Dostarlimab (Endometrial)

Indication
Advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency after platinum-based chemotherapy
(NICE TA779)

ICD-10 codes
C54

Regimen details
Cycle 1-4

Day	Drug	Dose	Route
1	Dostarlimab	500mg every 3 weeks	IV infusion

Cycle 5 onwards

Day	Drug	Dose	Route
1	Dostarlimab	1000mg every 6 weeks	IV infusion

Cycle frequency
Cycles 1-4: 21 days
Cycle 5 onwards: 42 days

Number of cycles
Until disease progression or unacceptable toxicity

Administration
Dostarlimab is administered in sodium chloride 0.9% at a concentration between 2-10mg/mL over 30 minutes.

For moderate (Grade 2) reactions, the infusion may be restarted at 50% of the original infusion rate with close monitoring. If reaction recurs despite adequate premedication treatment should be permanently discontinued.

Pre-medication
If a patient experiences a Grade 2 infusion related reaction the following premedication regimen is recommended 1-2 hours prior to future dostarlimab infusions:
Chlorphenamine 10mg IV
Paracetamol 500mg-1g PO/IV

Emetogenicity
This regimen has low emetogenic potential – refer to local policy

Additional supportive medication
Nil

Extravasation
Dostarlimab is neutral (group 1)

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U&E (including creatinine)	14 days
LFT	14 days
Thyroid function	14 days
Calcium	14 days
Glucose	14 days
Cortisol	14 days

Investigations – pre subsequent cycles

Investigation	Validity period
FBC	7 days
U&E (including creatinine)	7 days
LFT	7 days
Thyroid function	Every other cycle
Calcium	As clinically indicated
Glucose	Prior to each cycle for the first 4 cycles then every other cycle
Cortisol	Prior to each cycle for the first 4 cycles then every other cycle

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	Limit
Neutrophil count	≥ 1.0 x 10^9/L
Platelets	≥ 75 x 10^9/L
Creatinine Clearance (CrCl)	≥ 30mL/min
Bilirubin	≤ 1.5 x ULN
ALT/AST	≤ 2.5 x ULN (or ≤ 5 x ULN if liver metastases)
Alkaline Phosphatase	< 5 x ULN

Dose modifications

Dose reduction is not recommended. Dosing delay or discontinuation may be required to manage toxicity.

- **Haematological toxicity**

Discuss with prescriber/consultant if:
Neutrophils <1.0 x 10^9/L
Platelets <75 x 10^9/L

- **Renal impairment**

No dose adjustment is recommended for patients with mild or moderate renal impairment. There is limited data in patients with severe renal impairment (<30ml/min) or those undergoing dialysis.

- **Hepatic impairment**

No dose adjustment is recommended for patients with mild hepatic impairment (bilirubin < 1.5 x ULN or ALT <2.5 x ULN). There is limited data in patients with moderate or severe hepatic impairment.

Derangement of LFTs during treatment may indicate immunotherapy-induced hepatitis. See below for management.

- **Other toxicities**

Immune-related Adverse Reactions

Toxicity	Definition	Dose adjustment
Colitis	Grade 2-3	Withhold dose. Restart dosing when toxicity resolves to grade 0-1.
	Grade 4	Permanently discontinue
Hepatitis	Grade 2: AST/ALT 3-5 x ULN *or* Bilirubin 1.5-3 x ULN	Withhold dose. Restart dosing when toxicity resolves to grade 0-1.
	Grade ≥ 3 AST/ALT > 5 x ULN *or* Bilirubin > 3 x ULN	Permanently discontinue*
Type 1 diabetes mellitus (T1DM)	Grade 3 to 4 hyperglycaemia	Withhold dose. Restart dosing in appropriately managed, clinically and metabolically stable patients.
Hypophysitis or adrenal insufficiency	Grade 2 to 4	Withhold dose. Restart dosing when toxicity resolves to Grade 0 or 1. Permanently discontinue for recurrence or worsening whilst on adequate hormonal therapy.
Hypothyroidism or hyperthyroidism	Grade 3 to 4	Withhold dose. Restart dosing when toxicity resolves to grade 0 to 1.
Pneumonitis	Grade 2	Withhold dose. Restart dosing when toxicity resolves to grade 0 to 1. If Grade 2 recurs, permanently discontinue.
	Grade 3 to 4	Permanently discontinue
Nephritis	Grade 2	Withhold dose. Restart dosing when toxicity resolves to grade 0 to 1.
	Grade 3 to 4	Permanently discontinue
Immune-mediated rash	Grade 3	Withhold dose. Restart dosing when toxicity resolves to grade 0 to 1.
	Grade 4	Permanently discontinue
Other immune-related adverse reactions (e.g. myositis, myocarditis, encephalitis, Guillain Barré syndrome, pancreatitis, uveitis, diabetic ketoacidosis, anaemia, arthralgia)	Grade 3	Withhold dose. Restart dosing when toxicity resolves to grade 0 to 1.
	Grade 4	Permanently discontinue

*unless patient has liver metastases and commenced treatment with AST/ALT 3-5 x ULN. In these patients if AST/ALT increases by ≥ 50% from baseline and lasts for a week or more then treatment should be discontinued.

Recurrence of immune-related adverse reactions at Grade 3 or 4, after resolution of the previous reaction to ≤ Grade 1, requires permanent discontinuation of treatment (excluding pneumonitis – see above).

Infusion related reactions

Dostarlimab can cause infusion-related reactions which can be severe. For severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions or a recurrent moderate (Grade 2) reactions despite adequate premedication, the infusion should be stopped and treatment permanently discontinued.

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Pneumonitis
Colitis
Hepatitis
Nephritis
Endocrinopathies
Pancreatitis

- **Frequently occurring side effects**

Anaemia
Arthralgia
Nausea
Diarrhoea
Vomiting
Pruritis, rash
Pyrexia
Hypothyroidism

- **Other side effects**

Uveitis

Significant drug interactions – for full details consult product literature/ reference texts

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.

Corticosteroids: use of systemic corticosteroids at baseline, before starting dostarlimab, should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of dostarlimab. However, systemic corticosteroids or other immunosuppressants can be used after starting dostarlimab to treat immune-related adverse reactions.

Additional comments

Patients should be issued with the Jemperli (dostarlimab) patient card and keep this with them at all times for at least 4 months after the last dose of dostarlimab.

References

- National Institute for Health and Clinical Excellence TA779 accessed 31st March 2022 via www.nice.org.uk
- Summary of Product Characteristics Dostarlimab - Jemperli®(GSK) accessed 31st March 2022 via www.medicines.org.uk
- Oaknin, A., *et al.* Safety and anti-tumour activity of dostarlimab in patients with advanced or recurrent DNA mismatch repair deficient/microsatellite instability-high (dMMR/MSI-H) or proficient/stable (MMRp/MSS) endometrial cancer: interim results from GARNET – a phase 1, single-arm study. J Immunother Cancer 2022:10(1)

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