Pembrolizumab Carboplatin Pemetrexed Protocol (neoadjuvant NSCLC)

Indication

Metastatic non-squamous non-small-cell lung cancer (NSCLC)

Regimen details

Cycles 1-4

Pembrolizumab 200mg intravenous or 395mg subcutaneous
Pemetrexed 500mg/m^2 intravenously
Carboplatin AUC5 intravenously

Cycle 5 onwards

Pembrolizumab 200mg intravenous or 395mg subcutaneous
Pemetrexed 500mg/m^2 intravenously

Cycle frequency

Every 3 weeks

Number of cycles

For 2 years (for a total of 35 cycles) or until disease progression or intolerable toxicity (whichever occurs first)

Administration

Pembrolizumab (intravenous)

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.

Pembrolizumab (subcutaneous)

Inject into the subcutaneous tissue of the thigh or abdomen, avoiding the 5 cm area around the navel. Do not inject into skin that is damaged, sore, bruised, scarred, scaly, or has red patches. Rotate injection sites for subsequent injections.

- Inject 395mg over 1 minute

Pemetrexed

Pemetrexed should be administered before carboplatin
Pemetrexed is given in 100ml 0.9% sodium chloride over 10 minutes.

Carboplatin

Carboplatin is given in 500ml 5% dextrose 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, refer to the alliance protocol for management of hypersensitivity.

Pre-medication

Folic acid 400μg OD orally beginning 1-2 weeks prior to the first dose of pemetrexed continuing 3 weeks after the last dose of pemetrexed.
Vitamin B_{12} 1000μg IM injection 1-2 weeks prior to the first dose of pemetrexed repeated every 9 weeks until 3 weeks after the last dose of pemetrexed.
Dexamethasone 4mg BD should be taken the day before, the day of and the day after treatment with pemetrexed

Emetogenicity

Moderately emetogenic (carboplatin and pemetrexed)
Pembrolizumab given alone has minimal emetogenicity

Additional supportive medication

See above for vitamin supplementation for pemetrexed

Extravasation

Pemetrexed is an inflammitant
Carboplatin is an irritant
Pembrolizumab IV is neutral

Investigations – pre first cycle

Standard pre-SACT investigations

Investigations –pre subsequent cycles

FBC, U+E (including creatinine), LFT (including AST), calcium
ECG if clinically indicated

Standard limits for administration to go ahead

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

Investigation	**Limit**
Neutrophil count	≥ 1.5 x 10^9/L
Platelet count	≥ 100 x 10^9/L
Creatinine clearance	≥ 45 mL/min for pemetrexed See under Dose Modifications for adjustment of carboplatin dose
Bilirubin	≤ 1.5 x ULN
AST	<3 x ULN or < 5 x ULN in presence of liver metastases
Alkaline phosphatase	<3 x ULN or < 5 x ULN in presence of liver metastases

Consider immunotherapy driven toxicity as a potential reason for all changing laboratory results and discuss with a consultant if any concerns.

Dose modifications

Haematological toxicity

If neutrophils < 1.5 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 doses of carboplatin and pemetrexed to 75%.

Renal impairment

Pemetrexed should NOT be administered if CrCl <45 ml/min

Carboplatin dose should be recalculated if the serum creatinine increases by >20% from baseline

Hepatic impairment

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

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

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

Any other grade 3-4 toxicity
Reduce carboplatin and pemetrexed to 75% of previous dose

Treatment of immunotherapy toxicities
Immunotherapy toxicities should be aggressively managed as can cause permanent and life-threatening complications.
Refer to UKONS and ESMO guidance for treatment of immune related toxicities.
Available at:

https://www.healthierlsc.co.uk/application/files/7916/8977/4069/UKONS_AO_initial_management_Guidelines_FINAL_VERSION_2023.pdf

https://www.healthierlsc.co.uk/application/files/8916/8744/0377/ESMO_IO_Toxicity_Treatment_Guidance.pdf

Adverse effects –

for full details consult product literature/ reference texts

- **Serious side effects**

Myelosuppression
Infertility
Ototoxicity
Nephrotoxicity
Peripheral neuropathy
Immunotherapy toxicities

- **Frequently occurring side effects**

Myelosuppression
Nausea and vomiting
Mucositis, stomatitis
Oedema
Haematuria
Rash, pruritis

- **Other side effects**

Alopecia
Rash
Fatigue

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.

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 because of their potential interference with the pharmacodynamic activity and efficacy of pembrolizumab. However, systemic corticosteroids or other immunosuppressants can be used after starting pembrolizumab to treat immune-related adverse reactions.

Additional comments

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

References

Ghandi et al. Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer. N Engl J Med 2018;378:2078-2092

Keytruda sc SPC: https://www.medicines.org.uk/emc/product/101752/smpc
Keytruda IV SPC: https://www.medicines.org.uk/emc/product/2498/smpc
Carboplatin SPC: https://www.medicines.org.uk/emc/product/3787/smpc
Alimta SPC: https://www.medicines.org.uk/emc/product/3862/smpc

This protocol has been reviewed by Dr Portner consultant oncologist

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

Date: March 2026
Review: March 2028
VERSION: 3