PEMBROLIZUMAB (Keytruda) PEMETREXED CARBOPLATIN (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.
Carboplatin to start 30 minutes after completing pemetrexed

Day 1 PEMBROLIZUMAB 395mg subcutaneous* (2.4ml) over 1 minute
Pre-medication: Dexamethasone 4mg bd for 3 days (starting the day before chemotherapy)

PEMETREXED	500mg/m^2 in #ml diluent IV infusion over 10 minutes
CARBOPLATIN	AUC 5 in #ml glucose 5% IV 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 and 15 (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.
Carboplatin to start 30 minutes after completing pemetrexed

Day 1 PEMBROLIZUMAB 200mg in 100ml sodium chloride 0.9% IV infusion over 30 minutes
Pre-medication: Dexamethasone 4mg bd for 3 days (starting the day before chemotherapy)

PEMETREXED	500mg/m^2 in #ml diluent IV infusion over 10 minutes
CARBOPLATIN	AUC 5 in #ml glucose 5% IV 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 or licensed dose

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.
Pemetrexed	Ensure premedication taken Dexamethasone 4mg bd for 3 days (starting the day before chemotherapy) Folic acid 400mcg/day orally starting 1 to 3 weeks before chemotherapy continuing until 21 days after the last dose of pemetrexed. Hydroxycobalamin 1000mcg IM every 9 weeks starting 1 to 3 weeks before chemotherapy (give with every 3rd cycle of chemotherapy)

EXTRAVASATION AND TYPE OF LINE / FILTERS

Carboplatin – irritant
Pembrolizumab - neutral
Pemetrexed IV - inflammatory

Pembrolizumab IV – Use low protein binding 0.2 to 5micron in-line or add-on filter
Peripheral line

INVESTIGATIONS

Blood results required before SACT administration
FBC, U&E and LFTs every cycle
Mg^{++} baseline and then as clinically indicated
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. Patients with hydronephrosis or serum creatinine ≥100micromol/L need a serum creatinine checked every cycle.
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.
Pembrolizumab	Immune related toxicities - pneumonitis, colitis or hepatitis etc Pembrolizumab SC skin reactions at site of administration route
Pemetrexed	Skin reactions Pneumonitis

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.
Pemetrexed	Aminogycosides – increased risk of nephrotoxicity and ototoxicity NSAIDs Avoid for at least 5 days prior to and 2 days after pemetrexed dose.

DOSE MODIFICATIONS

Haematological

Pemetrexed
Delay treatment until resolution then treat with appropriate dose modification.
Nadir neutrophils <0.5 and nadir platelets >50 — 75% of previous dose
Nadir platelets ≤50 regardless of nadir neutrophils — 50% of previous dose
Treatment with pemetrexed should be discontinued if a patient experiences any haematologic or non-haematologic grade 3 or 4 toxicity after 2 dose reductions.

Non-haematological

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.

Pemetrexed

Any grade 3 or 4 non-haematological toxicities except mucositis	Give 75% of previous dose
Any diarrhoea requiring hospitalisation (irrespective of grade) or grade 3 or 4 diarrhoea	Give 75% of previous dose
Grade 3 or 4 mucositis	Give 50% of previous dose
Neurotoxicity grade 3 or 4	Discontinue therapy
If a patient experiences any haematological or non-haematological grade 3 or 4 toxicity after 2 dose reductions or immediately if grade 3 or 4 neurotoxicity is observed.	Discontinue therapy

Hepatic impairment

Pembrolizumab

No dose adjustment is needed

Pemetrexed

Total bilirubin should be ≤1.5xULN.

Alk phos, AST and ALT ≤3xULN. (Alk phos, AST, and ALT ≤5x normal is acceptable if liver has tumour involvement). Clinical decision

Renal impairment

Carboplatin

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

Pembrolizumab

No dose adjustment is needed

Pemetrexed

CrCl ≤45ml/min	Not recommended

REFERENCES

1. CDF