 (0.2)	1 (0.2)
Endocrine disorders			
Hypothyroidism	Very common	68 (11.2)[a]	0
Hyperthyroidism	Common	32 (5.3)	1 (0.2)
Adrenal insufficiency	Common	8 (1.3)	4 (0.7)
Thyroiditis	Uncommon	4 (0.7)[b]	0
Hypophysitis	Uncommon	3 (0.5)[c]	0
Metabolism and nutrition disorders			
Type 1 diabetes mellitus	Uncommon	1 (0.2)	1 (0.2)
Diabetic ketoacidosis	Uncommon	1 (0.2)	1 (0.2)
Nervous system disorders			
Encephalitis	Uncommon	2 (0.3)	2 (0.3)
Myasthenia gravis	Uncommon	1 (0.2)	0
Eye disorders			
Uveitis	Uncommon	2 (0.3)[d]	0
Respiratory, thoracic and mediastinal disorders			
Pneumonitis	Common	25 (4.1)[e]	7 (1.2)[f]
Gastrointestinal disorders			
Diarrhoea	Very common	157 (26)	8 (1.3)
Nausea	Very common	156 (25.8)	13 (2.1)
Vomiting	Very common	115 (19.0)	10 (1.7)
Colitis	Common	13 (2.1)[g]	5 (0.8)[h]
Pancreatitis	Common	7 (1.2)[i]	6 (1.0)[i]

System Organ Class/Adverse Reaction	Dostarlimab monotherapy	All Grades n (%)	Grades 3-4 n (%)
Gastritis	Common	6 (1.0)	1 (0.2)
Oesophagitis	Uncommon	1 (0.2)	1 (0.2)
Hepatobiliary disorders			
Hepatitis	Common	7 (1.2)[j]	4 (0.7)[j]
Skin and subcutaneous tissue disorders			
Rash	Very common	126 (20.8)[k]	9 (1.5)[l]
Pruritus	Very common	86 (14.2)	2 (0.3)
Musculoskeletal and connective tissue disorders			
Myalgia	Common	46 (7.6)	0
Immune-mediated arthritis	Uncommon	3 (0.5)	1 (0.2)
Polymyalgia rheumatica	Uncommon	2 (0.3)	0
Immune-mediated myositis	Uncommon	1 (0.2)	1 (0.2)
Renal and urinary disorders			
Nephritis	Uncommon	4 (0.7)[m]	0
General disorders and administration site conditions			
Pyrexia	Very common	75 (12.4)	1 (0.2)
Chills	Common	24 (4.0)	1 (0.2)
Investigations			
Transaminases increased	Very common	90 (14.9)[n]	20 (3.3)[o]
Injury, poisoning and procedural complications			
Infusion-related reaction	Common	8 (1.3)[p]	1 (0.2)

[a] Includes hypothyroidism and autoimmune hypothyroidism

[b] Includes thyroiditis and autoimmune thyroiditis

[c] Includes hypophysitis and lymphocytic hypophysitis

[d] Includes uveitis and iridocyclitis

[e] Includes pneumonitis, interstitial lung disease and immune-mediated lung disease

[f] Includes pneumonitis and interstitial lung disease

[g] Includes colitis, enterocolitis and immune-mediated enterocolitis

[h] Includes colitis and immune-mediated enterocolitis

[i] Includes pancreatitis and pancreatitis acute

[j] Includes hepatitis, autoimmune hepatitis and hepatic cytolysis

[k] Includes rash, rash maculopapular, erythema, rash macular, rash pruritic, rash erythematous, rash papular, erythema multiforme, skin toxicity, drug eruption, toxic skin eruption, exfoliative rash and pemphigoid

[l] Includes rash, rash maculo-papular and drug eruption

[m] Includes nephritis and tubulointerstitial nephritis

[n] Includes alanine aminotransferase increased, aspartate aminotransferase increased, transaminases increased and hypertransaminasaemia

[o] Includes alanine aminotransferase increased, aspartate aminotransferase increased and transaminases increased

[p] Includes infusion-related reaction and hypersensitivity

Table 5. Adverse reactions in patients with solid tumours treated with dostarlimab in combination therapy

System Organ Class/Adverse Reaction	Dostarlimab combination therapy	All Grades n (%)	Grades 3-4 n (%)
Endocrine disorders			
Hypothyroidism	Very common	36 (14.9)[a]	0
Hyperthyroidism	Common	10 (4.1)	1 (0.4)
Adrenal insufficiency	Uncommon	2 (0.8)	1 (0.4)
Thyroiditis	Uncommon	1 (0.4)	0
Metabolism and nutrition disorders			
Type 1 diabetes mellitus	Uncommon	1 (0.4)	1 (0.4)
Nervous system disorders			
Myasthenic syndrome	Uncommon	1 (0.1)	1 (0.1)
Guillain-Barré syndrome	Uncommon	3 (0.5)[b]	2 (0.3)
Eye disorders			
Uveitis	Uncommon	1 (0.4)	1 (0.4)
Cardiac disorders			
Myocarditis	Uncommon	2 (0.2)[c]	2 (0.2)[c]
Respiratory, thoracic and mediastinal disorders			
Pneumonitis	Common	5 (2.1)	1 (0.4)
Gastrointestinal disorders			
Colitis	Common	4 (1.1)[d]	3 (0.8)[d]
Pancreatitis	Common	3 (1.2)	2 (0.8)
Immune mediated gastritis	Uncommon	1 (0.1)	1 (0.1)
Vasculitis gastrointestinal	Uncommon	1 (0.1)	1 (0.1)

System Organ Class/Adverse Reaction	Dostarlimab combination therapy	All Grades n (%)	Grades 3-4 n (%)
Skin and subcutaneous tissue disorders			
Rash	Very common	86 (35.7)[e]	17 (7.1)[e]
Dry skin	Very common	24 (10.0)	0
Musculoskeletal and connective tissue disorders			
Immune-mediated arthritis	Uncommon	1 (0.4)	1 (0.4)
Myositis	Uncommon	2 (0.4)	1 (0.2)
General disorders and administration site conditions			
Pyrexia	Very common	31 (12.9)	0
Systemic inflammatory response syndrome	Uncommon	2 (0.4)	2 (0.4)
Investigations			
Alanine aminotransferase increased	Very common	31 (12.9)	5 (2.1)
Aspartate aminotransferase increased	Very common	29 (12.0)	5 (2.1)

[a] Includes hypothyroidism and immune-mediated hypothyroidism

[b] Includes Guillain-Barré syndrome and demyelinating polyneuropathy

[c] Includes myocarditis (combination with chemotherapy) and immune-mediated myocarditis from ongoing blinded trial of dostarlimab in combination; estimated frequency category

[d] Includes colitis (combination with chemotherapy) and enteritis reported from ongoing trials of dostarlimab in combination

[e] Includes rash and rash maculo-papular

Description of selected adverse reactions

Other adverse events

Table 6 summarises other adverse events that occurred in 10% or more of patients with solid tumours treated with dostarlimab monotherapy in the GARNET study. Fatigue and asthenia are the only adverse events reported in at least 20% of patients. Grade 4 events included asthenia (N=1 patient, 0.2%) and dyspnoea (N=2 patients, 0.3%).

Table 6. Other adverse events in ≥10% of patients with solid tumours treated with dostarlimab monotherapy

System Organ Class/Adverse Event	All Grades n (%)	Grades 3-4 n (%)
Gastrointestinal disorders		
Constipation	109 (18.0)	4 (0.7)
Abdominal pain	106 (17.5)	21 (3.5)
General disorders and administration site conditions		
Fatigue	155 (25.6)	17 (2.8)
Asthenia	126 (20.8)	13 (2.1)
Infections and infestations		
Urinary tract infection	86 (14.2)	9 (1.5)
Musculoskeletal and connective tissue disorders		
Arthralgia	103 (17.0)	5 (0.8)
Back pain	78 (12.9)	10 (1.7)
Metabolism and nutrition disorders		
Decreased appetite	108 (17.9)	6 (1.0)
Nervous system disorders		
Headache	61 (10.1)	0
Respiratory, thoracic and mediastinal disorders		
Cough	96 (15.9)	1 (0.2)
Dyspnoea	79 (13.1)	20 (3.3)

Table 7 summarises other adverse events that occurred in 10% or more of patients with endometrial cancer treated with dostarlimab in combination with chemotherapy in the RUBY study. Grade 4 events included neutrophil count decreased (N=9 patients, 3.7%), neutropenia (N=8 patients, 3.3%), thrombocytopenia and white blood cell count decreased (N=3 patients each, 1.2%), and pruritus, hypomagnesaemia, hypokalaemia, blood creatinine increased, hypertension and infusion related reaction (N=1 patient each, 0.4%).

Table 7. Other adverse events in ≥10% of patients with endometrial cancer treated with dostarlimab in combination with chemotherapy

System Organ Class/Adverse events	All Grades n (%)	Grades 3-4 n (%)
Gastrointestinal disorders		
Nausea	131 (54.4)	7 (2.9)
Constipation	84 (34.9)	1 (0.4)
Diarrhoea	76 (31.5)	4 (1.7)
Vomiting	49 (20.3)	4 (1.7)
Abdominal pain	38 (15.8)	4 (1.7)
Dyspepsia	26 (10.8)	0
Nervous system disorders		
Neuropathy peripheral	106 (44.0)	5 (2.1)
Peripheral sensory neuropathy	51 (21.2)	6 (2.5)
Headache	39 (16.2)	1 (0.4)
Dizziness	37 (15.4)	0
Dysgeusia	27 (11.2)	0
General disorders and administration site conditions		
Fatigue	126 (52.3)	4 (1.7)
Oedema peripheral	32 (13.3)	0
Skin and subcutaneous tissue disorders		
Alopecia	130 (53.9)	0
Pruritus	47 (19.5)	1 (0.4)
Infections and infestations		
Urinary tract infection	43 (17.8)	7 (2.9)
Musculoskeletal and connective tissue disorders		
Arthralgia	90 (37.3)	3 (1.2)
Myalgia	64 (26.6)	0
Back pain	39 (16.2)	1 (0.4)

System Organ Class/Adverse events	All Grades n (%)	Grades 3-4 n (%)
Pain in extremity	30 (12.4)	1 (0.4)
Metabolism and nutrition disorders		
Hypomagnesaemia	53 (22.0)	2 (0.8)
Decreased appetite	52 (21.6)	5 (2.1)
Hypokalaemia	47 (19.5)	12 (5.0)
Investigations		
Neutrophil count decreased	33 (13.7)	20 (8.3)
White blood cell count decreased	32 (13.3)	16 (6.6)
Platelet count decreased	31 (12.9)	5 (2.1)
Blood creatinine increased	28 (11.6)	2 (0.8)
Blood and lymphatic system disorders		
Anaemia	91 (37.8)	36 (14.9)
Neutropenia	33 (13.7)	23 (9.5)
Thrombocytopenia	26 (10.8)	8 (3.3)
Respiratory, thoracic and mediastinal disorders		
Dyspnoea	46 (19.1)	3 (1.2)
Cough	34 (14.1)	0
Vascular disorders		
Hypertension	32 (13.3)	17 (7.1)
Injury, poisoning and procedural complications		
Infusion related reactions	33 (13.7)	2 (0.8)
Psychiatric disorders		
Insomnia	39 (16.2)	0

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralising antibody) positivity in an assay may be influenced by several factors including assay methodology, sample

handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to dostarlimab in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

In the GARNET study, anti-drug antibodies (ADA) were tested in 384 patients who received dostarlimab monotherapy and the incidence of dostarlimab treatment-emergent ADAs was 2.1%. Neutralising antibodies were detected in 1.0% of patients.

Co-administration with chemotherapy did not affect dostarlimab immunogenicity. In the RUBY study, of the 225 patients who were treated with dostarlimab in combination with chemotherapy and evaluable for the presence of ADAs, there was no incidence of dostarlimab treatment-emergent ADA or treatment emergent neutralising antibodies.

In the patients who developed anti-dostarlimab antibodies in either study, there was no evidence of altered pharmacokinetics, efficacy or safety of dostarlimab. Because of the small number of patients who developed ADAs, the impact of immunogenicity on the efficacy and safety of dostarlimab is inconclusive.

Paediatric population

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

Reporting of suspected adverse reactions

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

4.9 Overdose

If overdose is suspected, the patient should be monitored for any signs or symptoms of adverse reactions or effects, and appropriate standard of care measures should be instituted immediately.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-neoplastic agents, monoclonal antibodies, ATC code: L01FF07

Mechanism of action

Dostarlimab is an anti-programmed cell death protein-1 (PD-1) immunoglobulin G4 (IgG4) humanised monoclonal antibody (mAb), derived from a stable Chinese hamster ovary (CHO) cell line.

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. Dostarlimab is a humanised mAb of IgG4 isotype that binds

to PD 1, resulting in inhibition of binding to PD-L1 and PD-L2, releasing inhibition of PD-1 pathway-mediated immune response, including the anti-tumour immune response. In syngeneic mouse tumour models, blocking PD-1 activity resulted in decreased tumour growth.

Pharmacodynamic effects

Based on exposure efficacy and safety relationships, there are no clinically significant differences in efficacy and safety within the exposure range attained under the recommended therapeutic dosing regimen (500 mg administered intravenously every 3 weeks for 4 doses, followed by 1,000 mg every 6 weeks thereafter). Full receptor occupancy as measured by both the direct PD-1 binding and IL-2 production functional assay was maintained throughout the dosing interval at the recommended therapeutic dosing regimen.

Clinical efficacy and safety

RUBY: Randomised controlled study of combination therapy in treatment of primary advanced or recurrent EC

The efficacy and safety of dostarlimab in combination with carboplatin-paclitaxel were investigated in RUBY, a multicentre, randomised, double-blinded, placebo-controlled Phase 3 study conducted in patients with primary advanced or recurrent EC.

Patients were randomised (1:1) to receive dostarlimab 500 mg plus carboplatin AUC 5 mg/mL/min and paclitaxel 175 mg/m2 every 3 weeks for 6 cycles followed by dostarlimab 1000 mg every 6 weeks (n = 245) or placebo plus carboplatin AUC 5 mg/mL/min and paclitaxel 175 mg/m2 every 3 weeks for 6 cycles followed by placebo every 6 weeks (n = 249). Randomisation was stratified by MMR/MSI status, prior external pelvic radiotherapy, and disease status (recurrent, primary Stage III, or primary Stage IV).

The key eligibility criteria for the study were International Federation of Gynaecology and Obstetrics (FIGO) primary Stage III or Stage IV disease, including Stage IIIA to IIIC1 disease with presence of evaluable or measurable disease per RECIST v.1.1, Stage IIIC1 patients with carcinosarcoma, clear cell, serous, or mixed histology (containing ≥10% carcinosarcoma, clear cell, or serous histology) regardless of presence of evaluable or measurable disease on imaging, Stage IIIC2 or Stage IV disease regardless of presence of evaluable or measurable disease. The study also included patients with first recurrent EC with a low potential for cure by radiation therapy or surgery alone or in combination, including patients who had first recurrent disease and were naïve to systemic anticancer therapy or who had received prior neo-adjuvant/adjuvant systemic anticancer therapy and had a recurrence or progressive disease ≥6 months after completing treatment (first recurrence). Treatment continued for up to 3 years or until unacceptable toxicity, disease progression or investigator decision. Assessment of tumour status was performed every 6 weeks through week 25, every 9 weeks through week 52 and every 12 weeks thereafter.

The primary efficacy outcome measures were progression-free survival (PFS), assessed by the investigator according to RECIST v1.1 in subjects with dMMR/microsatellite instability-high (MSI-H) primary advanced or recurrent EC and in all subjects (overall population) with primary advanced or recurrent EC, and overall survival (OS) in all subjects (overall population) with primary advanced or recurrent EC. Secondary endpoints included objective response rate (ORR), duration of response (DOR), and disease control rate (DCR) as assessed by blinded independent central radiologists' (BICR) review and investigator assessment according to RECIST v1.1, and PFS2, defined as the time from treatment randomisation to the date of assessment of progression on the first subsequent anticancer therapy following study treatment or death by any cause, whichever was earlier.

A total of 494 patients with EC were evaluated for efficacy in the RUBY study. Baseline demographics and characteristics of the overall study population were: median age 65 years (51% age 65 years or older); 77% White, 12% Black, 3% Asian; and Eastern Cooperative Oncology Group (ECOG) performance score (PS) 0 (63%) or 1 (37%); and primary stage III 18.6%; primary stage IV 33.6%; recurrent EC 47.8%.

The identification of dMMR/MSI-H tumour status was prospectively determined based on local testing assays (IHC, PCR or NGS), or central testing (IHC) when no local result was available.

Efficacy results are shown in Table 8 and Figures 1, 2 and 3. Dostarlimab plus carboplatin-paclitaxel demonstrated statistically significant improvements in PFS both the dMMR/MSI-H and overall populations and OS in the overall population versus placebo plus carboplatin-paclitaxel.

Table 8. Efficacy results in RUBY for patients with EC

Endpoint	**Overall population[a]**		**dMMR/MSI-H population[a]**	
	Dostarlimab + carboplatin-paclitaxel (N=245)	**Placebo + carboplatin-paclitaxel (N=249)**	**Dostarlimab + carboplatin-paclitaxel (N=53)**	**Placebo + carboplatin-paclitaxel (N=65)**
Primary endpoints				
Progression free survival (PFS)				
Median in months (95% CI)[b]	11.8 (9.6, 17.1)	7.9 (7.6, 9.5)	Not reached	7.7 (5.6, 9.7)
Number (%) of patients with event	135 (55.1)	177 (71.1)	19 (35.8)	47 (72.3)
Hazard ratio (95% CI)[c]	0.64 (0.51, 0.80)		0.28 (0.16, 0.50)	
p-value[d]	<0.0001		<0.0001	
Probability of PFS at 12 months (95% CI)[e]	48.2 (41.3, 54.8)	29.0 (23.0, 35.2)	63.5 (48.5, 75.3)	24.4 (13.9, 36.4)
Probability of PFS at 24 months (95% CI)[e]	36.1 (29.3, 42.9)	18.1 (13.0, 23.9)	61.4 (46.3, 73.4)	15.7 (7.2, 27.0)
Overall survival (OS)[f, g]				
Median in months (95% CI)[b]	44.6 (32.6, NE)	28.2 (22.1, 35.6)	Not reached	31.4 (20.3, NE)
Number (%) of patients with event	109 (44.5)	144 (57.8)	12 (22.6)	35 (53.8)
Hazard ratio (95% CI)[c]	0.69 (0.54, 0.89)		0.32 (0.17, 0.63)	
p-value[d]	0.0020		NA[f]	
Probability of OS at 12 months (95% CI)[e]	83.3 (77.9, 87.4)	80.9 (75.4, 85.3)	86.8 (74.2, 93.5)	79.9 (67.9, 87.8)

Endpoint	Overall population[a]		dMMR/MSI-H population[a]	
	Dostarlimab + carboplatin-paclitaxel (N=245)	**Placebo + carboplatin-paclitaxel (N=249)**	**Dostarlimab + carboplatin-paclitaxel (N=53)**	**Placebo + carboplatin-paclitaxel (N=65)**
Probability of OS at 24 months (95% CI)[e]	70.1 (63.8, 75.5)	54.3 (47.8, 60.3)	82.8 (69.5, 90.7)	57.5 (44.4, 68.6)
Secondary endpoints				
Objective response rate (ORR)[h]				
Number of participants with evaluable disease at baseline (n)	212	219	49	58
ORR, n (%) (95% CI)	149 (70.3) (63.6, 76.3)	142 (64.8) (58.1, 71.2)	38 (77.6) (63.4, 88.2)	40 (69.0) (55.5, 80.5)
Complete response rate, n (%)	53 (25.0)	43 (19.6)	15 (30.6)	12 (20.7)
Partial response rate, n (%)	96 (45.3)	99 (45.2)	23 (46.9)	28 (48.3)
Duration of response (DOR)[h, i]				
Number of responder (n)	149	142	38	40
Median in months (95% CI)[b]	10.6 (8.2, 17.6)	6.2 (4.4, 6.7)	Not reached	5.4 (3.9, 8.1)
Patients with duration ≥ 6 months, n (%)	94 (63.1)	69 (48.6)	28 (73.7)	18 (45.0)
Patients with duration ≥ 12 months, n (%)	60 (40.3)	29 (20.4)	22 (57.9)	7 (17.5)
PFS 2[g]				
Median in months (95% CI)[b]	32.3 (24.6, NE)	18.4 (14.9, 22.0)	Not reached	21.6 (13.4, 39.1)
Hazard ratio (95% CI)[c]	0.66 (0.52, 0.84)		0.33 (0.18, 0.63)	
Probability of PFS2 at 24 months (95% CI)[e]	56.8 (50.0, 63.1)	40.8 (34.4, 47.0)	77.6 (63.1, 86.9)	46.8 (33.9, 58.6)

CI = Confidence interval; NA = not applicable; NE = not estimable.

[a] Efficacy data with a median follow-up of 25 months (cut-off date 28 Sept 2022).

[b] By Brookmeyer and Crowley method.

[c] Based on stratified Cox regression model.

[d] One-sided p-value based on stratified log-rank test.

[e] By Kaplan-Meier method.

[f] OS is a primary endpoint for the overall population only.

[g] Median follow-up of 37 months (cut-off date 22 Sept 2023).

[h] Assessed by investigator according to RECIST v1.1.

[i] For patients with a partial or complete response.

Pre-specified exploratory analyses of PFS and OS were performed in patients with MMRp/MSS EC (n = 376). The PFS HR was 0.76 (95% CI: 0.59, 0.98) with a median PFS of 9.9 months for dostarlimab plus carboplatin-paclitaxel (n = 192) versus 7.9 months for placebo plus carboplatin-paclitaxel (n = 184) (cut-off date 28 Sept 2022). The OS HR was 0.79 (95% CI: 0.60, 1.04) with a median OS of 34 months for dostarlimab plus carboplatin-paclitaxel versus 27 months for placebo plus carboplatin-paclitaxel (cut-off date 22 Sept 2023).

Figure 1. Kaplan-Meier curve of progression-free survival per investigator assessment in all patients (overall population) with EC (RUBY study)

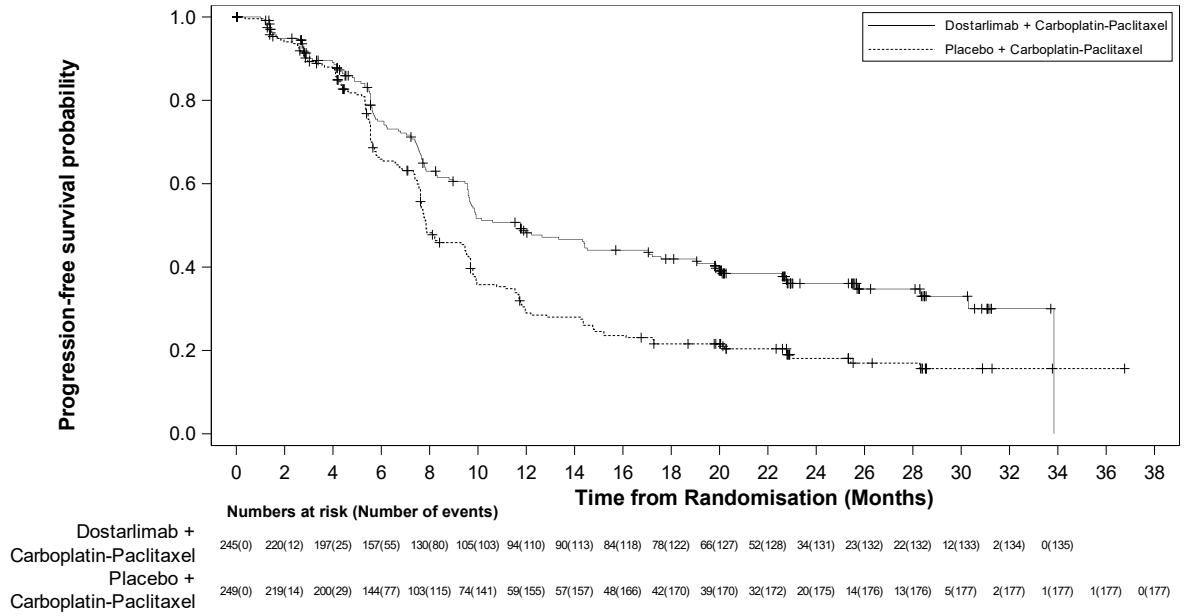


Figure 2. Kaplan-Meier curve of progression-free survival per investigator assessment in patients with dMMR/MSI-H EC (RUBY study)

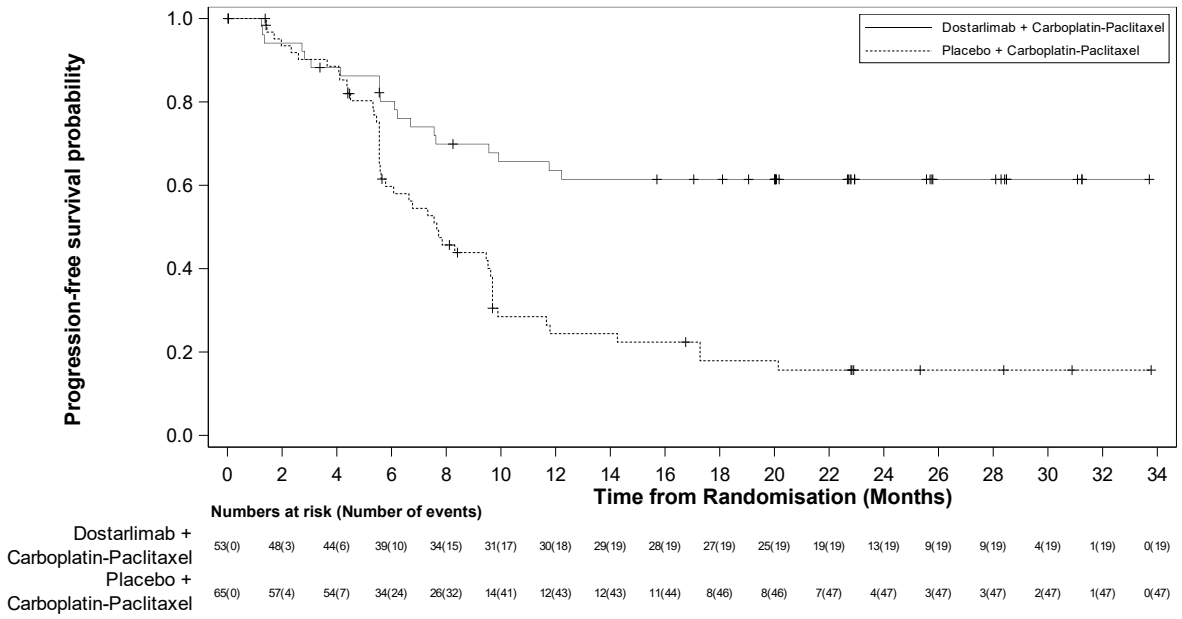
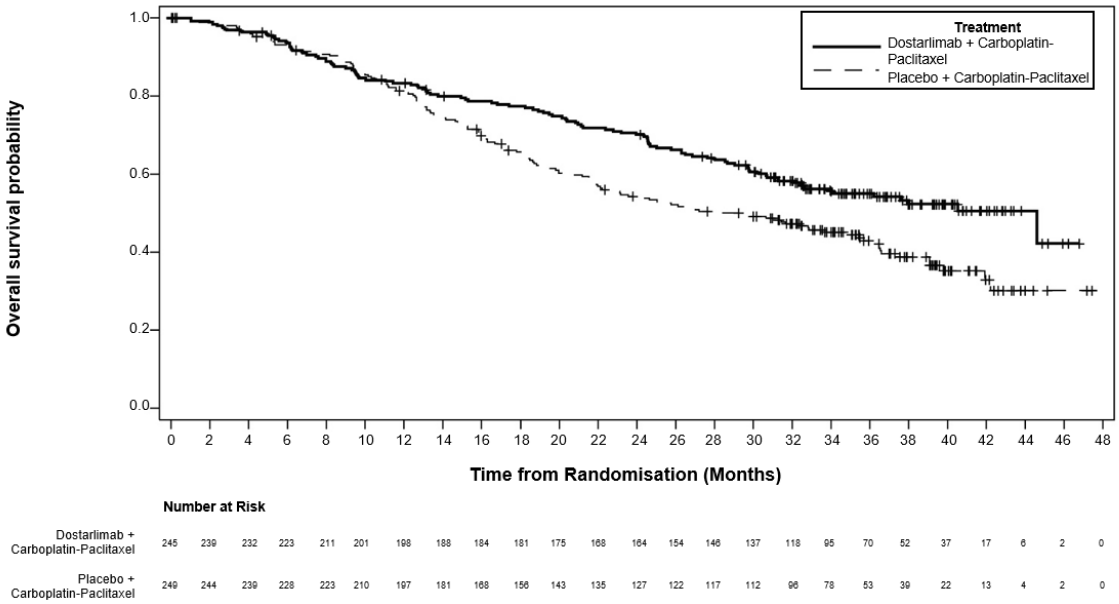


Figure 3. Kaplan-Meier curve of overall survival in all patients (overall population) with EC (RUBY study)



Patient-reported outcomes (PROs) were assessed using European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC) QLQ-C30 and EORTC QLQ-EN24. Throughout the first 6 dosing cycles of the study, quality of life was maintained in both the overall population and MMRp/MSS population with no notable differences between treatment arms. Patients in the dMMR/MSI-H population receiving dostarlimab plus carboplatin-paclitaxel demonstrated greater observed improvements as compared to placebo plus carboplatin-paclitaxel relative to baseline after the first 6 dosing

cycles in global quality of life, role function, social function, nausea, pain, and insomnia (assessed by a difference of ≥10 points between arms relative to the baseline assessment).

GARNET: patients with recurrent or advanced dMMR/MSI-H EC who have progressed on or after treatment with a platinum-containing regimen

The efficacy and safety of dostarlimab as monotherapy were investigated in GARNET, a multicentre, open-label, Phase 1 dose escalation study conducted in patients with recurrent or advanced EC that has progressed on or after treatment with a platinum-containing regimen.

The GARNET study included expansion cohorts in subjects with recurrent or advanced solid tumours who have limited available treatment options. Cohort A1 enrolled patients with mismatch repair deficient (dMMR) EC that has progressed on or after a platinum-containing regimen.

Patients received dostarlimab 500 mg every 3 weeks for 4 cycles followed by 1,000 mg every 6 weeks. Treatment continued until unacceptable toxicity or disease progression for up to two years. The major efficacy outcome measures were objective response rate (ORR) and duration of response (DOR) as assessed by blinded independent central radiologists' (BICR) review according to RECIST v1.1. The secondary endpoints included disease control rate (DCR) and PFS both assessed by BICR review according to RECIST v1.1; and OS.

All patients included in both the primary and secondary efficacy analysis set had a minimum follow-up period of 24 weeks from first dose, regardless of whether they had a post-treatment scan.

A total of 141 patients with dMMR EC were evaluated for efficacy in the GARNET study. Among these 141 patients, the baseline characteristics were: median age 65.0 years (50% age 65 or older); 76.6% White, 3.5% Asian, 2.8% Black; and Eastern Cooperative Oncology Group (ECOG) PS 0 (38.3%) or 1 (61.7%). The median number of prior therapies for recurrent or advanced endometrial cancer was one: 63% of patients had one prior line, 37% had two or more prior lines. Forty-eight patients (34%) received treatment only in the neoadjuvant or adjuvant setting before participating in the study.

The identification of dMMR/MSI-H tumour status was prospectively determined based on local testing.

Local diagnostic assays (IHC, PCR or NGS) available at the sites were used for the detection of the dMMR/MSI-H expression in tumour material. Most of the sites used IHC as it was the most common assay available.

Efficacy results are shown in Table 9 and Figure 4.

Table 9. Efficacy results in GARNET for patients with dMMR endometrial cancer

Endpoint	**Dostarlimab (N=141)**[a]
Primary endpoints	
Objective response rate (ORR)	
ORR n (%) (95% CI)	64 (45.4) (37.0, 54.0)
Complete response rate, n (%)	22 (15.6)

Partial response rate, n (%)	42 (29.8)
Duration of response (DOR)[b]	
Median in months	Not reached
Patients with duration ≥ 12 months, n (%)	51 (79.7)
Patients with duration ≥ 24 months, n (%)	28 (43.8)
Secondary endpoints	
Progression free Survival (PFS)	
Median in months (95% CI)[c]	5.6 (4.1, 16.6)
Number (%) of patients with event	83 (58.9)
Probability of PFS at 6-months, (95% CI)[c]	49.2% (40.6, 57.2)
Probability of PFS at 9-months, (95% CI)[c]	47.6% (39.0, 55.7)
Probability of PFS at 12-months, (95% CI)[c]	46.0% (37.4, 54.1)
Overall Survival (OS)	
Median in months	Not reached
Number (%) of patients with event	55 (39.0)
Disease control rate (DCR)[d]	
DCR n (%) (95% CI)	86 (60.3) (51.7, 68.4)

CI = Confidence interval

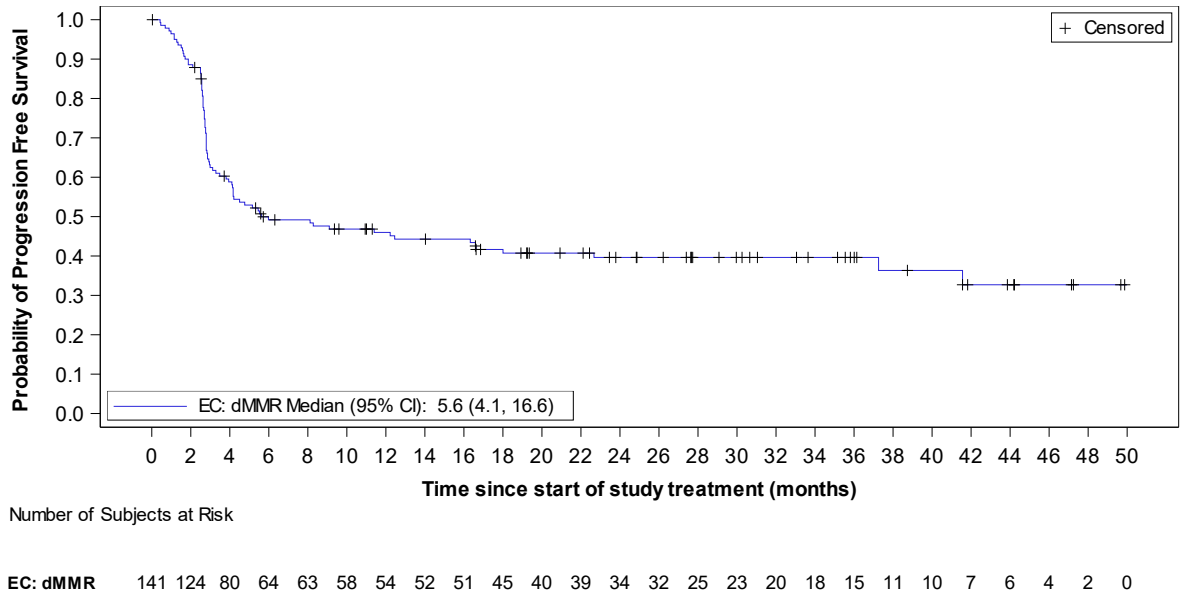
[a] Efficacy data with a median follow-up of 27.6 months (cut-off date 01 Nov 2021)

[b] For patients with a partial or complete response

[c] by Kaplan-Meier method

[d] includes patient with complete response, partial response and stable disease for at least 12 weeks

Figure 4. Kaplan-Meier Plot for Progression Free Survival per RECIST 1.1 - Based on BICR Assessment (Primary Efficacy Analysis Set) in patients with dMMR EC (N = 141)



Number of Subjects at Risk

EC: dMMR	141	124	80	64	63	58	54	52	51	45	40	39	34	32	25	23	20	18	15	11	10	7	6	4	2	0

Elderly patients

Of the 515 patients treated with dostarlimab monotherapy (IA1 GARNET population at time of data cut-off 01 March 2020), 51% were under 65 years, 38% were 65 75 years, and 12% were 75 years or older. Safety risks were not observed to be increased in older subjects compared to younger subjects.

In the 72 patients with dMMR/MSI-H EC (IA1 population at time of data cut-off 01 March 2020) in the efficacy analysis, the ORR by BICR (95 % CI) was 43.2 % (27.1 %, 60.5 %) in patients under 65 years and 48.6 % (31.4 %, 66.0 %) in patients 65 years and older.

In the 105 patients with dMMR/MSI-H EC (IA2 population at time of data cut-off 01 March 2020) in the efficacy analysis, the ORR by BICR (95 % CI) was 45.3 % (31.6 %, 59.6%) in patients under 65 years and 44.2% (30.5 %, 58.7 %) in patients 65 years and older.

Paediatric population

The safety and efficacy of dostarlimab in children and adolescents below 18 years of age have not been established.

5.2 Pharmacokinetic properties

The pharmacokinetics (PK) of dostarlimab was assessed as monotherapy and when administered in combination with chemotherapy.

Dostarlimab PK as monotherapy or in combination with chemotherapy were characterised using population PK analysis from 869 patients with various solid tumours, including 546 patients with EC. The PK of dostarlimab are approximately dose proportional. When dosed at the recommended therapeutic dose for monotherapy (500 mg administered intravenously every 3 weeks for 4 doses, followed by 1,000 mg every 6 weeks), or at the recommended therapeutic dose for combination with chemotherapy (500 mg administered intravenously every 3 weeks for 6 doses, followed by 1000 mg every 6 weeks), dostarlimab

shows an approximate two-fold accumulation (C_{min}) , consistent with the terminal half-life. The exposure of dostarlimab as monotherapy and/or in combination with chemotherapy was similar.

Absorption

Dostarlimab is administered via the intravenous route and therefore estimates of absorption are not applicable.

Distribution

The geometric mean volume of distribution of dostarlimab at steady state is approximately 5.81 L (CV% of 14.2%).

Biotransformation

Dostarlimab is a therapeutic mAb IgG4 that is expected to be catabolised into small peptides, amino acids, and small carbohydrates by lysosome through fluid-phase or receptor-mediated endocytosis. The degradation products are eliminated by renal excretion or returned to the nutrient pool without biological effects.

Elimination

The geometric mean clearance is 0.00681 L/h (CV% of 30.2%) at steady state. The geometric mean terminal half-life ($t_{1/2}$) at steady state is 23.2 days (CV% of 20.8%).

Dostarlimab clearance was estimated to be 7.8% lower when dostarlimab was given in combination with chemotherapy. There was no meaningful impact on dostarlimab exposure.

Linearity/non-linearity

Exposure (both maximum concentration [Cmax] and the area under the concentration-time curve, [AUC0-tau] and [AUC0-inf]) was approximately dose proportional.

Special patient populations

A population PK analysis of the patient data indicates that there are no clinically important effects of age (range: 24 to 86 years), sex or race, ethnicity, or tumour type on the clearance of dostarlimab. This population PK model also indicates that alterations in renal function (normal to moderate) and hepatic function (normal to mild impairment) do not alter the disposition of dostarlimab.

5.3 Preclinical safety data

Genotoxicity

No studies have been performed to assess the potential of dostarlimab for genotoxicity.

Carcinogenicity

No studies have been performed to assess the potential of dostarlimab for carcinogenicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium citrate dihydrate

Citric acid monohydrate

Arginine hydrochloride

Sodium chloride

Polysorbate 80

Water for injection

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store in a refrigerator 2°C to 8°C.

Do not freeze.

Store in the original carton until time of preparation in order to protect from light. The prepared dose may be stored either:

- At room temperature up to 25ºC for no more than 6 hours from the time of dilution until the end of infusion.
- Under refrigeration at 2°C to 8°C for no more than 24 hours from time of dilution until end of infusion. If refrigerated, allow the diluted solution to come to room temperature prior to administration.

<u>After preparation of infusion</u>

To reduce microbiological hazard, use as soon as practicable after reconstitution/preparation. If not used immediately, and infusion dilution was performed aseptically, in-use chemical and physical stability have been demonstrated for up to 24 hours at 2°C to 8°C and up to 6 hours at room temperature (up to 25°C) from time of vial puncture to the end of administration.

Due to the lack of preservative, the product must not be used beyond these storage times.

Product is for single use in one patient only, discard any residue.

6.5 Nature and contents of container and special equipment for use, administration or implantation

10 mL Type I borosilicate clear glass vial, with a grey chlorobutyl elastomer stopper laminated with fluoropolymer, sealed with an aluminium flip-off cap containing 500 mg dostarlimab.

6.6 Special precautions for disposal

Any unused medicine or waste material should be disposed of by taking to your local pharmacy.

Dilution

For the 500 mg dose, withdraw 10 mL of dostarlimab from a vial and transfer into an intravenous (IV) bag containing sodium chloride 9 mg/mL (0.9%) solution for injection, or glucose 50 mg/mL (5%) solution for injection. The final concentration of the diluted solution should be between 2 mg/mL and 10 mg/mL. The total volume of the infusion solution must not exceed 250 mL. This may require withdrawing a volume of diluent from the IV bag prior to adding a volume of dostarlimab into the IV bag.

- For example, if preparing a 500 mg dose in a 250 mL diluent IV bag, to achieve a 2 mg/mL concentration would require withdrawing 10 mL of diluent from the 250 mL IV bag. Then, 10 mL of dostarlimab would be withdrawn from the vial and transferred into the IV bag.

For the 1,000 mg dose, withdraw 10 mL of dostarlimab from each of two vials (withdraw 20 mL total) and transfer into an IV bag containing sodium chloride 9 mg/mL (0.9%) solution for injection or glucose 50 mg/mL (5%) solution for injection. The final concentration of the diluted solution should be between 4 mg/mL and 10 mg/mL. The total volume of the infusion solution must not exceed 250 mL. This may require withdrawing a volume of diluent from the IV bag prior to adding a volume of dostarlimab into the IV bag.

- For example, if preparing a 1,000 mg dose in a 250 mL diluent IV bag, to achieve a 4 mg/mL concentration would require withdrawing 20 mL of diluent from the 250 mL IV bag. Then, 10 mL of dostarlimab would be withdrawn from each of two vials, totaling 20 mL, and transferred into the IV bag.

Mix diluted solution by gentle inversion. Do not shake the final infusion bag. Discard any unused portion left in the vial.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

GlaxoSmithKline NZ Limited
Private Bag 106600
Downtown
Auckland
New Zealand

Phone: (09) 367 2900
Facsimile: (09) 367 2910

9. DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine: 6 July 2023

10. DATE OF REVISION OF THE TEXT

29 May 2025

Summary table of changes:

Section changed	Summary of new information
4.1	Update to indication for combination therapy
4.8	Update to safety data based on the RUBY clinical study Interim Analysis 2
5.1	Addition of efficacy data from the RUBY clinical study Interim Analysis 2 Update to text on Patient Reported Outcomes

Version 6.0