PEMBROLIZUMAB (Keytruda) PEMETREXED CISPLATIN

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/) (PEMB8)

1. Pembrolizumab in combination with pemetrexed-based combination chemotherapy for treating untreated PD-L1-positive or negative locally advanced or metastatic stage IIIB or IV stage IIIB or IV non-squamous non-small-cell lung cancer. Not received prior treatment with an anti PD-1, anti-PD-L1, anti-PD-L2, anti-CD137 or anti-cytotoxic T-lymphocyte-associated antigen-4 (CTL-4) antibody unless the patient completed or discontinued checkpoint inhibitor immunotherapy as art of adjuvant/neoadjuvant/maintenance therapy without disease progression on treatment and at least 6 months elapsed between the date of last immunotherapy treatment and the date of first diagnosis of relapse with recurrent or metastatic disease. No symptomatically active brain metastases or leptomeningeal metastases. On completion of 4 cycles of pembrolizumab plus pemetrexed-based chemotherapy in combination with carboplatin and in the absence of disease progression, treatment with pembrolizumab in combination with 'maintenance' pemetrexed. PS 0 or 1. (TA683)

REGIMEN (SC)

Cycles 1 to 4 (Pembrolizumab before chemotherapy. Cisplatin 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 IV infusion over 10 minutes
Prehydration
CISPLATIN 75mg/m^2 in 1000ml sodium chloride 0.9% IV infusion over 2 hours
Post hydration

Cycles 5 to 35

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 IV infusion over 10 minutes

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

REGIMEN (IV)

Cycles 1 to 4 (Pembrolizumab before chemotherapy. Cisplatin to start 30 minutes after completing pemetrexed)

Day 1 PEMBROLIZUMAB 200mg in 100ml sodium chloride IV infusion over 30 minutes
Pre-medication: Dexamethasone 4mg bd for 3 days (starting the day before chemotherapy)
PEMETREXED 500mg/m^2 in #ml IV infusion over 10 minutes
Prehydration
CISPLATIN 75mg/m^2 in 1000ml sodium chloride 0.9% IV infusion over 2 hours
Post hydration

Cycles 5 to 35

Day 1 PEMBROLIZUMAB 200mg in 100ml sodium chloride IV infusion over 30 minutes
Pre-medication: Dexamethasone 4mg bd for 3 days (starting the day before chemotherapy)
PEMETREXED 500mg/m^2 in #ml IV infusion over 10 minutes

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

CYCLE FREQUENCY AND NUMBER OF CYCLES

Combination every 21 days for 4 cycles. A formal medical review as to whether treatment with pembrolizumab in combination with pemetrexed plus cisplatin should continue or not will be scheduled to occur at least by the end of the first 6 weeks of treatment.
Pembrolizumab and pemetrexed every 21 days cycles 5 to 35 cycles (up to maximum 2 years).

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

High risk day cycles 1 to 4
Low risk day cycles 5 to 35

CONCURRENT MEDICATION REQUIRED

Cisplatin	Ensure adequate pre and post hydration. If urine output is <100ml/hour or if patient gains >2kg in weight during IV administration post cisplatin give 20-40mg furosemide PO/IV.
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

Cisplatin - exfoliant
Pembrolizumab IV – neutral
Pemetrexed - inflammatory

Pembrolizimab 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 and LFTs every cycle
Neutrophils x 10^9/L ≥1.5
Platelets x 10^9/L ≥100
Serum creatinine 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

Cisplatin	Nephrotoxicity – ensure adequate pre and post hydration is prescribed. Ototoxicity – assess patient for tinnitus or hearing abnormalities.
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)

Pemetrexed	Aminogycosides – increased risk of nephrotoxicity and ototoxicity NSAIDs Avoid all 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

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

Pembrolizumab

No dose adjustment is needed

Renal impairment

Cisplatin

CrCl >60ml/min	give 100% dose
CrCl 50-59ml/min	give 75% dose
CrCl 40-49ml/min	give 50% dose (curative intent) not recommended (palliative intent)
CrCl <40ml/min	not recommended

Pembrolizumab

No dose adjustment is needed

Pemetrexed

CrCl ≤45ml/min	Not recommended

REFERENCES

1. Gandhi, L et al; NEJM 2018; 378: 2078-2092