PEMBROLIZUMAB (Keytruda) GEMCITABINE 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)

(Pembrolizumab before chemotherapy. Gemcitabine and carboplatin can be given in any order)

Cycles 1 to 4

Day 1 PEMBROLIZUMAB 395mg subcutaneous* (2.4ml) over 1 minute
GEMCITABINE 1000mg/m^2 infusion in #ml diluent IV infusion over 30 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)
Day 8 GEMCITABINE 1000mg/m^2 infusion in #ml diluent IV infusion over 30 minutes

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)

(Pembrolizumab before chemotherapy. Gemcitabine and carboplatin can be given in any order)

Cycles 1 to 4

Day 1 PEMBROLIZUMAB 200mg in 100ml sodium chloride 0.9% IV infusion over 30 minutes
GEMCITABINE 1000mg/m^2 infusion in #ml diluent IV infusion over 30 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)
Day 8 GEMCITABINE 1000mg/m^2 infusion in #ml diluent IV infusion over 30 minutes

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 emetic risk day 1 cycles 1 to 4
Low risk day 8
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 H_2 antagonist Carboplatin should be given at a slower rate e.g. 2-4 hours.

EXTRAVASATION AND TYPE OF LINE / FILTERS

Carboplatin – irritant
Gemcitabine – neutral
Pembrolizumab IV - neutral

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 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.
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.
Gemcitabine	Diarrhoea – see dose modifications, treat with ,loperamide or codeine Mucositis – see dose modifications, use routine mouthcare
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)

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.

DOSE MODIFICATIONS

Haematological

Gemcitabine

Neutrophils >1.5x10^9/L and platelets >100x10^9/L	give 100% dose
Neutrophils<1.5x10^9/L or platelets <100x10^9/L	delay treatment (day 1) or omit treatment (day 8)

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.

Gemcitabine

Diarrhoea and/or mucositis grade 2 toxicity	omit until toxicity resolved then restart at 100% dose
Diarrhoea and/or mucositis grade 3	omit until toxicity resolved then restart at 75% dose
Diarrhoea and/or mucositis grade 4	omit until toxicity resolved then restart at 50% dose

Hepatic impairment

Gemcitabine

Bilirubin >27µmol/L	initiate treatment with 80% dose

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