PEMBROLIZUMAB (Keytruda) PACLITAXEL CARBOPLATIN weekly 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 chemotherapy as neoadjuvant treatment and then continued as adjuvant monotherapy after definitive surgery for patients with previously untreated locally advanced early stage (M0) triple negative breast cancer at high risk of recurrence (T1c N1-2 or T2-4 N0-2 disease. T1c N1-2 disease or T2 N0 disease or T2 N1-2 disease or T3 N0 disease or T3 N1-2 disease or T4 N0 disease or T4 N1-2 disease). PS 0 or 1. (TA851)

REGIMEN

Cycles 1 to 4 (Paclitaxel to be administered 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
	CARBOPLATIN	AUC 1.5 (if CrCl used maximum 220mg) in #ml glucose 5% IV infusion over 30 minutes
	Dose calculated by EDTA GFR or calculated (CrCl + 25) x AUC.	
Day 1	PEMBROLIZUMAB	200mg in 100ml sodium chloride 0.9% IV infusion over 30 minutes

diluent volume for dose prescribed as per national standardised product specification

Cycles 5 to 8

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

Cycles 9, 11, 13, 15 and 17 (even number cycles no treatment)

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

CYCLE FREQUENCY AND NUMBER OF CYCLES

Paclitaxel and carboplatin - every 7 days for 12 weeks (4 x 21 days)
EC every 21 days for 4 cycles
Pembrolizumab every 21 days for 8 cycles then every 42 days for 5 cycles (intent to start within 2 months of surgery).
A formal medical review as to how pembrolizumab and neoadjuvant chemotherapy are being tolerated and whether neoadjuvant chemotherapy should continue or not will be scheduled to occur at least by the end of the first 6 weeks of treatment.
If patient has progressive disease despite neoadjuvant treatment and/or does not have definitive surgery then the patient will NOT proceed to adjuvant pembrolizumab therapy.

ANTI-EMETICS

Moderate risk day 1, 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 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 – neutral

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

Central line

INVESTIGATIONS

Blood results required before SACT administration
FBC, U&E and LFTs every dose
Neutrophils $x10^9$/L ≥1.0
Platelets $x10^9$/L ≥100
Thyroid function baseline, then every cycle
Random cortisol baseline, then every cycle
Random glucose every cycle
ECG (possible ECHO) required if patient has preexisting cardiac disease
Baseline weight and every cycle

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

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

Cyclophosphamide	Cytochrome P450 enzyme inducers (e.g. 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 (e.g. erythromycin, fluoxetine, gemfibrozil) use with caution. inducors (e.g. 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 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

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

REFERENCES
CDF