NIVOLUMAB (Opdivo) VINORELBINE (oral) CARBOPLATIN

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
	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

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 days 1 and 8

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
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
Ideally EDTA GFR should be used
Creatinine clearance (GFR) calculated, at the Consultants discretion
Serum creatinine
Baseline weight and every cycle

MAIN TOXICITES AND ADVERSE REACTIONS

Carboplatin	Ototoxicity - monitor Neurotoxicity – monitor.
Vinorelbine	Neurological disorders Stomatitis Constipation
Nivolumab	Immune related toxicities - pneumonitis, colitis or hepatitis etc

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
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
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