PROTOCOL

Systemic Anti Cancer Therapy Protocol

Tepotinib
Advanced NSCLC with (MET) exon 14 skipping alterations

PROTOCOL REF: MPHATASA
(Version No.: 1.0)

Approved for use:

As monotherapy for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) harbouring mesenchymal-epithelial transition factor gene (MET) exon 14 (METex14) skipping alterations as first or subsequent-line treatment and satisfies the following criteria:

- Tumour is EGFR wild type (WT) and negative for both ALK and ROS1 gene rearrangements.
- No known brain metastases or if the patient does have brain metastases then the patient is symptomatically stable before staring tepotinib.
- ECOG performance status (PS) score of 0 or 1.

**************Blueteq Form Required**************

Dosage:

Drug	Dosage	Route	Frequency
Tepotinib	450mg	Oral	Once daily continuously

Until unacceptable toxicity or disease progression whichever is first.

Four weeks supply will be issued at each SACT treatment visit.

Administration:

Tepotinib is available as 225 mg film-coated tablets. It should be swallowed whole (tablets should not crushed or chewed before swallowing).with water after food at roughly the same time each day.

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

Tepotinib can affect ability to drive and use machines.

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

Emetogenic risk:

Mildly emetogenic.

Supportive treatments:

- Metoclopramide 10mg orally three times a day.
- Loperamide 4mg immediately after first episode of loose stool then 2mg to be taken after each subsequent episode (maximum of 8 tablets in 24 hours) as required for management of diarrhoea.

Dosing in renal and hepatic impairment:

Renal	CrCl ≥ 30 ml/min: no dose adjustment CrCL < 30 ml/min: not studied, discuss with clinical team. Haemodialysis: not studied discuss with clinical team

	Creatinine Clearance (CrCL) calculated using Cockcroft and Gault formula (please use the application available on the Remote Citrix Web Portal).

Hepatic

Mild hepatic impairment (Child-Pugh Class A) to Moderate (Child-Pugh Class B) - no dose adjustment is recommended

Severe (Child-Pugh Class C) hepatic impairment - not studied this patient group use with caution.

Parameters	1 point	2 points	3 points
Total bilirubin (µmol/L)	< 34	34–50	> 50
Serum albumin (g/L)	> 35	28–35	< 28
Prothrombin time, prolongation (s) *Or* INR	< 4 < 1.7	4–6 1.7-2.3	> 6 >2.3
Ascites	None	Mild to Moderate (diuretic responsive)	Severe (diuretic refractory)
Hepatic encephalopathy	None	Grade I–II (or suppressed with medication)	Grade III–IV (or refractory to medication)

INR: International Normalised Ratio.
Child-Pugh Class A = 5-6 points
Child-Pugh Class B = 7-9 points
Child-Pugh Class C = 10 or more points
Please note: assessment of Child-Pugh Class is to help guide clinical teams when prescribing and pharmacists when screening.
Refer to 'Dose Modifications and Toxicity Management' section for entrectinib-induced hepatotoxicity.

Interactions:

This list is not exhaustive, for full list of interactions please refer to SmPC or consult with a member of the pharmacy team.

CYP inducers and P-gp inducers

Tepotinib is a substrate for P-glycoprotein (P-gp). Strong P-gp inducers may have the potential to decrease tepotinib exposure. Strong CYP inducers may also decrease tepotinib exposure. Concomitant use of strong CYP inducers and P-gp inducers (e.g. carbamazepine, phenytoin, rifampicin, St. John's wort) should be avoided.

Dual strong CYP3A inhibitors and P-gp inhibitors

The effect of strong CYP3A inhibitors or P-gp inhibitors on tepotinib has not been studied clinically. However, metabolism and in vitro data suggest concomitant use of medicinal products that are strong CYP3A inhibitors and P gp inhibitors may increase tepotinib exposure, which may increase the incidence and severity of adverse reactions of tepotinib. Concomitant use of tepotinib with dual strong CYP3A and P-gp inhibitors (e.g. itraconazole) should be avoided.

P-gp substrates

Tepotinib can inhibit the transport of sensitive substrates of P-gp. Monitoring of the clinical effects of P-gp-dependent substances with a narrow therapeutic index (e.g. digoxin) is recommended during co-administration with tepotinib.

BCRP substrates

Tepotinib can inhibit the transport of sensitive substrates of the Breast Cancer Resistance Protein (BCRP). Monitoring of the clinical effects of sensitive BCRP substrates is recommended during co-administration with tepotinib.

Metformin

Based on in vitro data, tepotinib or its metabolite may have the potential to alter the exposure to co-administered metformin in humans through inhibition of metformin's renal excretion or hepatic uptake mediated via OCT1 and 2 and MATE1 and 2. Monitoring of the clinical effects of metformin is recommended during co-administration with tepotinib.

Main toxicities:

The most common (all grades)	**Very common:** Oedema Fatigue/Asthenia Nausea Diarrhoea Low albumin **Common:** Abdominal pain Constipation Vomiting
The most common severe (grade ≥ 3)	Oedema Low albumin Increased ALT Increase in lipase Increase in amylase
The most common laboratory abnormalities	low albumin Increase in ALT Increase in AST Increase in ALP Increase in creatinine Increase in amylase Increase in lipase

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 1 D15	Cycle 2	Cycle 2 D15	Cycle 3	Cycle 3 D15	Cycle 4	Ongoing
Informed Consent	x								
Clinical Assessment	x			x				x	As clinically indicated or every 3 months
SACT Assessment (to include PS and toxicities*)	x	x		x		x		x	Every cycle
On treatment review			x		x		x		To be organized and completed by chemotherapy day unit nursing staff
FBC	x	x		x		x		x	Every cycle
LFTs (ALT, AST and Bilirubin)	x	x	x	x	x	x	x	x	Baseline then every 2 weeks for the first 3 months of treatment, then every cycle or as clinically indicated.
U&E & Magnesium**	x	x		x		x		x	Every Cycle
CrCl (Cockcroft and Gault)	x	x		x		x		x	Every cycle
CT scan	x							x	Every 3 months or as clinically indicated
ECG									If clinically indicated
Full Observations		x		x		x		x	Every cycle*
Weight recorded	x	x		x		x		x	Every cycle
Height	x								

* Monitor patients for (refer to 'Non-haematological Toxicity 'section):
  - New or worsening pulmonary symptoms indicative of ILD/pneumonitis (e.g. shortness of breath, cough, and fever),.
  - Peripheral, generalised or localised oedema (e.g. oedema of the face, periorbital oedema, genital oedema)

Dose Modifications and Toxicity Management:

Dosing should be modified based on tepotinib toxicity.

Table 1. Recommended tepotinib dose reduction levels

Dose reduction level	Dose
First dose reduction	225 mg (1 tablet) once daily
Tepotinib should be permanently discontinued if patients are unable to tolerate 225 mg daily	

Table 2. Recommended dose modifications for Tepotinib

Adverse reaction	Severity	Dose modification
Interstitial Lung Disease (ILD) Monitor for new or worsening pulmonary symptoms indicative for ILD-like reactions (e.g. dyspnoea, cough, fever)	Any grade	Withhold tepotinib if ILD is suspected. Permanently discontinue tepotinib if ILD is confirmed.
Increased ALT and/or AST without increased total bilirubin	**Grade 3** >5.0 - 20.0 x ULN if baseline was normal >5.0 - 20.0 x baseline if baseline was abnormal	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 >20.0 x ULN if baseline was normal >20.0 x baseline if baseline was abnormal	Permanently discontinue tepotinib.

Increased ALT and/or AST with increased total bilirubin in the absence of cholestasis or hemolysis	ALT and/or AST > 3 x ULN AND total bilirubin > 2 x ULN	Permanently discontinue tepotinib.
Increased total bilirubin without concurrent increased ALT and/or AST	**Grade 3** >3.0 - 10.0 x ULN if baseline was normal >3.0 - 10.0 x baseline if baseline was abnormal	Withhold tepotinib until recovery to baseline bilirubin. If recovered to baseline within 7 days, then resume tepotinib at a reduced dose; otherwise permanently discontinue.
	Grade 4 >10.0 x ULN if baseline was normal >10.0 x baseline if baseline was abnormal	Permanently discontinue tepotinib.
Other adverse reactions	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.

Haematological toxicity:

Tepotinib is not known to cause bone marrow suppression or predispose to infections.

Non- Haematological toxicity:

Hepatotoxicity

ALT and AST increases from baseline were reported on 42.0% and 32.9% of patients, respectively. Grade 3 or higher ALT and AST were reported in 3.9% and 2.4% of patients, respectively.. These elevations improved or resolved with dose modification or

permanent discontinuation of treatment, The median time to resolution was 5.0 weeks. Refer to 'Dose Modification' section.

ALP increase from baseline was reported in 47.5% of patients. Grade 3 or 4 occurred in 1.6% of patients. The median time to first onset for ALP increase of any grade was 5.7 weeks and the median time to resolution was 9.8 weeks. The observed ALP increase was not associated with cholestasis and did not lead to dose modification.

Interstitial Lung Disease (ILD)/Pneumonitis

Patients should be monitored for new or worsening pulmonary symptoms indicative for ILD-like reactions (e.g. dyspnoea, cough, fever). Immediately withhold in patients with suspected ILD/pneumonitis and contact the clinical team. **Permanently discontinue if no other potential causes of ILD/pneumonitis are identified.**

Oedema

Oedema was observed in almost 70% of patients. It includes peripheral oedema, which was the most frequent at 60.0%, generalised oedema and localised oedema (e.g. oedema of the face, periorbital oedema, genital oedema). The median time to onset of any-grade oedema was 7.9 weeks and the median time to resolution was approximately 67.0 weeks. Refer to Table 2 for dose modifications.

References:

Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Published: November 27, 2017

Tepotinib 225 mg film-coated tablets, summary of Product Characteristics, Merck Serono Ltd available via https://www.medicines.org.uk/emc (last updated 25th May 2022).

Paik, P. K. et al. (2020). Tepotinib in non–small-cell lung cancer with MET exon 14 skipping mutations. *NEJM*, 383(10), 931-943.

NICE TA 789, Tepotinib for treating advanced non-small-cell lung cancer with MET gene alterations. Published 18th May 2022.

Circulation/Dissemination

Date added into Q-Pulse	14th November 2022
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Version History

Date	Version	Author name and designation	Summary of main changes
November 2022	1.0	**Hala Ghoz** **Lung SRG Pharmacist**	V1.0 New Regimen Protocol