Summary of Product characteristics

1. NAME OF THE MEDICINAL PRODUCT

JEMPERLI

The marketing of Jemperli is subject to risk mangment plan (RMP) including Patient information card that emphasizes important safety information patients should be aware of before and during treatment.
Please explain to the patient the need to review the card before starting treatment.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of 10 mL concentrate for solution for infusion contains 500 mg of dostarlimab.

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

Dostarlimab is an anti-programmed cell death protein-1 (PD-1) immunoglobulin G4 (IgG4) humanised monoclonal antibody (mAb), produced by recombinant DNA technology in mammalian Chinese hamster ovary (CHO) cells.

Excipients with known effect
2 mg of polysorbate 80 in each dosage unit.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

Clear to slightly opalescent colourless to yellow solution, essentially free from visible particles.

The concentrate for solution for infusion has a pH of approximately 6.0 and an osmolality of approximately 300 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

JEMPERLI is indicated in combination with carboplatin and paclitaxel for the first-line treatment of adult patients with primary advanced or recurrent endometrial cancer (EC) and who are candidates for systemic therapy.

JEMPERLI is indicated as monotherapy for the treatment of adult patients with mismatch repair deficient (dMMR)/ microsatellite instability-high (MSI-H) recurrent or advanced EC that has progressed on or following prior treatment with a platinum-containing regimen.

4.2 Posology and method of administration

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

The identification of dMMR/MSI-H tumour status should be determined using a validated testing method such as IHC, PCR or NGS* (see section 5.1 for information on assays used in the studies).
*IHC=immunohistochemistry; PCR=polymerase chain reaction; NGS=next-generation sequencing.

Posology

JEMPERLI in combination with carboplatin and paclitaxel

When JEMPERLI is administered in combination with carboplatin and paclitaxel, refer to the full Prescribing Information for the combination products (see also section 5.1).

The recommended dose is 500 mg dostarlimab every 3 weeks in combination with carboplatin and paclitaxel every 3 weeks for 6 cycles followed by 1000 mg dostarlimab as monotherapy every 6 weeks for all cycles thereafter.

The dosage regimen in combination with carboplatin and paclitaxel is presented in Table 1.

Table 1. Dosage regimen for JEMPERLI in combination with carboplatin and paclitaxel

	500 mg once every 3 weeks in combination with carboplatin and paclitaxel[a] (1 Cycle = 3 weeks)						**1000 mg once every 6 weeks as monotherapy until disease progression or unacceptable toxicity, or for a duration of up to 3 years (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	

3 weeks between Cycle 6 and Cycle 7

[a] Administer dostarlimab prior to carboplatin and paclitaxel on the same day.

Administration of dostarlimab should continue according to the recommended schedule until disease progression or unacceptable toxicity, or for a duration of up to 3 years (see section 5.1).

JEMPERLI monotherapy

The recommended dose as monotherapy is 500 mg dostarlimab 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 dostarlimab should continue according to the recommended schedule until disease progression or unacceptable toxicity (see section 5.1).

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.

Table 3. Recommended dose modifications for JEMPERLI		
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 with 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 with 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[f], TEN[g], DRESSh)	Suspected	Withhold dose for any grade. Restart dosing if not confirmed and when toxicity resolves to grade 0 or 1.

Table 3. Recommended dose modifications for JEMPERLI		
Immune-related adverse reactions	**Severity grade[a]**	**Dose modification**
	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 (including but not limited to myositis, , sarcoidosis, autoimmune haemolytic anaemia, pancreatitis, iridocyclitis, uveitis, diabetic ketoacidosis, arthralgia, solid organ transplant rejection, graft-versus-host disease)	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 increase of 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.

[f] SJS = Stevens-Johnson syndrome
[g] TEN = toxic epidermal necrolysis
[h] DRESS = drug reaction with eosinophilia and systemic symptoms.

Patient Card

All prescribers of JEMPERLI should inform patients about the Patient Card, explaining what to do should they experience any symptom of immune-related adverse reactions. The physician will provide the Patient Card to each patient.

Special populations

Elderly
No dose adjustment is recommended for patients who are aged 65 years or over.

There are limited clinical data with dostarlimab in patients aged 75 years or over (see section 5.1).

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).

Hepatic impairment
No dose adjustment is recommended for patients with mild hepatic impairment. There are limited data in patients with moderate hepatic impairment and no data in patients with severe hepatic impairment (see section 5.2).

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

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 section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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. Patients should be monitored for symptoms and signs of immune-related adverse reactions. Haematological and clinical chemistries, including liver, kidney and thyroid function tests, should be evaluated 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, treatment with 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). Upon improvement to grade ≤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. Hormone replacement therapy for endocrinopathies should be instituted as warranted.

Treatment with 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). 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).

Immune-related colitis
Dostarlimab can cause immune-related colitis (see section 4.8). Patients should be monitored for signs and symptoms of colitis and managed with dostarlimab treatment modifications, anti-diarrhoeal agents and corticosteroids (see section 4.2).

Immune-related hepatitis
Dostarlimab can cause immune-related hepatitis (see section 4.8). Patients should be monitored for changes in liver function periodically as indicated, based on clinical evaluation and managed with dostarlimab treatment modifications and corticosteroids (see section 4.2).

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).

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.

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.

Immune-related nephritis
Dostarlimab can cause immune-related nephritis (see section 4.8). Patients should be monitored for changes in renal function and manage with dostarlimab treatment modifications and corticosteroids (see section 4.2).

Immune-related rash
Immune-related rash has been reported in patients receiving dostarlimab, including pemphigoid (see section 4.8). Patients should be monitored for signs and symptoms of rash. Exfoliative dermatologic conditions should be managed as recommended in section 4.2. 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 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.

Immune-related arthralgia
Immune-related arthralgia has been reported in patients receiving dostarlimab (see section 4.8). Patients should be monitored for signs and symptoms of arthralgia. Suspected immune-related arthralgia should be confirmed and other causes excluded. Patients should be managed with dostarlimab treatment modifications and corticosteroids (see section 4.2).

Other immune-related adverse reactions
Given the mechanism of action of dostarlimab other potential immune-related adverse reactions may occur, including potentially serious events [e.g. myositis, myocarditis, encephalitis, demyelinating neuropathy (including Guillain Barré syndrome), sarcoidosis]. Clinically significant immune-related adverse reactions reported in less than 1 % of patients treated with dostarlimab as monotherapy in clinical studies include encephalitis, autoimmune haemolytic anaemia, pancreatitis, iridocyclitis and uveitis. Patients should be monitored for signs and symptoms of immune-related adverse reactions and managed as described in section 4.2. Solid organ transplant rejection has been reported in the post-marketing 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
Dostarlimab can cause infusion-related reactions, which can be severe (see section 4.8). For severe (grade 3) or life-threatening (grade 4) infusion-related reactions, the infusion should be stopped and treatment should be permanently discontinued (see section 4.2).

Patients excluded from clinical studies
Patients with the following status were excluded from the GARNET study: Eastern Cooperative Oncology Group (ECOG) baseline performance score (PS) ≥ 2; uncontrolled central nervous system metastases or carcinomatous meningitis; other malignancies within the last 2 years; immunodeficiency or receiving immunosuppressive therapy within 7 days; active HIV, hepatitis B or hepatitis C infection; active autoimmune disease requiring systemic treatment in the past 2 years excluding replacement therapy; history of interstitial lung disease; or receiving live vaccine within 14 days.

Patients with the following status were excluded from the RUBY study: has a concomitant malignancy, or has a prior non-endometrial invasive malignancy who has been disease-free for <3 years or who received any active treatment in the last 3 years for that malignancy; uncontrolled central nervous system metastases or carcinomatous meningitis, or both; known history of HIV or active hepatitis B or hepatitis C; immunodeficiency or receiving immunosuppressive therapy within 7 days; considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease, or active infection requiring systemic therapy; or receiving a live vaccine within 30 days before first dose of study treatment, during study treatment, and for up to 180 days after receiving the last dose of study treatment.

After careful consideration of the potential increased risk, dostarlimab may be used with appropriate medical management in these patients.

Polysorbate 80 content

This medicinal product contains polysorbate 80 (see section 2), which may cause allergic reactions.

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per 500 mg dose, i.e. essentially 'sodium-free'. This medicinal product may be diluted in sodium chloride 9 mg/mL (0.9%) solution for infusion. This should be taken into consideration for patients on a controlled sodium diet (see section 6.6).

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. Monoclonal antibodies (mAb) such as dostarlimab are not substrates for cytochrome P450 or active substance transporters. Dostarlimab is not a cytokine and is unlikely to be a cytokine modulator. Additionally, pharmacokinetic (PK) interaction of dostarlimab with small molecule active substances is not expected. There is no evidence of interaction mediated by non-specific clearance of lysosome degradation for antibodies.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception

There is a risk associated with the administration of dostarlimab to women of childbearing potential. Women of childbearing potential must use effective contraception during treatment with dostarlimab and until 4 months after the last dose of dostarlimab.

Pregnancy

There are no or limited amount of data on the use of dostarlimab in pregnant women. Based on its mechanism of action, dostarlimab can cause foetal harmful pharmacological effects when administered during pregnancy.

Animal reproduction and development studies have not been conducted with dostarlimab; however, inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing foetus resulting in foetal death (see section 5.3). Human immunoglobulins (IgG4) are known to cross the placental barrier, and therefore, being an IgG4, dostarlimab has the potential to be transmitted from the mother to the developing foetus.

JEMPERLI is not recommended during pregnancy and in women of childbearing potential not using effective contraception.

Breast-feeding

It is unknown whether dostarlimab/metabolites are excreted in human milk.

A risk to the newborns/infants cannot be excluded.

JEMPERLI should not be used during breast-feeding and breast-feeding should be avoided for at least 4 months after the last dose of dostarlimab.

Fertility

Fertility studies have not been conducted with dostarlimab (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile
Dostarlimab is most commonly associated with immune-related adverse reactions. Most of these, including severe reactions, resolved following initiation of appropriate medical therapy or withdrawal of dostarlimab (see "Description of selected adverse reactions" below).

Dostarlimab in monotherapy

The safety of dostarlimab has been evaluated in 605 patients with EC or other advanced solid tumours who received dostarlimab monotherapy in the GARNET study, including 153 patients with advanced or recurrent dMMR/MSI-H EC. Patients received doses of 500 mg every 3 weeks for 4 cycles followed by 1000 mg every 6 weeks for all cycles thereafter.

In patients with advanced or recurrent solid tumours (N = 605), the most common adverse reactions (> 10 %) were anaemia (28.6 %), diarrhoea (26.0 %), nausea (25.8 %), vomiting (19.0 %), arthralgia (17.0 %), pruritus (14.2 %), rash (13.2 %), pyrexia (12.4 %), aspartate aminotransferase increased (11.2 %) and hypothyroidism (11.2 %). JEMPERLI was permanently discontinued due to adverse reactions in 38 (6.3 %) patients; most of them were immune-related events. Adverse reactions were serious in 11.2 % of patients; most serious adverse reactions were immune-related adverse reactions (see section 4.4).

The safety profile for patients with dMMR/MSI-H EC in the GARNET study (N=153) was not different from that of the overall monotherapy population presented in Table 4.

Dostarlimab in combination with carboplatin and paclitaxel

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

In patients with primary advanced or recurrent EC (N = 241), the most common adverse reactions (≥ 10 %) were rash (23.2 %), rash maculopapular (14.5%), hypothyroidism (14.5 %), pyrexia (12.9 %), alanine aminotransferase increased (12.9 %), aspartate aminotransferase increased (12.0 %) and dry skin (10.0 %). JEMPERLI was permanently discontinued due to adverse reactions in 12 (5.0 %) patients; most were immune-related events. Adverse reactions were serious in 5.8 % of patients. The most frequent (>1 %) serious adverse reaction was pyrexia (2.9 %). The most frequent (>10 %) immune-related adverse reaction was hypothyroidism (12.0 %), with maculo-papular rash (1.2 %) the most frequent (>1 %) immune-related adverse reaction leading to treatment discontinuation (see section 4.4).

Tabulated list of adverse reactions

Adverse reactions reported in clinical trials of dostarlimab as a monotherapy or in combination with chemotherapy are listed in Table 4 by system organ class and by frequency. The frequencies of adverse reactions listed in the dostarlimab monotherapy column are based on all-cause adverse event frequency identified in 605 patients with advanced or recurrent solid tumours from the GARNET study exposed to dostarlimab monotherapy for a median duration of treatment of 24 weeks (range: 1 week to 229 weeks). Unless otherwise stated, the frequencies of adverse reactions listed in the dostarlimab in combination with chemotherapy column are based on all-cause adverse event frequency identified in 241 patients with primary advanced or recurrent EC from the RUBY study exposed to dostarlimab in combination with carboplatin and paclitaxel for a median duration of treatment of 43 weeks (range: 3 to 193 weeks). For additional safety information when dostarlimab is administered in combination with carboplatin and paclitaxel, refer to the respective Prescribing Information for the combination products.

Adverse reactions known to occur with dostarlimab as monotherapy, or with carboplatin or paclitaxel given alone, may occur during treatment with these medicinal products in combination, even if these reactions were not reported in clinical studies with dostarlimab in combination with carboplatin and paclitaxel. These 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 (≥ 1/1000 to < 1/100); rare (≥ 1/10000 to < 1/1000); very rare (< 1/10000); and not known (cannot be estimated from the available data).

Table 4: Adverse reactions in patients treated with dostarlimab

	Dostarlimab monotherapy	**Dostarlimab in combination with chemotherapy**
Blood and lymphatic system disorders		
Very common	Anaemia[a]	
Endocrine disorders		
Very common	Hypothyroidism*[b]	Hypothyroidism[e]
Common	Hyperthyroidism*, adrenal insufficiency*	Hyperthyroidism
Uncommon	Thyroiditis*[c], hypophysitis[d]	Thyroiditis, adrenal insufficiency
Metabolism and nutrition disorders		
Uncommon	Type 1 diabetes mellitus, diabetic ketoacidosis	Type 1 diabetes mellitus
Nervous system disorders		
Uncommon	Encephalitis, myasthenia gravis	Myasthenic syndrome† Guillain-Barré syndrome†[f]
Eye disorders		
Uncommon	Uveitis[g]	Uveitis
Cardiac disorders		
Uncommon		Myocarditis†[h]
Respiratory, thoracic and mediastinal disorders		
Common	Pneumonitis*[i]	Pneumonitis
Gastrointestinal disorders		
Very common	Diarrhoea, nausea, vomiting	
Common	Colitis*[j], pancreatitis[k], gastritis	Colitis†[l], pancreatitis
Uncommon	Oesophagitis	Immune mediated gastritis†, vasculitis gastrointestinal†

	Dostarlimab monotherapy	Dostarlimab in combination with chemotherapy
Hepatobiliary disorders		
Common	Hepatitis*[m]	
Skin and subcutaneous tissue disorders		
Very common	Rash*[n], pruritus	Rash[o], dry skin
Musculoskeletal and connective tissue disorders		
Very common	Arthralgia*	
Common	Myalgia	
Uncommon	Immune-mediated arthritis, polymyalgia rheumatica, immune-mediated myositis	Immune-mediated arthritis, myositis[†]
Renal and urinary disorders		
Uncommon	Nephritis*[p]	
General disorders and administration site conditions		
Very common	Pyrexia	Pyrexia
Common	Chills	
Uncommon		Systemic inflammatory response syndrome[†]
Investigations		
Very common	Transaminases increased[q]	Alanine aminotransferase increased, aspartate aminotransferase increased
Injury, poisoning and procedural complications		
Common	Infusion-related reaction*[r]	

[†] Includes events identified from other clinical trials in patients with solid tumours receiving dostarlimab in combination with various types of anticancer therapies.

[*] See section 'Description of selected adverse reactions.'

[a] Includes anaemia and autoimmune haemolytic anaemia

[b] Includes hypothyroidism and autoimmune hypothyroidism

[c] Includes thyroiditis and autoimmune thyroiditis

[d] Includes hypophysitis and lymphocytic hypophysitis

[e] Includes hypothyroidism and immune-mediated hypothyroidism

[f] Includes Guillain-Barré syndrome and demyelinating polyneuropathy

[g] Includes uveitis and iridocyclitis

[h] Includes myocarditis and immune-mediated myocarditis

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

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

[k] Includes pancreatitis and pancreatitis acute

[l] Includes colitis and enteritis

[m] Includes hepatitis, autoimmune hepatitis and hepatic cytolysis

[n] 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

[o] Includes rash and rash maculo-papular

[p] Includes nephritis and tubulointerstitial nephritis

[q] Includes transaminases increased, alanine aminotransferases increased, aspartate aminotransferases increased and hypertransaminasaemia

[r] Includes infusion-related reaction and hypersensitivity.

Description of selected adverse reactions

The selected adverse reactions described below are based on the safety of dostarlimab in a combined monotherapy safety database of 605 patients in the GARNET study in patients with EC or other advanced solid tumours. Immune-related adverse reactions were defined as events of grade 2 and

above; the frequencies below exclude grade 1 events. The management guidelines for these adverse reactions are described in section 4.2.

Immune-related adverse reactions (see section 4.4)

Immune-related pneumonitis
Immune-related pneumonitis occurred in 14 (2.3 %) patients, including grade 2 (1.3 %), grade 3 (0.8 %) and grade 4 (0.2 %) pneumonitis. Pneumonitis led to discontinuation of dostarlimab in 8 (1.3 %) patients.

Systemic corticosteroids (prednisone ≥ 40 mg per day or equivalent) were required in 11 (78.6%) patients experiencing pneumonitis. Pneumonitis resolved in 11 (78.6 %) patients.

Immune-related colitis
Colitis occurred in 8 (1.3 %) patients, including grade 2 (0.7 %) and grade 3 (0.7 %) colitis. Colitis did not lead to discontinuation of dostarlimab in any patients.

Systemic corticosteroids (prednisone ≥ 40 mg per day or equivalent) were required in 5 (62.5 %) patients. Colitis resolved in 5 (62.5 %) patients experiencing colitis.

Immune-related hepatitis
Hepatitis occurred in 3 (0.5 %) patients, all of which were grade 3. Systemic corticosteroids (prednisone ≥ 40 mg per day or equivalent) were required in 2 (66.7 %) patients. Hepatitis led to discontinuation of dostarlimab in 1 (0.2%) patient and resolved in 2 of the 3 patients.

Immune-mediated endocrinopathies
Hypothyroidism occurred in 46 (7.6 %) patients, all of which were grade 2. Hypothyroidism did not lead to discontinuation of dostarlimab and resolved in 17 (37.0 %) patients.

Hyperthyroidism occurred in 14 (2.3 %) patients, including grade 2 (2.1 %) and grade 3 (0.2 %). Hyperthyroidism did not lead to discontinuation of dostarlimab and resolved in 10 (71.4 %) patients.

Thyroiditis occurred in 3 (0.5 %) patients; all were grade 2. None of the events of thyroiditis resolved; there were no discontinuations of dostarlimab due to thyroiditis.

Adrenal insufficiency occurred in 7 (1.2 %) patients, including grade 2 (0.5 %), and grade 3 (0.7 %). Adrenal insufficiency resulted in discontinuation of dostarlimab in 1 (0.2 %) patient and resolved in 4 (57.1 %) patients.

Immune-mediated nephritis
Nephritis, including tubulointerstitial nephritis, occurred in 3 (0.5 %) patients; all were grade 2. Systemic corticosteroids (prednisone ≥ 40 mg per day or equivalent) were required in 2 (66.7 %) patients experiencing nephritis. Nephritis led to discontinuation of dostarlimab in 1 (0.2 %) patient and resolved in all 3 patients.

Immune-related rash
Immune-related rash (rash, rash maculo-papular, rash macular, rash pruritic, pemphigoid, drug eruption, skin toxicity, toxic skin eruption) occurred in 31 (5.1 %) patients, including grade 3 in 9 (1.5 %) patients receiving dostarlimab. The median time to onset of rash was 57 days (range 2 days to 1485 days). Systemic corticosteroids (prednisone ≥ 40 mg per day or equivalent) were required in 9 (29.0 %) patients experiencing rash. Rash led to discontinuation of dostarlimab in 1 (0.2 %) patient and resolved in 24 (77.4 %) patients.

Immune-related arthralgia
Immune-related arthralgia occurred in 34 (5.6 %) patients. Grade 3 immune-related arthralgia was reported in 5 (0.8 %) patients receiving dostarlimab. The median time to onset of arthralgia was 94.5 days (range 1 day to 840 days). Systemic corticosteroids (prednisone ≥ 40 mg per day or

equivalent) were required in 3 (8.8 %) patients experiencing arthralgia. Arthralgia led to discontinuation of dostarlimab in 1 (0.2 %) patient and resolved in 19 (55.9 %) patients experiencing arthralgia.

Infusion-related reactions
Infusion-related reactions including hypersensitivity occurred in 6 (1.0 %) patients, including grade 2 (0.3 %) and grade 3 (0.2 %) infusion-related reactions. All patients recovered from the infusion-related reaction.

Immune checkpoint inhibitor class effects

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

Immunogenicity
In the GARNET study, anti-drug antibodies (ADA) were tested in 315 patients who received dostarlimab and the incidence of dostarlimab treatment-emergent ADAs was 2.5 %. Neutralising antibodies were detected in 1.3 % of patients. Co-administration with carboplatin and paclitaxel did not affect dostarlimab immunogenicity. In the RUBY study, of the 225 patients who were treated with dostarlimab in combination with carboplatin and paclitaxel 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 ADAs, there was no evidence of altered efficacy or safety of dostarlimab.

Elderly population

Of the 605 patients treated with dostarlimab monotherapy, 51.6 % were under 65 years, 36.9 % were 65 to less than 75 years, and 11.5 % were 75 years or older. Of the 241 patients treated with dostarlimab in combination with carboplatin-paclitaxel, 52.3% were under 65 years, 36.5% were 65 to less than 75 years, and 11.2% were 75 years or older. No overall differences in safety were reported between elderly (≥ 65 years) and younger patients (< 65 years).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/.
Additionally, you should also report to GSK Israel (il.safety@gsk.com).

4.9 Overdose

If overdose is suspected, the patient should be monitored for any signs or symptoms of adverse reactions or effects, and appropriate symptomatic treatment instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-neoplastic agents, monoclonal antibodies and antibody drug conjugates, ATC code: L01FF07

Mechanism of action

Dostarlimab is a humanised mAb of the IgG4 isotype that binds to PD-1 receptors and blocks the interactions of binding with its ligands PD-L1 and PD-L2. The inhibition of PD-1 pathway-mediated immune response results in reactivation of T-cell function such as proliferation, cytokine production, and cytotoxic activity. Dostarlimab potentiates T-cell responses, including anti-tumour immuno responses through blockade of PD-1 binding to PD-L1 and PD-L2. In syngeneic mouse tumour models, blocking PD-1 activity resulted in decreased tumour growth.

Clinical efficacy and safety

RUBY: Randomised controlled study of dostarlimab in combination with carboplatin and paclitaxel in treatment of adult patients with primary advanced or recurrent EC

The efficacy and safety of dostarlimab in combination with carboplatin-paclitaxel were investigated in 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). 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. After a median follow-up of 37 months, 27 out of 245 patients randomised to dostarlimab plus carboplatin-paclitaxel have received treatment for >3 years (cut-off date 22 Sep 2023).

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). Prior radiation was not permitted within 21 days of study treatment excluding palliative radiotherapy which was permitted within up to 1 week of study treatment.

The primary efficacy outcome measures were progression-free survival (PFS) assessed by the investigator according to RECIST v1.1 in patients with dMMR/MSI-H primary advanced or recurrent EC and in all patients (overall population) with primary advanced or recurrent EC, and overall survival (OS) in all patients (overall population) with primary advanced or recurrent EC.

A total of 494 patients with EC were evaluated for efficacy in the RUBY study. Baseline demographics and characteristics were: median age 65 years (38% aged 65 to 74 years and 13% aged 75 years or older); 77% White, 12% Black, 3% Asian; ECOG PS 0 (63%) or 1 (37%); primary stage III 19%, primary stage IV 34%, recurrent EC 48%; endometrioid carcinoma 55%, mixed carcinoma 4%, carcinosarcoma 9%, clear cell carcinoma 3 %, serous carcinoma 21%, other 8%; and prior surgery 91%, prior radiotherapy (28%), prior anti-cancer therapy (20%).

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 and 2. PFS is presented at the primary analysis with median follow up of 25 months. OS results are based on the second interim analysis with a median follow up of 37 months. Dostarlimab plus carboplatin-paclitaxel demonstrated statistically significant improvements in PFS by investigator (dMMR/MSI-H and overall populations) and OS (overall population) versus placebo plus carboplatin-paclitaxel.

Table 5: Efficacy results in RUBY for overall population and patients with dMMR/MSI-H EC

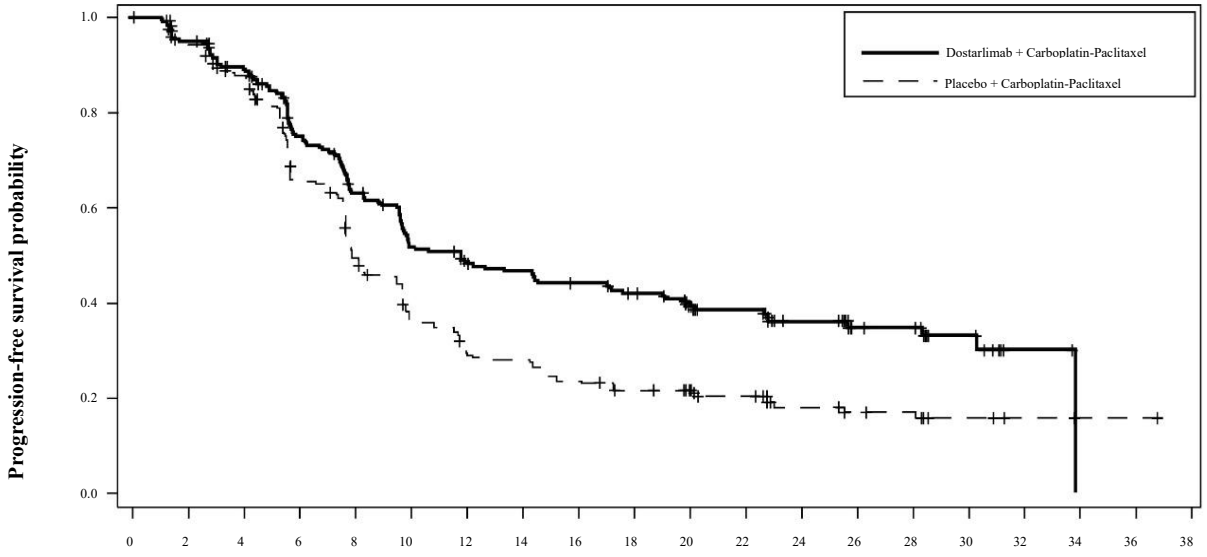
Endpoint	**Overall population**		**dMMR/MSI-H population**	
	Dostarlimab + carboplatin-paclitaxel (N=245)	**Placebo + carboplatin-paclitaxel (N=249)**	**Dostarlimab + carboplatin-paclitaxel (N=53)**	**Placebo + carboplatin-paclitaxel (N=65)**
Progression free-survival (PFS)[a]				
Median in months (95% CI)[b]	11.8 (9.6, 17.1)	7.9 (7.6, 9.5)	Not reached (11.8, NR)	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	
Overall survival (OS)[e, f]				
Median in months (95% CI)[b]	44.6 (32.6, NR)	28.2 (22.1, 35.6)	Not reached (NR, NR)	31.4 (20.3, NR)
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[g]	
Objective response rate (ORR)[h]				
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)
Duration of response (DOR)[h, i]				
Median in months (95% CI)[b]	10.6 (8.2, 17.6)	6.2 (4.4, 6.7)	Not reached (10.1, NR)	5.4 (3.9, 8.1)

CI: confidence interval; NA = not applicable; NR = not reached.
[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] OS is a primary endpoint for the overall population only.
[f] Median follow-up of 37 months (cut-off date 22 Sept 2023).
[g] Not statistically significant since no hypothesis testing was performed for overall survival in the dMMR/MSI-H population.
[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 mismatch repair proficient (MMRp)/ microsatellite stable (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).

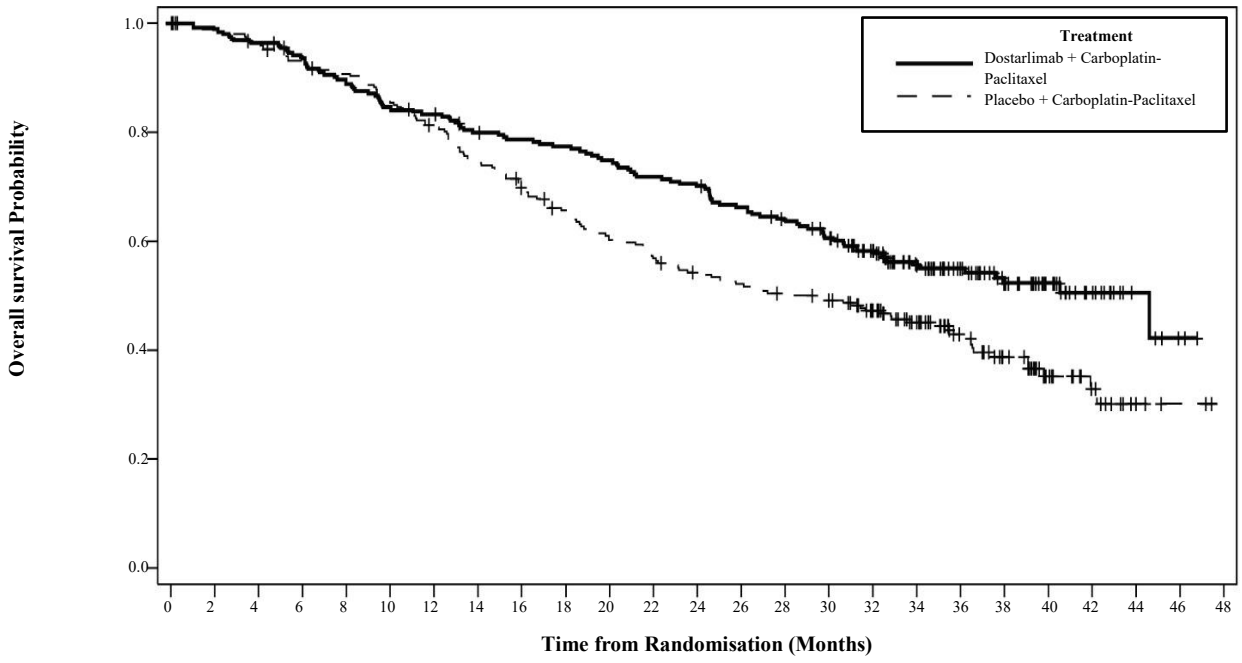
Figure 1. Kaplan-Meier curve of progression-free survival per investigator assessment in all patients (overall population) with EC (RUBY study)



Numbers at Risk (Number of events)

Dostarlimab + Carboplatin-Paclitaxel	245(0)	220(12)	197(25)	157(55)	130(80)	105(103)	94(110)	90(113)	84(118)	78(122)	66(127)	52(128)	34(131)	23(132)	22(132)	12(133)	2(134)	0(135)	
Placebo + Carboplatin-Paclitaxel	249(0)	219(4)	200(29)	144(77)	103(115)	74(141)	59(155)	57(157)	48(166)	42(170)	39(170)	32(172)	20(175)	14(176)	13(176)	5(177)	2(177)	1(177)	1(177)	0(177)

Figure 2. Kaplan-Meier curve of overall survival in all patients (overall population) with EC (RUBY study)



Number at Risk

Dostarlimab + Carboplatin-Paclitaxel	245	239	232	223	211	201	198	188	184	181	175	168	164	154	146	137	118	95	70	52	37	17	6	2	0
Placebo + Carboplatin-Paclitaxel	249	244	239	228	223	210	197	181	168	156	143	135	127	122	117	112	96	78	53	39	22	13	4	2	0

GARNET: adult 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 monotherapy were investigated in the GARNET study, a multicentre, uncontrolled, multiple parallel cohort, open-label study. The GARNET study included expansion cohorts in patients 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 500 mg dostarlimab every 3 weeks for 4 cycles followed by 1000 mg dostarlimab 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 response evaluation criteria in solid tumours (RECIST) v 1.1. The efficacy population was defined as patients who had measurable disease by BICR at baseline and had minimum of 24 weeks follow-up or had less than 24 weeks of follow-up and discontinued due to adverse events or disease progression.

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 of 65 years (52 % aged 65 years or older); 77 % white, 3.5 % Asian, 2.8 % black; and ECOG PS 0 (39 %) or 1 (61 %). At the time of diagnosis, 21 % of the patients with dMMR/MSI-H EC were FIGO Stage IV. At study entry (the most recent FIGO stage), 67 % of the patients were FIGO Stage IV. 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.

Table 6 includes the efficacy data for the 143 patients. The overall median treatment duration in weeks was 34 (range 2 to 220). Twenty four percent of patients who received any amount of dostarlimab received treatment >102 weeks (2 years).

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

Endpoint	**Results (N=143)**[a]
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)
Patients with duration ≥ 24 months, n (%)	29 (44.6)
Disease control rate (DCR)[c]	

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] Includes patient with complete response, partial response and stable disease for at least 12 weeks.

Efficacy and PD-L1 status

Clinical activity was observed regardless of tumour PD-L1 combined positive score (CPS) by IHC. The relationship between PD-L1 status and efficacy was analysed post-hoc in patients with available tissue samples (N = 81) among the efficacy population from Cohort A1 of the GARNET study using a data cut-off date of 01 March 2020. Among 23 patients with PD-L1 CPS < 1 %, ORR was 30.4 % (7/23, 95 % CI 13.2, 52.9) and among 58 patients with PD-L1 CPS ≥ 1 %, ORR was 55.2 % (32/58, 95 % CI 41.5, 68.3).

Elderly patients

Of the 108 patients treated with dostarlimab in the GARNET study efficacy population, 50.0 % were older than 65 years.

Consistent results were observed in the elderly population, where the ORR by BICR (95% CI) was 42.6 % (29.2 %, 56.8 %) in patients ≥ 65 years.

5.2 Pharmacokinetic properties

The pharmacokinetics (PK) of dostarlimab were assessed as a monotherapy and when administered in combination with carboplatin and paclitaxel.

Dostarlimab monotherapy or in combination with carboplatin and paclitaxel was characterised using population PK analysis from 869 patients with various solid tumours, including 546 patients with EC. 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 carboplatin and paclitaxel (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 ($t_{1/2}$). The exposure of dostarlimab as monotherapy and/or in combination with carboplatin and paclitaxel was similar.

Absorption

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

Distribution

The mean volume of distribution of dostarlimab at steady state is approximately 5.8 L (CV % of 14.9 %).

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 mean clearance is 0.007 L/h (CV % of 30.2 %) at steady state. The $t_{1/2}$ 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 carboplatin and paclitaxel. 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, [$AUC_{0\text{-}tau}$] and [$AUC_{0\text{-}inf}$]) was approximately dose proportional.

Pharmacokinetic/pharmacodynamic relationship

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 interleukin 2 (IL-2) production functional assay was maintained throughout the dosing interval at the recommended therapeutic dosing regimen.

Special populations

A population PK analysis of the patient data indicates that there are no clinically important effects of age (range: 24 to 86 years), gender or race, ethnicity, or tumour type on the clearance of dostarlimab.

Renal impairment

Renal impairment was evaluated based on the estimated creatinine clearance [CL_{CR} mL/min] (normal: $CL_{CR} \geq 90$ mL/min, n = 305; mild: CL_{CR} = 60-89 mL/min, n = 397; moderate: CL_{CR} = 30-59 mL/min, n = 164; severe: CL_{CR} = 15-29 mL/min, n = 3 and ESRD: $CL_{CR} < 15$ mL/min, n = 1). The effect of renal impairment on the clearance of dostarlimab was evaluated by population pharmacokinetic analyses in patients with mild or moderate renal impairment compared to patients with normal renal function. No clinically important differences in the clearance of dostarlimab were found between patients with mild or moderate renal impairment and patients with normal renal function. There are limited data in patients with severe renal impairment.

Hepatic impairment

Hepatic impairment was evaluated as defined using the US National Cancer Institute criteria of hepatic dysfunction by total bilirubin and AST (Normal: total bilirubin (TB) & AST < = upper limit of normal (ULN), n = 772; mild: TB > ULN to 1.5 ULN or AST > ULN, n = 92; and moderate: TB > 1.5-3 ULN, any AST, n = 5). The effect of hepatic impairment on the clearance of dostarlimab was evaluated by population pharmacokinetic analyses in patients with mild hepatic impairment compared to patients with normal hepatic function. No clinically important differences in the clearance of dostarlimab were found between patients with mild hepatic impairment and normal hepatic function. There are limited data in patients with moderate hepatic impairment and no data in patients with severe hepatic impairment.

5.3 Preclinical safety data

Nonclinical data reveal no special hazard for humans based on repeat-dose toxicity studies of duration up to 3 months in the cynomolgus monkey. No studies have been performed to assess the potential of dostarlimab for carcinogenicity or genotoxicity. Animal reproduction and development toxicity studies have not been conducted with dostarlimab. 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. These

results indicate a potential risk that administration of dostarlimab during pregnancy could cause foetal harm, including increased rates of abortion or stillbirth.

No notable effects on the male and female reproductive organs were observed in monkeys in the 1-month and 3-month repeat-dose toxicology studies; however, these results may not be representative at all of the potential clinical risk because of the immaturity of the reproductive system of animals used in the studies. Therefore, fertility toxicity remains unknown.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-arginine hydrochloride
Trisodium citrate dihydrate
Sodium chloride
Citric acid monohydrate
Polysorbate 80
Water for injection

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vial

The expiry date of the vaccine is indicated on the label and packaging.

After dilution

If not used immediately, chemical and physical in-use stability has been demonstrated for 24 hours at 2 °C – 8 °C and 6 hours at room temperature (up to 25 °C) from the time of preparation/dilution until the end of administration.

6.4 Special precautions for storage

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

Do not freeze.

Store in the original package in order to protect from light.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 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 dostarlimab.

Each carton contains one vial.

6.6 Special precautions for disposal and other handling

Preparation/dilution

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 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 intravenous 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 intravenous bag, to achieve a 2 mg/mL concentration would require withdrawing 10 mL of diluent from the 250 mL intravenous bag. Then, 10 mL of JEMPERLI would be withdrawn from the vial and transferred into the intravenous bag.

For the 1000 mg dose, withdraw 10 mL of JEMPERLI from each of two vials (withdraw 20 mL total) and transfer into an intravenous 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 JEMPERLI into the intravenous bag.

-For example, if preparing a 1000 mg dose in a 250 mL diluent intravenous bag, to achieve a 4 mg/mL concentration would require withdrawing 20 mL of diluent from the 250 mL intravenous bag. Then, 10 mL of JEMPERLI would be withdrawn from each of two vials, totaling 20 mL, and transferred into the intravenous 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 25 ºC 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 JEMPERLI.

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.

7. MANUFACTURER

GlaxoSmithKline Trading Services Limited , Dublin, Ireland

8. LICENSE HOLDER

GlaxoSmithKline (Israel) Ltd., 25 Basel St., Petach Tikva

9. LICENSE NUMBER

169-79-36883

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