DURVALUMAB (Imfinzi) VINORELBINE (oral) 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

Day 1 DURVALUMAB 1500mg in 250ml sodium chloride 0.9% IV infusion over 60 minutes
VINORELBINE 60mg/m^2 (maximum dose 120mg) capsule once daily oral
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 VINORELBINE 60mg/m^2 (maximum dose 120mg) capsule once daily oral

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

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 emetic risk days 1 and 8 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.
Vinorelbine	Consider concomitant laxatives particularly in patients with a history of constipation or those receiving opioid analgesics.

EXTRAVASATION AND TYPE OF LINE / FILTERS

Carboplatin – irritant
Durvalumab - neutral

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 days 1 and 8 every cycle
Mg^{++} baseline and then as clinically indicated
Neutrophils x 10^9/L ≥1.5
Platelets x 10^9/L ≥100
Serum creatinine
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
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
Vinorelbine	Neurological disorders Stomatitis Constipation

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.
Vinorelbine	Caution with strong inducers or inhibitors eg rifampicin, carbamazepine, phenytoin, clarithromycin, fluconazole, itraconazole etc

DOSE MODIFICATIONS

Haematological

Vinorelbine
Omit day 8 based on platelets - clinical decision

Non-haematological

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

Hepatic impairment

Durvalumab
No dose adjustment is needed for patients with hepatic impairment.

Vinorelbine
Mild liver impairment (bilirubin <1.5xULN and ALT and/or AST from 1.5-2.5xULN) 60mg/m²/week.
Moderate liver impairment (bilirubin 1.5-3xULN, whatever the levels of ALT and AST) 50mg/m²/week.
Severe hepatic impairment contra-indicated.

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.

REFERENCES
1. CDF