Tepotinib (Lung)

Indication
Advanced non-small-cell lung cancer (NSCLC) with mesenchymal-epithelial transition factor gene exon 14 (METex14) skipping alterations for any line of treatment.

(NICE TA789)

ICD-10 codes
C34

Regimen details

Drug	Dose	Route
Tepotinib	450mg OD	Oral

Cycle frequency
Continuous

Number of cycles
Until disease progression or unacceptable toxicity

Administration
Tepotinib is available as 225mg tablets.

Tepotinib should be taken with food and tablets should be swallowed whole, not crushed or chewed.

If a dose is missed, it can be taken as soon as remembered on the same day, unless the next dose is due within 8 hours.

Pre-medication
Nil

Emetogenicity
This regimen has low emetic potential – refer to local policy

Additional supportive medication
Loperamide as required

Extravasation
N/A

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U&Es (including creatinine)	14 days
LFTs	14 days
Albumin	14 days
Lipase/Amylase	14 days

Investigations – pre subsequent cycles

Investigation	Validity period
FBC	Monthly
U&Es (including creatinine)	Monthly
LFTs	Every 2 weeks for the first 3 months then monthly
Lipase/Amylase	Monthly
Albumin	Monthly

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	≥ 1.5 x 10^9/L
Platelets	≥ 100 x 10^9/L
ALT/AST	< 3 x ULN
Bilirubin	< 1.5 x ULN
Creatinine clearance (CrCl)	≥ 30ml/min

Dose modifications

The recommended dose reduction for management of adverse reactions is to 225mg OD. If patients are unable to tolerate 225mg OD then tepotinib should be permanently discontinued.

- **Haematological toxicity**

If neutrophils < 1.5 x 10^9/L or platelets < 100 x 10^9/L withhold tepotinib and discuss with consultant/prescriber.

- **Renal impairment**

No dose adjustment is recommended for patients with mild or moderate renal impairment (CrCl 30-89ml/min). The pharmacokinetics and safety of tepotinib in patients with severe renal impairment (CrCl <30ml/min) have not been studied.

See toxicity section below for information on increase in serum creatinine during treatment.

- **Hepatic impairment**

No dose adjustment is recommended for patients with mild (Child-Pugh Class A) or moderate hepatic impairment (Child-Pugh Class B). The pharmacokinetics and safety of tepotinib in patients with severe hepatic impairment (Child-Pugh Class C) have not been studied.

See toxicity section below for management of deranged LFTs during treatment.

- **Other toxicities**

Toxicity	Definition	Action/Dose adjustment
Interstitial lung disease (ILD)	Any grade	Withhold tepotinib if ILD is suspected Permanently discontinue tepotinib if ILD is confirmed
Other adverse reaction	Grade 2	Maintain dose level. If intolerable, consider withholding tepotinib until resolved, then resume tepotinib at a reduced dose
	Grade 3	Withhold tepotinib until resolved, then resume tepotinib at a reduced dose
	Grade 4	Permanently discontinue tepotinib

Hepatotoxicity

Toxicity	Definition	Action/Dose adjustment
Increased ALT and/or AST without increased total bilirubin	Grade 3 (ALT/AST > 5 – 20 x ULN)	Withhold tepotinib until recovery to baseline ALT/AST If recovered to baseline within 7 days, then resume tepotinib at the same dose; otherwise resume tepotinib at a reduced dose.
	Grade 4 (ALT/AST > 20 x ULN)	Permanently discontinue tepotinib
Increased ALT and/or AST with increased total bilirubin in the absence of cholestasis or haemolysis	ALT and/or AST > 3 x ULN with bilirubin > 2 x ULN	Permanently discontinue tepotinib
Increased total bilirubin without concurrent increased ALT and/or AST	Grade 3 (Bilirubin > 3 – 10 x ULN)	Withhold tepotinib until recovery to baseline bilirubin If recovered to baseline within 7 days, then resume tepotinib at a reduced dose; otherwise permanently discontinue tepotinib.
	Grade 4 (Bilirubin > 10 x ULN)	Permanently discontinue tepotinib

Increased Creatinine

Tepotinib or its main metabolite inhibit renal tubular transporter proteins OCT2 and MATE1 and 2. Creatinine is a substrate of these transporters and observed increases in creatinine may be the result of inhibition of active tubular secretion rather than renal injury. Renal function estimates that rely on serum creatinine (CrCl or eGFR) should be interpreted with caution considering this effect. In case of blood creatinine increase whilst on treatment, it is recommended that further assessment of the renal function be performed to exclude renal impairment.

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

- **Serious side effects**

Interstitial lung disease
Pleural effusion
Pneumonia
Oedema (peripheral, generalised, localised)
Hepatic failure

- **Frequently occurring side effects**

Hypoalbuminaemia
Nausea, vomiting
Diarrhoea, constipation
Increased transaminases
Fatigue
Increased creatinine
Abdominal pain
Musculoskeletal pain

- **Other side effects**

Increased amylase
Increased lipase

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

Strong CYP inducers and P-gp inducers e.g. carbamazepine, phenytoin, rifampicin, St John's Wort: may reduce tepotinib exposure. Concomitant use should be avoided.
Dual strong CYP3A inhibitors and P-gp inhibitors e.g. itraconazole: may increase tepotinib exposure and therefore incidence and severity of adverse effects. Concomitant use should be avoided.
P-gp substrates: tepotinib can inhibit the transport of P-gp substrates. Monitoring the clinical effect of P-gp dependent substances with a narrow therapeutic index (e.g. digoxin) is recommended.
BCRP substrates: tepotinib can inhibit the transport of BCRP substrates. Monitoring the clinical effect of BCRP substrates is recommended during co-administration with tepotinib.
Metformin: tepotinib may alter exposure to metformin through inhibition of metformin's renal excretion or hepatic uptake mediated via OCT1 and 2 and MATE1 and 2. Monitoring clinical effects of metformin is recommended.

Additional comments

Tepotinib tablets contain lactose. Patients with hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Women of childbearing potential and male patients with female partners of childbearing potential should use effective methods of contraception during treatment and for at least 1 week after the last dose.

References

- National Institute for Health and Care Excellence (NICE TA789) accessed 28th July 2022 via www.nice.org.uk
- Summary of Product Characteristics – Tepotinib (Merck) accessed 28th July 2022 via www.medicines.org.uk
- Paik, K. *et al*. Tepotinib in Non-Small-Cell Lung Cancer with MET Exon 14 Skipping Mutations. N Engl J Med 2020; 383:931-943

Written/reviewed by: Dr W Owadally (Consultant Oncologist, UHBW NHS Trust)

Checked by: Kate Gregory (Lead Pharmacist for SACT Protocols, SWAG Cancer Alliance)

Authorised by: Dr J Braybrooke (Consultant Oncologist, UHBW NHS Trust, SWAG Cancer Alliance)

Date: August 2022