PEMBROLIZUMAB (Keytruda) CARBOPLATIN PACLITAXEL (neoadjuvant then adjuvant)

INDICATION (ICD10) C34

Check the most recent Blueteq eligibility criteria before prescribing. Blueteq registration required. (www.england.nhs.uk/publication/national-cancer-drugs-fund-list/) (PEMB30)

1. Pembrolizumab in combination with chemotherapy for neoadjuvant treatment and then continued as adjuvant monotherapy in adults with previously untreated UICC/AJCC 8th edition stage IIA or IIB or IIIA or N2 only IIIB M0 disease non-small cell lung cancer (without EGFR 19 or 21 mutation or an ALK gene fusion) AND who are candidates for potentially curative surgery (undergo resection within 20 weeks of the 1st dose of neoadjuvant therapy and any form of post-operative radiotherapy is for this to start no later than 8 weeks after surgery and for adjuvant pembrolizumab to commence no later than 4 weeks after completion of radiotherapy). PS 0 or 1. (TA1017)

REGIMEN (SC)

Cycles 1 to 4 (pembrolizumab before chemotherapy)

Day 1 PEMBROLIZUMAB 395mg subcutaneous* (2.4ml) over 1 minute
Premedication 30 minutes prior to infusion:
Dexamethasone 20 mg IV bolus
Chlorphenamine 10 mg IV bolus
PACLITAXEL 175mg/m^2 in #ml sodium chloride 0.9% infusion over 3 hours
CARBOPLATIN AUC 5 in #ml glucose 5% infusion over 30 minutes
Dose calculated by EDTA GFR or calculated CrCl + 25 x AUC.
(Maximum dose when using CrCl 125+25 x AUC)

Cycles 5, 7, 9, 11, 13, 15 and 17 (only given following surgery, radiotherapy or chemoradiotherapy)
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 chemotherapy)

Day 1 PEMBROLIZUMAB 200mg in 100ml sodium chloride 0.9% IV infusion over 30 minutes
Premedication 30 minutes prior to infusion:
Dexamethasone 20 mg IV bolus
Chlorphenamine 10 mg IV bolus
PACLITAXEL 175mg/m^2 in #ml sodium chloride 0.9% infusion over 3 hours
CARBOPLATIN AUC 5 in #ml glucose 5% infusion over 30 minutes
Dose calculated by EDTA GFR or calculated CrCl + 25 x AUC.
(Maximum dose when using CrCl 125+25 x AUC)

Cycles 5, 7, 9, 11, 13,15 and 17 (only given following surgery, radiotherapy or chemoradiotherapy)
Day 1 PEMBROLIZUMAB 400mg in 100ml sodium chloride 0.9% IV infusion over 30 minutes
diluent volume for dose prescribed as per national standardised product specification

CYCLE FREQUENCY AND NUMBER OF CYCLES

Combination treatment every 21 days for 4 cycles. A formal medical review as to how pembrolizumab plus chemotherapy is being tolerated and whether treatment with pembrolizumab plus chemotherapy should be completed or not will be scheduled to occur at least by the end of the second cycle of treatment.
Pembrolizumab monotherapy every 42 days (ie cycles 5, 7, 9, 11, 13, 15 and 17). Pembrolizumab will be stopped earlier than the 7 monotherapy cycles, if there is any local or distant disease progression at any time in the neoadjuvant, peri-operative and adjuvant phases of treatment or unacceptable toxicity.

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
Minimal risk day 1 cycles 5, 7, 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

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^{++} and LFTs, every cycle
Neutrophils x 10^9/L ≥1.5
Platelets x 10^9/L ≥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 (or as specified in Trust guideline)
Random glucose every cycle
Hba1c baseline
Baseline weight 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)

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 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

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 dose adjustment is needed

Renal impairment

Carboplatin

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

Pembrolizumab

No dose adjustment is needed

REFERENCES

1. CDF