Dostarlimab, Carboplatin & Paclitaxel (Endometrial)

Indication

Advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency.

(NICE TA963)

ICD-10 codes

C54

Regimen details

Cycles 1-6 – combination treatment

Day	Drug	Dose	Route
1	Dostarlimab	500mg	IV infusion
1	Paclitaxel	175mg/m^2	IV infusion
1	Carboplatin	AUC 5*	IV infusion

* Carboplatin dose calculated using the Calvert equation: **Carboplatin dose (mg) = AUC (CrCl +25).** CrCl should be capped at 125mL/min.

Cycle 7 onwards – dostarlimab maintenance

Day	Drug	Dose	Route
1	Dostarlimab	1000mg	IV infusion

Cycle frequency

Cycles 1-6 (combination treatment): 21 days
Cycle 7 onwards (dostarlimab maintenance): 42 days

Number of cycles

Until disease progression or unacceptable toxicity up to a maximum of 3 years treatment.

Administration

Dostarlimab is administered in sodium chloride 0.9% at a concentration between 2-10mg/mL over 30 minutes.

For moderate (Grade 2) reactions, the infusion may be restarted at 50% of the original infusion rate with close monitoring. If reaction recurs despite adequate premedication treatment should be permanently discontinued.

Paclitaxel should be administered prior to carboplatin.

Paclitaxel is administered in a 500mL sodium chloride 0.9% non-PVC infusion bag with a 0.22 micron in-line filter over 3 hours.
Blood pressure and pulse should be monitored regularly (e.g. every 30 minutes) during paclitaxel infusion.

Carboplatin should be administered in 250-500mL glucose 5% over 30-60 minutes.

Patients should be observed closely for hypersensitivity reactions, particularly during the first and second infusions. Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of paclitaxel or carboplatin. Facilities for the treatment of hypotension and bronchospasm **must** be available.

If hypersensitivity reactions occur, minor symptoms such as flushing or localised cutaneous reactions do not require discontinuation of therapy. The infusion may be temporarily interrupted and when symptoms improve restarted at a slower infusion rate. Chlorphenamine 10mg IV may be administered. Severe reactions, such as hypotension, bronchospasm or generalised rash/erythema require immediate discontinuation of paclitaxel or carboplatin and appropriate therapy should be initiated.

Pre-medication

30 minutes prior to each paclitaxel infusion:
Chlorphenamine 10mg IV slow bolus
Dexamethasone 16-20mg IV slow bolus

Consider administering hydrocortisone 100mg IV prior to carboplatin if there has been a 6 month or longer gap from previous carboplatin-containing course of treatment due to possible carboplatin antibodies.

If a patient experiences a Grade 2 infusion related reaction to dostarlimab the following premedication regimen is recommended 1-2 hours prior to future dostarlimab infusions (where not already administered as part of paclitaxel premedication regimen):
Chlorphenamine 10mg IV
Paracetamol 500mg-1g PO/IV

Emetogenicity

This regimen has moderate-high emetic potential – refer to local policy

Additional supportive medication

Proton pump inhibitor if required.
Loperamide if required.
Laxatives if required
Mouthwashes as per local policy

Extravasation

Dostarlimab is neutral (group 1)
Carboplatin – irritant (Group 3)
Paclitaxel – vesicant (Group5)

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U&E (including creatinine)	14 days
LFT	14 days
Thyroid function	14 days
Calcium	14 days
Magnesium	14 days
Glucose	14 days
Cortisol	14 days

Investigations – pre cycles 2-6 (combination treatment)

Investigation	Validity period
FBC	96 hours
U&E (including creatinine)	7 days
LFT	7 days
Thyroid function	7 days
Calcium	7 days
Magnesium	7 days
Glucose	7 days
Cortisol	7 days

Investigations – pre cycle 7 onwards (dostarlimab maintenance)

Investigation	Validity period
FBC	7 days
U&E (including creatinine)	7 days
LFT	7 days
Thyroid function	Every other cycle
Calcium	As clinically indicated
Glucose	Every other cycle or as clinically indicated
Cortisol	Every other cycle or as clinically indicated

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	Limit
Neutrophil count	≥ 1.0 x 10^9/L
Platelets	≥ 100 x 10^9/L
Creatinine Clearance (CrCl)	≥ 30mL/min (and < 10% change)
Bilirubin	< ULN
ALT/AST	≤ 2.5 x ULN (or ≤ 5 x ULN if liver metastases)

Dose modifications

Dostarlimab: Dose reductions are not recommended for dostarlimab. Toxicity should be managed with dose delay/omission or discontinuation.

Paclitaxel:

Dose level	Paclitaxel dose
Full dose	175mg/m^2
First dose reduction	135mg/m^2
Second dose reduction	90mg/m^2
Third dose reduction	Discontinue

Carboplatin: reduce by dose by 1 x AUC

- **Haematological toxicity**

Neutrophils (x 10^9/L)		**Platelets** (x 10^9/L)	**Carboplatin dose**	**Paclitaxel dose**
≥ 1.0	and	≥ 100	100%	100%
< 1.0	or	< 100	Delay 1 week (or until recovery) then reduce dose by 1 x AUC	Delay 1 week (or until recovery)
< 1.0	and	< 100	Delay 1 week (or until recovery) then reduce dose by 1 x AUC	Delay 1 week (or until recovery) then reduce dose to next dose reduction level.

In the case of febrile neutropenia (neutrophils < 0.5 × 10^9/L and fever > 38.5°C requiring IV antibiotics) reduce paclitaxel to 135mg/m^2 and carboplatin by 1 x AUC for all future cycles.

Dostarlimab: Discuss with prescriber/consultant if neutrophils <1.0 x 10^9/L or platelets <75 x 10^9/L

- **Renal impairment**

Dostarlimab: No dose adjustment is recommended for patients with mild or moderate renal impairment. There is limited data in patients with severe renal impairment (<30ml/min) or those undergoing dialysis. Reduction in creatinine clearance during treatment may indicate immunotherapy-induced nephritis. See below for management.

Paclitaxel: No need for dose adjustment

Carboplatin:

CrCl (mL/min)	**Carboplatin dose**
> 30	100%
20-30	Measured GFR then 100% dose (or consider changing to non-nephrotoxic regimen, discuss with consultant)
< 20	Discuss with consultant

- **Hepatic impairment**

Dostarlimab: No dose adjustment is recommended for patients with mild hepatic impairment (bilirubin < 1.5 x ULN or ALT <2.5 x ULN). There is limited data in patients with moderate or severe hepatic impairment. Derangement of LFTs during treatment may indicate immunotherapy-induced hepatitis. See below for management.

Paclitaxel:

Bilirubin (x ULN)		**AST/ALT** (x ULN)	**Paclitaxel dose**
≤1.25	and	<10	100%
1.25-2	and		135mg/m^2
2-5	and		90mg/m^2
> 5	or	≥10	Not recommended (consultant decision)

Carboplatin: no need for dose adjustment expected. Consultant decision if bilirubin > 5 x ULN or ALT ≥ 10 x ULN.

- **Other toxicities**

Immune-related Adverse Reactions

Toxicity	Definition	Dose adjustment
Colitis	Grade 2-3	Withhold dose. Restart dosing when toxicity resolves to grade 0-1.
	Grade 4	Permanently discontinue
Hepatitis	Grade 2: AST/ALT 3-5 x ULN *or* Bilirubin 1.5-3 x ULN	Withhold dose. Restart dosing when toxicity resolves to grade 0-1.
	Grade ≥ 3 AST/ALT > 5 x ULN *or* Bilirubin > 3 x ULN	Permanently discontinue*
Type 1 diabetes mellitus (T1DM)	Grade 3 to 4 hyperglycaemia	Withhold dose. Restart dosing in appropriately managed, clinically and metabolically stable patients.
Hypophysitis or adrenal insufficiency	Grade 2 to 4	Withhold dose. Restart dosing when toxicity resolves to Grade 0 or 1. Permanently discontinue for recurrence or worsening whilst on adequate hormonal therapy.
Hypothyroidism or hyperthyroidism	Grade 3 to 4	Withhold dose. Restart dosing when toxicity resolves to grade 0 to 1.
Pneumonitis	Grade 2	Withhold dose. Restart dosing when toxicity resolves to grade 0 to 1. If Grade 2 recurs, permanently discontinue.
	Grade 3 to 4	Permanently discontinue
Nephritis	Grade 2 (creatinine 1.5-3x ULN)	Withhold dose. Restart dosing when toxicity resolves to grade 0 to 1.
	Grade 3 to 4 (creatinine >3 x ULN)	Permanently discontinue
Exfoliative dermatological conditions (e.g. Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Drug Rash with eosinophilia and Systemic Symptoms(DRESS))	Suspected	Withhold dose. Restart dosing if not confirmed, when toxicity resolves to grade 0 to 1.
	Confirmed	Permanently discontinue
Myocarditis	Grade 2-4	Permanently discontinue
Severe neurological toxicities (e.g myasthenic syndrome, myasthenia gravis, Guillain-Barré syndrome, encephalitis, transverse myelitis)	Grade 2-4	Permanently discontinue
Other immune-related adverse reactions (e.g. myositis, pancreatitis, uveitis, diabetic ketoacidosis, anaemia, arthralgia)	Grade 3	Withhold dose. Restart dosing when toxicity resolves to grade 0 to 1.
	Grade 4	Permanently discontinue

*unless patient has liver metastases and commenced treatment with AST/ALT 3-5 x ULN. In these patients if AST/ALT increases by ≥ 50% from baseline and lasts for a week or more then treatment should be discontinued.

Recurrence of immune-related adverse reactions at Grade 3 or 4, after resolution of the previous reaction to ≤ Grade 1, requires permanent discontinuation of treatment (excluding pneumonitis – see above).

Infusion related reactions

Dostarlimab can cause infusion-related reactions which can be severe. For severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions or a recurrent moderate (Grade 2) reactions despite adequate premedication, the infusion should be stopped and treatment permanently discontinued.

Carboplatin and Paclitaxel toxicities

Toxicity	Definition	Carboplatin dose	Paclitaxel dose
Fatigue	Grade 3	100%	1st occurrence – 135mg/m^2, if persistent 90mg/m^2 or omit
Neuropathy	Grade 2	100%	1st occurrence – 135mg/m^2 for all future cycles, if persistent 90mg/m^2 or omit
	Grade ≥ 3		Withhold until ≤ Grade 1, restart at 90mg/m^2.
Arthralgia/Myalgia	Grade ≥ 2	100%	Consider diclofenac +/- co-codamol. If persists reduce dose to 135mg/m^2

For all other grade 3 toxicities (except alopecia and nausea and vomiting) withhold until grade ≤ 1 and continue with carboplatin with 1 x AUC dose reduction and paclitaxel reduced to next dose reduction level. If further toxicity, consider additional dose reduction, discuss with consultant.

For any grade 4 toxicity (except alopecia and nausea and vomiting) withhold and discuss with consultant.

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Myelosuppression
Hypersensitivity reactions
Pulmonary fibrosis
Nephrotoxicity
Electrolyte disturbances
Arrhythmias
Cardiac failure
Febrile Neutropenia

- **Frequently occurring side effects**

Nausea and vomiting
Mucositis, stomatitis
Myelosuppression
Diarrhoea, constipation
Peripheral neuropathy
Oedema
Phlebitis
Myalgia, arthralgia
Alopecia
Fatigue

- **Other side effects**

Flu-like symptoms
Taste changes

Headache
Abdominal pain
Deranged liver function
Rash
Ototoxicity
Elderly patients may have a higher incidence of severe neuropathy, severe myelosuppression, or cardiovascular events compared to younger patients.

Significant drug interactions – for full details consult product literature/ reference texts

Corticosteroids: use of systemic corticosteroids at baseline, before starting dostarlimab, should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of dostarlimab. However, systemic corticosteroids or other immunosuppressants can be used after starting dostarlimab to treat immune-related adverse reactions.
Warfarin/coumarin anticoagulants: increased or fluctuating anticoagulant effects. Avoid if possible, consider switching patient to a low molecular weight heparin or DOAC during treatment or if the patient continues taking an oral anticoagulant monitor the INR at least once a week and adjust dose accordingly.

Clozapine: increased risk of agranulocytosis, avoid concomitant use.

Paclitaxel is a CYP 2C8 and CYP 3A4 substrate. Drug levels may be increased by inhibitors of these enzymes and decreased by inducers of these enzymes.

Carboplatin only:
Aminoglycoside antibiotics: increased risk of nephrotoxicity and ototoxicity
Diuretics: increased risk of nephrotoxicity and ototoxicity
Nephrotoxic drugs: increased nephrotoxicity ; not recommended
Phenytoin: carboplatin reduces absorption and efficacy of phenytoin

Additional comments

Patients should be issued with the Jemperli (dostarlimab) patient card and be advised to keep this with them at all times for at least 4 months after the last dose of dostarlimab.

References

- National Institute for Health and Clinical Excellence TA 963) accessed 4th April 2024 via www.nice.org.uk
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- Summary of Product Characteristics Carboplatin (Hospira) accessed 7th March 2024 via www.medicines.org.uk
- Summary of Product Characteristics Paclitaxel (Hospira) accessed 7th March 2024 via www.medicines.org.uk
- Mirza, M.R. et al. Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer. N Engl J Med. 2023; 388:2145-2158

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