PEMBROLIZUMAB (Keytruda) PACLITAXEL CARBOPLATIN EC

INDICATION (ICD10) C50

Check the most recent Blueteq eligibility criteria before prescribing. Blueteq registration required. (www.england.nhs.uk/publication/national-cancer-drugs-fund-list/) (PEMB21)

1. Pembrolizumab in combination with sequential chemotherapy as neoadjuvant treatment and then continued as adjuvant monotherapy after definitive surgery for patients with previously untreated locally advanced or early stage triple negative breast cancer (M0) disease at high risk of recurrence (high risk as specified in Blueteq criteria). PS 0 or 1. (TA851)

REGIMEN (SC)

Cycles 1 to 4 (Pembrolizumab before all chemotherapy. Paclitaxel before carboplatin)

Days 1, 8 and 15	Premedication 30 minutes prior to infusion:	
	Dexamethasone	8mg IV bolus
	Chlorphenamine	10mg IV bolus
	PACLITAXEL	80mg/m^2 in #ml sodium chloride 0.9% IV infusion over 60 minutes
Day 1	PEMBROLIZUMAB	395mg subcutaneous* (2.4ml) over 1 minute
	CARBOPLATIN	AUC 5 (if CrCl used maximum 700mg) in #ml glucose 5% IV infusion over 30 minutes
	Dose calculated by EDTA GFR or calculated (CrCl + 25) x AUC.	

Cycles 5 to 8 (pembrolizumab before chemotherapy)

Day 1	PEMBROLIZUMAB	395mg subcutaneous* over 1 minute
	EPIRUBICIN	90mg/m^2 IV bolus
	CYCLOPHOSPHAMIDE	600mg/m^2 IV bolus

Cycles 9, 11, 13, 15 and 17

Day 1	PEMBROLIZUMAB	790mg subcutaneous* (4.8ml) over 2 minutes

*Into the thigh or abdomen, avoiding the 5cm area around the navel

REGIMEN (IV)

Cycles 1 to 4 (Pembrolizumab before all chemotherapy. Paclitaxel before carboplatin)

Days 1, 8 and 15	Premedication 30 minutes prior to infusion:	
	Dexamethasone	8mg IV bolus
	Chlorphenamine	10mg IV bolus
	PACLITAXEL	80mg/m^2 in #ml sodium chloride 0.9% IV infusion over 60 minutes
Day 1	PEMBROLIZUMAB	200mg in 100ml sodium chloride 0.9% IV infusion over 30 minutes
	CARBOPLATIN	AUC 5 (if CrCl used maximum 700mg) in #ml glucose 5% IV infusion over 30 minutes
	Dose calculated by EDTA GFR or calculated (CrCl + 25) x AUC.	

Cycles 5 to 8

Day 1	PEMBROLIZUMAB	200mg in 100ml sodium chloride 0.9% IV infusion over 30 minutes
	EPIRUBICIN	90mg/m^2 IV bolus
	CYCLOPHOSPHAMIDE	600mg/m^2 IV bolus

Cycles 9, 11, 13, 15 and 17

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

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

CYCLE FREQUENCY AND NUMBER OF CYCLES

Paclitaxel weekly and carboplatin every 21 day for 4 cycles. A formal medical review is required before the end of the first 6 weeks of treatment.

EC every 21 days for 4 cycles

Pembrolizumab every 21 days for 8 cycles (neoadjuvant) then every 42 days for 5 cycles (adjuvant). Adjuvant pembrolizumab (cycle 9) to start within 2 months of surgery unless has progressive disease despite neoadjuvant treatment and/or does not have definitive surgery then the patient will NOT proceed to adjuvant pembrolizumab therapy.

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 4

Low risk days 8 and 15 cycles 1 to 4

High risk day 1 cycles 5 to 8

Minimal risk day 1 cycles 9, 11, 13, 15 and 17

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
GCSF	3 days following each weekly paclitaxel, 7 days in EC arm

EXTRAVASATION AND TYPE OF LINE / FILTERS

Carboplatin – possible irritant
Cyclophosphamide – neutral
Epirubicin – vesicant
Paclitaxel – vesicant
Pembrolizumab IV – neutral

Administer Paclitaxel via polyethylene lined or DEHP free administration set with ≤0.22micron filter.
Administer pembrolizumab IV via low protein binding 0.2 to 5micron in-line or add-on filter

Central (or peripheral) line

INVESTIGATIONS

Blood results required before SACT administration:
Paclitaxel Carboplatin Pembrolizumab
FBC every dose. U&E and LFTs every dose (unless no concerns on day 1, then every cycle).
Neutrophils x 10^9/L ≥1.0 day 1, ≥0.8 on days 8 and 15 if not omit (clinician discretion)
Platelets x 10^9/L ≥100 day 1, ≥80 days 8 and 15 if not omit (clinician discretion)
Thyroid function baseline, then every cycle
Random cortisol baseline, then every cycle (or as specified in Trust guideline)
Random glucose every cycle
Hba1c baseline
ECHO required if patient has preexisting cardiac disease or risk factors eg smoking or age.
Baseline weight and every cycle

EC Pembrolizumab
FBC every dose. U&E and LFTs every dose (unless no concerns on day 1, then every cycle).
Neutrophils x 10^9/L ≥1.0 day 1
Platelets x 10^9/L ≥100 day 1
Thyroid function baseline, then every cycle
Random cortisol baseline, then every cycle
Random glucose every cycle
ECHO required if patient has pre-existing cardiac disease
Weight every cycle

Pembrolizumab
FBC, U&E and LFTs every dose
Neutrophils x 10^9/L ≥1.0 day 1
Platelets x 10^9/L ≥100 day 1
Thyroid function baseline, then every dose
Random cortisol baseline, then every dose
Random glucose every dose
Weight every dose

MAIN TOXICITES AND ADVERSE REACTIONS

Carboplatin	Ototoxicity – monitor Neurotoxicity - monitor
Cyclophosphamide	may irritate bladder, drink copious volumes of water.
Epirubicin	Cardiotoxicity – monitor cardiac function. Epirubicin may be stopped in future cycles if signs of cardiotoxicity e.g. cardiac arrhythmias, pericardial effusion, tachycardia with fatigue.
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)

Cyclophosphamide	Cytochrome P450 enzyme inducers (eg rifampicin, carbamazepine, phenytoin, St Johns Wort, corticosteroids): may increase active cyclophosphamide metabolites. Allopurinol, Cimetidine and protease inhibitors: may increase active metabolites. Aprepitant, Ciprofloxacin, Fluconazole, Itraconazole: may reduce activation of cyclophosphamide and alter the effectiveness of treatment. Grapefruit juice: decreased or delayed activation of cyclophosphamide. Patients should be advised to avoid grapefruit juice for 48 hours before and on day of cyclophosphamide dose.
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 (eg erythromycin, fluoxetine, gemfibrozil) use with caution. inducors (eg rifampicin, carbamazepine, phenytoin, phenobarbital, efavirenz, nevirapine) use with caution.

DOSE MODIFICATIONS

Epirubicin maximum lifetime dose
= 650mg/m^2 (in patients with cardiac dysfunction or exposed to mediastinal irradiation)
= 1000mg/m^2 (with normal cardiac function)

Haematological

Previous neutropenic sepsis, Symptoms including diarrhoea, mucositis and leucopenia, discuss with Registrar or Consultant

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 paclitaxel dose reduction
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

Epirubicin

Bilirubin 24-51micromol/L	give 50% dose
Bilirubin 52-85micromol/L or AST >4xULN	give 25% dose
Bilirubin >86micromol/L or Child Pugh C	not recommended

Paclitaxel
In the absence of Gilbert's syndrome:

Transaminase <10xULN and bilirubin ≤1.25xULN	no dose reduction
Transaminase <10xULN and bilirubin 1.26-2xULN	clinician discretion
Transaminase <10xULN and bilirubin 2·01-5xULN	clinician discretion
Transaminase ≥10xULN or bilirubin >5xULN	contraindicated

Pembrolizumab
No dose adjustment is needed

Renal impairment

Carboplatin

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

Cyclophosphamide

CrCl 10-29ml/min	Consider giving 75% dose
CrCl <10ml/min	not recommended, if unavoidable consider 50% of original dose

Paclitaxel
No dose adjustment is needed

Pembrolizumab
No dose adjustment is needed

REFERENCES
CDF