NIVOLUMAB (Opdivo) CARBOPLATIN PACLITAXEL

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) (NIV25)

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)
2. Nivolumab plus chemotherapy for previously untreated 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 (stage M0 without an EGFR 19 or 21 mutation or ALK gene fusion))) non-small cell lung cancer AND and who are candidates for potentially curative surgery within 20 weeks of the 1st dose of neoadjuvant therapy 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. (TA1127)

REGIMEN

Cycles 1-3 **(NIV23)**, Cycles 1-4 **(NIV25)**

Day 1 NIVOLUMAB 360mg IV infusion in 100ml sodium chloride IV infusion over 30 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)

Cycles 5-17 **NIV25 patients only** (separate regimen on Aria)

Day 1 NIVOLUMAB 1200mg subcutaneous over 3 to 5 minutes

diluent volume for dose prescribed as per national standardised product specification

CYCLE FREQUENCY AND NUMBER OF CYCLES

Neoadjuvant only (NIV23) - every 21 days for maximum 3 cycles (must be formally reviewed before end of 2nd cycle).

Neoadjuvant then adjuvant (NIV25) - every 21 days for maximum 4 cycles, followed by adjuvant SC nivolumab monotherapy to commence no later than 12 weeks after surgery (any form of post-operative radiotherapy is to start no later than 8 weeks after surgery and for adjuvant nivolumab to commence no later than 4 weeks after completion of radiotherapy) every 4 weeks for a maximum 13 cycles (use adjuvant SC nivolumab NIV25 regimen on Aria).

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.
Paclitaxel	Ensure premedication given before paclitaxel

EXTRAVASATION AND TYPE OF LINE / FILTERS

Carboplatin – irritant
Nivolumab IV – neutral
Paclitaxel – vesicant

Nivolumab IV use low protein binding 0.2 to 1.2micron in-line or add-on filter.
Paclitaxel via polyethylene lined or DEHP free administration set with ≤0.22micron filter
Central or 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
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)

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.
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
Nivolumab
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
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.

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

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

REFERENCES

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