Chemotherapy Protocol

GYNACOLOGICAL CANCER

Dostarlimab

Regimen

- Endometrial - Dostarlimab

Indication

- Dostarlimab is indicated for patients with;
  - proven histological diagnosis of endometrial carcinoma
  - recurrent or locally advanced or metastatic disease
  - tumour has a documented presence of microsatellite instability-high (MSI-H) or DNA mismatch repair deficiency (dMMR) confirmed by validated testing
  - progressive disease during or following previous platinum-based therapy for recurrent/locally advanced/metastatic endometrial carcinoma
  - no symptomatic brain or leptomeningeal metastases
  - who has not received any prior treatment with an anti-PD-1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody unless the patient has been treated with dostarlimab in a company early access scheme and all other treatment criteria on this form apply

- ECOG performance status (PS) of 0 or 1

Toxicity

Drug	Adverse Effect
Dostarlimab	Immune mediated effects including colitis, hepatitis, diabetes, adrenal insufficiency, thyroid disorders, pneumonitis, nephritis and rash among others

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Monitoring

- FBC, LFTs and U&Es prior to day 1 and 22 for the first two cycles and then day 1 from cycle 3 onwards

Dose Modifications

The dose modifications listed are for haematological, liver and renal function and some drug specific toxicities. Dose adjustments may be necessary for other toxicities as well.

Dostarlimab belongs to the immunotherapy class of cancer treatments. Autoimmune toxicities are most frequently noted and can be life threatening. If autoimmune toxicities occur delaying treatment should be considered while investigations or treatments are organised. Some, but not all, toxicities mandate cessation of treatment. Please seek guidance from relevant site-specific specialist teams or oncologists / haematologists with experience of prescribing these agents.

Haematological

Consider blood transfusion or erythropoietin if patient symptomatic of anaemia or has a haemoglobin of less than 8g/dL (80g/L)

There is little need to adjust the dose of dostarlimab for haematological toxicity.

Dose escalation or reduction is not recommended.

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

Hepatitis is a known adverse effect of dostarlimab. During treatment the following dose reductions apply.

Drug	Bilirubin µmol/L		ALT/AST units/L	Dose (% of original dose)
Dostarlimab	1.5 - 3xULN	or	3-5xULN	Withhold dose. Restart treatment when toxicity resolves to grade 0 or 1
	Greater than 3xULN	or	Greater than 5xULN	Permanently discontinue

The dostarlimab should be permanently discontinued when the hepatic injury does not improve to at least NCI-CTC grade 1 within 12 weeks of the last dose, the corticosteroid dose cannot be reduced to 10mg or less of prednisolone or equivalent per day within 12 weeks or any NCI-CTC grade 3 or above reaction.

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

Severe nephritis or renal dysfunction has been observed with dostarlimab treatment. Patients should be monitored for signs and symptoms of nephritis and renal dysfunction. Most patients present with asymptomatic increases in serum creatinine. Disease-related aetiologies should be ruled out. During treatment the following dose reductions apply.

Drug	NCI-CTC Grade	Dose (% of original dose)
Dostarlimab	2	Withhold dose. Restart dosing when toxicity resolves to grade 0-1.
	3 or above	Permanently discontinue

For NCI-CTC Grade 2 or 3 serum creatinine elevation, dostarlimab should be withheld and consideration given to prescribing of corticosteroids. Upon improvement to NCI-CTC grade 1

initiate corticosteroid taper over at least one month. Dostarlimab may be resumed when the reaction remains at NCI-CTC grade 1 or below following tapering of the corticosteroid.

The dostarlimab should be permanently discontinued when the serum creatinine does not improve to at least NCI-CTC grade 1 within 12 weeks of the last dose, the corticosteroid dose cannot be reduced to 10mg or less of prednisolone or equivalent per day within 12 weeks or in the case of a recurrent NCI-CTC grade 3 reaction.

For NCI-CTC Grade 4 serum creatinine elevation, dostarlimab must be permanently discontinued, and corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.

Other

Dose reductions or interruptions in therapy are not necessary for those toxicities that are considered unlikely to be serious or life threatening. For example, alopecia, altered taste or nail changes.

Dostarlimab is associated with inflammatory adverse reactions resulting from increased or excessive immune activity, likely to be related to its pharmacology.

Immune-related adverse reactions, which can be severe or life-threatening, may involve the gastrointestinal, liver, skin, nervous, endocrine, or other organ systems. Most occur during treatment, however, onset months after the last dose has been reported. Unless an alternate aetiology has been identified, diarrhoea, increased stool frequency, bloody stool, LFT elevations, rash and endocrinopathy must be considered inflammatory and durvalumab-related. Early diagnosis and appropriate management are essential to minimise life threatening complications.

Dostarlimab should be permanently discontinued for:

- any NCI-CTC grade 3 or 4 pneumonitis or hepatitis;
- any other life threatening NCI-CTC grade 4 reaction (including colitis and renal impairment);
- any recurrence of a severe or NCI-CTC grade 3 reaction;
- any persistent NCI-CTC grade 2 or 3 treatment-related adverse reaction that does not recover to grade 1 or resolve within 12 weeks after the last dose.

Immune-related adverse reaction	Severity (NCI-CTC Grade)	Treatment modification
Immune-related pneumonitis (see below for further detailed guidance)	Grade 2	Withhold until symptoms resolve, radiographic abnormalities improve, and management with corticosteroids is complete. If there is a recurrence of a grade 2 pneumonitis permanently discontinue the dostarlimab
	Grade 3 or 4	Permanently discontinue
Immune- related colitis (see below for further detailed	Grade 2 or 3	Withhold until symptoms resolve to grade 0 or 1 and management with corticosteroids, if needed, is complete

guidance)	Grade 4	Permanently discontinue
Immune-related diabetes mellitus	Grade 3 or 4	Withhold dose. Restart dosing in appropriately managed, clinically and metabolically stable patients.
Immune-related hypophysitis or adrenal insufficiency (see below for adrenal crisis management and further detailed guidance)	Grade 2 or above	Withhold dose. Restart dosing when toxicity resolves to grade 0 to 1. Permanently discontinue for recurrence or worsening while on adequate hormonal therapy.
Immune-related thyroid disease	Grade 3 or above	Withhold dose. Restart dosing when toxicity resolves to grade 0 to 1. Isolated hypothyroidism can be managed with replacement therapy, without treatment interruption or corticosteroids.
Immune-related rash	Grade 3 rash	Withhold dose until symptoms resolve and management with corticosteroids is complete
	Grade 4 rash	Permanently discontinue

Do not resume dostarlimab if the patient is still receiving immunosuppressive doses of corticosteroids or other immunosuppressive therapy.

Treatment with dostarlimab should be permanently discontinued for grade 2 or 3 immune-related adverse reactions that persist in spite of treatment modifications or a reduction of corticosteroid dose to 10 mg prednisolone, or equivalent, cannot be achieved.

Endocrine

Dostarlimab can cause inflammation of the endocrine system organs, specifically hypophysitis, hypopituitarism, adrenal insufficiency, and hypothyroidism. This may present with nonspecific symptoms resembling other causes such as brain metastasis or underlying disease.

If there are any signs of adrenal crisis such as severe dehydration, hypotension, or shock, immediate administration of intravenous corticosteroids with mineralocorticoid activity is recommended, the patient must be evaluated for presence of sepsis or infections. If there are signs of adrenal insufficiency but the patient is not in crisis, further investigations should be considered including laboratory and imaging assessment. Evaluation of laboratory results to assess endocrine function may be performed before corticosteroid therapy is initiated. If pituitary imaging or laboratory tests of endocrine function are abnormal, a short course of high-dose corticosteroid therapy is recommended to treat the gland inflammation. The scheduled dose of dostarlimab should be omitted. It is currently unknown if the corticosteroid treatment reverses the gland dysfunction. Appropriate hormone replacement should also be

initiated. Long-term hormone replacement therapy may be necessary.

Once symptoms or laboratory abnormalities are controlled and overall patient improvement is evident, treatment with dostarlimab may be resumed and initiation of corticosteroid taper should be based on clinical judgment.

Hypophysitis can present as a diffuse, heterogenous enlargement of the pituitary on a brain MRI but can be completely normal. When hypophysitis with pituitary dysfunction is suspected, blood tests including thyroid stimulating hormone (TSH), free T4, adrenocorticotropic stimulating hormone, cortisol, leutinizing hormone, and follicle-stimulating hormone should be obtained in women, and the first four plus testosterone in men. Typically the anterior pituitary axis is involved, affecting thyroid, gonadal, and adrenal function, but isolated axis dysfunction can be seen. Hypophysitis will cause low free T4 as well as TSH. Hypophysitis with clinically significant adrenal insufficiency and hypotension, dehydration, and electrolyte abnormalities such as hyponatremia and hyperkalemia constitutes adrenal crisis. Hospitalization and intravenous steroids with mineralocorticoid activity, such as methylprednisolone, should be initiated while waiting for laboratory results. Infection and sepsis should be ruled out with appropriate cultures and imaging. Prednisolone 1 mg/kg by mouth should be administered if patients are clinically stable. Steroids can usually be tapered over 30 days to achieve physiologic replacement levels. Thyroid hormone and/or testosterone replacement therapy may not be permanent, as the need for those hormones may wane over months in some patients. Cortisone replacement may also not be permanent in a modest portion of patients.

Gastrointestinal

Gastro-intestinal immune reactions include diarrhoea, increased frequency of bowel movements, abdominal pain or haematochezia, with or without fever. Diarrhoea or colitis occurring after initiation of dostarlimab must be promptly evaluated to exclude infectious or other alternate causes. Immune-related colitis is often associated with evidence of mucosal inflammation, with or without ulcerations and lymphocytic and neutrophilic infiltration.

NCI-CTC grade 1 diarrhoea or suspected mild colitis may continue on dostarlimab. Symptomatic treatment and close monitoring are advised.

For a NCI-CTC grade 2 - 3 diarrhoea or colitis withhold the dostarlimab and administer corticosteroids. Upon improvement to NCI-CTC grade 1 begin to taper the corticosteroid over a period of one month. The dostarlimab may be re-started when the diarrhoea or colitis remains at NCI-CTC grade 1 following corticosteroid taper.

The dostarlimab should be permanently discontinued when the diarrhoea or colitis does not improve to at least NCI-CTC grade 1 within 12 weeks of the last dose, the corticosteroid dose cannot be reduced to 10mg or less of prednisolone or equivalent per day within 12 weeks or in the case of a recurrent NCI-CTC grade 3 reaction.

For Grade 4 diarrhoea or colitis, dostarlimab must be permanently discontinued, and corticosteroid treatment initiated.

Lung

Interstitial lung disease including pneumonitis and acute interstitial pneumonitis are associated with dostarlimab. For NCI-CTC grade 1 events (asymptomatic with radiographic findings only) then the dostarlimab may be continued with close monitoring. Radiologic findings should be followed on serial imaging studies and consideration given to pulmonary

consultation and/or bronchoscopy, if clinically indicated. For NCI-CTC grade 2 events withhold the dostarlimab and consider pulmonary consultation with bronchoscopy and biopsy/bronchoalveolar lavage (BAL) and pulmonary function tests. Treat with systemic corticosteroids at a dose of 1 to 2mg/kg/day prednisone or equivalent. When symptoms improve to NCI-CTC grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Treatment with dostarlimab may be resumed if the event improves to NCI-CTC grade 0 or 1 within 12 weeks and corticosteroids have been reduced to the equivalent of prednisolone 10 mg oral daily or less. Repeat chest imaging monthly as clinically indicated.

Should a second episode of pneumonitis occur then discontinue the dostarlimab.

For NCI-CTC grade 3 or 4 events discontinue dostarlimab and consider pulmonary function tests and seek advice from a lung specialist. A bronchoscopy with biopsy and / or BAL should be considered. Treatment involves corticosteroid therapy such as intravenous methylprednisolone 125mg. When symptoms improve to NCI-CTC grade 1 or less, a high dose oral steroid such as prednisone 1 to 2 mg/kg once per day can be considered. A reducing schedule should be considered over a period of at least four weeks.

Infusion reactions

Severe infusion-related reactions have been reported in patients receiving dostarlimab. Monitor for signs and symptoms of an infusion-related reaction. For a NCI-CTC grade 2 reaction stop the infusion. If symptoms resolve within one hour of stopping the dostarlimab infusion may be re-started at 50% of the original infusion rate, consider pre-medication with chlorpheniramine and hydrocortisone if these have not already been given. For a grade 3 or above infusion permanently discontinue treatment.

Regimen

The product literature states dostarlimab is given as a 500mg dose every 21 days for 4 cycles followed by 1000mg every 42 days thereafter. To allow this to be one continuous regimen on ARIA the initial phase has been set as a 42 day cycle with treatment given on days 1 and 22.

Treatment is continued until disease progression, unacceptable toxicity occurs or the patient chooses to stop. A medical review as to whether treatment with dostarlimab should continue should occur by at least the second cycle. Nine cycles will be set in ARIA (54 weeks in total).

Cycles 1 and 2 – 42 day cycle

Drug	Dose	Days	Administration
Dostarlimab	500mg	1, 22	Intravenous infusion in 100ml sodium chloride 0.9% over 30 minutes

Cycles 3 onwards – 42 day cycle

Drug	Dose	Days	Administration
Dostarlimab	1000mg	1	Intravenous infusion in 100ml sodium chloride 0.9% over 30 minutes

Administration Information

Extravasation

- Dostarlimab - neutral

Additional Therapy

- No antiemetics are required
- For the treatment of infusion related reactions;

  - chlorphenamine 10mg intravenous once only when required for infusion related reactions
  - hydrocortisone 100mg intravenous once only when required for infusion related reactions
  - salbutamol 2.5mg nebule when required for infusion related bronchospasm

- Loperamide 4mg oral initially followed by 2mg after each loose stool when required for the relief of diarrhoea (maximum 16mg/24 hours).
- Gastric protection with a proton pump inhibitor or a H_2 antagonist may be considered in patients considered at high risk of GI ulceration or bleed

Additional Information

- The use of systemic corticosteroids, before starting treatment with dostarlimab should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of the agent. However, systemic corticosteroids can be used after starting dostarlimab to treat immune-related adverse reactions. The use of systemic corticosteroids after starting treatment does not appear to impair the efficacy of dostarlimab.

References
1. NICE Technology Appraisal TA779. Dostarlimab for previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency. Published 16/03/22. DOH.

REGIMEN SUMMARY

Dostarlimab

Cycles 1 and 2

Day 1 and 22

1. Dostarlimab 500mg intravenous infusion in 100ml sodium chloride 0.9% over 30 minutes

2. Chlorphenamine 10mg intravenous injection once only when required for infusion related reactions.

3. Hydrocortisone 100mg intravenous injection once only when required for infusion related reactions

4. Salbutamol 2.5mg nebule once only when required for infusion related bronchospasm

Cycle 3 onwards

Day 1

5. Dostarlimab 1000mg intravenous infusion in 100ml sodium chloride 0.9% over 30 minutes

6. Chlorphenamine 10mg intravenous injection once only when required for infusion related reactions.

7. Hydrocortisone 100mg intravenous injection once only when required for infusion related reactions

8. Salbutamol 2.5mg nebule once only when required for infusion related bronchospasm

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	July 2022		Dr Deborah Wright Pharmacist	Dr Clare Green Consultant Medical Oncologist

This chemotherapy protocol has been developed as part of the chemotherapy electronic prescribing project. This was and remains a collaborative project that originated from the former CSCCN. These documents have been approved on behalf of the following Trusts;

Hampshire Hospitals NHS Foundation Trust
NHS Isle of Wight
Portsmouth Hospitals NHS Trust
Salisbury Hospital NHS Foundation Trust
University Hospital Southampton NHS Foundation Trust
Western Sussex Hospitals NHS Foundation Trust

All actions have been taken to ensure these protocols are correct. However, no responsibility can be taken for errors that occur as a result of following these guidelines.