NIVOLUMAB (Opdivo) GEMCITABINE 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 (Gemcitabine and carboplatin can be given in any order)

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

Day 1	NIVOLUMAB	360mg IV infusion in 100ml sodium chloride IV infusion over 30 minutes
	GEMCITABINE	1000 or 1250mg/m^2 infusion in #ml sodium chloride 0.9% IV infusion over 30 minutes
	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	GEMCITABINE	1000 or 1250mg/m^2 infusion in #ml sodium chloride 0.9% IV infusion over 30 minutes

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 or licensed dose

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

Low risk day 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 H_2 antagonist Carboplatin should be given at a slower rate e.g. 2-4 hours.

EXTRAVASATION AND TYPE OF LINE / FILTERS

Carboplatin – irritant
Gemcitabine – neutral
Nivolumab IV – neutral

Nivolumab IV use low protein binding 0.2 to 1.2micron in-line or add-on 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.
Baseline weight and every cycle

MAIN TOXICITES AND ADVERSE REACTIONS

Carboplatin	Ototoxicity - monitor Neurotoxicity – monitor.
Gemcitabine	Diarrhoea – see dose modifications, treat with, loperamide or codeine Mucositis – see dose modifications, use routine mouthcare
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.

DOSE MODIFICATIONS

Haematological

Gemcitabine

Neutrophils >1.5x10^9/L and platelets >100x10^9/L	give 100% dose
Neutrophils<1.5x10^9/L or platelets <100x10^9/L	delay treatment (day 1) or omit treatment (day 8)

Non-haematological

Nivolumab

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

Gemcitabine

Diarrhoea and/or mucositis grade 2 toxicity	omit until toxicity resolved then restart at 100% dose
Diarrhoea and/or mucositis grade 3	omit until toxicity resolved then restart at 75% dose
Diarrhoea and/or mucositis grade 4	omit until toxicity resolved then restart at 50% dose

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.

Gemcitabine

Bilirubin >27µmol/L	initiate treatment with 80% dose

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