DOSTARLIMAB (Jemperli) CARBOPLATIN PACLITAXEL

INDICATION (ICD10) C54

Check the most recent Blueteq eligibility criteria before prescribing. Blueteq registration required. (www.england.nhs.uk/publication/national-cancer-drugs-fund-list/) (DOS2)

1. Dostarlimab in combination with platinum-containing chemotherapy (carboplatin and paclitaxel) for the 1st line treatment of mismatch repair deficient or microsatellite instability-high endometrial carcinoma in adult patients who have recurrent or primary advanced disease and who are not candidates for potentially curative surgery or radiotherapy or chemoradiotherapy but are eligible for systemic therapy. Has not previously received any systemic chemotherapy for the endometrial carcinoma or the only systemic therapy has been as neoadjuvant or adjuvant chemotherapy or chemoradiotherapy and the patient has progressed or recurred at least 6 months since the completion of such chemotherapy but has not received any prior antibody treatment which targets PD-1 or PD-L1 or PD-L2 or CD137 or OX40 or anti-cytotoxic CTLA-4. Note: patients with carcinosarcoma (Mixed Mullerian tumour) are eligible but otherwise uterine sarcomas of any kind are NOT eligible for dostarlimab in this indication. Has no symptomatically active brain metastases or leptomenigeal metastases. PS 0 or 1.

REGIMEN

Cycles 1 to 6

Day 1 Premedication 30 minutes prior to infusion:
Dexamethasone 20 mg IV bolus
Chlorphenamine 10 mg IV bolus
DOSTARLIMAB 500mg in 250ml sodium chloride 0.9% IV infusion over 30 minutes
PACLITAXEL 175mg/m^2 in #ml sodium chloride 0.9% IV infusion over 3 hours
CARBOPLATIN AUC 5 in #ml glucose 5% IV infusion over 30 minutes
Dose calculated by EDTA GFR or calculated (CrCl + 25) x AUC.
Maximum dose when using CrCl (125+25 x AUC)mg

Cycles 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51 and 53

Day 1 DOSTARLIMAB 1000mg in 250ml sodium chloride 0.9% IV infusion over 30 minutes

diluent volume for dose prescribed as per national standardised product specification

CYCLE FREQUENCY AND NUMBER OF CYCLES

Cycle every 21 days for up to 3 calendar years
A formal medical review as to how dostarlimab and carboplatin and paclitaxel are being tolerated, and whether treatment with this combination should continue or not, will be scheduled to occur at least by the end of the first 6 weeks of treatment.

ANTI-EMETICS

Moderate risk day 1 cycles 1 to 6
None required cycle 7 onwards

CONCURRENT MEDICATION REQUIRED

Carboplatin	Anaphylaxis treatment should be prescribed if the patient has had an anaphylactic episode previously. Dexamethasone 20mg IV bolus Chlorphenamine 10mg IV bolus H_2 antagonist Carboplatin should be given at a slower rate e.g. 2-4 hours.
Paclitaxel	Ensure premedication given before paclitaxel

EXTRAVASATION AND TYPE OF LINE / FILTERS

Carboplatin - irritant
Dostarlimab – neutral
Paclitaxel – vesicant

Administer paclitaxel via polyethylene lined administration set with ≤0.22micron filter
Central or peripheral line

INVESTIGATIONS

Blood results required before SACT administration
FBC, U&E and LFTs, creatinine every cycle
Neutrophils x 10^9/L ≥1.5
Platelets x 10^9/L ≥100
Thyroid function baseline, then every cycle
Random cortisol baseline, then every cycle
Random glucose every cycle
GFR assessed using EDTA result or calculated creatinine clearance at the Consultant's discretion.
CA125 baseline and day 1 every cycle
Baseline weight and every cycle

MAIN TOXICITES AND ADVERSE REACTIONS

Carboplatin	Ototoxicity – monitor Neurotoxicity - monitor
Dostarlimab	Immune related toxicities - pneumonitis, colitis or hepatitis etc
Paclitaxel	(2% risk of severe hypersensitivity) Reactions range from mild hypotension (light-headedness) to full cardiac collapse (anaphylactic shock). Discontinue infusion and resuscitate appropriate to reaction. If reaction is mild and settles promptly (i.e. within 5-10 minutes), cautiously restart at a slower rate under close supervision. If further reactions occur stop treatment.

INTERACTIONS WHICH MAY REQUIRE DOSE MODIFICATIONS
(not exhaustive list check SPC/BNF/Stockleys)

Paclitaxel	DOACs to be used with caution, need dose modifications or to be avoided eg apixaban Clopidogrel interacts with paclitaxel Paclitaxel is catalysed, by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. inhibitors (e.g. erythromycin, fluoxetine, gemfibrozil) use with caution. inducors (e.g. rifampicin, carbamazepine, phenytoin, phenobarbital, efavirenz, nevirapine) use with caution.

DOSE MODIFICATIONS

Non-haematological

Dostarlimab

Immune-related adverse reactions – refer to TV immune-oncology agent immune-related adverse event clinical guideline.

Recurrence of immune-related adverse reactions after resolution to ≤grade 1 (except for pneumonitis)

Grade 3 to 4	Permanently discontinue

Colitis

Grade 2 to 3	Withhold dose, Restart dosing when toxicity resolves to grade 0-1.
Grade 4	Permanently discontinue

Hepatitis

Grade 2 with AST or ALT >3 and up to5xULN or total bilirubin >1.5 and up to 3xULN	Withhold dose. Restart dosing when toxicity resolves to grade 0 to 1.
Grade ≥3 with AST or ALT >5xULN or total bilirubin >3xULN	Permanently discontinue. For patients with liver metastases who begin treatment with grade 2 increase of AST or ALT, if AST or ALT increase by ≥50% relative to baseline and lasts for at least 1 week, then treatment should be discontinued.

Hypophysitis or adrenal insufficiency

Grade 2 to 4	Withhold dose. Restart dosing when toxicity resolves to grade 0 to 0 to 1. Permanently discontinue for recurrence or worsening while on adequate hormonal therapy.

Hypothyroidism or hyperthyroidism

Grade 3 to 4	Withhold dose. Restart dosing when toxicity resolves to grade 0 to 0 to 1.

Infusion-related reactions

Grade 2	Withhold dose, If resolved with 1 hour of stopping, may be restarted at 50% of the original infusion rate, or restart when symptoms resolve with premedication, permanently discontinue.
Grade 3 to 4	Permanently discontinue

Nephritis

Grade 2	Withhold dose, Restart dosing when toxicity resolves to grade 0-1.
Grade 3 to 4	Permanently discontinue

Pneumonitis

Grade 2	Withhold dose, Restart dosing when toxicity resolves to grade 0-1. If grade 2 recurs, permanently discontinue.
Grade 3 to 4	Permanently discontinue

Immune-mediated rash

Grade 3	Withhold dose, Restart dosing when toxicity resolves to grade 0-1.
Grade 4	Permanently discontinue

Other immune-related adverse reactions (including but not limited to myositis, myocarditis, encephalitis, demyelinating neuropathy including Guillane Barre syndrome, sarcoidosis, autoimmune haemalytic anaemia, pancreatitis, iridocyclitis, uveitis, diabetic ketoacidosis, arthralgia, solid organ transplant injection, graft versus-host disease).

Grade 3	Withhold dose, Restart dosing when toxicity resolves to grade 0-1.
Grade 4	Permanently discontinue

Type 1 diabetes mellitus (T1DM)

Grade 3 to 4 (hyperglycaemia)	Withhold dose, Restart dosing in appropriately managed, clinically and metabolically stable patients.

Paclitaxel
If patient complains of tinnitus, tingling of fingers and/or toes or motor weakness
discuss with Consultant or Registrar before administration
If grade ≥2 neuropathy, consider paclitaxel dose reduction
If grade >3 peripheral neuropathy is >grade 3 omit further paclitaxel

Hepatic impairment
Dostarlimab
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.

Paclitaxel
In the absence of Gilbert's syndrome:

Transaminase <10xULN and bilirubin ≤1.25xULN	no dose reduction
Transaminase <10xULN and bilirubin 1.26-2xULN	give 77% of original dose
Transaminase <10xULN and bilirubin 2·01-5xULN	give 51% of original dose
Transaminase ≥10xULN or bilirubin >5xULN	contraindicated

Renal impairment
Carboplatin

GFR/ calculated CrCl ≤20ml/min or ≤30ml/min with pre-existing severe renal impairment	contraindicated

Dostarlimab
No dose adjustment is recommended for patients with mild or moderate renal impairment. There are limited data in patients with severe renal impairment of end-stage renal disease undergoing dialysis.

REFERENCES

CDF