NIVOLUMAB (Opdivo) VINORELBINE (oral) CISPLATIN

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
Pre-hydration
VINORELBINE 60mg/m^2 (maximum dose 120mg) capsule once daily oral
CISPLATIN 75mg/m^2 in 1000ml sodium chloride 0.9% IV infusion over 2 hours
Post hydration

Day 8 VINORELBINE 60mg/m^2 (maximum dose 120mg) capsule once daily oral

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

Day 1 NIVOLUMAB 1200mg subcutaneous over 3 to 5 minutes

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

High emetic risk day 1
Moderate emetic risk day 8

CONCURRENT MEDICATION REQUIRED

Cisplatin	Ensure adequate pre and post hydration. If urine output is <100 ml/hour or if patient gains >2kg in weight during IV administration post cisplatin give 20-40 mg furosemide PO/IV or 200ml mannitol 10% IV.
Vinorelbine	Consider concomitant laxatives particularly in patients with a history of constipation or those receiving opioid analgesics.

EXTRAVASATION AND TYPE OF LINE / FILTERS

Cisplatin – exfoliant
Nivolumab IV - neutral

Nivolumab IV 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 days 1 and 8 every cycle
Neutrophils x 10^9/L ≥1.5
Platelets x 10^9/L ≥100
Creatinine clearance (GFR) calculated, at the Consultants discretion
Serum creatinine
Baseline weight and every cycle

MAIN TOXICITES AND ADVERSE REACTIONS

Cisplatin	Nephrotoxicity – ensure adequate pre and post hydration is prescribed. Ototoxicity – assess patient for tinnitus or hearing abnormalities.
Nivolumab	Immune related toxicities - pneumonitis, colitis or hepatitis etc
Vinorelbine	Neurological disorders Stomatitis Constipation

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

Cisplatin	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

If patient complains of tinnitus, tingling of fingers and/or toes, discuss with SpR or Consultant before administration.

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

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.

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
Cisplatin

CrCl >60ml/min	give 100% dose
CrCl 50-59ml/min	give 75% dose
CrCl 40-49ml/min	give 50% dose (curative intent)
CrCl <40ml/min	not recommended

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