DRUP – Drug specific manual for TEPOTINIB (Tepmetko)

1. Drug specific in- and exclusion criteria

Tepotinib specific criteria are highlighted in light grey.

Inclusion criteria	Yes	No	n.a.
1. Patients must be ≥18 years of age.			
2. Histologically-proven locally advanced or metastatic solid tumor, multiple myeloma, non-Hodgkin lymphoma or T-cell prolymphocytic leukemia, with symptomatic or radiological disease progression after standard anti-cancer therapy, or for whom no such treatment is no longer available or indicated.			
a. <u>For patients with a primary brain tumor</u>: histologically confirmed recurrent or de novo primary brain tumor, with unequivocal progression after prior therapy, at least 3 months after radiotherapy (either first line chemo-radiotherapy or re-irradiation), and with stable or decreasing dosage of steroids for at least 7 days prior to the baseline MRI scan.			
3. Presence of an oncogenic mutation that can potentially be targeted by tepotinib (please refer to the list of drugs and acceptable profiles for further definitions). A complete sequencing report, confirming the actionable mutation, has to be submitted for patient enrollment.			
4. ECOG performance status 0-2			
5. Patients must have acceptable organ and bone marrow function measured within 4 weeks prior to administration of study treatment as defined below:			
a. Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L			
b. Hemoglobin > 5.6 mmol/l			
c. Platelet count ≥ 100 x 10^9/L			
d. Total bilirubin < 1.5 x ULN			
e. AST (SGOT) and ALT (SGPT) < 2.5 x institutional ULN (or < 5 x ULN in patients with known hepatic metastases)			
f. Serum creatinine ≤ 1.5 × ULN or calculated or measured creatinine clearance ≥ 50 mL/min/1.73 m^2			
6. Objectively measurable disease (by physical or radiographic examination, according to RECIST v1.1 for patients with solid tumors, or according to IMWG, Lugano, RANO or GCIG criteria, resp., for patients with multiple myeloma, non-Hodgkin lymphoma and T-cell prolymphocytic leukemia, primary brain tumors or ovarian cancer in case of CA125-based evaluation).			

Inclusion criteria	Yes	No	n.a.
7. A new (obtained ≤2 months before inclusion, and without any type of anti-cancer therapy within those ≤2 months) fresh frozen tumor biopsy specimen for extensive biomarker testing is mandatory before the start of treatment with a targeted agent included in the protocol. Alternatively, fresh frozen tumor tissue acquired in the context of a standard care procedure may be used, provided that no systemic anti-cancer treatment was given between the procedure and start of study treatment within DRUP. The following exceptions are made: a) An exception is made for patients with a primary brain tumor or other tumor types with only intracerebral lesions, only if the mandatory DRUP pre-treatment biopsy for biomarker analysis cannot safely be obtained: i. The fresh frozen tumor biopsy sample may be replaced by fresh frozen tumor tissue, obtained earlier from recurrent disease, as part of standard of care surgical procedure (i.e., performed at progression) ii. If no fresh frozen tumor tissue is available for NGS, and the risk of obtaining a new tumor biopsy is considered too high, no biopsy will be required. In this case, the study coordinators must be informed in advance, and there will be no reimbursement for the biopsy procedure. b) In case WGS is performed on tumor tissue outside the context of a clinical trial before inclusion, and without any type of anti-cancer therapy between the collection of tissue and inclusion in DRUP, this can replace the DRUP pre-treatment biopsy, provided that the patient gives consent to use his/her WGS data for biomarker analysis in DRUP. c) An exception is made for patients that underwent an allogeneic hematopoietic stem cell transplantation prior to study enrollment, since this will prevent a correct WGS analysis due to a mismatch between the biopsy specimen and the required blood sample.			
8. Ability to understand and the willingness to sign a written informed consent document.			
9. For orally administered drugs, the patient must be able to swallow and tolerate oral medication and must have no known malabsorption syndrome.			
10. Women of child-bearing potential and men must agree to the use of two highly effective forms of contraception in combination for the duration of study participation, and for at least one week after the last dose.			

Exclusion criteria	Yes	No	n.a.
1. Patients who are eligible for on-label treatment or ongoing trials with tepotinib are excluded from treatment with tepotinib within the DRUP trial.			
2. Known hypersensitivity to tepotinib or any of the excipients of the product.			
3. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.			
4. Ongoing toxicity ≥ grade 2, other than alopecia or grade 2 peripheral neuropathy.			

Exclusion criteria	Yes	No	n.a.
5. Patient is receiving any other anti-cancer therapy (cytotoxic, biologic, radiation, or hormonal other than for replacement). Required wash out period prior to starting study treatment is at least two weeks. An exception is made for patients suffering from CRPC, who are allowed to continue androgen deprivation therapy.			
6. Patient is pregnant or nursing.			
7. Patients with brain metastases. Patients with previously treated brain metastases are eligible, provided that the patient has not experienced a seizure or had a clinically significant change in neurological status within the 3 months prior to registration. All patients with previously treated brain metastases must be stable for at least 1 month after completion of treatment and off steroid treatment prior to study enrollment.			
For patients with a primary brain tumor: *a. Patients who require anti-convulsant therapy must be taking non-enzyme inducing antiepileptic drugs (non-EIAED). EIAED are prohibited. Patients previously on EIAED must be switched to non-EIAED at least 2 weeks prior to randomization.* *b. No radiotherapy within the three months prior to the diagnosis of progression.* *c. No radiotherapy with a dose over 65 Gy, stereotactic radiosurgery or brachytherapy unless the recurrence is histologically proven.*			
8. Patients with clinically significant preexisting cardiac conditions, including uncontrolled or symptomatic angina, uncontrolled atrial or ventricular arrhythmias, or symptomatic congestive heart failure are not eligible.			
9. Patients with known left ventricular ejection fraction (LVEF) < 40% are not eligible.			
10. Patients with stroke (including TIA) or acute myocardial infarction within 3 months before the first dose of study treatment are not eligible.			
11. Patients with any other clinically significant medical condition which, in the opinion of the treating physician, makes it undesirable for the patient to participate in the study or which could jeopardize compliance with study requirements including, but not limited to: ongoing or active infection, or severe psychiatric illness/social situations.			

NB Please note that official prescription instructions, as outlined in the Summary of Product Characteristics (SPC, most recent version can be downloaded from https://www.ema.europa.eu/en/medicines) and / or any other official documents concerning this drug, will always take precedence over this manual. This manual is provided for practical support; treatment can be performed according to local standard-of-care protocols.

2. Treatment schedule

	Screening (≤28 days before treatment start)	After screening, before start	D1 of every treatment cycle (1 cycle = 28 days)	At the end of every 2nd treatment cycle	After end of treatment (≤30 days)
Concurrent meds	x		x		
Adverse events			x		
Physical exam	x		x[1]		
Vital signs	x		x[1]		
Performance Status	x		x[1]		
Hb, neutrophil count, platelets	x		x[1]		
Serum chemistry	x		x[1]		
ALT, AST, total bilirubin	x[2]				
Serum pregnancy test	x[3]		x[3]		
Electrocardiogram	x[4]				
Tepotinib (Tepmetko)			x (continuous dosing)		
Tumor biopsy		x[5]			x[5]
Response evaluation	x[6]			x[6]	

1. According to local standard clinical practice, or as clinically indicated.
2. Monitor liver function tests (including ALT, AST, and total bilirubin) prior to the start of tepotinib.
3. During screening, a serum test should be performed, and then serum of urine pregnancy testing at day 1 of every treatment cycle.
4. Electrocardiogram should be done prior to start treatment to check for QTc prolongation.
5. Tumor biopsy: after screening is positive, a mandatory DRUP pre-treatment biopsy should be taken. After termination of DRUP treatment, a post-treatment biopsy can be taken. The post-treatment biopsy is optional.
6. A baseline scan should be performed <28 days before start of treatment. Tumor assessments will initially be repeated every 8 weeks after treatment initiation. If the patient continues treatment beyond 3 response evaluations (i.e., 24 weeks), response evaluation will thereafter be performed at the end of every 3rd treatment cycle (i.e., every 12 weeks).

3. Administration and starting dosage

The recommended dose is 450 mg tepotinib (2 tablets) taken once daily. Treatment should continue until disease progression or unacceptable toxicity.
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.

4. How supplied

Tepotinib is supplied as film-coated tablets containing 225 mg of tepotinib (as hydrochloride hydrate). Drugs can be (re-)ordered by filling in the required fields in the eCRF. Drugs will be shipped to the site's pharmacy. Per shipment, sufficient drug can be ordered to treat the patient until the next response evaluation (and 1 cycle beyond for the first order, to cover the period in between response evaluation and re-supply).

5. Dose modifications for toxicity

Please refer to Summary of Product Characteristics (SPC), or to section 6 'Warnings and precautions' below.

6. Warnings and precautions

The recommended dose reduction level for the management of adverse reactions is 225 mg (1 tablet) daily. Detailed recommendations for dose modification are provided in the table hereafter.

Table 1: Recommended dose modifications for tepotinib

Adverse reaction	Severity	Dose modification
Interstitial Lung Disease (ILD) /Pneumonitis	Any grade	Withhold tepotinib if ILD is suspected. Permanently discontinue tepotinib if ILD is confirmed.
Increased ALT and/or AST without increased total bilirubin	ALT and/or AST greater than 5 times up to 20 times 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.
	ALT and/or AST greater than 20 times ULN	Permanently discontinue tepotinib.
Increased ALT and/or AST with increased total bilirubin in the absence of cholestasis or hemolysis	ALT and/or AST greater than 3 times ULN with total bilirubin greater than 2 times ULN	Permanently discontinue tepotinib.
Other adverse reactions	Grade 3 or higher	Reduce tepotinib to 225 mg until the adverse reaction recovers to ≤ grade 2. A temporary interruption of tepotinib treatment for no more than 21 days can also be considered.

ULN = upper limit of normal

<u>Special populations:</u>

Renal impairment
No dose adjustment is recommended in patients with mild or moderate renal impairment (creatinine clearance 30 to 89 mL/min). The pharmacokinetics and safety of tepotinib in patients with severe renal impairment (creatinine clearance below 30 mL/min) have not been studied. The use of tepotinib in patients with severe renal impairment is therefore not recommended.
Renal function estimates that rely on serum creatinine (creatinine clearance or estimated glomerular filtration rate) should be interpreted with caution.

Hepatic impairment
No dosage modification is recommended in patients with mild (Child Pugh Class A) or moderate (Child Pugh Class B) hepatic impairment. The pharmacokinetics and safety of tepotinib in patients with severe hepatic impairment (Child Pugh Class C) have not been studied. The use of tepotinib in patients with severe hepatic impairment is therefore not recommended.

Elderly
No dose adjustment is necessary in patients aged 65 years and above.

<u>Warnings and precautions:</u>

Interstitial Lung Disease (ILD) and pneumonitis
Interstitial lung disease (ILD) or ILD-like adverse reactions including pneumonitis have been reported in patients who received tepotinib monotherapy at the recommended dose regimen and may be fatal.
Patients should be monitored for pulmonary symptoms indicative for ILD-like reactions. Tepotinib should be withheld and patients should be promptly investigated for alternative diagnosis or specific aetiology of interstitial lung disease. Tepotinib must be permanently discontinued if interstitial lung disease is confirmed and the patient be treated appropriate.

Monitoring of liver enzymes
Increase in ALT and/or AST have been reported in patients who received tepotinib monotherapy at the recommended dose regimen. Liver enzymes (ALT and AST) and bilirubin should be monitored prior to the start of tepotinib treatment and thereafter as clinically indicated. If grade 3 or higher increases (ALT and/or AST greater than 5 times ULN) occur, dose adjustment or discontinuation is recommended (see Table 1).

QTC prolongation
QTc prolongation was reported in a limited number of patients. In patients at risk of developing QTc prolongation, including patients with known electrolyte disturbances or taking concomitant medicinal products known to have QTc prolongation effects, monitoring is recommended as clinically indicated (e.g. ECG, electrolytes).

Embryo-foetal toxicity
Tepotinib can cause foetal harm when administered to pregnant women. Pregnancy testing is recommended in women of childbearing potential prior to initiating treatment with tepotinib. Women of childbearing potential and males with female partners of childbearing potential should use effective contraception during tepotinib treatment and for at least 1 week after the last dose (see Fertility, pregnancy and lactation).

Interpretation of laboratory tests
In vitro studies suggest that tepotinib or its main metabolite inhibit the renal tubular transporter proteins organic cation transporter (OCT) 2 and multidrug and toxin extrusion transporters (MATE) 1 and 2. Creatinine is a substrate of these transporters, and the 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 (creatinine clearance or estimated glomerular filtration rate) should be interpreted with caution considering this effect. In case of blood creatinine increase while on treatment, it is recommended that further assessment of the renal function be performed to exclude renal impairment.

Lactose content
Tepotinib contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

<u>Fertility, pregnancy and lactation:</u>

Women of childbearing potential/Contraception in males and females
Pregnancy testing is recommended in women of childbearing potential prior to initiating treatment with tepotinib.

Women of childbearing potential should use effective contraception during tepotinib treatment and for at least 1 week after the last dose. Women using systemically acting hormonal contraceptives should add a barrier method during TEPMETKO treatment and for at least 1 week after the last dose. Male patients with female partners of childbearing potential should use barrier contraception during tepotinib treatment and for at least 1 week after the last dose.

Pregnancy
There are no clinical data on the use of tepotinib in pregnant women. Studies in animals have shown teratogenicity. Based on the mechanism of action and findings in animals tepotinib can cause foetal harm when administered to pregnant women.
Tepotinib should not be used during pregnancy, unless the clinical condition of the woman requires treatment with tepotinib. Women of childbearing potential or male patients with female partners of childbearing potential should be advised of the potential risk to a foetus.

Breast-feeding
There are no data regarding the secretion of tepotinib or its metabolites in human milk or its effects

on the breast-fed child or milk production. Breast-feeding should be discontinued during treatment with tepotinib and for at least 1 week after the last dose.

Fertility
No human data on the effect of tepotinib on fertility are available. No morphological changes in male or female reproductive organs were seen in the repeat-dose toxicity studies in rats and dogs, except for reduced secretion in seminal vesicles of male rats at comparable human clinical exposure.

<u>Effects of other medicinal products on tepotinib</u>

CYP and P-gp inducers
Tepotinib is a substrate for P-glycoprotein (P-gp). In healthy participants, co-administration of a single 450 mg tepotinib dose with the strong inducer carbamazepine (300 mg twice daily for 14 days) decreased tepotinib AUCinf by 35% and Cmax by 11% compared to administration of tepotinib alone. The decreased exposure is not clinically relevant.

Dual strong CYP3A inhibitors and P-gp inhibitors
In healthy participants, co-administration of a single 450 mg tepotinib dose with the strong CYP3A inhibitor and P-gp inhibitor itraconazole (200 mg once daily for 11 days) increased tepotinib AUCinf by 22% with no change in tepotinib Cmax compared to administration of tepotinib alone. This is classified as a weak interaction, and the observed changes in systemic exposure to tepotinib are not considered clinically relevant. Therefore, CYP3A and P-gp inhibitors are not expected to influence tepotinib exposure.

Acid-reducing agents
Co-administration of omeprazole under fed conditions had no clinically relevant effect on the pharmacokinetic profile of a single dose of tepotinib 450 mg and its metabolites (geometric mean ratio for tepotinib of 110% for AUCinf (90% CI: 102; 119) and of 104% for Cmax (90% CI: 93; 117); similar effect on metabolites observed).

<u>Effects of tepotinib on other medicinal products</u>

P-gp substrates
Tepotinib is an inhibitor of P-gp. Administration of tepotinib 450 mg orally once daily for 8 days increased the AUC of the sensitive P-gp substrate dabigatran etexilate by approximately 50% and Cmax by approximately 40%. Dose adjustment of dabigatran etexilate may be needed in case of concomitant use. Caution and monitoring for adverse reactions of other P-gp-dependent substances with a narrow therapeutic index (e.g. digoxin, aliskiren, everolimus, sirolimus) is recommended during co-administration with tepotinib.

BCRP substrates
Tepotinib can inhibit the transport of substrates of the breast cancer resistance protein (BCRP) in vitro. Monitoring for adverse reactions of sensitive BCRP substrates (e.g. rosuvastatin, methotrexate, topotecan) is recommended during co-administration with tepotinib.

Substrates of OCT and MATE

Based on in vitro data, tepotinib or its metabolite may have the potential to alter the exposure of substrates of the transporters OCT1 and 2 and MATE1 and 2. The most clinically relevant example of substrates of these transporters is metformin. Monitoring of the clinical effects of metformin is recommended during co-administration with tepotinib.

CYP3A4 substrates

Multiple administrations of 450 mg tepotinib orally once daily had no clinically relevant effect on the pharmacokinetics of the sensitive CYP3A4 substrate midazolam.

Hormonal contraceptives

It is currently unknown whether tepotinib may reduce the effectiveness of systemically acting hormonal contraceptives. Therefore, women using systemically acting hormonal contraceptives should add a barrier method during tepotinib treatment and for at least 1 week after the last dose.

<u>Effects on ability to drive and use machines</u>

Tepotinib has no influence on the ability to drive and use machines.