PROTOCOL

Systemic Anti Cancer Therapy Protocol

# Maintenance Pemetrexed Non-Small Cell Lung Cancer (NSCLC)

PROTOCOL REF: MPHAMAPELU
(Version No.1.2)

## Approved for use in:

The maintenance treatment of **locally advanced or metastatic non-squamous NSCLC** in adults where:

- Their disease has not progressed immediately after 4 cycles of platinum-based (cisplatin/carboplatin) chemotherapy in combination with pemetrexed, gemcitabine, paclitaxel or docetaxel induction therapy.
- ECOG performance status (PS) is 0 or 1 at the start of maintenance treatment

## Dosage:

| Drug | Dose | Route | Frequency |
|---|---|---|---|
| **Pemetrexed** | **500 mg/m$^2$** | IV infusion | Every 21 days |

To be continued until disease progression or an unacceptable toxicity.

## Emetogenic risk:

Low emetogenic risk

## Supportive treatments:

- Vitamin B12 1000 micrograms via intra muscular injection, to commence in the week preceding the 1st cycle of treatment. If this is not possible or has been missed then to be administered on cycle 1 day 1 of treatment.
- Vitamin B12 should be given every 9 weeks thereafter (every 3rd treatment cycle) on the same day as treatment.
- Folic acid 400 micrograms once daily during treatment starting at least five days before the first dose of pemetrexed, and continuing until 21 days after the last dose of pemetrexed. If this is not possible or has been missed then to be administered on cycle 1 day 1 of treatment.
- Dexamethasone 4mg twice daily for 3 days starting the day before pemetrexed.treatment. If dexamethasone oral premedication has not been commenced then administer dexamethasone sodium phosphate 6.6mg intravenously (equivalent to dexamethasone 8mg oral dose) 30 minutes prior to starting treatment with pemetrexed. The remaining doses are to be given via the oral route, dexamethasone 4mg twice a day for 1 day.
- Metoclopramide 10mg oral tablets, up to 3 times a day or as required (total of 5 days supply).

## Extravasation risk:

Pemetrexed- NEUTRAL

Refer to the CCC policy for the 'Prevention and Management of Extravasation Injuries'.

## Dosing in renal and hepatic impairment:

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| **Renal** | GFR ≥ 45mL/min- no dose adjustment is needed<br>GFR <45 ml/min: not recommended<br>**GFR 45-79 ml/min- Refer to 'Interactions' Section** |

| | |
|---|---|
| **Hepatic** | Mild (bilirubin >1.0-1.5 x ULN and any AST or bilirubin ≤ULN and AST >ULN) to moderate (bilirubin 1.5-3 x ULN, with any AST)- no need for dose adjustment is expected.<br>Severe (bilirubin >3.0-10 x ULN, with any AST)- not recommended, based on the risk of pemetrexed induced liver dysfunction.<br>**NOTE: ALP, AST and ALT ≤ 5 times ULN is acceptable if liver has tumour involvement.** |

## Patient Counselling Points

Women of childbearing potential should use effective contraception throughout treatment and for at least 6 months following the last dose of pemetrexed. Sexually mature males are advised to use effective contraceptive measures during the treatment and up to 3 months thereafter.

Contact the triage team for the following:

- New or worsening cough, chest pain or shortness of breath
- Uncontrolled diarrhoea or constipation.
- Jaundice, severe nausea or vomiting, or easy bruising or bleeding.
- Signs of an infection such as fever, shaking, chills, severe sore throat, productive cough, pain or burning when you pass urine, cloudy or foul smelling urine.
- Signs of bleeding problems such as black, tarry stools; extensive bruising; blood in urine or pinpoint red spots on skin.
- Skin rash and/or itching

## Interactions:

Refer to SmPC for full list of interactions.

| **Vaccines** |
| --- |
| Concomitant use of yellow fever vaccine is contraindicated- risk of fatal disease. Concomitant use of live attenuated vaccines not recommended- risk of systemic, possibly fatal, disease. The risk is increased in subjects who are already immunosuppressed by their underlying disease. Use an inactivated vaccine where it exists |
| **Nephrotoxic Drugs**<br>**aminoglycosides loop diuretics, platinum compounds, cyclosporine, Non-steroidal anti-inflammatory drugs (NSAIDs)** |
| Pemetrexed is mainly eliminated unchanged renally by tubular secretion and to a lesser extent by glomerular filtration. Concomitant administration of nephrotoxic drugs [e.g. **aminoglycosides (gentamycin, neomycin, amikacin tobramycin), loop diuretics (fusosemide, bumetanide, indapamide), platinum compounds, cyclosporine]** could potentially result in delayed clearance of pemetrexed. This combination should be used with caution and renal function monitored closely.<br><br>Patients with mild to moderate renal insufficiency (CrCl 45 to 79 ml/min):<br><br>• Short-acting NSAIDs (e.g. **ibuprofen or diclofenac**) and **aspirin** (> 1.3 g daily) should be avoided for 2 days before, on the day of, and 2 days following pemetrexed administration.<br>• NSAIDs with long elimination half-lives (e.g. **rofecoxib, naproxen, meloxicam and piroxicam**) should be interrupted for at least 5 days prior to, on the day of, and at least 2 days following pemetrexed administration. |

- If concomitant administration of NSAIDs is necessary, patients should be monitored closely for toxicity, especially myelosuppression and gastrointestinal toxicity.

## Treatment schedule:

| Day | Drug | Dose | Route | Diluent and rate |
|---|---|---|---|---|
| 1 | **Pemetrexed** | **500mg/m$^2$** | **IV** | In 100mL sodium chloride 0.9% over 10 minutes |

**Every 21 days until progression or unacceptable toxicity**

## Main toxicities:

Refer to SmPC for full list of toxicities.

| **Very common** | |
|---|---|
| **Myelosupression** | anaemia, neutropenia, leukopenia, thrombocytopenia |
| **Infections and infestations** | Infection, pharyngitis |
| **Gastrointestinal** | Stomatitis, mucositis, anorexia, nausea, vomiting, diarrhoea, constipation |
| **Skin** | Rash and skin exfoliation |
| **Renal and urinary disorders** | Raises serum creatinine and reduced CrCl |
| **Less Common** | |
| **Radiation recall** | **Radiation pneumonitis or oesophagitis**- can occur in patients treated with radiation either prior (weeks or years |

| | |
|---|---|
| | previously**)**, during, or subsequent to their pemetrexed therapy. |
| **Cardiovascular events** | Cardiac failure and arrhythmia<br>Angina, myocardial infarction, coronary artery disease and cerebrovascular events have been reported |
| **Ocular** | Conjunctivitis<br>Dry eye<br>Lacrimation increased<br>Keratoconjunctivitis sicca<br>Eyelid oedema<br>Ocular surface disease |
| **Hepatobiliary disorders** | Increases in ALT and AST |
| **CNS** | Taste disorder, peripheral motor neuropathy, peripheral sensory neuropathy, dizziness |

## Investigations and treatment plan:

| | Pre | Cycle 1 | Cycle 2 | Cycle 3 | Cycle 4 | Ongoing |
|---|---|---|---|---|---|---|
| Informed Consent | X | | | | | |
| Clinical Assessment | X | | | | X | Every three cycles |
| SACT Assessment (to include PS and toxicities) | X | X | X | X | X | Every cycle |
| FBC | X | X | X | X | X | Every cycle |
| U&E & LFTs & Magnesium | X | X | X | X | X | Every Cycle |
| CrCl (Cockcroft and Gault) | X | X | X | X | X | Every cycle |
| CT scan** | X | | | | X | Every three months |
| ECG | | | | | | If clinically indicated |
| Full set of observations (*BP, heart rate, temperature, respiratory rate and $O_2$ sats*) | X | X | X | X | X | Every cycle |
| Weight recorded | X | X | X | X | X | Every cycle |
| Height | X | | | | | |

## Dose Modifications and Toxicity Management:

**Pemetrexed should be discontinued** if a patient experiences any Grade 3 or 4 haematologic or non-haematologic toxicity after 2 dose reductions or immediately if Grade 3 or 4 neurotoxicity is observed.

## Haematological toxicity:

Proceed on day 1 if-

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|---|---|
| ANC ≥ 1.0 x $10^9$/L | Plt ≥ 100 x $10^9$/L |

Delay 1 week on day 1 if-

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|---|---|
| ANC ≤ 0.9 x $10^9$/L | Plt ≤ 99 x $10^9$/L |

These haematological guidelines assume that patients are well with good performance status, that other acute toxicities have resolved and the patient has not had a previous episode of neutropenic sepsis.

Table 1: Dose modifications for pemetrexed due to haematological toxicities

| **Haematological Parameters** | **Dose** |
|---|---|
| ANC < 0.5 x $10^9$/L and Plt ≥ 50 x $10^9$/L | 75% |
| Plt < 50 x $10^9$/L irrespective of ANC | 75% |
| Plt < 50 x $10^9$/L with bleeding irrespective of ANC | 50% |

## Non-haematological toxicity:

Table 2: Dose modifications for pemetrexed for non-haematological toxicities

| Toxicity | Grade | Dose |
|---|---|---|
| Any persistent/un-resolving toxicity (despite treatment breaks and supportive measures) | 2 | 75% |
| Diarrhoea | Any grade requiring hospitalization | 75 % |
| | 3 or 4 | 75 % |
| Mucositis | 3 or 4 | 50 % |
| Neurotoxicity | 3 or 4 | Discontinue |

## References:

1. Krens S D, Lassche, Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. Lancet Oncol 2019; 20: e201–08.
2. Pemetrexed 25mg/ml concentrate for solution for infusion SmPC, Eli Lilly and Company Ltd. Available from www.medicines.org.uk/emc/medicine. Last updated 31st August 2022.
3. NICE TA (TA402): Pemetrexed maintenance treatment for non-squamous non-small-cell lung cancer after pemetrexed and cisplatin. Published: 24 August 2016
4. NICE TA (TA190): Pemetrexed for the maintenance treatment of non-small-cell lung cancer. Last updated: 10 August 2017

## Circulation/Dissemination

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|---|---|
| Date added into Q-Pulse | 7th September 2023 |
| Date document posted on the Intranet | N/A |

## Version History

| Date | Version | Author name and designation | Summary of main changes |
|---|---|---|---|
| | 1.0 | **Tara Callagy**<br>**Lung SRG Pharmacist** | New protocol<br>V1.0 |
| | 1.1 | **Tara Callagy**<br>**Lung SRG Pharmacist** | **Updated in line with NICE TAs**<br>**V1.1** |
| June 2023 | 1.2 | **Hala Ghoz**<br>**Lung SRG Pharmacist** | **Routine protocol update**<br>**V1.2** |
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