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. (TA939)

REGIMEN SC (pembrolizumab before chemotherapy)

Cycles 1 to 6

Day 1	**PEMBROLIZUMAB**	395mg	Subcutaneous	over 1 minute
	BEVACIZUMAB	15mg/kg	IV infusion	#ml sodium chloride 0.9%
	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 (maximum 700mg)	IV infusion	#ml glucose 5% 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**	790mg	Subcutaneous	over 2 minutes
	BEVACIZUMAB	15mg/kg	IV infusion	#ml sodium chloride 0.9%

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

Day 1	**BEVACIZUMAB**	15mg/kg	IV infusion	#ml sodium chloride 0.9%

REGIMEN IV (pembrolizumab before chemotherapy)
Cycles 1 to 6

Day 1	**PEMBROLIZUMAB**	200mg	IV infuson	100ml sodium chloride 0.9% IV infusion over 30 minutes
	BEVACIZUMAB	15mg/kg	IV infusion	#ml sodium chloride 0.9%
	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 (maximum 700mg)	IV infusion	#ml glucose 5% 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	IV infuson	100ml sodium chloride 0.9% IV infusion over 30 minutes
	BEVACIZUMAB	15mg/kg	IV infusion	#ml sodium chloride 0.9%

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	IV infusion	#ml sodium chloride 0.9%

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

diluent volume for dose prescribed as per national standardised product specification

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

ADMINISTRATION
Pembrolizumab SC - withdraw the required volume using a transfer needle (18-21G recommended). To avoid needle clogging, change the needle to a 25-30G, 13 mm hypodermic injection needle immediately prior to SC injection.
Do not administer other medicinal products for injection at the same site as the pembrolizumab.

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 IV - neutral

Paclitaxel via polyethylene lined or DEHP free administration set with ≤0.22micron filter
Pembrolizumab IV – 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 including Mg^{++} (>0.4) and LFTs Neutrophils $x10^9$/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, then every cycle
Random cortisol	baseline, then every cycle (or as specified in Trust guideline)
Random glucose	baseline, then every cycle
Hba1c	baseline
Blood pressure	baseline and before every bevacizumab dose
Urinalysis for proteinuria	baseline and before every bevacizumab dose
Virology	before cycle 1 if not previously checked
Weight	baseline and every cycle

MAIN TOXICITES 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 - pneumonitis, colitis or hepatitis etc Pembrolizumab SC skin reactions at site of administration route

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

Carboplatin	Aminoglycosides increased risk of nephrotoxicity and ototoxicity. Renal function should be well monitored and audiometric tests as required. Carboplatin can cause a decrease in phenytoin serum levels. This may lead to reappearance of seizures and may require an increase of phenytoin dosages.
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

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 Acute Oncology Initial Management guidelines
If the drug-related toxicity does not resolve to grade 0-1 within 12 weeks after onset of toxicity, discontinuation is recommended.

Hepatic impairment
Bevacizumab
No need for dose adjustment

Carboplatin
No need for dose adjustment is expected

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

Pembrolizumab
No need for dose adjustment is expected

Renal impairment
Bevacizumab
No need for dose adjustment

Carboplatin

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

Paclitaxel
No need for dose adjustment is expected

Pembrolizumab
No need for dose adjustment is expected

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