NIVOLUMAB (Opdivo) PEMETREXED CARBOPLATIN

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/) (NIV23)

1. Nivolumab plus chemotherapy for the neoadjuvant treatment of adults with previously untreated UICC/AJCC 8th edition stage IIA or IIB or IIIA or N2 only IIIB non-small cell lung cancer (stage M0 without an EGFR 19 or 21 mutation or ALK gene fusion)) tumours at least 4 cm or node positive and who are candidates for potentially curative surgery within 6 weeks of completing the 3rd cycle and have been assessed by thoracic surgical team to be eligible for a potentially curative resection and has the necessary fitness to undergo such surgery Check Blueteq criteria carefully for eligibility for future treatments. PS 0 or 1. (TA876)

REGIMEN

Carboplatin to start 30 minutes after completing pemetrexed

Day 1 NIVOLUMAB 360mg IV infusion 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 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)

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

CYCLE FREQUENCY AND NUMBER OF CYCLES

Every 21 days for maximum 3 cycles (must be formally reviewed before end of 2nd cycle)

ANTI-EMETICS

Moderate emetic risk day 1

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
Nivolumab – neutral
Pemetrexed - inflammatory

Nivolumab use low protein binding 0.2 to 1.2micron in-line or add-on filter.
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
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.
Baseline weight and every cycle

MAIN TOXICITES AND ADVERSE REACTIONS

Carboplatin	Ototoxicity - monitor Neurotoxicity – monitor.
Nivolumab	Immune related toxicities - pneumonitis, colitis or hepatitis etc
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

Nivolumab
Immune-related adverse reactions - refer to TV immune-oncology agent immune related adverse event clinical guideline.

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

Nivolumab

Data from patients with moderate or severe hepatic impairment are too limited to draw conclusions. Nivolumab should be administered with caution in patients with moderate or severe hepatic impairment ie bilirubin >1.5xULN and any AST.

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

Nivolumab

Data from patients with severe renal impairment (CrCl <30ml/min) are too limited to draw conclusions.

Pemetrexed

CrCl ≤45ml/min	Not recommended

REFERENCES

1. Forde et al NEJM N Engl J Med 2022; 386:1973-1985