

Pembrolizumab Cisplatin Pemetrexed Protocol (metastatic NSCLC)

Indication

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

Regimen details

Cycles 1-4

Pembrolizumab 200mg intravenous or 395mg subcutaneous
Pemetrexed 500mg/m² intravenously
Cisplatin 75mg/m² intravenously

Cycle 5 onwards

Pembrolizumab 200mg intravenous or 395mg subcutaneous
Pemetrexed 500mg/m² 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 cisplatin

Pemetrexed is given in 100ml 0.9% sodium chloride over 10 minutes.

Cisplatin

Cisplatin should be given according to the schedule below

Drug	Fluid	Time
Potassium chloride 20mmol, magnesium sulphate 10mmol	1 litre 0.9% sodium chloride	2 hours
Cisplatin 75mg/m ²	1 litre 0.9% sodium chloride	2 hours
Potassium chloride 20mmol, magnesium sulphate 10mmol	1 litre 0.9% sodium chloride	2 hours

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 B₁₂ 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

Highly emetogenic (cisplatin)

Pemetrexed and pembrolizumab have minimal emetogenicity

Additional supportive medication

See above for vitamin supplementation for pemetrexed

Extravasation

Pemetrexed is an inflammitant

Cisplatin is an exfoliant

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 ≥ 50 mL/min (60 ml/min prior to cycle 1) for cisplatin
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 10⁹/L and platelets < 100 x 10⁹/L delay for 1 week. If resolved, then continue with 100% dose. If 2 or more delays then reduce doses of cisplatin and pemetrexed to 75%.

Renal impairment

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

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

Cisplatin: No dose modification required

Mucositis

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

Neurotoxicity

Grade 2: reduce cisplatin to 50% dose and continue with 100% dose pemetrexed.

Grade 3-4: discontinue cisplatin.

Any other grade 3-4 toxicity

Reduce cisplatin 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

Lancashire & South Cumbria Cancer Network

Systemic Anticancer Treatment Protocol

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>

Cisplatin SPC: <https://www.medicines.org.uk/emc/product/100546/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

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VERSION: 3
