

BEVACIZUMAB 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 of 0 or 1.

REGIMEN

Day 1 PEMBROLIZUMAB 200mg in 100ml sodium chloride 0.9% IV infusion over 30 minutes
 BEVACIZUMAB 15mg/kg in 100ml sodium chloride 0.9% IV infusion
 Premedication 30 minutes prior to infusion:
 Dexamethasone 20 mg IV bolus
 Chlorphenamine 10 mg IV bolus
 PACLITAXEL 175mg/m² in 500ml* sodium chloride 0.9% IV infusion over 3 hours
 CARBOPLATIN AUC 5 in 500ml 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)

* doses 84mg to 144mg in 250ml sodium chloride 0.9%

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
 BEVACIZUMAB 15mg/kg in 100ml sodium chloride 0.9% IV infusion

Cycles 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34 and 36 onwards

Day 1 BEVACIZUMAB 15mg/kg in 100ml sodium chloride 0.9% IV infusion

Bevacizumab - The initial dose should be administered over 90 minutes, if tolerated well the second infusion may be administered over 60 minutes.

If the 60 minute infusion is well tolerated all subsequent infusions may be administered 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.

Bevacizumab every 21 days with Pembrolizumab every 42 days cycles 7 to 35 (up to 2 years)

Bevacizumab monotherapy every 21 days cycle 36 (2 years) onwards until disease progression

ANTI-EMETICS

Moderate risk day 1 cycles 1 to 6

Minimal risk day 1 cycles 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

Bevacizumab – neutral
 Carboplatin - irritant
 Paclitaxel – vesicant
 Pembrolizumab - neutral

Paclitaxel via polyethylene lined administration set with ≤ 0.22 micron 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 $10^9/L \geq 1.5$
 Platelets x $10^9/L \geq 100$
 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
 Blood pressure every cycle
 Urinalysis for proteinuria every cycle
 Baseline weight and every cycle

MAIN TOXICITIES AND ADVERSE REACTIONS

Bevacizumab	Arterial thromboembolism Gastrointestinal perforation Haemorrhage Hypertension Wound healing complications
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.
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DOSE MODIFICATIONS

Non-haematological

Bevacizumab

Hypertension

Baseline blood pressure should be <150/100mmHg.

Diastolic increase >20mmHg above baseline or BP rises to >150/100mmHg	Antihypertensive therapy may be required.
Blood pressure >180/110mmHg	It is advised that bevacizumab therapy is withheld until blood pressure controlled.

Proteinuria

Urine dipstick result. 1+ or 2+ on dipstick (0.3–2.9g/L)	Continue with bevacizumab. No additional evaluation required.
3+ on dipstick (3-19g/L)	May have dose of bevacizumab as scheduled, but 24 hour urine to measure 24 hour protein to be done a few days before next cycle due. If 24hr protein result <2g, continue with bevacizumab, with continued proteinuria monitoring via 24 hour urine before each dose. If the 24 hour protein level falls to <1g/24hr, return to dipstick analysis. If ≥2g, withhold bevacizumab until repeat 24 hour urine collection shows <2g protein. Then re-introduce bevacizumab, with continued proteinuria monitoring via 24 hour urine.
4+ on dipstick (≥20g/L)	Withhold bevacizumab. 24 hour urine required. Follow 24 hour urine monitoring and guidance as for 3+ on dipstick.

Wound healing

Bevacizumab may adversely affect the wound healing process. Therapy should not be initiated for at least 28 days following major surgery or until the surgical wound is fully healed. Therapy should also be withheld for at least 28–60 days before elective surgery.

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 \leq 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 \geq 10xULN or bilirubin >5xULN	contraindicated

Renal impairment

Carboplatin

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

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