PEMBROLIZUMAB (Keytruda) CARBOPLATIN PACLITAXEL

INDICATION (ICD10) C56, C54

Check the most recent Blueteq eligibility criteria before prescribing. Blueteq registration required. (www.england.nhs.uk/publication/national-cancer-drugs-fund-list/) (PEMB22) (PEMB32) (PEMB33)

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. (TA939)
2. Pembrolizumab in combination with platinum-containing chemotherapy (carboplatin and paclitaxel) for the 1st line treatment of mismatch repair deficient (dMMR) or microsatellite instability-high **endometrial** carcinoma in adult patients who have 1st recurrence or primary advanced disease and who are not candidates for potentially curative surgery or radiotherapy or chemoradiotherapy but are eligible for systemic therapy (patients with carcinosarcoma (Mixed Mullerian tumour) are eligible, but otherwise uterine sarcomas of any kind are NOT eligible for pembrolizumab in this indication). 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. Has no symptomatically active brain metastases or leptomeningeal metastases. PS 0, 1 or 2. (TA1092)
3. Pembrolizumab 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 1st recurrence or primary advanced disease and who are not candidates for potentially curative surgery or radiotherapy or chemoradiotherapy but are eligible for systemic therapy (patients with carcinosarcoma (Mixed Mullerian tumour) are eligible, but otherwise uterine sarcomas of any kind are NOT eligible for pembrolizumab in this indication). 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. Has no symptomatically active brain metastases or leptomeningeal metastases. PS 0, 1 or 2. (TA1092)

REGIMEN SC (pembrolizumab before chemotherapy)

Cycles 1 to 6

Day 1	**PEMBROLIZUMAB**	395mg	Subcutaneous	over 1 minute
	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

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

REGIMEN IV (pembrolizumab before chemotherapy)
Cycles 1 to 6

Day 1	**PEMBROLIZUMAB**	200mg	IV infusion	100ml 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

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

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

*Dose calculated by EDTA GFR or calculated CrCl + 25 x AUC.
Maximum dose when using CrCl 125+25 x AUC

#or diluent and diluent volume for dose prescribed as per national standardised product specification

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 (cycle 35)

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, 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 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 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 (or as specified in Trust guideline)
Random glucose	baseline and every cycle
HbA1c	Baseline then every 3 months
CA125	baseline and day 1 every cycle or as required
Virology	before cycle 1 if not previously checked
Weight	baseline 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 - 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

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

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 75% of original dose
Transaminase <10xULN and bilirubin 2·01-5xULN	give 50% of original dose
Transaminase ≥10xULN or bilirubin >5xULN	contraindicated

Pembrolizumab

No need for dose adjustment is expected

Renal impairment

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

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
HbA1c	X			X		Every 3 months
Random cortisol	X	X	X	X	X	Every cycle
Blood pressure	X	X	X	X		After 1st week, then every 2 weeks for 2 months then 2 monthly
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