Jemperli

Versión GDSv08-IPIv07

Jemperli

Dostarlimab

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).

Clear to slightly opalescent colourless to yellow solution in a single-dose vial.

Clinical Information

Indications

Endometrial Cancer

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)/microsatellite instability-high (MSI-H) endometrial cancer (EC) that has progressed on or following prior treatment with a platinum-containing regimen in any setting.

Dosage and Administration

Pharmaceutical Form

Concentrate for solution for infusion.

Posology

JEMPERLI in Combination with Chemotherapy

When *JEMPERLI* is administered in combination with chemotherapy, refer to the full Prescribing Information for the combination products (*see also Clinical Studies*).

The recommended dose as combination therapy is 500 mg dostarlimab administered as an intravenous infusion over 30 minutes every 3 weeks for 6 cycles 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 *JEMPERLI* 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 Q6W
Week	1	4	7	10	13	16	19	25	31	

a Administer dostarlimab prior to chemotherapy on the same day.

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

JEMPERLI Monotherapy

The recommended dose as monotherapy is 500 mg *JEMPERLI* administered as an intravenous infusion over 30 minutes every 3 weeks for 4 cycles followed by 1000 mg every 6 weeks for all cycles thereafter.

The dosage regimen as monotherapy is presented in Table 2.

Table 2. Dosage regimen for *JEMPERLI* as monotherapy

500 mg once every 3 weeks (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	Continue dosing Q6W
Week	1	4	7	10	13	19	25	

3 weeks between Cycle 4 and Cycle 5

Administration of *JEMPERLI* 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 *Warnings and Precautions*.

Table 3. Recommended dose modifications for JEMPERLI

Immune-related adverse reactions	Severity gradea	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.
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 gradea**	**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.

Method of Administration

JEMPERLI is for intravenous infusion only. *JEMPERLI* should be administered by intravenous infusion using an intravenous infusion pump over 30 minutes.

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

For instructions on dilution of the medicinal product before administration, *see Use and Handling*.

Children

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

Elderly

No dose adjustment is recommended for patients who are 65 years of age or over. There are limited clinical data with *JEMPERLI* in patients 75 years of age or over.

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 Pharmacokinetics*).

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 Pharmacokinetics*).

Contraindications

None

Warnings and Precautions

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 *JEMPERLI*. 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, *JEMPERLI* 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 Posology, 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.

JEMPERLI 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 *JEMPERLI* (*see Adverse Reactions*). 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 *JEMPERLI* treatment modifications and corticosteroids (*see Posology*).

Immune-Related Colitis

JEMPERLI can cause immune-related colitis (*see Adverse Reactions*). Monitor patients for signs and symptoms of colitis and manage with *JEMPERLI* treatment modifications, anti-diarrhoeal agents and corticosteroids (*see Posology*).

Immune-Related Hepatitis

JEMPERLI can cause immune-related hepatitis. Monitor patients for changes in liver function periodically as indicated based on clinical evaluation and manage with *JEMPERLI* treatment modifications and corticosteroids (*see Posology*).

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 *JEMPERLI* (*see Adverse Reactions*).

Hypothyroidism and Hyperthyroidism

Immune-related hypothyroidism and hyperthyroidism (including thyroiditis) occurred in patients receiving *JEMPERLI*, 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 *Posology*.

Adrenal Insufficiency

Immune-related adrenal insufficiency occurred in patients receiving *JEMPERLI*. Patients should be monitored for clinical signs and symptoms of adrenal insufficiency. For symptomatic adrenal insufficiency, patients should be managed as recommended in *Posology*.

Immune-Related Nephritis

JEMPERLI can cause immune-related nephritis (*see Adverse Reactions*). Monitor patients for changes in renal function and manage with *JEMPERLI* treatment modifications and corticosteroids (*see Posology*).

Immune-Related Rash

Immune-related rash has been reported in patients receiving *JEMPERLI*, including pemphigoid (*see Adverse Reactions*). Patients should be monitored for signs and symptoms of rash. Exfoliative dermatologic conditions should be managed as recommended (*see Posology*). Events of Stevens-Johnson Syndrome or toxic epidermal necrolysis have been reported in patients treated with PD-1 inhibitors.

Caution should be used when considering the use of *JEMPERLI* 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 *JEMPERLI* other potential immune-related adverse reactions may occur. Clinically significant immune-related adverse reactions reported in less than 1% of patients treated with *JEMPERLI* 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 *Posology*.

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.

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

JEMPERLI can cause infusion-related reactions, which can be severe (*see Adverse Reactions*). For severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions, stop infusion and permanently discontinue *JEMPERLI* (*see Posology*).

Interactions

No drug-drug interaction studies have been conducted with *JEMPERLI*. Monoclonal antibodies (mAbs) such as *JEMPERLI* are not substrates for cytochrome P450 or drug transporters. *JEMPERLI* is not a cytokine and is unlikely to be a cytokine modulator. Additionally, pharmacokinetic (PK) drug-drug interaction of *JEMPERLI* with small molecule drugs is not expected. There is no evidence of drug-drug interaction mediated by non-specific clearance of lysosome degradation for antibodies.

Pregnancy and Lactation

Fertility

Fertility studies have not been conducted with dostarlimab.

Pregnancy

There are no available data on the use of *JEMPERLI* in pregnant women. Animal reproduction studies have not been conducted with dostarlimab to evaluate its effect on reproduction and foetal development. Based on its mechanism of action, *JEMPERLI* can cause foetal harm when administered to a pregnant woman. Animal models link the PD-1/PD-L1 signaling pathway with maintenance of pregnancy through induction of maternal immune tolerance to foetal 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 foetus. Advise women of the potential risk to a foetus.

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

Lactation

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 *JEMPERLI*.

Effects on Ability to Drive and Use Machines

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

Adverse Reactions

Clinical Trial Data

The safety of *JEMPERLI* as monotherapy has been evaluated in 605 patients with recurrent or advanced EC or other solid tumours in the GARNET study. Patients received doses of *JEMPERLI* 500 mg every 3 weeks for 4 cycles followed by 1000 mg every 6 weeks for all cycles thereafter.

The safety of *JEMPERLI* in combination with chemotherapy has been evaluated in 241 patients with primary advanced or recurrent EC in the RUBY study. Patients received doses of *JEMPERLI* 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 *JEMPERLI* monotherapy in the GARNET study, and who received dostarlimab in combination with chemotherapy in the RUBY study, are listed in Table 4. Additional adverse reactions identified from other clinical trials in patients with solid tumors receiving dostarlimab in combination with various types of anticancer therapies are also included in Table 4.

Adverse reactions known to occur with *JEMPERLI* or with combination therapy components 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 *JEMPERLI* is administered in combination, refer to the local labels for the respective combination therapy components prior to initiation of treatment.

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

System Organ Class	JEMPERLI monotherapy	JEMPERLI in combination therapy
Blood and lymphatic system disorders	Very common • Anaemia Uncommon • Autoimmune haemolytic anaemia	
Endocrine disorders	Very common • Hypothyroidism[a] Common • Hyperthyroidism, adrenal insufficiency Uncommon • Thyroiditis[c], hypophysitis[d]	Very common • Hypothyroidism[b] Common • Hyperthyroidism Uncommon • Thyroiditis, adrenal insufficiency
Metabolism and nutrition disorders	Uncommon • Type 1 diabetes mellitus, diabetic ketoacidosis	Uncommon • Type 1 diabetes mellitus
Nervous system disorders	Uncommon • Encephalitis, Myasthenia gravis	Uncommon • Myasthenic syndrome, Guillain-Barré syndrome[e]
Eye disorders	Uncommon • Uveitis[f]	Uncommon • Uveitis
Cardiac disorders		Uncommon • Myocarditis[g]
Respiratory, thoracic and mediastinal disorders	Common • Pneumonitis[h]	Common • Pneumonitis
Gastrointestinal disorders	Very common • Diarrhoea, nausea, vomiting Common • Colitis[i], pancreatitis[j], gastritis Uncommon • Oesophagitis	Common • Colitis[k], pancreatitis Uncommon • Immune mediated gastritis, vasculitis gastrointestinal
Hepatobiliary disorders	Common Hepatitis[l]	
Skin and subcutaneous tissue disorders	Very common Rash[m], pruritus	Very common • Rash[n], dry skin
Musculoskeletal and connective tissue disorders	Common • Myalgia Uncommon • Immune-mediated arthritis, polymyalgia rheumatica, immune-mediated myositis	Uncommon • Immune-mediated arthritis, myositis

System Organ Class	JEMPERLI monotherapy	JEMPERLI in combination therapy
Renal and urinary disorders	Uncommon • Nephritis[o]	
General disorders and administration site conditions	Very common • Pyrexia Common • Chills	Very common • Pyrexia Uncommon • Systemic inflammatory response syndrome
Investigations	Very common • Transaminases increased[p]	Very common • Alanine aminotransferase increased, aspartate aminotransferase increased
Injury, poisoning and procedural complications	Common • Infusion related reaction[q]	

[a] Includes hypothyroidism and autoimmune hypothyroidism
[b] Includes hypothyroidism and immune-mediated hypothyroidism
[c] Includes thyroiditis and autoimmune thyroiditis
[d] Includes hypophysitis and lymphocytic hypophysitis
[e] Includes Guillain-Barré syndrome and demyelinating polyneuropathy
[f] Includes uveitis and iridocyclitis
[g] Includes myocarditis and immune-mediated myocarditis
[h] Includes pneumonitis, interstitial lung disease, and immune-mediated lung disease
[i] Includes colitis, enterocolitis and immune-mediated enterocolitis
[j] Includes pancreatitis and pancreatitis acute
[k] Includes colitis and enteritis
[l] Includes hepatitis, autoimmune hepatitis and hepatic cytolysis
[m] Includes rash, rash maculo-papular, erythema, rash macular, rash pruritic, rash erythematous, rash papular, erythema multiforme, skin toxicity, drug eruption, toxic skin eruption, exfoliative rash and pemphigoid
[n] Includes rash and rash maculo-papular
[o] Includes nephritis and tubulointerstitial nephritis
[p] Includes alanine aminotransferase increased, aspartate aminotransferase increased, transaminases increased and hypertransaminasaemia
[q] Includes infusion related reaction and hypersensitivity.

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 *JEMPERLI* 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 *JEMPERLI* 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 *JEMPERLI* treatment-emergent ADA or treatment-emergent neutralising antibodies.

In the patients who developed ADAs, there was no evidence of altered pharmacokinetics, efficacy or safety of *JEMPERLI*.

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.

Pharmacological Properties

Pharmacodynamics

Pharmacotherapeutic group: Anti-neoplastic agents, monoclonal antibodies and antibody drug conjugates.

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 signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumours. Dostarlimab is a humanised mAb of the 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 when doubling the exposure of dostarlimab. 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.

Pharmacokinetics

The pharmacokinetics (PK) of dostarlimab were 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 1000 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 14.9%).

Metabolism

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 [C_{max}] and the area under the concentration-time curve, [AUC_{0-tau}] and [AUC_{0-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.

Clinical Studies

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/m^2 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/m^2 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. Treatment could continue beyond 3 years or beyond disease progression if the patient was clinically stable and considered to be deriving clinical benefit by the investigator. 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/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) and duration of response (DOR) 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 5 and Figures 1, 2 and 3. Dostarlimab plus carboplatin-paclitaxel demonstrated statistically significant improvements in PFS in both the dMMR/MSI-H and overall populations and OS in the overall population versus placebo plus carboplatin-paclitaxel.

Table 5. 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)

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)
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)
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)

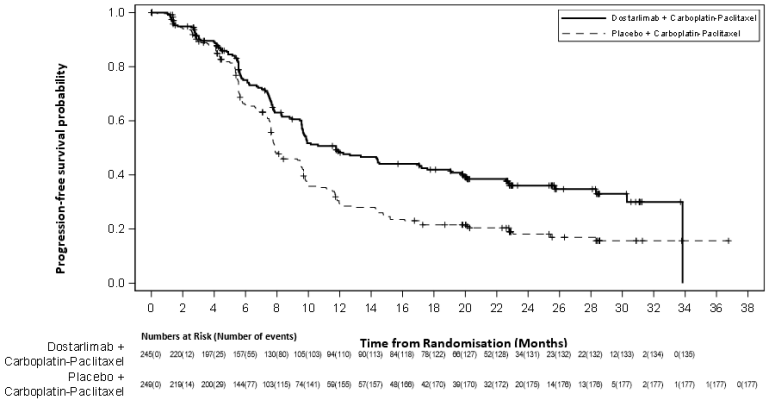


Figure 2. Kaplan-Meier curve of progression-free survival per investigator assessment in patients with dMMR/MSI-H EC (RUBY study)

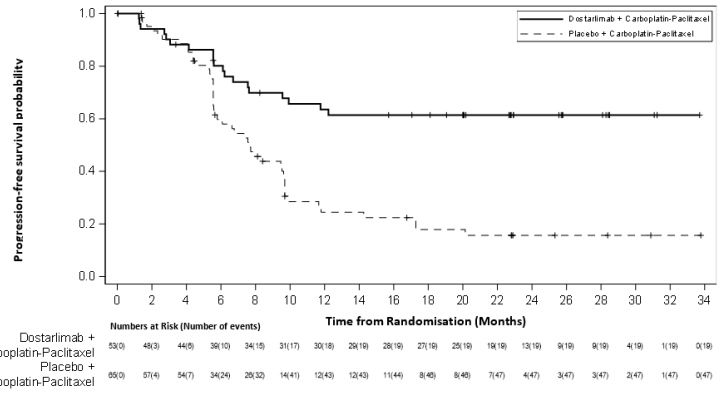
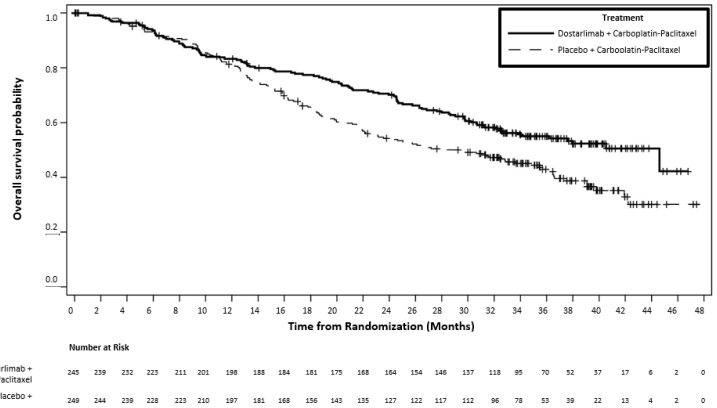


Figure 3. Kaplan-Meier curve of overall survival in all patients (overall population) with EC (RUBY study)



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 who have 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 dMMR/MSI-H EC who have progressed on or after a platinum-containing regimen.

Patients received dostarlimab 500 mg every 3 weeks for 4 cycles followed by 1000 mg every 6 weeks. Treatment continued until unacceptable toxicity or disease progression that was either symptomatic, rapidly progressive, required urgent intervention, or occurred with a decline in performance status. A maximum of 220 weeks (51 months) of treatment with dostarlimab was administered, and 24% of subjects who received any amount of dostarlimab received treatment >102 weeks (2 years). The primary efficacy outcome measures were ORR and DOR as assessed by 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 143 patients with dMMR/MSI-H EC were evaluated for efficacy in the GARNET study. Among these 143 patients, the baseline characteristics were: median age 65 years (52% age 65 or older); 77% White, 3% Asian, 3% Black; and Eastern Cooperative Oncology Group (ECOG) PS 0 (39%) or 1 (61%). The median number of prior lines of therapy was one: 63% of patients had one prior line, 37% had two or more prior lines. Forty-nine 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 6 and Figure 4.

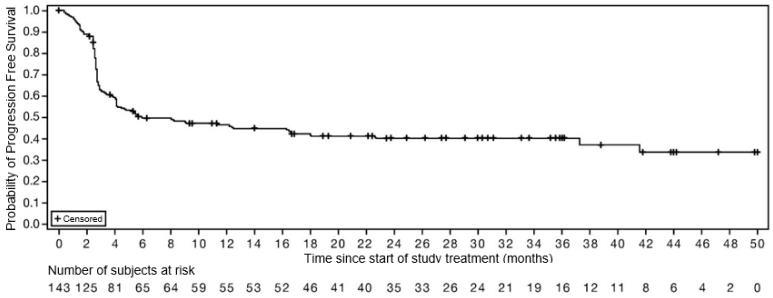
Table 6. Efficacy results in GARNET for patients with dMMR/MSI-H EC

Endpoint	Dostarlimab (N=143)[a]
Primary endpoints	
Objective response rate (ORR)	
ORR n (%) (95% CI)	65 (45.5) (37.1, 54.0)
Complete response rate, n (%)	23 (16.1)
Partial response rate, n (%)	42 (29.4)
Duration of response (DOR)b	
Median in months	Not reached
Patients with duration ≥ 12 months, n (%)	52 (80.0)

Endpoint	Dostarlimab (N=143)[a]
Patients with duration ≥ 24 months, n (%)	29 (44.6)
Secondary endpoints	
Progression-free Survival (PFS)	
Median in months (95% CI)[c]	6.0 (4.1, 18.0)
Number (%) of patients with event	83 (58.0)
Probability of PFS at 6 months, (95% CI)[c]	49.5% (41.0, 57.5)
Probability of PFS at 9 months, (95% CI)[c]	48.0% (39.4, 56.0)
Probability of PFS at 12 months, (95% CI)[c]	46.4% (37.8, 54.5)
Overall Survival (OS)	
Median in months	Not reached
Number (%) of patients with event	55 (38.5)
Disease control rate (DCR)d	
DCR n (%) (95% CI)	86 (60.1) (51.6, 68.2)

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 curve of progression-free survival per RECIST v1.1, BICR, in patients with dMMR/MSI-H EC (GARNET study) (N=143)



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.

Non-Clinical Information

Carcinogenesis/Mutagenesis

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

Reproductive Toxicology

Animal reproduction studies have not been conducted with dostarlimab. The PD-1/PD-L1 pathway is thought to be involved in maintaining tolerance to the foetus throughout pregnancy. Blockade of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to the foetus and to result in an increase in foetal loss.

Fertility

Animal fertility studies have not been conducted with dostarlimab. In 1-month and 3-month repeat-dose toxicology studies in monkeys, there were no notable effects in the male and female reproductive organs; however, many animals in these studies were not sexually mature.

Pregnancy

Animal Toxicology and/or Pharmacology

The nonclinical safety of dostarlimab was evaluated in 1-month and 3-month repeat-dose toxicity studies in Cynomolgus monkeys administered intravenous doses of 10, 30 or 100 mg/kg/week. No findings of toxicological significance were observed in both studies except that one male monkey dosed at 10 mg/kg/week was euthanized due to chronic, unresolved generalised skin findings in the 3-month study. The no observed adverse effect level (NOAEL) was ≥ 100 mg/kg in the 1-month study, corresponding to exposure multiples of 35 and 28 times the exposure in humans at doses of 500 and 1000 mg, respectively. The NOAEL was not determined in the 3-month study as the relationship of the premature euthanasia of the animal to dostarlimab could not be ruled out.

Pharmaceutical Information

List of Excipients

Trisodium citrate dihydrate

Citric acid monohydrate

L arginine hydrochloride

Sodium chloride

Polysorbate 80

Water for injection.

Shelf Life

Unopened Vial

The expiry date is indicated on the packaging.

After Preparation of Infusion

If not used immediately, 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.

Storage

The storage conditions are detailed on the packaging.

Do not freeze. Store in the original package in order to protect from light.

For storage conditions after dilution of the medicinal product, see *Use and Handling*.

Nature and Contents of Container

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 *JEMPERLI*.

Each carton contains one vial.

Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Use and Handling

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

JEMPERLI 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.

For the 500-mg dose, withdraw 10 mL of *JEMPERLI* 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 *JEMPERLI* 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 *JEMPERLI* would be withdrawn from the vial and transferred into the IV bag.

For the 1000-mg dose, withdraw 10 mL of *JEMPERLI* 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 to 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 *JEMPERLI* into the IV bag.

- For example, if preparing a 1000 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 *JEMPERLI* 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.

Storage

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.

Administration

JEMPERLI should be administered by intravenous infusion using an intravenous infusion pump over 30 minutes by a health care practitioner. 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.

JEMPERLI must not be administered as an intravenous push or bolus injection. Do not co-administer other medicinal products through the same infusion line.

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

Not all presentations are available in every country.

Version number: GDSv08-IPIv07
Date of issue: 13 August 2024