Indication	Previously treated advanced renal cell carcinoma with clear cell component. NB Patients treated with more than 1 line of VEGF-targeted therapy for advanced/metastatic disease are not eligible. NB Patients should not have received previous treatment with either lenvatinib or everolimus.
Treatment Intent	Palliative treatment
Frequency and number of cycles	Every 28 days Continue until progressive disease or unacceptable toxicity / patient choice
Monitoring parameters pre-treatment	• Monitor FBC and U&E's prior to each cycle, in particular potassium, calcium and magnesium. Abnormalities in electrolytes should be corrected before starting treatment. • If neuts <1.0 or platelets <75 defer 1 week. • LFTs should be monitored before cycle 1, then every 2 weeks for the first 2 cycles and then before each cycle. • Thyroid function and 9am cortisol level must be assessed at baseline then every 8 weeks. • Blood pressure (BP) should be well controlled prior to treatment. BP should be monitored after 1 week, then every 2 weeks for the first 2 cycles, and then prior to each cycle. • ECG prior to cycle 1 and then every 8 weeks • Urine protein should be monitored prior to each cycle If >/=2+ see table 1. • Monitoring of fasting serum glucose is recommended prior to the start of treatment and then every 3 months thereafter. More frequent monitoring is recommended when Everolimus is co-administered with other medicinal products that may induce hyperglycaemia. When possible, optimal glycaemic control should be achieved before starting treatment. • Dyslipidaemia (including hypercholesterolaemia and hypertriglyceridaemia) has been reported with everolimus. Monitoring of blood cholesterol and triglycerides prior to the start of Everolimus therapy and every 3 months thereafter, as well as management with appropriate medical therapy, is recommended. • <u>Hepatic impairment</u>: In patients with severe (Child-Pugh C) hepatic impairment, if benefits are considered to outweigh risks, the recommended starting dose of lenvatinib is 10 mg taken once daily and everolimus 5mg on alternate days. • <u>Renal impairment</u>: In patients with severe renal impairment, the recommended starting dose is 10 mg of lenvatinib with 5 mg of

	everolimus taken once daily. Not recommended for patients with end-stage renal disease. • <u>Management of adverse reactions and dose adjustments:</u> • Grade 1 or 2 adverse reactions, continue treatment unless adverse events intolerable to the patient despite optimal management. • >/= Grade 3 or intolerable adverse reactions require interruption of treatment until improvement of the reaction to Grade 0-1 or baseline. • For toxicities thought to be related to both lenvatinib and everolimus, lenvatinib should be reduced prior to reducing everolimus. • For toxicities thought to be related to lenvatinib see table 1. • Toxicities related to everolimus include e.g non-infectious pneumonitis, stomatitis, hyperglycaemia, dyslipidaemia, haematological toxicities. • Treatment should be discontinued in case of life-threatening reactions (e.g. Grade 4) with the exception of laboratory abnormalities judged to be non-life-threatening, in which case they should be managed as severe reactions (e.g. Grade 3). • When dose modifications of lenvatinib are required, the 1st dose reduction (DR) should be to 14mg, the 2nd DR to 10mg and the 3rd DR to 8 mg (limited data below 8mg). • Gastrointestinal toxicity should be actively managed in order to reduce the risk of development of renal impairment or renal failure. • <u>Cautions</u> • Use with caution in patients who have had an arterial thromboembolism within the previous 6 month. • Lenvatinib should not be started in patients with fistulae and should be permanently discontinued in patients with oesophageal or tracheobronchial tract involvement and any Grade 4 fistula • Lenvatinib may adversely affect the wound healing process. • Patients should be advised to report promptly any new or worsening respiratory symptoms which could be indicative of everolimus induced non-infectious pneumonitis. The use of corticosteroids may be indicated for moderate (Grade 2) or severe (Grade 3) non-infectious pneumonitis until clinical symptoms resolve. • Use of live vaccines should be avoided during treatment with everolimus. • Everolimus has immunosuppressive properties and may pre-dispose patients to bacterial, fungal, viral and protozoan infections including reactivation of hepatitis B. Ensure patients are monitored appropriately • Patients should be advised to be cautious when driving or using machines if they experience fatigue

	• <u>Concomitant medication / Drug interactions</u> • Caution should be taken in patients receiving agents acting on the renin-angiotensin aldosterone system as there may be a higher risk for acute renal failure. • Patients taking concomitant ACE inhibitor (e.g. ramipril) therapy may be at increased risk for angioedema. • Caution in those taking medicinal products known to prolong the QT interval, including Class Ia and III antiarrhythmics. • Co-administration with inhibitors (e.g ketoconazole, itraconazole, clarithromycin) and inducers (e.g rifampicin, dexamethasone, phenytoin, and carbamazepine) of CYP3A4 and/or the multidrug efflux pump P-glycoprotein (PgP) should be avoided. If co-administration of a ***moderate*** CYP3A4 and/or PgP inhibitor or inducer cannot be avoided, dose adjustments of everolimus may be considered. Concomitant treatment with ***potent*** CYP3A4 inhibitors (e.g ketoconazole, itraconazole, clarithromycin) result in dramatically increased plasma concentrations of everolimus. There are currently not sufficient data to allow dosing recommendations in this situation and concomitant treatment of everolimus and ***potent*** inhibitors is not recommended. • Caution should be exercised when in combination with orally administered CYP3A4 substrates with a narrow therapeutic index (e.g. pimozide, terfenadine, astemizole, cisapride, quinidine or ergot alkaloid derivatives), and the patient should be monitored for undesirable effects. • For oral self-administration: <u>refer to local Trust policy on oral anti-cancer medicines</u> and supply Patient Information Leaflet.
Reference(s)	SpC (Kisplyx® and Afinitor®) accessed online 12/12/17

NB For funding information, refer to the SACT funding spreadsheet

Table 1: Adverse reactions related to lenvatinib

Adverse reaction	**Severity**	**Action**	**Dose reduce and resume lenvatinib**
Hypertension	Grade 3 (despite optimal antihypertensive therapy)	Interrupt	Resolves to Grade 0, 1 or 2. See detailed guidance in Table 2
	Grade 4	Discontinue	Do not resume
Proteinuria	≥ 2 gm / 24 hours	Interrupt	Resolves to less than 2 gm / 24 hours.
Nephrotic syndrome	-------	Discontinue	Do not resume
Renal impairment or failure	Grade 3	Interrupt	Resolves to Grade 0-1 or baseline.
	Grade 4*	Discontinue	Do not resume
Cardiac dysfunction	Grade 3	Interrupt	Resolves to Grade 0-1 or baseline.
	Grade 4	Discontinue	Do not resume
PRES/RPLS	Any grade	Interrupt	Consider resuming at reduced dose if resolves to Grade 0-1.
Hepatotoxicity	Grade 3	Interrupt	Resolves to Grade 0-1 or baseline.
	Grade 4*	Discontinue	Do not resume
Arterial thromboembolisms	Any grade	Discontinue	Do not resume
Haemorrhage	Grade 3	Interrupt	Resolves to Grade 0-1.
	Grade 4	Discontinue	Do not resume
GI perforation or fistula	Grade 3	Interrupt	Resolves to Grade 0-1 or baseline.
	Grade 4	Discontinue	Do not resume
Non-GI fistula	Grade 4	Discontinue	Do not resume
QT interval prolongation	>500 ms	Interrupt	Resolves to <480 ms or baseline
Diarrhoea	Grade 3	Interrupt	Resolves to Grade 0-1 or baseline.

	Grade 4 (despite medical management)	Discontinue	Do not resume
*Grade 4 laboratory abnormalities judged to be non-life-threatening, may be managed as severe reactions (e.g., Grade 3)			

Table 3 Recommended management of hypertension associated with lenvatinib

Blood pressure (BP) level	**Recommended action**
Systolic BP ≥140 mmHg up to <160 mmHg or diastolic BP ≥90 mmHg up to <100 mmHg	Continue lenvatinib and initiate antihypertensive therapy, if not already receiving OR Continue lenvatinib and increase the dose of the current antihypertensive therapy or initiate additional antihypertensive therapy
Systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg despite optimal antihypertensive therapy	1. Withhold lenvatinib 2. When systolic BP ≤150 mmHg, diastolic BP ≤95 mmHg, and patient has been on a stable dose of antihypertensive therapy for at least 48 hours, resume lenvatinib at a reduced dose
Life-threatening consequences (malignant hypertension, neurological deficit, or hypertensive crisis)	Urgent intervention is indicated. Discontinue lenvatinib and institute appropriate medical management.

Repeat every 28 days

TTO	Drug	Dose	Route	Directions
	Lenvatinib (Kisplyx®)	18mg	po	Swallowed whole with water once a day with or without food. If a patient misses a dose, and it cannot be taken within 12 hours, then that dose should be skipped and the next dose should be taken at the usual time of administration.
	Everolimus (Afinitor®)	5mg	po	Swallowed whole with a glass of water once a day at the same time every day, consistently either with or without food. Grapefruit and grapefruit juice should be avoided.
	Metoclopramide	10mg	po	3 times a day when 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.