SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Dostarlimab
Endometrial Adenocarcinoma

PROTOCOL REF: MPHADOST
(Version No. 1.0)

Approved for use in:

Dostarlimab as monotherapy is approved for the treatment of recurrent, locally advanced or metastatic endometrial adenocarcinoma that exhibits mismatch repair deficiency (dMMR) or microsatellite instability-high (MSI-H) providing the following conditions are met:

- ECOG performance status or 0 or 1
- Progressed on or following platinum-containing regimen for recurrent/locally advanced/metastatic disease.
- Patient has no symptomatic brain or leptomeningeal metastases
- No previous treatment with anti-PD-1, anti-PD-L2, anti-CD137 or CTLA-4 unless dostarlimab via an early access scheme
- Maximum treatment break is 12 weeks after expected 3- or 6-weekly cycle length, if longer then a treatment break approval form is required to be submitted

*******Blueteq registration is required*******

Exclusions

History of pneumonitis, organ transplantation, HIV infection, active hepatitis B or C infection
Active infection requiring systemic treatment
Less than 4 weeks from major surgery
History of clinically severe autoimmune disease (can proceed with immunotherapy if well controlled autoimmune disease at the discretion of the clinical team, this needs to be documented on Meditech)
Patient with active CNS disease or carcinomatosis meningitis

Dosage:

Cycles 1-4:

Drug	Dose	Route	Frequency
Dostarlimab	**500 mg**	IV infusion	Day 1 only of a 3 week cycle

Cycle 5 onwards:

Drug	Dose	Route	Frequency
Dostarlimab	**1000 mg**	IV infusion	Day 1 only of a 6 week cycle

- Treatment will be continued until disease progression or unacceptable toxicity
- Guidelines for permanent discontinuation or withholding of doses are contained in dose modifications

Patient Counselling Points

Women of childbearing potential should use effective contraception throughout treatment and for at least 4 months following the last dose of Dostarlimab.

Contact the triage team for the following:

- New or worsening cough, chest pain or shortness of breath
- Diarrhoea or severe abdominal pain (with or without blood/mucous)
- Jaundice, severe nausea or vomiting, or easy bruising or bleeding
- Persistent or unusual headache, extreme weakness, dizziness or fainting, or vision changes
- Monitor for signs of infection / sepsis

Emetogenic risk:

Mildly emetogenic.

Supportive treatments:

Metoclopramide 10mg orally up to three times a day when required for nausea and vomiting. To be taken for a maximum of 5 consecutive days.

Extravasation risk:

Monoclonal antibody- treat symptomatically, no sepsis recommendations

Refer to Clatterbridge Policy '[Prevention and Management of Extravasation Injuries]' for further guidance.

Dosing in renal and hepatic impairment(Prior to start of treatment ONLY/Baseline):

Renal	Dostarlimab	CrCl ≥ 30 ml/min- No dose adjustment. CrCl < 30ml/min- limited data. Use with caution.

Hepatic	Dostarlimab	Mild (bilirubin > ULN to 1.5 ULN or AST > ULN) No dose adjustment.
		Moderate (bilirubin >1.5-3 x ULN and normal or high AST) to Severe (Total bilirubin >3 x ULN and normal or high AST) Limited data. Use with caution

Interactions:

There are no known drug interactions. For full details please refer to the SmPC.

Treatment schedule:

Cycle 1 to 4

Day	Drug	Dose	Route	Diluent and rate
1	**Dostarlimab**	**500 mg**	**IV**	Sodium Chloride 0.9% 100mL over 30 minutes

Every 3 weeks

Cycle 5 onwards

Day	Drug	Dose	Route	Diluent and rate
1	**Dostarlimab**	**1000 mg**	**IV**	Sodium Chloride 0.9% 250mL over 30 minutes

Every 6 weeks until progression or unacceptable toxicity

Routine prophylaxis against infusion related reactions (IRRs) is not required. However the patient should be monitored during the infusion, and treatment given if necessary.

If patient experiences Grade 1 or more IRR refer to 'Dose Modification and Toxicity Management' section in conjunction with the CCC Hypersensitivity; Management Prevention Policy for guidance on management.

Main toxicities:

Dostarlimab is commonly associated with immune-related adverse reactions. For full details on assessment and management of immune-relate toxicities refer to immune-oncology toxicity specific guidance for adverse event management.

Report any suspected adverse reactions via the Yellow Card Scheme (YSC) Website.

Dostarlimab	
General and administration disorders	Pyrexia, chills and infusion-related reaction
Blood and lymphatic system disorders	Anaemia
Endocrine disorders	Hypothyroidism, Hyperthyroidism, adrenal insufficiency
Respiratory disorders	Pneumonitis
Gastrointestinal disorders	Nausea, diarrhoea, vomiting, colitis, pancreatitis
Hepatobiliary disorders	Hepatitis, transaminsases increased
Skin disorders	Pruritus, rash
Musculoskeletal disorders	Arthralgia, Myalgia
Renal and urinary disorders	Nephritis
Other immune-related adverse reactions	Including but not limited to myositis, myocarditis, encephalitis, demyelinating neuropathy including Guillain Barré syndrome, sarcoidosis, autoimmune haemolytic anaemia, pancreatitis, iridocyclitis, uveitis, diabetic ketoacidosis, arthralgia, solid organ transplant rejection, graft-versus-host disease

Investigations and treatment plan:

If suspicion of endocrinopathies: request TSH, T4, T3, ACTH, cortisol, LH, FSH, testosterone (men) and prolactin (women)

	Pre	Cycle 1	Cycle 2	Prior to Cycle 3	Cycle 3	Cycle 4	Cycle 5	Ongoing
Informed Consent	X							
Clinical Assessment	X			X				First review by the end of the 2nd 3-weekly cycle of treatment then 3 monthly or as clinically indicated
SACT Assessment (to include PS and toxicities)	X	X	X		X	X	X	Every cycle
Immunotherapy bloods as per Meditech order set: FBC, U&E/renal profile, Magnesium, LFTs, TFTs, cortisol, blood glucose	X	X	X		X	X	X	Every cycle
Fatigue profile as per Meditech order set: B12, folate, Iron profile, vitamin D, Zinc, Testosterone (men only), ESR	X							At baseline then if clinically indicated
CrCl (Cockcroft and Gault)	X	X	X		X	X	X	Every cycle only if baseline CrCL <40ml/min or creatinine increases above 1.5x upper limit of normal

CT scan	X					X		Every 12 weeks or if clinically indicated
Trop-T, CK, pro-BNP	X*							As clinically indicated ***At baseline for all Renal and Melanoma** (ECG to be reviewed by clinical team)
ECG	X*							
Full set of observations (BP, heart rate, temperature, respiratory rate and O2 saturations)		X	X		X	X	X	Every cycle
Weight recorded	X	X	X		X	X	X	Every cycle
Height	X							

Pregnancy test if applicable

Dose Modifications and Toxicity Management:

Haematological toxicity:

- Dosing delay or discontinuation may be required based on individual safety and tolerability.
- Guidelines for permanent discontinuation or withholding of doses are contained in dose modifications.
- Detailed guidelines for the management of immune-related adverse reactions are provided in the CCC Immuno-Oncology toxicity specific guidance for adverse event management

Proceed on day 1 if:-

Platelets Cycle 2 onwards[a]	Neutrophils	Serum Creatinine	Bilirubin	AST/ALT	Alkaline Phosphatase	TSH and Free T4
≥ 75 x 10^9/L	≥ 1.0 x 10^9/L	≤1.5 x ULN[b] or baseline	<3 x ULN	<5 x ULN	<5 x ULN	Within range or no change from base line

- **[a]Platelets must be within normal range prior to Cycle 1.**
- [b]ULN = upper limit of normal

Non-Haematological toxicity:

Detailed guidelines are provided in the CCC clinical network immunotherapy acute oncology guidelines. Systemic high-dose corticosteroid with or without additional immunosuppressive therapy may be required for management of severe immune-related adverse reactions.

Infusion-related reactions (IRRs)

Treatment-related adverse reaction	Severity	Treatment modification

Infusion-related reactions (IRRs)	Grade 1 **Mild transient reaction**; infusion interruption not indicated; intervention not indicated	Reduce infusion rate by 50%
	Grade 2 **Therapy or infusion interruption indicated but responds promptly to symptomatic treatment** (e.g., antihistamines, steroids, IV fluids); prophylactic medications indicated for 24 hrs or less	Withhold until adverse reactions recover to Grade 0-1; restart infusion at a 50% slower rate
	Recurrence of Grade 2 despite adequate premedication	Permanently discontinue
	Grade 3 **Prolonged** (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae OR Grade 4 **Life-threatening consequences**; urgent intervention indicated	

Other Toxicities

Toxicity Grade	**Action**
Grade 1 Mild	Continue treatment increase monitoring and provide symptomatic treatment.
Grade 2 Moderate	Withhold treatment until resolved to ≤ grade 1. Refer to Immuno-Oncology toxicity specific guidance for adverse event management.

Grade 3 and Grade 4 Severe	Withhold treatment. Treatment will be permanently discontinued for any unresolving grade 3-4, severe or life-threatening adverse reaction at the treating clinician's discretion. Refer to Immuno-Oncology toxicity specific guidance for adverse event management.

References:

1. JEMPERLI 500 mg concentrate for solution for infusion SmPC, GlaxoSmithKline UK. Last Updated 26th July 2021
2. NICE TA779 Dostarlimab for previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency. Published 16th March 2022.
3. Oaknin, A., et al. (2020). Clinical activity and safety of the anti–programmed death 1 monoclonal antibody dostarlimab for patients with recurrent or advanced mismatch repair–deficient endometrial cancer: A nonrandomized phase 1 clinical trial. *JAMA oncology*, 6(11), 1766-1772.
4. Oaknin, A., et al. (2020). LBA36 Safety and antitumor activity of dostarlimab in patients (pts) with advanced or recurrent DNA mismatch repair deficient (dMMR) or proficient (MMRp) endometrial cancer (EC): Results from GARNET. *Annals of Oncology*, 31, S1166.

Circulation/Dissemination

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Version History

		Author name and designation	Summary of main changes
		Sophie Hughes, Advanced Pharmacist	New Regimen Protocol V1.0