| **Protocol Contains CHECKPOINT INHIBITOR IMMUNOTHERAPY** | |
|---|---|
| **Indication** | Dostarlimab in combination with platinum-containing chemotherapy for the 1st line treatment of mismatch repair deficient (dMMR) / microsatellite instability-high (MSI-H) primary advanced or recurrent endometrial cancer (EC) in patients who are not candidates for potentially curative surgery or radiotherapy or chemoradiotherapy but are eligible for systemic therapy.<br><br>Patients should not have previously received any systemic chemotherapy for endometrial carcinoma unless it has been as neoadjuvant or adjuvant chemotherapy or chemoradiotherapy and the patient has progressed or recurred at least 6 months since the completion of treatment.<br><br>NB the patient must have not received any prior treatment with any PD-1 or PD-L1 or PD-L2 or CD137 or OX40 or anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) unless they have received dostarlimab for this indication via the EAMS scheme. |
| **Treatment Intent** | Palliative |
| **Frequency and number of cycles** | 6 cycles of dostarlimab in combination with chemotherapy followed by dostarlimab monotherapy.<br><br>Cycles 1-6 combination therapy repeat every 21 days<br><br>Cycle 7 onwards repeat every 42 days until disease progression, unacceptable toxicity, patient choice or to a maximum duration of 3 calendar years.<br><br>A formal medical review should take place after the first 6 weeks of treatment. |
| **Monitoring Parameters pre-treatment** | • **Virology screening:** All new patients referred for systemic anti-cancer treatment should be screened for hepatitis B and C and the result reviewed prior to the start of treatment. Patients not previously tested who are starting a new line of treatment, should also be screened for hepatitis B and C. Further virology screening will be performed following individual risk assessment and clinician discretion.<br>• **Thyroid function** must be assessed at baseline then at least every 6 weeks throughout treatment.<br>• Cortisol monitoring should be undertaken in line with ESMO immunotherapy toxicity guidance available on KMCC website (see link below). Cortisol level should not be taken within 24hours of the last steroid dose.<br>• **Pre-treatment cardiac assessment:**<br>  ○ **ECG** baseline and as clinically indicated.<br>  ○ Check **BNP**, and **Troponin T** prior to treatment.<br>• Monitor for signs and symptoms of myocarditis.<br>• **Cycles 1-6**<br>• EDTA/DTPA should be used to measure GFR prior to cycle 1. C+G may be used to estimate CrCl if there is a delay in obtaining EDTA result.<br>• Monitor U+Es, LFTs, FBC and glucose at each cycle. If CrCl falls by >25% repeat EDTA and d/w consultant.<br>• If neuts <1.5 and/or PLT <100 defer treatment by one week. Consider dose reduction on subsequent cycles.<br>• **Cycle 7 onwards**<br>• FBC, U&E, LFTs and glucose at each cycle.<br>• **Hepatic impairment:**<br>  ○ **Dostarlimab** - No recommended dose adjustment in mild hepatic impairment. Limited data in moderate impairment and no available data in severe impairment. |

- **Carboplatin** - No dose adjustment required.
- **Paclitaxel** - If bilirubin < 1.25 x ULN and transaminase < 10 x ULN, dose at full dose. Otherwise consider dose reduction, not recommended in severe hepatic impairment.

- **Renal impairment:**
  - **Dostarlimab** - No recommended dose adjustment in mild or moderate renal impairment. Limited data in severe impairment or end-stage renal disease undergoing dialysis.
  - **Carboplatin** - stop if CrCl<30ml/min
  - **Paclitaxel** - no dose reduction necessary.
- The use of systemic corticosteroids or immunosuppressants before starting dostarlimab should be avoided; dexamethasone is permitted as prescribed within this protocol. Systemic corticosteroids or other immunosuppressants can be used after starting dostarlimab to treat immune-related adverse reactions.
- **Infusion-related reactions:**
  - **Dostarlimab**
    For severe infusion reactions (grade 3-4), infusion should be stopped and dostarlimab permanently discontinued.
    Grade 2 reaction, withhold dose. If reaction resolves within 1 hour of stopping, the infusion 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.
  - **Paclitaxel**
    Patients developing hypersensitivity reactions to paclitaxel may be rechallenged with full dose paclitaxel following prophylactic medication (e.g. famotidine 40mg po given 4 hours prior to treatment plus hydrocortisone 100mg iv and chlorphenamine 10mg iv 30 minutes prior to treatment, then give paclitaxel over 3-6 hours (i.e. starting at over 6 hours and gradually increase rate if possible).
  - **Carboplatin**
  - Mild/moderate reactions (grade 1-2): If symptoms resolve after treatment with hydrocortisone and chlorphenamine, the infusion may be restarted at 50% rate for 30 mins, then, if no further reaction, increase to 100% rate.
  - If symptoms do not resolve after treatment with hydrocortisone and chlorphenamine, do not restart the infusion. At consultant's discretion, patients may be rechallenged at a later date with additional prophylaxis. In the event of further reaction (grade 1-3), stop infusion and consider alternative treatment.
  - Severe (grade 3): Do not restart infusion. Consider alternative treatment.
  - Anaphylaxis (grade 4): Follow anaphylaxis protocol. Discontinue permanently and consider alternative treatment.
- **Adverse reactions and dose modification:**
- **Immune-related adverse reactions** may appear during or after treatment with dostarlimab. The most common immune-related reactions are: anaemia (including autoimmune haemolytic anaemia), pneumonitis, colitis, hyperthyroidism, hypothyroidism and arthralgia. The following additional, immune related adverse reactions have been reported in patients receiving dostarlimab: type 1 diabetes, nephritis, hepatitis, pancreatitis, severe skin reactions, encephalitis, Guillain-Barre syndrome, myocarditis, iridocyclitis, uveitis and diabetic ketoacidosis.
  See guidelines for management of immune-related adverse reactions following immunotherapy: https://www.kmcc.nhs.uk/medicines-and-prescribing-incorporating-sact-pathways/immunotherapy/
- Cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported. If SJS or TEN is confirmed, dostarlimab should be permanently discontinued. Caution

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| | 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.<br>• **Dose Modification:**<br>o Dose reduction of either chemotherapy agents (paclitaxel or carboplatin) and not the other agent is appropriate if the toxicity is clearly related to one of the chemotherapy agents. If the toxicity is related to both agents, they should both be modified according to their recommended dose modification. If the toxicity is related to the combination of dostarlimab and both chemotherapy agents, the doses of the chemotherapy agents should be reduced, or the dose of all three drugs should be interrupted or discontinued. In patients who suffer a severe allergic reaction to paclitaxel or carboplatin which necessitates discontinuation of the drug causing the severe allergy, use of dostarlimab can continue with carboplatin **or** paclitaxel in combination.<br>Patients may have chemotherapy discontinued and continue dostarlimab as monotherapy, in the same way patients may discontinue dostarlimab and continue chemotherapy alone.<br>o **Dostarlimab -** Dose reduction is not recommended. 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 table 1). Upon improvement to Grade </=1, corticosteroid taper should be initiated and continued for 1 month or longer. 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 1.<br>o **Paclitaxel -** Dose reduce Paclitaxel by 20% in the event of >/= grade 2 neuropathy and consider delay until recovery to </= grade 1.<br>o Consider omitting paclitaxel in event of recurrent grade >/= 3 neuropathy OR recurrent or persistent >/= grade 2 neuropathy following a dose reduction.<br>o Dose reduction of **carboplatin** and **paclitaxel** should be considered if any other grade 3 or 4 non-haematological toxicity or repeat appearance of grade 2 (except N&V and alopecia). Delay until resolution of toxicity to </=grade 1.<br>• **Common drug interactions (for comprehensive list refer to BNF/SPC):**<br>**Dostarlimab -** No interaction studies have been performed.<br>**Paclitaxel -** Caution should be exercised when administering paclitaxel concomitantly with medicines known to inhibit either CYP2C8 or CYP3A4 (e.g. ketoconazole, erythromycin, fluoxetine, clopidogrel, cimetidine, ritonavir and nelfinavir); toxicity may be increased. CYP2C8 or CYP3A4 inducers (e.g. rifampicin, carbamazepine, phenytoin, efavirenz, nevirapine) may reduce efficacy.<br>**Carboplatin** - Caution with other nephrotoxic drugs.<br>• Each patient should be given a copy of the Jemperli ® patient alert card at each cycle.<br>Patients must be advised to contact the oncology team or the 24-hour hot-line immediately if they experience any side effect, as some side effects worsen rapidly. Prompt management of side effects can ensure that the patient continues with treatment |
| **References** | KMCC protocol GYN-049 V3 Gynae NOG and Immunotherapy working group agreed change regarding monitoring and carboplatin maximum dose. |

NB For funding information, refer to CDF and NICE Drugs Funding List

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| Protocol No | GYN-049 | Kent and Medway SACT Protocol<br>Disclaimer: No responsibility will be accepted for the accuracy of this information when used elsewhere. | |
| Version | V4 | Written by | M.Archer |
| Supersedes version | V3 | Checked by | C.Waters V4<br>O.Adebayo V3<br>V4 Update to carboplatin dose and cardiac monitoring guidance only. |
| Date | 04.06.2025 | Authorising consultant (usually NOG Chair) | L.Kivat V3 |

**Table 1: Dose modification for dostarlimab**

| **Immune-related adverse reactions** | **Severity grade** | **Dose modification** |
|---|---|---|
| Colitis | 2 to 3 | Withhold dose. Restart dosing when toxicity resolves to grade 0-1. |
| | 4 | Permanently discontinue. |
| Hepatitis | Grade 2 with AST or ALT > 3 and up to 5 × ULN<br>Or total bilirubin > 1.5 and up to 3 × ULN | Withhold dose. Restart dosing when toxicity resolves to grade 0 to 1. |
| | Grade >/=3 with AST or ALT > 5 × ULN<br>Or total bilirubin > 3 × ULN | Permanently discontinue (see exception below*) |
| Type 1 diabetes mellitus (T1DM) | 3 to 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 to 1. Permanently discontinue for recurrence or worsening while on adequate hormonal therapy. |
| Hypothyroidism or hyperthyroidism | 3 to 4 | Withhold dose. Restart dosing when toxicity resolves to grade 0 to 1. |
| Pneumonitis | 2 | Withhold dose. Restart dosing when toxicity resolves to grade 0-1. If grade 2 recurs, permanently discontinue. |
| | 3 to 4 | Permanently discontinue. |
| Nephritis | 2 | Withhold dose. Restart dosing when toxicity resolves to grade 0-1. |
| | 3 to 4 | Permanently discontinue. |
| Exfoliative dermatologic conditions (e.g., SJS, TEN, DRESS) | Suspected | Withhold dose for any grade. Restart dosing if not confirmed and when toxicity resolves to grade 0-1. |
| | Confirmed | Permanently discontinue. |
| Myocarditis | 2,3, or 4 | Permanently discontinue. |
| Severe neurological toxicities (myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome, encephalitis, transverse myelitis) | 2,3 or 4 | Permanently discontinue |
| Other immune-related adverse reactions (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 0-1. |
| | 4 | Permanently discontinue. |
| Recurrence of immune-related adverse reactions after resolution to ≤ grade 1 (except for pneumonitis, see above) | 3 to 4 | Permanently discontinue. |

*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.

**Cycle 1 to 6: Repeat every 21 days**

| Day | Drug | Dose | Route | Infusion Duration | Administration |
|---|---|---|---|---|---|
| 1 | **DOSTARLIMAB** | **500mg** | IV | 30mins | In 100ml Sodium Chloride 0.9% Administered via a 0.22 micron in-line filter |
| | **Give pre-meds 30 minutes prior to paclitaxel** | | | | |
| | Dexamethasone | 16mg | IV | Bolus | |
| | Chlorphenamine | 10mg | IV | Slow bolus | Through the side of a fast running Sodium Chloride 0.9% intravenous infusion. |
| | Ondansetron | <75yrs 16mg<br>≥75yrs 8mg | IV | 15 min | Sodium chloride 0.9% 50ml |
| | **PACLITAXEL** | **175mg/m²** | IV | 3 hrs | In 500ml Sodium Chloride 0.9% (if dose <150mg in 250ml Sodium Chloride 0.9%)<br>Use non-PVC bag and non-PVC administration set via in-line 0.22 microns filter.<br>Flush with sodium chloride 0.9% |
| | **CARBOPLATIN** | **AUC 5**<br>**Dose = AUC X (GFR + 25)**<br>(dose capped at 790mg on epx system) | IV | 30 mins | Glucose 5% 500ml<br><br>In clinical practice the dose is usually capped at either 700mg OR for a maximum calculated dose of GFR 125ml/min |
| TTO | Drug | Dose | Route | Directions | |
| Day 1 | Dexamethasone | 6mg | PO | OM for 3 days starting the day after paclitaxel dose. | |
| | Metoclopramide | 10mg | PO | Take 10mg THREE times a day for 3 days then take 10mg up to THREE times a day when required (Maximum of 30mg per day).<br>Do not take for more than 5 days continuously. | |
| | Loperamide | 2-4mg | PO | Take 4mg (2 capsules) initially, then 2mg (1 capsule) after each loose stool when required.<br>Maximum 16mg (8 capsules) a day.<br>Do not take for longer than 3 days without contacting the oncology team.<br>Dispense 30 capsules on cycle 1 then only if specified. | |

**Cycle 7 onwards repeat every 42 days (cycle 7 to be started 21 days after cycle 6)**

| Day | Drug | Dose | Route | Infusion Duration | Administration |
|---|---|---|---|---|---|
| 1 | **DOSTARLIMAB** | **1000mg** | IV | 30mins | In 100ml Sodium Chloride 0.9%<br>Administered via a 0.22 micron in-line filter |
| TTO | Drug | Dose | Route | Directions | |
| Day 1 | Metoclopramide | 10mg | PO | 10mg TDS PRN.<br>Do not take for more than 5 days continuously. | |