EVEROLIMUS + LENVATINIB (*Kisplyx*®)

This combination is indicated for the treatment of adult patients with advanced rcc, following one prior VEGF-targeted therapy, and with PS 0 - 1

Blueteq registration is required before treatment may start

Drug/Dosage:	**Everolimus**	initiate at 5mg po once daily continuous therapy
	Lenvatinib	initiate at 18mg po once daily continuous therapy

Administration: Everolimus is available as 2.5mg and 5mg tablets, which may be taken at the same time of day every day either with or without food, but not after a high fat meal. Grapefruit and grapefruit juice should be avoided while on everolimus.
Lenvatinib is available as 10mg and 4 mg capsules, brand name Kisplyx®.
Swallow whole with water, with or without food.

Frequency: continue for as long as there is clinical benefit, or unacceptable toxicity.

Main Toxicities: myelosuppression; increased risk of infection; hypertension; proteinuria; diarrhoea; nausea; mucositis; rash or dry skin or PPE; dysphonia; non-infectious pneumonitis (can be severe – any shortness of breath should be reported); headache; oedema; hyperglycaemia; hypertriglyceridaemia; hypothyroidism; fatigue

Anti- emetics: mildly emetogenic, but nausea very common (avoid domperidone)

Regular:	FBC	every 4 weeks
Investigations:	LFTs	every 2 weeks for the first 2 months, then every 4 weeks
	U&Es	every 4 weeks
	Ca^{2+}	every 4 weeks
	Blood pressure	after 1 week, then every 2 weeks for the first 2 months, then monthly
	Proteinuria	baseline, after 1 month, then as indicated
	QT interval	baseline, after 1 month, then periodically as indicated
	Thyroid function	baseline, then periodically as indicated
	Random blood glucose*	baseline, then: for non-diabetics: before the 2nd and 3rd month's supply is dispensed as a minimum for patients with a history of diabetes, or previous raised blood glucose: continue to monitor every month
	*Fasting glucose	only if random blood glucose > 11 mmol/l
	Triglycerides	baseline, then periodically, according to Consultant preference

Comments: Ensure patient has a supply of loperamide and metoclopramide.

Patients should be advised to apply moisturiser to their hands and feet regularly throughout treatment, and to minimise activities that put pressure on feet or hands if they start to develop sore hands or feet. Recommended moisturisers are Udderly Smooth or urea-containing moisturisers eg Eucerin.

Interactions: There is no data available regarding interactions with lenvatinib.

Lenvatinib has been shown to prolong the QT interval, so use with caution in patients taking other medicines that lead to QT prolongation (e.g. amiodarone, quinidine, sotalol, chloroquine, clarithromycin), and those with electrolyte disturbances such as hypokalaemia, hypocalcaemia,

or hypomagnesaemia. When using lenvatinib in these patients, periodic ECG, plus monitoring of magnesium and calcium should be considered.

Elimination of everolimus is mainly through hepatic metabolism. Concomitant use of enzyme inducers (e.g. carbamazepine, phenytoin, St Johns wort) with everolimus should be avoided, as this may increase the risk of therapeutic failure.
Co-administration of everolimus with potent CYP3A4 enzyme inhibitors (eg itraconazole, clarithromycin) or grapefruit juice is not recommended.
Co-administration with moderate enzyme inhibitors (eg erythromycin, fluconazole, verapamil) should be avoided. If this is not possible, the dose of everolimus may need to be reduced to 2.5mg daily.

Dose Modifications

Management of adverse reactions may require dose interruption, dose reduction, or discontinuation of combination therapy.

Mild to moderate adverse reactions (e.g., Grade 1 or 2) generally do not warrant interruption of the combination, unless intolerable to the patient despite optimal management.
Severe (e.g. Grade 3) or intolerable adverse reactions require interruption of the combination until improvement of the reaction to Grade 0-1 or baseline.

For Grade 3 toxicities thought to be lenvatinib-related, upon resolution/improvement of an adverse reaction to Grade 0-1 or baseline, treatment should be resumed at a reduced dose of lenvatinib.
For toxicities thought to be everolimus-related, everolimus should be interrupted, reduced to alternate day dosing or discontinued.
For toxicities thought to be related to both drugs, **lenvatinib should be reduced prior to reducing the everolimus dose.**

Dose modifications from recommended lenvatinib daily dose of 18mg

Dose level	Daily dose
First dose reduction	14 mg orally once daily
Second dose reduction	10 mg orally once daily
Third dose reduction	8 mg orally once daily

Adverse reactions requiring dose modification of lenvatinib			
Adverse reaction	**Severity**	**Action**	**When to resume lenvatinib at next step dose reduction**
Hypertension	Grade 3 (despite optimal antihypertensive therapy)	Interrupt	Resolves to Grade 0, 1 or 2. See detailed guidance below
	Grade 4	Discontinue	Do not resume
Proteinuria	≥ 2 gm / 24 hours	Interrupt	Resolves to less than 2 gm / 24 hrs
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 thromboembolism	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 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)

Hypertension:

Blood pressure (BP) should be well controlled prior to starting. If patients are known to be hypertensive, they should be on a stable dose of antihypertensive therapy for at least 1 week prior to starting.
The early detection and effective management of hypertension are important to minimise the need for lenvatinib dose interruptions and reductions. Antihypertensive agents should be started as soon as elevated BP is confirmed.
BP should be monitored after 1 week of treatment with lenvatinib, then every 2 weeks for the first 2 months, and monthly thereafter.
The choice of antihypertensive treatment should be individualised to the patient's clinical circumstances and follow standard medical practice.

Recommended management of hypertension

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 ≥ 48 hrs, 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.

Haematological Toxicity:

Neutrophils 0.5 – 0.99 x 10^9/l or Platelets 50 - 74 x 10^9/l	Interrupt treatment until neutrophils ≥ 1.0 x 10^9/l and platelets ≥ 75 x 10^9/l, then re-start both drugs at the same dose.
Neutrophils < 0.5 x 10^9/l or Platelets < 50 x 10^9/l	Interrupt treatment until neutrophils ≥ 1.0 x 10^9/l and platelets ≥ 75 x 10^9/l, then re-start with a reduced dose of everolimus
Grade 3 febrile neutropenia (neutrophils 0.5 - 0.9 x 10^9/l)	Interrupt treatment until fever resolved and neutrophils ≥ 1.25 x 10^9/l, then re-start with a reduced dose of everolimus
Grade 4 febrile neutropenia (neuts < 0.5)	Discontinue everolimus permanently.

Mucositis: Symptoms should be managed according to the Alliance guidelines for mucositis.

Grading of Mucositis	Management and advice for everolimus
Grade 2, first episode	Everolimus may continue if the patient can tolerate it. Otherwise, interrupt until ≤ Grade 1, then try and re-introduce at the same dose.
Grade 2, second episode	Interrupt treatment until ≤ Grade 1, then re-start everolimus at a reduced dose.
Grade 3	Everolimus treatment should be interrupted until ≤ Grade 1. Then re-start everolimus at a reduced dose. If Grade 3 toxicity recurs, consider stopping permanently
Grade 4	Discontinue everolimus permanently.

Non-infectious Pneumonitis: If radiological changes suggestive of everolimus-related pneumonitis, manage as follows:

Grading of Pneumonitis	Management
Grade 2 (symptomatic, not affecting ADL)	Consider interrupting therapy until symptoms resolve, then re-initiate everolimus at a reduced dose. Discontinue if symptoms do not resolve within 4 weeks.
Grade 3 (symptomatic, affecting ADL, requiring O_2)	Interrupt therapy until symptoms resolve. The use of corticosteroids may be indicated until symptoms resolve. Consider re-initiating everolimus at a reduced dose.
Grade 4 (life-threatening)	Discontinue everolimus. Corticosteroids may be required until symptoms resolve.

Hyperglycaemia or Dyslipidaemia: If blood glucose is raised at baseline, whenever possible, optimal glycaemic control should be achieved before starting everolimus. Once everolimus has started, follow the advice below:

Fasting glucose 14 - 27.8 mmol/l or Triglycerides 5.8 - 11.4 mmol/l - interrupt everolimus until resolved, and re-initiate everolimus at a reduced dose.
Fasting glucose > 27.8mmol/l or Triglycerides > 11.4mmol/l – permanently discontinue everolimus

Any other toxicities thought to be everolimus-related:

Other Everolimus-related Non-Haematological Toxicity	Management
Grade 2	If toxicity is tolerable, no dose adjustment required. If toxicity becomes intolerable, interrupt everolimus until recovery to Grade ≤1. Re-initiate treatment at same dose. If toxicity recurs at Grade 2, interrupt treatment until recovery to Grade ≤1. Re-initiate treatment at a reduced dose.
Grade 3	Interrupt everolimus until recovery to Grade ≤1. Consider re-initiating treatment at a reduced dose. If toxicity recurs at Grade 3, consider discontinuation.
Grade 4	Discontinue everolimus permanently

Hepatic Impairment: No adjustment of starting dose of either drug is required on the basis of hepatic function in patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment.
In patients with severe (Child-Pugh C) hepatic impairment, use only if the desired benefit outweighs the risk, and then the starting dose for lenvatinib is 10mg od and the starting dose for everolimus is 2.5mg od.

Renal Impairment: No adjustment of starting dose is required on the basis of renal function in patients with mild or moderate renal impairment.
In patients with severe renal impairment (CrCl < 30ml/min), the recommended starting dose is 10 mg of lenvatinib with 5mg of everolimus, both taken once daily.

Reference: Motzer, R et al; Lancet Oncology 2015; 16 (15): 1473 - 1482