Systemic Anti Cancer Treatment Protocol

Tivozanib

PROTOCOL REF: MPHATIVOUR
(Version No: 1.2)

This protocol has been temporarily amended – please see the Oral SACT Operational Changes during Covid-19. Amendments may include less frequent blood monitoring, telephone SACT assessments and longer durations of treatment being dispensed.

Approved for use in:

Tivozanib is indicated for the first line treatment of advanced / metastatic renal cell carcinoma in patients with a clear cell component.

ECOG performance status of 0 or 1

The patient is treatment naïve to systemic therapy and in particular has previously received neither any vascular endothelial growth factor (VEGF)-targeted systemic therapy nor mTOR pathway inhibitor-targeted treatment unless prior treatment with pazopanib or sunitinib has had to be stopped solely as a consequence of dose-limiting toxicity and in the clear absence of progression.

Blueteq registration required.

Dosage:

Drug	Dosage	Route	Frequency
Tivozanib	1340micrograms	oral	Once daily for 21 days followed by 7 days rest

Capsules will be supplied at 28 day intervals and are available as 1340 micrograms and 890 micrograms.

Treatment to continue until disease progression or unacceptable toxicity.

Supportive treatments:

- Loperamide 2mg capsules, to be taken after each loose stool

Extravasation risk:

Not applicable

Administration:

- Tivozanib is for oral administration.
- It may be taken with or without food. The capsules should be swallowed whole with a glass of water and must not be opened.
- If a dose is missed the patient should not be given an additional dose. The patient should take the usual prescribed dose on the following day.

Drug Interactions

Tivozanib is metabolized by the cytochrome CYP3A4 pathway and therefore drugs that induce or inhibit this enzyme should be avoided where possible.

Herbal preparations containing St. John's wort are contraindicated.
If a patient is already taking St John's wort, this should be stopped before starting treatment. The inducing effect of St John's wort may persist for at least 2 weeks after cessation of treatment.

INDUCERS (lowers Tivozanib levels): Carbamazepine, phenobarbital, phenytoin, dexamethasone, rifabutin, rifampicin, St John's Wort, troglitazone, pioglitazone
The clinical effects of strong CYP3A4 inducers on repeated daily dosing of tivozanib has not been studied but potentially the average time to reach steady-state and the average steady-state serum concentration of tivozanib may be reduced, due to the reduction in half-life.

Moderate CYP3A4 inducers are not expected to have a clinically relevant effect on tivozanib exposure.

CYP3A4 INHIBITORS: Indinavir, nelfinavir, ritonavir, clarithromycin, erythromycin, itraconazole, ketoconazole, nefazodone, grapefruit juice, verapamil, diltiazem, cimetidine, amiodarone, fluvoxamine, mibefradil

Tivozanib exposure is unlikely to be altered by CYP3A4 inhibitors.

Caution should be exercised if tivozanib is co-administered with rosuvastatin.

Contraceptives

It is currently unknown whether tivozanib may reduce the effectiveness of hormonal contraceptives, and therefore women using hormonal contraceptives should add a barrier method.

Main Toxicities:

Hypertension, dysphonia, fatigue, diarrhoea, decreased appetite, headache, hypertension, dyspnoea, cough, abdominal pain, nausea, stomatitis, hand & foot syndrome, back pain, weight loss.

Please refer to SPC for the full list.

Investigations and Treatment Plan:

	Pre	C1	C1	C2	C3	Pre	C4 D1	Ongoing
Week		1	3	5	9	12	13	→
Medical Assessment	X		X		X		X	Every 12 weeks after cycle 3
Nursing Assessment	X	X		X	X		X	Every cycle
FBC	X		X	X	X		X	Every cycle
U&E & LFT	X		X	X	X		X	Every Cycle
Thyroid function tests	X				X			Every other cycle
CT scan	X					X		Every 12 weeks
Informed Consent	X							
ECG *								If clinically indicated
Blood pressure measurement	X	X	X	X	X		X	Every cycle
PS recorded	X	X	X	X	X		X	Every cycle
Toxicities documented	X	X	X	X	X		X	Every cycle
Weight recorded	X	X	X	X	X		X	Every cycle
Urine dipstick for protein								If clinically indicated

A formal medical review as to whether treatment with tivozanib should continue or not will be scheduled to occur at least by the end of the first 8 weeks of treatment.

*QT/QTc interval prolongation may lead to an increased risk for ventricular arrhythmias. It is recommended that tivozanib be used with caution in patients with a history of QT interval prolongation or other relevant pre-existing cardiac disease and those receiving other medications known to increase the QT interval. Baseline and periodic monitoring

of electrocardiograms and maintenance of electrolytes (e.g. calcium, magnesium, potassium) within the normal range is recommended.

Assessment visits

Review on week 3 for the first cycle and arrange 2 weekly BP checks with GP

Thereafter patient can be seen every 28 days on day 1 of each cycle

Dose Modifications and Toxicity Management:

There is a correlation between overall survival and the cumulative dose exposure and it is therefore recommended that attempts be made to manage toxicity before a dose reduction is made.

Haematological toxicity

Tivozanib is not myelosuppressive; however FBC should be reviewed prior to each cycle.

Non-haematological toxicity

The occurrence of undesirable effects may require temporary interruption and/or dose reduction of tivozanib therapy. In the pivotal study, the dose was reduced for grade 3 events and interrupted for grade 4 events.

When dose reduction is necessary, the tivozanib dose can be reduced to 890 microgram once daily with the normal treatment schedule of 21 days of dosing, followed by a 7-day rest period.

Tivozanib	
Hypertension	Patients should be screened for hypertension and controlled as appropriate. Temporary suspension is recommended in patients with severe hypertension that is not controlled with medical management. Treatment may be resumed once hypertension is appropriately controlled.

	The decision should not be based on single elevated BP reading and should be based on repeated evidence of elevation to eliminate possible contribution from 'white coat syndrome'. Patient should be advised to involve their GP for regular monitoring and if necessary treatment. Serial home BP monitoring can provide additional useful information. *Systolic 140-150 mmHg or Diastolic <90 mmHg:* -Continue treatment but need to monitor blood pressure closely and follow relevant steps as necessary. *Systolic 150-160mmHg or Diastolic 90-100mmgh:* -Continue treatment at same dose. -Repeat BP at GP, treatment needed if remained elevated or higher. -Continue with vigilant BP monitoring until BP <140/90mmHg. *Systolic 160-180 mmHg or diastolic 100-110 mmHg (at least 2 readings 30 minutes apart):* -Continue treatment at same dose -Instigate BP treatment, to be reviewed at GP within 5 days. -Continue with vigilant BP monitoring until BP <140/90mmHg. *Severe hypertension (>200mmHg systolic or >110mmHg diastolic)* Temporary suspension is recommended in patients with severe hypertension that is not controlled with medical management. Treatment at reduced dose may be resumed once hypertension is appropriately controlled.

	The choice of antihypertensive treatment should be individualised to the patient's clinical circumstances and follow standard medical practice – use NICE Clinical Guideline CG 127 – Hypertension in adults diagnosis and management Verapamil and diltiazem should be avoided due to their inhibition of CYP3A4 enzymes. Accessible here: https://www.nice.org.uk/guidance/CG127Hypertension in adults: diagnosis and management | Guidance and guidelines | NICE In the case of persistent hypertension despite use of anti-hypertensive therapy, the tivozanib dose should be reduced, or the treatment interrupted and re-initiated at a lower dose once the blood pressure is controlled, according to clinical judgment. Discontinuation of treatment should be considered in cases of persistent severe hypertension, posterior reversible encephalopathy syndrome, or other complications of hypertension. Patients receiving anti-hypertensive medication should still be monitored for hypotension when tivozanib is either interrupted or discontinued.
Skin and tissue disorders	The patients should be advised to avoid hot water and to wear gloves when performing housework. Use simple moisturising creams to keep the skin moist and limit peeling.

	Consideration of temporary interruption and/or reduction in treatment dose or, in severe or persistent cases, permanent discontinuation of treatment.
Proteinuria	Monitoring for proteinuria before initiation of, and periodically throughout treatment is recommended, using a urine dipstick. Patients who show 2+ protein level on dipstick should have a 24 hour protein assessment. For patients who develop Grade 2 (> 1.0-3.4 g/24 hours) or Grade 3 (≥ 3.5 g/24 hours) proteinuria, the dose of tivozanib has to be reduced or the treatment temporarily interrupted. If the patient develops Grade 4 proteinuria (nephrotic syndrome) tivozanib has to be discontinued. Risk factors for proteinuria include high blood pressure.
Thyroid dysfunction	Hypothyroidism has been observed to occur early as well as late during treatment with Tivozanib. Therefore, TFTs require routine monitoring prior to initiation of treatment and throughout the course. Hypothyroidism should be treated according to standard medical practice.
QT interval prolongation	QT/QTc interval prolongation has been reported and may lead to an increased risk for ventricular arrhythmias. It is recommended that tivozanib be used with caution in patients with a history of QT interval prolongation or other relevant pre-

	existing cardiac disease and those receiving other medications known to increase the QT interval. Baseline and periodic monitoring of electrocardiograms and maintenance of electrolytes (e.g. calcium, magnesium, potassium) within the normal range is recommended.
Posterior Reversible Encephalopathy Syndrome. PRES	Neurological disorder which can present with headache, seizure, lethargy, confusion, blindness and other visual and neurologic disturbances. Mild to severe hypertension may be present. Magnetic Resonance Imaging is necessary to confirm the diagnosis of PRES. Tivozanib must be discontinued in patients developing signs or symptoms of PRES. The safety of re-initiating tivozanib therapy in patients previously experiencing PRES is not known and tivozanib should only be used with caution in these patients.

Hepatic Impairment

Tivozanib should be used with caution in patients with mild and moderate hepatic impairment with close monitoring of tolerability.

Mild	No dose adjustment required
Moderate	Tivozanib 1340 micrograms **EVERY OTHER DAY**, as they may be at an increased risk of adverse reactions due to increased exposure
Severe	Tivozanib is <u>not</u> recommended

Renal Impairment

No dose adjustment is required in patients with mild or moderate renal impairment. Caution is advised in patients with severe renal impairment due to limited experience and in patients undergoing dialysis as there is no experience of tivozanib in this patient population.

References:

EMC. *Fotiva 1340mcg hard capsules.* Available from https://www.medicines.org.uk/emc/product/8995/smpc [accessed on 4/3/19]

NICE. *Tivozanib for treating advanced renal cell carcinoma.* Available from https://www.nice.org.uk/guidance/ta512/resources/tivozanib-for-treating-advanced-renal-cell-carcinoma-pdf-82606776648901 [Accessed on 4/3/19]