Nivolumab, Pemetrexed and Platinum (Lung)

Indication

Nivolumab in combination with platinum- based chemotherapy for neoadjuvant treatment of resectable non-small-cell lung cancer (NSCLC) who satisfy the following criteria:

i) Tumours ≥ 4 cm or node positive (stage IIA or IIB or IIIA or N2 only IIIB tumour according to the UICC/AJCC TNM 8th edition).
ii) NEGATIVE for EGFR 19 or 21 mutation or an ALK gene fusion (NOT a requirement for squamous histology).
iii) Potentially curative resection to proceed within 6 weeks of completing the final cycle of neoadjuvant nivolumab plus chemotherapy.
iv) ECOG performance status (PS) of 0 or 1.

Following neoadjuvant SACT and successful resection:

i) Adjuvant chemotherapy, radiotherapy or chemoradiotherapy is PERMITTED if indicated.
ii) Adjuvant immunotherapy is NOT PERMITTED.

During neoadjuvant SACT:

i) If disease progression occurs, then further immunotherapy is NOT funded IN ANY INDICATION.
ii) If no disease progression but deemed not for surgical resection, further immunotherapy is ONLY PERMITTED following a disease response of at least 6 months (duration from last Nivolumab dose to progressive disease). UNLESS stage III disease and treated with concurrent chemoradiotherapy then potentially eligible for maintenance durvalumab

(NICE TA 876)

ICD-10 codes

Codes with prefix C34

Regimen details

With Carboplatin:

Day	Drug	Dose	Route
1	Nivolumab	360mg	IV infusion
1	Carboplatin	AUC5	IV infusion
1	Pemetrexed	500mg/m^2	IV infusion

With Cisplatin

Day	Drug	Dose	Route
1	Nivolumab	360mg	IV infusion
1	Cisplatin	75mg/m^2	IV infusion
1	Pemetrexed	500mg/m^2	IV infusion

Cycle frequency

Every 3 weeks

Number of cycles

3 cycles

Administration

Nivolumab may be administered without dilution as a 10mg/mL solution or in sodium chloride 0.9% or glucose 5% at a concentration between 1-10mg/mL over 30 minutes. Nivolumab should be administered via an infusion set with an in-line sterile, non-pyrogenic, low protein binding filter (pore size 0.2 – 1.2µm).

Patients should be monitored (blood pressure, pulse and temperature) every 30 minutes during the infusion for infusion related reactions. For mild to moderate reactions, decrease the infusion rate and closely monitor. Premedication with paracetamol and chlorphenamine should be used for further doses. For severe infusion related reactions discontinue treatment.

Pemetrexed is administered in 100mL sodium chloride 0.9% over 10 minutes.

Carboplatin is administered in 250-500mL glucose 5% over 30-60 minutes.

Patients should be observed closely for hypersensitivity reactions, particularly during the first and second infusions. Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of carboplatin. Facilities for the treatment of hypotension and bronchospasm must be available.

If hypersensitivity reactions occur, minor symptoms such as flushing or localised cutaneous reactions do not require discontinuation of therapy. The infusion may be temporarily interrupted and when symptoms improve restarted at a slower infusion rate. Chlorphenamine 10mg IV may be administered. Severe reactions, such as hypotension, bronchospasm or generalised rash/erythema require immediate discontinuation of carboplatin and appropriate therapy.

Cisplatin is administered in 500mL sodium chloride 0.9% over 60 minutes following the pre and post hydration protocol below.

Infusion Fluid & Additives	**Volume**	**Infusion Time**
Sodium Chloride 0.9%	1000mL	60 minutes
Mannitol 20% **OR** Mannitol 10%	200mL 400mL	10 minutes 15 minutes
Ensure urine output > 100mL / hour prior to giving cisplatin. Give a single dose of furosemide 20mg iv if necessary.		
Cisplatin	500mL	60 minutes
Sodium Chloride 0.9% + 2g $MgSO_4$ + 20mmol KCl	1000mL	2 hours
TOTAL	**2700 or 2900mL**	**4 hours 10 minutes or 4 hours 15 minutes**

Note: Patients with magnesium or potassium below the normal range should have 2g $MgSO_4$ and 20mmol KCl added to the pre-hydration bag and the duration of the infusion increased to 2 hours.
Patients should be advised to drink at least 2 litres of fluid over the 24 hours following cisplatin.

Pre-medication

Vitamin B12 (hydroxycobalamin) 1mg IM should be administered in the week preceding the first cycle Pemetrexed should be administered no earlier than 48 hours after vitamin B12 injection for the first dose.
Folic acid 400 microgram PO OD should be started at least 1 week before first cycle (with a minimum of 5 doses taken in the 7 days preceding the first dose) and continued until 3 weeks after last cycle.
Dexamethasone 4mg PO BD for 3 days should be started 24 hours before chemotherapy.
Antiemetics as per local guidelines.

Emetogenicity

Carboplatin based regimen: moderate emetic potential – refer to local policy
Cisplatin based regimen: high emetic potential – refer to local policy

Additional supportive medication

Loperamide if required. Proton pump inhibitor if required.
Mouthwashes as per local policy.
If magnesium levels < normal reference range refer to local magnesium replacement guidelines

Extravasation

Nivolumab is neutral (Group 1)
Pemetrexed is an inflammatant (Group 2)
Carboplatin is an exfoliant (Group 4)
Cisplatin is an exfoliant (Group 4)

Investigations – pre first cycle

Investigation	**Validity period** (or as per local practice)
FBC	14 days
U+E (including creatinine)	14 days
LFTs	14 days
Magnesium	14 days
Calcium	14 days
Thyroid function	14 days
Glucose	14 days
Cortisol	At consultant discretion

Investigations – pre subsequent cycles

Investigation	**Validity period** (or as per local practice)
FBC	96 hours
U+E (including creatinine)	7 days
LFTs	7 days
Magnesium	7 days
Calcium	7 days
Thyroid function	6 weekly
Glucose	As clinically indicated
Cortisol	At consultant discretion

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	**Limit**
Neutrophils	≥1.0 x 10^9/L
Platelets	≥100 x 10^9/L
Creatinine Clearance (CrCl)	> 60mL/min (if cisplatin based regimen) >45ml/min (if carboplatin based regimen)
Bilirubin	<1.5 x ULN
ALT/AST	<3 x ULN
Alkaline phosphatase	<3 x ULN

Dose modifications

- **Haematological toxicity**

If neutrophils < 1.0 x 10^9/L and platelets < 100 x 10^9/L delay for 1 week. If resolved, then continue with 100% dose. If 2 or more delays, then reduce dose of pemetrexed to 75% and cisplatin to 75% or carboplatin to AUC4.

- **Renal impairment**

Nivolumab – no need for dose adjustment is expected

Carboplatin is contraindicated if CrCl <20mL/min.

Pemetrexed should NOT be administered if CrCl <45 mL/min.

CrCl (mL/min)	**Cisplatin dose**
≥ 60	100%
50-59	75%
40-49	50% (consider switching to carboplatin AUC 5)
< 40	Contraindicated

- **Hepatic impairment**

Nivolumab: no need for dose adjustment is expected. See below for management of immune-mediated hepatitis.

Pemetrexed: No information available for patients with bilirubin > 1.5 x ULN and/or AST/ALT > 3 x ULN (5 x ULN if liver metastases present) – consultant decision.

Carboplatin: No dose modification required.

Cisplatin: No dose modification required.

- **Other toxicities**

Mucositis
Grade 3-4: reduce pemetrexed to 50% dose and continue with 100% dose cisplatin/carboplatin.

Neurotoxicity
Grade 2: reduce cisplatin to 50% dose or carboplatin to AUC4 and continue with 100% dose pemetrexed.
Grade 3-4: discontinue cisplatin/carboplatin

Any other grade 3-4 toxicity: reduce cisplatin and pemetrexed to 75% of previous dose. For carboplatin, reduce to AUC4. Patients must be advised to seek specialist advice if they experience side effects as these can worsen rapidly.

Nivolumab

Immune reactions may occur during or after completion of treatment. Management may require treatment delay and corticosteroids (initial dose of 1-2 mg/kg/day prednisolone or equivalent followed by a taper).

Toxicity	Definition	Action
Colitis	Grade 1	Continue and closely monitor
	Grade 2-3	Withhold until symptoms resolve to ≤ grade 1
	Grade 4	Permanently discontinue Nivolumab
Pneumonitis	Grade 1	Continue and closely monitor
	Grade 2	Withhold until symptoms resolve to ≤ grade 1
	Grade 3-4 or recurrent grade 2	Permanently discontinue Nivolumab
Nephritis	Grade 2 (creatinine 1.5-3 x ULN)	Withhold until symptoms resolve to ≤ grade 1
	Grade 3 (creatinine > 3 x ULN) or Grade 4	Permanently discontinue Nivolumab
Endocrine	Symptomatic hypophysitis	Withhold until symptoms resolve to ≤ grade 1
	Type 1 diabetes with grade > 3 hyperglycaemia (glucose > 13.9 mmol/L) or ketoacidosis	Withhold until ≤ grade 2 May consider recommencing after corticosteroid taper or discontinue.
	Hyperthyroidism ≥ grade 3	Withhold until ≤ grade 2 May consider recommencing after corticosteroid taper or discontinue.
	Hypothyroidism	Continue and manage with replacement therapy
Hepatitis	AST/ALT 3-5 x ULN or Bilirubin > 1.5-3 x ULN	Withhold until resolves to ≤ grade 1
	AST/ALT > 5 x ULN or Bilirubin > 3 x ULN	Permanently discontinue Nivolumab
	If liver metastasis with baseline AST/ALT 3-5 x ULN: - If AST/ALT increases ≥ 50% for ≥ 1 week	Permanently discontinue Nivolumab
Infusion-related reactions	Grade 3-4	Permanently discontinue Nivolumab

Nivolumab should be permanently discontinued if:

- Grade 4 toxicity (except for endocrinopathies that are controlled with replacement hormones)
- Corticosteroid dosing cannot be reduced to ≤10 mg prednisolone or equivalent per day within 12 weeks
- Treatment-related toxicity does not resolve to Grade 0-1 within 12 weeks after last dose
- Any event occurs a second time at Grade ≥ 3 severity

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Myelosuppression
Infertility
Ototoxicity
Nephrotoxicity
Peripheral neuropathy
Pneumonitis
Colitis
Hepatitis
Nephritis
Endocrinopathies
Pancreatitis

- **Frequently occurring side effects**

Myelosuppression
Nausea and vomiting
Mucositis, stomatitis
Diarrhoea
Oedema
Haematuria
Reduced appetite
Headache
Dizziness
Dry eyes
Cough
Rash, pruritis
Fatigue
Hyperglycaemia
Hypocalcaemia
Hyperthyroidism, hypothyroidism

- **Other side effects**

Alopecia
Arthralgia

Significant drug interactions – for full details consult product literature/ reference texts

Warfarin/coumarin anticoagulants: increased or fluctuating anticoagulant effects. Avoid if possible, consider switching patient to a low molecular weight heparin during treatment or if the patient continues taking an oral anticoagulant monitor the INR at least once a week and adjust dose accordingly.
Aminoglycoside antibiotics: increased risk of nephrotoxicity and ototoxicity.
Clozapine: increased risk of agranulocytosis, avoid concomitant use.
Diuretics: increased risk of nephrotoxicity and ototoxicity.
Nephrotoxic drugs: increased nephrotoxicity; not recommended.
Phenytoin: cisplatin/carboplatin reduces absorption and efficacy of phenytoin.
Anti-gout agents: cisplatin/carboplatin may increase plasma concentration of uric acid therefore dose adjustments may be required to control hyperuricaemia and gout.

Non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided from 5 days before each dose of pemetrexed until 2 days after each dose.

Corticosteroids: use of systemic corticosteroids at baseline, before starting Nivolumab, should be avoided (except for the standard dexamethasone required with pemetrexed) because of their potential interference with the pharmacodynamic activity and efficacy of Nivolumab. However, additional systemic corticosteroids or other immunosuppressants can be used after starting Nivolumab to treat immune-related adverse reactions (as above).

Additional comments

Women of childbearing potential should use effective contraception during treatment and for at least 8 weeks after the last dose of Nivolumab.

References

- Forde PM, et al. CheckMate 816 Investigators. Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer. N Engl J Med. 2022 May 26;386(21):1973-1985.
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- Summary of Product Characteristics Pemetrexed (Lilly) accessed via www.medicines.org.uk on 31 August 2023
- Summary of Product Characteristics Carboplatin (Hospira) accessed via www.medicines.org.uk on 31 August 2023
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