PEMBROLIZUMAB (Keytruda) CARBOPLATIN PACLITAXEL

INDICATION (ICD10) C56

Check the most recent Blueteq eligibility criteria before prescribing. Blueteq registration required. (www.england.nhs.uk/publication/national-cancer-drugs-fund-list/) (PEMB22)

1. For the treatment of persistent, recurrent or metastatic cervical cancer, no symptomatically active brain metastases or leptomeningeal metastases, not amenable to curative treatment (such as with surgery or radiotherapy or chemoradiotherapy), in patients whose tumour PD-L1 expression test results have a combined positive score (CPS) of 1 or more, not previously treated with systemic chemotherapy (except as radiosensitiser). ECOG PS 0 or 1.

REGIMEN

Cycles 1 to 6

Day 1 PEMBROLIZUMAB 200mg in 100ml sodium chloride 0.9% IV infusion over 30 minutes
Premedication 30 minutes prior to infusion:
Dexamethasone 20 mg IV bolus
Chlorphenamine 10 mg IV bolus
PACLITAXEL 175mg/m^2 in 500ml sodium chloride 0.9% infusion over 3 hours
CARBOPLATIN AUC 5 in 500ml glucose 5% infusion over 30 minutes
Dose calculated by EDTA GFR or calculated CrCl + 25 x AUC.
(Maximum dose when using CrCl 125+25 x AUC)

Cycles 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33 and 35

Day 1 PEMBROLIZUMAB 400mg in 100ml sodium chloride 0.9% IV infusion over 30 minutes

CYCLE FREQUENCY AND NUMBER OF CYCLES

Combination every 21 days for 6 cycles. Formal review by the end of first 6 weeks treatment.
Pembrolizumab monotherapy every 42 days starting from cycle 7 up to 2 years

ANTI-EMETICS

Moderate risk day 1 cycles 1 to 6
Minimal risk day 1 cycles 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33 and 35

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
Paclitaxel – vesicant
Pembrolizumab - neutral

Paclitaxel via polyethylene lined administration set with ≤0.22micron filter
Pembrolizumab – Use low protein binding 0.2 to 5micron in-line or add-on filter
Central or peripheral line

INVESTIGATIONS

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

MAIN TOXICITES AND ADVERSE REACTIONS

Carboplatin	Ototoxicity – monitor Neurotoxicity - monitor
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.
Pembrolizumab	Immune related toxicities

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

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 giving 75% dose
If grade >3 peripheral neuropathy is >grade 3 omit further paclitaxel

Pembrolizumab
Immune-related adverse reactions - refer to TV immune-oncology agent immune related adverse event clinical guideline.
If the drug-related toxicity does not resolve to grade 0-1 within 12 weeks after onset of toxicity, discontinuation is recommended.

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

REFERENCES

1. Colombo et al. N Engl J Med 2021; 385:1856-1867

REGIMEN

Cycles 1 to 4

Day 1 PEMBROLIZUMAB 200mg in 100ml sodium chloride 0.9% IV infusion over 30 minutes
Premedication 30 minutes prior to infusion:
Dexamethasone 20 mg IV bolus
H_2 antagonist
Chlorphenamine 10 mg IV bolus
PACLITAXEL 200mg/m^2 in 500ml sodium chloride 0.9% infusion over 3 hours
CARBOPLATIN AUC 6 in 500ml glucose 5% infusion over 30 minutes
Dose calculated by EDTA GFR or calculated CrCl + 25 x AUC.
(Maximum dose when using CrCl 125+25 x AUC)

Cycles 5 to 35

Day 1 PEMBROLIZUMAB 200mg in 100ml sodium chloride 0.9% IV infusion over 30 minutes

CYCLE FREQUENCY AND NUMBER OF CYCLES

Combination every 21 days for 4 cycles
Pembrolizumab monotherapy cycles 5 up to 35 cycles

ANTI-EMETICS

Moderate risk day 1 cycles 1 to 4
Minimal risk day 1 cycles 5 to 35

CONCURRENT MEDICATION REQUIRED

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Random cortisol baseline, then every cycle
Random glucose every cycle
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REFERENCES

1. Paz-Ares, L et al; NEJM 2018; 379: 2040-2051