Carboplatin, Pemetrexed and Pembrolizumab

Indication

First-line treatment of metastatic non-squamous, non-small cell lung cancer (NSCLC) for patients who do not have epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) positive mutations.

(NICE TA683)

ICD-10 codes

Codes pre-fixed with C34.

Regimen details

Cycles 1-4

Day	Drug	Dose	Route
1	Pembrolizumab	200mg	IV infusion
1	Pemetrexed	500mg/m²	IV infusion
1	Carboplatin	AUC 5*	IV infusion

* Carboplatin dose calculated using the Calvert equation: **Carboplatin dose (mg) = AUC (CrCl +25)**
The creatinine clearance (CrCl) is calculated using the Cockcroft and Gault equation, however for patients where the creatinine level may not truly reflect renal function (e.g. in extremes of BSA or debilitated patients) an EDTA should be performed as per local policy.
CrCl should be capped at 125mL/min.

Subsequent cycles

Day	Drug	Dose	Route
1	Pembrolizumab	200mg*	IV infusion
1	Pemetrexed	500mg/m²	IV infusion

* Pembrolizumab may also be administered at a dose of 400mg every 6 weeks i.e. with alternate cycles of pemetrexed

Cycle frequency

21 days

Number of cycles

Up to 4 cycles in combination with platinum chemotherapy.
Maintenance pemetrexed and pembrolizumab may continue for a total of 2 years (or a maximum of 35 3-weekly cycles) or until disease progression or unacceptable toxicity, whichever occurs first.

Administration

Pembrolizumab should be administered in 100mL sodium chloride 0.9% over 30 minutes.

Pembrolizumab should be administered via an infusion set with an in-line sterile, non-pyrogenic, low protein binding filter (pore size 0.2 – 5.0µm).

After the infusion the line should be flushed with 30mL sodium chloride 0.9%.

Patients should be monitored every 30 minutes during the infusion (blood pressure, pulse and temperature) and 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.

Pre-medication

Vitamin B12 (hydroxycobalamin) 1mg IM in the week preceding the first cycle and then approximately every 9 weeks (i.e. every 3 cycles) until pemetrexed treatment is completed. Pemetrexed should be administered no earlier than 48 hours after vitamin B12 injection for the first dose. Subsequent vitamin B12 injections may be administered on the same day as pemetrexed.

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

This regimen has severe emetic potential.

Additional supportive medication

Antiemetics as per local guidelines.
Loperamide if required.
H_2 antagonist or proton pump inhibitor if required.
Mouthwashes as per local policy.

Extravasation

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

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

Consider formal EDTA measurement of creatinine clearance in patients with a low body surface area.

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)	> 45 mL/min
Bilirubin	<1.5 x ULN
ALT/AST	<3 x ULN
Alkaline phosphatase	<3 x ULN

Dose modifications

For non-haematological toxicity delay treatment until resolved to ≤ grade 1.

- ### Haematological toxicity

If neutrophils < 1.0 x 10^9/L and/or platelets < 100 x 10^9/L delay for 1 week. If resolved then continue with 100% dose. If 2 or more delays then reduce doses of carboplatin to AUC 4 and pemetrexed to 75%. Continue with full dose pembrolizumab.

- ### Renal impairment

Carboplatin is contraindicated if CrCl <20mL/min.

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

Pembrolizumab

The safety and efficacy of pembrolizumab has not been studied in patients with renal impairment. No specific dose adjustments are recommended in mild to moderate renal impairment.

Discuss with consultant if CrCl <30mL/min or if deteriorating renal function from baseline, as this may represent immunotherapy-induced nephritis.

- ### Hepatic impairment

Carboplatin

No dose modification required.

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.

Pembrolizumab

The safety and efficacy of pembrolizumab has not been studied in patients with hepatic impairment. No specific dose adjustments are recommended in mild hepatic impairment. See below for management of hepatitis.

- **Other toxicities**

Carboplatin and Pemetrexed:

Mucositis

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

Neurotoxicity

Grade 2: reduce carboplatin to AUC 4 and continue with 100% dose pemetrexed.
Grade 3-4: discontinue carboplatin.

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

Pembrolizumab:

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 pembrolizumab
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 pembrolizumab
Nephritis	Grade 2 (creatinine 1.5-3 x ULN)	Withhold until symptoms resolve to ≤ grade 1
	Grade 3 (creatinine > 3 x ULN)	Permanently discontinue pembrolizumab
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 pembrolizumab
	If liver metastasis with baseline AST/ALT 3-5 x ULN: - If AST/ALT increases ≥ 50% for ≥ 1 week	Permanently discontinue pembrolizumab
Infusion-related reactions	Grade 3-4	Permanently discontinue pembrolizumab

Pembrolizumab 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.

Carboplatin:
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: carboplatin reduces absorption and efficacy of phenytoin.

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

Additional comments

Women of child bearing potential should use effective contraception during treatment and for at least 4 months after the last dose of pembrolizumab.

References

- National Institute of Health and Clinical Excellence Guideline TA683. Accessed 21 September 2023 via www.nice.org.uk
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- Summary of Product Characteristics Pemetrexed (Lilly) accessed 27 February 2019 via www.medicines.org.uk
- Summary of Product Characteristics Pembrolizumab (MSD) accessed 27 February 2019 via www.medicines.org.uk
- Leena Gandhi, et al. Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer N Engl J Med 2018; 378:2078-2092

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