DURVALUMAB (Imfinzi) CARBOPLATIN PACLITAXEL (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
Premedication 30 minutes prior to infusion:
Dexamethasone 20 mg IV bolus
Chlorphenamine 10 mg IV bolus
PACLITAXEL 175mg/m^2 in #ml sodium chloride 0.9% infusion over 3 hours
CARBOPLATIN AUC 5 in #ml glucose 5% 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

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).
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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.
Paclitaxel	Ensure premedication given before paclitaxel

EXTRAVASATION AND TYPE OF LINE / FILTERS

Carboplatin - irritant
Durvalumab - neutral
Paclitaxel – vesicant

Paclitaxel via polyethylene lined or DEHP free administration set with ≤0.22micron filter
Durvalumab – Use low protein binding 0.2 or 0.22micron in-line or add-on filter
Central or peripheral line

INVESTIGATIONS

Blood results required before SACT administration
FBC, U&E including Mg^{++} 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.
Thyroid function baseline, then every 1 to 2 cycles
Random cortisol baseline, then every 1 to 2 cycles
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
Paclitaxel	(2% risk of severe hypersensitivity) Reactions range from mild hypotension (light-headedness) to full cardiac collapse (anaphylactic shock). Discontinue infusion and resuscitate appropriate to reaction. If reaction is mild and settles promptly (i.e. within 5-10 minutes), cautiously restart at a slower rate under close supervision. If further reactions occur stop treatment.

INTERACTIONS WHICH MAY REQUIRE DOSE MODIFICATIONS
(not exhaustive list check SPC/BNF/Stockleys)

Paclitaxel	DOACs to be used with caution, need dose modifications or to be avoided eg apixaban Clopidogrel interacts with paclitaxel Paclitaxel is catalysed, by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. inhibitors (e.g. erythromycin, fluoxetine, gemfibrozil) use with caution. inducors (e.g. rifampicin, carbamazepine, phenytoin, phenobarbital, efavirenz, nevirapine) use with caution.

DOSE MODIFICATIONS

Non-haematological

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

Paclitaxel
If patient complains of tinnitus, tingling of fingers and/or toes or motor weakness discuss with Consultant or Registrar before administration
If grade ≥2 neuropathy, consider paclitaxel dose reduction
If grade >3 peripheral neuropathy is >grade 3 omit further paclitaxel

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

Paclitaxel
In the absence of Gilbert's syndrome:

Transaminase <10xULN and bilirubin ≤1.25xULN	no dose reduction
Transaminase <10xULN and bilirubin 1.26-2xULN	give 77% of original dose
Transaminase <10xULN and bilirubin 2·01-5xULN	give 51% of original dose
Transaminase ≥10xULN or bilirubin >5xULN	contraindicated

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