Indication	For metastatic or inoperable locally advanced renal cell carcinoma with a clear cell component. Note: papillary, chromophobe and Xp11 translocation sub types can be treated as per clear cell pathway. Tivozanib is either being used as 1st line treatment for renal carcinoma or as 2nd line treatment in patients previously treated with 1st line nivolumab plus ipilimumab or pembrolizumab plus lenvatinib or nivolumab plus cabozantinib or avelumab plus axitinib. The patient must not previously have received any vascular endothelial growth factor (VEGF)-targeted systemic therapy unless the patient commenced 1st line treatment with whichever of pazopanib or sunitinib or cabozantinib as the immediate prior therapy and this had to be stopped within 3 months of its start solely because of dose-limiting toxicity and in the clear absence of disease progression.
Treatment Intent	Palliative treatment
Frequency and number of cycles	Every 28 days Tivozanib is to be continued until progressive disease or unacceptable toxicity or patient choice to stop treatment, or tivozanib can be stopped for a planned treatment break following the protocol used in the STAR trial; i.e. following 24 weeks of continuous therapy, and if there is no evidence of disease progression on therapy, patients and clinicians may choose to stop treatment for a planned drug free interval/treatment break and then restart tivozanib on disease progression. (Further planned treatments breaks following the same strategy are allowed). Review by the end of the first 8 weeks of treatment
Monitoring parameters pre-treatment	• **Virology screening:** All new patients referred for systemic anti-cancer treatment should be screened for hepatitis B and C and the result reviewed prior to the start of treatment. Patients not previously tested who are starting a new line of treatment, should also be screened for hepatitis B and C. Further virology screening will be performed following individual risk assessment and clinician discretion. • Monitor FBC, LFT's (AST, ALT, bilirubin, and AP) and U&E's prior to each cycle. Calcium, magnesium and potassium should be maintained within the normal range. • If neuts <1.0 and/or PLT <50 d/w consultant • **Hepatic impairment:** Not recommended in severe hepatic impairment. Patients with moderate hepatic impairment should be treated with 1340 microgram every other day. No dose adjustment is required in mild hepatic impairment. Tivozanib should be used with caution in patients with mild and moderate hepatic impairment with close monitoring of tolerability. • **Renal impairment:** No dose adjustment is required in patients with mild or moderate renal impairment. Caution in patients with severe (<30ml/min) renal impairment (limited data). • Thyroid function should be monitored before initiation of treatment, and every 8 weeks throughout. • **ECG** prior to initiating treatment and then as clinically indicated. • **ECHO** at baseline for at risk patients and repeated every 6 months. • **Hypertension and proteinuria:** BP should be well controlled prior to treatment. Monitor blood pressure (BP) every 2 weeks for the first 2 months and then before each cycle. Hypertension should be treated as needed with anti-hypertensive therapy. Patients receiving anti-hypertensive medication should be monitored for hypotension when tivozanib is either interrupted or discontinued. 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 BP is controlled. Proteinuria should be checked prior to starting treatment and before each cycle. Dose reduce or interrupt treatment in patients who develop Grade 2 (> 1.0-3.4 g/24 hours) or Grade 3 (≥ 3.5 g/24 hours) proteinuria. • **Venous / arterial thromboembolic events:** Use with caution in patients at risk of, or who have a history of arterial thromboembolic events. Use of tivozanib in patients who are at risk of VTEs, should be based on individual patient benefit/risk assessment. • **Cardiac failure:** Signs or symptoms of cardiac failure should be periodically monitored throughout treatment. • **QT interval prolongation:** Use 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. • **Bleeding / wound healing:** Use with caution in patients who are at risk of, or who have a history of bleeding, GI perforation or fistula. Temporary interruption of tivozanib therapy is recommended in patients undergoing major surgical procedures. The decision to resume tivozanib therapy after surgery should be based on clinical judgment of adequate wound healing. • **Posterior reversible encephalopathy syndrome (PRES):** The safety of re-initiating tivozanib in patients previously experiencing PRES is not known and tivozanib should only be used with caution in these patients. • **Hand Foot Skin Reaction:** Emollients should be initiated at first sign of hand foot skin reaction, cream containing 10% urea are recommended. Consider temporary interruption and/or reduction in treatment dose. • **Dose modifications / interruption of treatment***:* Reduce dose to 890 microgram once daily for 21 days followed by a 7 day rest period for grade 3 events and interrupt treatment for grade 4 events. • Discontinuation of treatment should be considered in cases of persistent severe hypertension, cardiac failure events, hand foot skin reaction, posterior reversible encephalopathy syndrome, or other complications of hypertension. Discontinue if the patient develops Grade 4 proteinuria (nephrotic syndrome). • **Missed dose / vomiting:** The next dose should be taken at the next scheduled time. • **Drug and food interactions:** Co-administration with herbal preparations containing St. John's wort is contraindicated. The inducing effect of St John's wort may persist for at least 2 weeks after stopping St John's wort. It is recommended that concomitant administration of tivozanib with strong CYP3A4 inducers, if used, should be undertaken with caution. Moderate CYP3A4 inducers are not expected to have a clinically relevant effect on tivozanib exposure. Tivozanib inhibits the transporter protein BCRP *in vitro*, caution should be exercised if tivozanib is co-administered with rosuvastatin. • Tivozanib may cause fatigue/dizziness patients should be advised to take caution when driving or operating machinery. • For oral self-administration: refer to local Trust policy on oral anti-cancer medicines and supply Patient Information Leaflet and Macmillan information sheet.
Reference(s)	SPC accessed online 18.10.2024 KMCC protocol RCC-009 V3 CDF list V1.376 accessed online

NB For funding information, refer to CDF and NICE Drugs Funding List

Repeat every 28 days

Day	Drug	Dose	Route	Administration Details
1	**TIVOZANIB**	**1340 micrograms**	PO	OD for 21 days, followed by a 7-day rest period. Can be taken with or without food. The capsules must be swallowed whole with a glass of water and must not be opened. Available as 1340mcg and 890mcg capsules.
TTO	Drug	Dose	Route	Directions
Day 1	Metoclopramide	10mg	PO	10mg up to 3 times a day as required. Do not take for more than 5 days continuously.
	Loperamide	2-4mg	PO	Take 4mg (2 capsules) initially, then 2mg (1 capsule) after each loose stool when required. Maximum 16mg (8 capsules) a day. Dispense 30 capsules on cycle 1 then only if specified.