DURVALUMAB (Imfnzi) 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/) (DUR3)

1. For the treatment of 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 non-small cell lung cancer staged as having M0 disease (EGFR 19 or 21 mutation or an ALK gene fusion) AND who are candidates for potentially curative surgery. PS 0 or 1.

REGIMEN

Cycles 1 to 4

Carboplatin to start 30 minutes after completing pemetrexed

Day 1 DURVALUMAB 1500mg in 250ml sodium chloride 0.9% IV infusion over 60 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)

Resection should occur within 20 weeks of starting cycle 1.

Cycles 5 to 16 (cycle 5 should start within 12 weeks of resection, or within 4 weeks of completion of any radiotherapy, which should start within 8 weeks of resection)
Day 1 DURVALUMAB 1500mg in 250ml sodium chloride 0.9% IV infusion over 60 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 durvalumab plus chemotherapy is being tolerated and whether treatment with durvalumab plus chemotherapy should be completed or not will be scheduled to occur at least by the end of the second cycle of treatment.
Durvalumab every 28 days cycles 5 to 16 (maximum 12 cycles) (should start within 12 weeks of resection including any radiotherapy).

ANTI-EMETICS

Moderate risk day 1 cycles 1 to 4
Minimal risk day 1 cycles 5 to 16

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
Durvalumab - neutral
Pemetrexed - inflammatory

Durvalumab – Use low protein binding 0.2 or 0.22micron 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
Random glucose every cycle
Baseline weight and every cycle cycles 1 to 4, then every 3rd cycle cycles 5 to 16

MAIN TOXICITES AND ADVERSE REACTIONS

Carboplatin	Ototoxicity - monitor Neurotoxicity – monitor.
Durvalumab	Immune related toxicities
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

Durvalumab

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

Durvalumab

No dose adjustment is needed for patients with 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

Renal impairment

Carboplatin

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

Durvalumab

No dose adjustment is required in mild or moderate renal impairment. There is insufficient data from patients with severe renal impairment (CrCl <30ml/min) for dosing recommendations.

Pemetrexed

CrCl ≤45ml/min	Not recommended

REFERENCES

1. CDF