

DOSTARLIMAB (Jemperli) CARBOPLATIN PACLITAXEL

INDICATION (ICD10) C54

Check the most recent Blumetq eligibility criteria before prescribing. Blumetq registration required. (www.england.nhs.uk/publication/national-cancer-drugs-fund-list/) (DOS2) (DOS3)

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 leptomeningeal metastases. PS 0 or 1. (TA897)
2. Dostarlimab in combination with platinum-containing chemotherapy (carboplatin and paclitaxel) for the 1st line treatment of mismatch repair proficient (pMMR) or microsatellite stable 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. 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 leptomeningeal metastases. PS 0 or 1. (TA1117)

REGIMEN

Cycles 1 to 6

Day 1	DOSTARLIMAB	500mg	IV infusion	#ml sodium chloride 0.9% over 30 minutes
	Premedication 30 minutes prior to paclitaxel: Chlorphenamine 10mg IV bolus Dexamethasone 20mg IV bolus			
	PACLITAXEL	175mg/m ²	IV infusion	#ml sodium chloride 0.9% over 3 hours
	CARBOPLATIN	AUC* 5	IV infusion	#ml glucose 5% over 30 minutes

Cycle 7 and then odd number cycles up to 3 calendar years from day 1 of cycle 1

Day 1	DOSTARLIMAB	1000mg	IV infusion	#ml sodium chloride 0.9% over 30 minutes
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*Dose calculated by EDTA GFR or calculated (CrCl + 25) x AUC.

Maximum dose when using CrCl (125+25 x AUC)mg

diluent volume for dose prescribed as per national standardised product specification

CYCLE FREQUENCY AND NUMBER OF CYCLES

Calendar years - maximum duration of treatment from initiation of the treatment, the treatment must stop at that maximum time duration irrespective of any breaks in treatment.

Cycle every 21 days for up to 3 **calendar** years from day 1 cycle 1 of combination.

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 or DEHP free administration set with ≤0.22micron filter.

Administer dostarlimab via 0.2 or 0.22micron in-line polyethersulfone (PES) filter.

Central or peripheral line

INVESTIGATIONS

Blood results required before SACT administration

FBC, U&E including Mg ⁺⁺ (>0.4) and LFTs Neutrophils x 10 ⁹ /L ≥1.0 provided patient is well Platelets ≥100x10 ⁹ /L	baseline and every cycle
GFR assessed using EDTA result (BMI <19 or >30 or calculated creatinine clearance at the Consultant's discretion	baseline and every cycle
Serum creatinine	baseline and every cycle
Thyroid function	baseline and every cycle
Random cortisol	baseline and every cycle
Random glucose	baseline and every cycle
CA125	baseline and day 1 every cycle or as required
Virology	before cycle 1 if not previously checked
Weight	baseline and every cycle

MAIN TOXICITIES 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.
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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 \leq grade 1 (except for pneumonitis)

Grade 3 to 4	Permanently discontinue
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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 to $5 \times$ ULN or total bilirubin >1.5 and up to $3 \times$ ULN	Withhold dose. Restart dosing when toxicity resolves to grade 0 to 1.
Grade ≥ 3 with AST or ALT $>5 \times$ ULN or total bilirubin $>3 \times$ ULN	Permanently discontinue. For patients with liver metastases who begin treatment with grade 2 increase of AST or ALT, if AST or ALT increase by $\geq 50\%$ 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.
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Hypothyroidism or hyperthyroidism

Grade 3 to 4	Withhold dose. Restart dosing when toxicity resolves to grade 0 to 0 to 1.
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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 haemolytic anaemia, pancreatitis, iridocyclitis, uveitis, diabetic ketoacidosis, arthralgia, solid organ transplant rejection, 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.
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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 $> \text{grade } 3$ omit further paclitaxel

Hepatic impairment

Carboplatin

No need for dose adjustment is expected

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
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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.

Paclitaxel

No need for dose adjustment is expected

REFERENCES

CDF

Assessments

	Pre	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Ongoing
Clinical assessment	X		Pre cycle		Pre cycle	Every cycle
SACT assessment (PS and toxicities)	X	X	X	X	X	Every cycle
FBC	X	X	X	X	X	Every cycle
U&E, calcium, magnesium & LFT	X	X	X	X	X	Every cycle
Thyroid function	X	X	X	X	X	Every cycle
Random glucose	X	X	X	X	X	Every cycle
Random cortisol	X	X	X	X	X	Every cycle
CA125	X	X	X	X	X	Every cycle as required
CrCl	X	X	X	X	X	Every cycle
CT scan	X					At cycle 6, Inform consultant team if not booked
Informed consent	X					Verbal each cycle
Height	X					
Weight recorded	X	X	X	X	X	Every cycle