Systemic Anti Cancer Treatment Protocol

Lenvatinib (Kisplyx) and Everolimus in Renal Cell Carcinoma

PROTOCOL REF: MPHALEVEUR
(Version No: 1.1)

The 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:

Lenvatinib and everolimus combination is for the treatment of adult patients with metastatic disease or inoperable advanced renal cell carcinoma (RCC) where the following criteria is met:

- The patient has a confirmed diagnosis of renal cell carcinoma with a clear cell component.
- The patient has previously received only one prior vascular endothelial growth factor (VEGF)-targeted therapy.
- The patient has progressed on previous treatment or within six months of discontinuing previous treatment.
- Performance status of either 0 or 1
- The patient has either brain metastases that are symptomatically stable or they have no brain metastases.

No treatment break of more than six weeks beyond the expected cycle length is allowed.

***Blue-teq registration required ***

Dosage:

Drug	Dosage	Route	Frequency
Lenvatinib	18mg	Oral	Daily
Everolimus	5mg	Oral	Daily

Until disease progression or unacceptable toxicity

Supportive treatments:

Cyclizine 50mg oral tablets, up to three times a day as required

Loperamide 2mg when required (max 16mg in 24hours)

Extravasation risk:

N/A

Administration:

Lenvatinib and everolimus should be administered orally once daily at the same time every day, consistently either with or without food.

For patients with swallowing difficulty, lenvatinib capsules must not be opened but may be dissolved using the following instructions;

> *Pour a tablespoon of water or apple juice into a small glass and put the capsules into the liquid without breaking or crushing them. Leave for at least 10 minutes then stir for at least 3 minutes to dissolve the capsule shells. Drink the mixture. After drinking, add the same amount of water or apple juice, swirl and swallow.*

If a patient misses a dose and it cannot be taken within 12 hours; then that dose should be skipped and the next dose taken at the usual time of administration.

Everolimus tablets should be swallowed whole with a glass of water. The tablets should not be chewed or crushed. Avoid Grapefruit juice.

Drug Interactions

Lenvatinib

No significant drug-drug interaction is therefore expected between lenvatinib and other CYP3A4/Pgp substrates.

Lenvatinib can prolong QT interval therefore caution should be used when using in combination with other QT prolonging drugs such as amiodarone, ciprofloxacin, citalopram, erythromycin, fluoxetine, fluconazole and ondansetron.

Oral contraceptives

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

Everolimus

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

INDUCERS (lowers everolimus levels): Carbamazepine, phenobarbital, phenytoin, dexamethasone, rifampicin, St John's Wort.

INHIBITORS (increases everolimus levels): Indinavir, nelfinavir, ritonavir, clarithromycin, erythromycin, itraconazole, ketoconazole, nefazodone, grapefruit juice, verapamil, diltiazem, cimetidine, amiodarone, fluvoxamine, mibefradil, ciclosporin, fluconazole.

ACE inhibitors may increase the risk for angioedema.

Main Toxicities:

Hypertension, diarrhoea, neutropenia, fatigue, dyspnoea, anaemia, thrombocytopenia, stomatitis, skin reaction, headaches, nausea, pneumonitis, oedema, hyperglycaemia.

Please refer to the SPC for more information on toxicities for both medicines.

Investigations and Treatment Plan:

	Pre	C1		C2		C3	C4	C5	Ongoing
		Wk1	Wk3	Wk5	Wk7	Wk9	Wk13	Wk17	
Informed Consent	X								
Clinical Assessment	X			X		X		X	For the first three cycles then after each CT scan
SACT assessment (including PS & toxicities)	X	X	X	X	X	X	X	X	Every Cycle
FBC	X		X	X	X	X	X	X	Two weekly for the 1st 2 cycles then every cycle
U&E & LFT	X		X	X	X	X	X	X	Every 2 weeks for the 1st 2months then monthly
Mg &Ca	X			X		X	X	X	Every cycle
Blood Glucose	X			X		X	X	X	Every cycle
Fasting lipids and cholesterol	X						X		Every 12 weeks
CT scan	X						X		Every 12 weeks
TFTs & TSH	X			X		X	X	X	Every cycle

Weight	X	X	X	X	X	X	X	X	Every cycle
Height	X								
ECG	X								If clinically indicated
Urine dipstick for Protein	X		X	X	X				Then every 12 weeks (unless clinically indicated)
Blood Pressure	X		X	X	X	X	X	X	Monitor after 1 week of treatment,* then every 2 weeks for the first two cycles, then every 4 weeks

*Blood pressure check during week 2 can be arranged at GP surgery or for patient to attend chemotherapy clinic.

Dose Modifications and Toxicity Management:

- For toxicities thought to be related to lenvatinib upon resolution/improvement of an adverse reaction to Grade 0-1 or baseline, treatment should be resumed at a reduced dose of lenvatinib as suggested below.
- For toxicities thought to be related to everolimus, treatment should be interrupted, reduced to 5mg on alternate days.
- For toxicities thought to be related to both lenvatinib and everolimus- lenvatinib should be reduced prior to reducing everolimus.

Adverse reactions requiring dose modification of lenvatinib			
Adverse reaction	**Severity**	**Action**	**Dose reduce and resume lenvatinib**
Hypertension	Grade 3 (despite optimal antihypertensive therapy)	Interrupt	Stop lenvatinib until it resolves to Grade 0, 1 or 2. Can continue on with everolimus. Grade 3- Stop both medications
	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)			

Adverse reactions requiring dose modification of everolimus		
Adverse reaction	**Severity**	**Action**
Non-infectious pneumonitis	Grade 2	Consider interruption of therapy until symptoms improve to Grade ≤1. Consider dose reduction Discontinue treatment if failure to recover within 4 weeks.
	Grade 3	Interrupt treatment until symptoms resolve to Grade ≤1 Consider dose reduction If toxicity recurs at Grade 3, consider discontinuation.
	Grade 4	Discontinue treatment.
Stomatitis	Grade 2	Temporary dose interruption until recovery to Grade ≤1. Re-initiate treatment at same dose. If stomatitis recurs at Grade 2, interrupt dose until recovery to Grade ≤1. Consider dose reduction
	Grade 3	Temporary dose interruption until recovery to Grade ≤1. Consider dose reduction

	Grade 4	Discontinue treatment.
Other non-haematological toxicities (excluding metabolic events)	Grade 2	If toxicity is tolerable, no dose adjustment required. If toxicity becomes intolerable, temporary dose interruption until recovery to Grade ≤1. Re-initiate treatment at same dose. If toxicity recurs at Grade 2, interrupt treatment until recovery to Grade ≤1 Consider dose reduction
	Grade 3	Temporary dose interruption until recovery to Grade ≤1. Consider dose reduction If toxicity recurs at Grade 3, consider discontinuation.
	Grade 4	Discontinue treatment.
Metabolic events (e.g. hyperglycaemia, dyslipidaemia)	Grade 2	No dose adjustment required.
	Grade 3	Temporary dose interruption. Consider dose reduction
	Grade 4	Discontinue treatment.
Thrombocytopenia	Grade 2 (<75, ≥50x10^9/l)	Temporary dose interruption until recovery to Grade ≤1 (≥75x10^9/l). Re-initiate treatment at same dose.
	Grade 3 & 4 (<50x10^9/l)	Temporary dose interruption until recovery to Grade ≤1 (≥75x10^9/l). Consider dose reduction
Neutropenia	Grade 2 (≥1x10^9/l)	No dose adjustment required.
	Grade 3 (<1, ≥0.5x10^9/l)	Temporary dose interruption until recovery to Grade ≤2 (≥1x10^9/l). Re-initiate treatment at same dose.
	Grade 4 (<0.5x10^9/l)	Temporary dose interruption until recovery to Grade ≤2 (≥1x10^9/l). Consider dose reduction

Hypertension

- Usually occurs early on in the course of treatment.
- Blood pressure (BP) should be well controlled prior to treatment with lenvatinib and, if patients are known to be hypertensive, they should be on a stable dose of antihypertensive therapy for at least 1 week prior to treatment 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.

Proteinuria

- Usually occurs early on in the course of treatment therefore urine protein should be monitored regularly.
- If urine dipstick proteinuria ≥2+ is detected, withhold treatment dose interruptions, adjustments, or discontinuation may be necessary.

Lenvatinib should be discontinued in the event of nephrotic syndrome and not to be resumed.

Dose modifications from recommended lenvatinib daily dose

Dose level	Daily dose	Number of capsules
Recommended daily dose	18 mg orally once daily	One 10 mg capsule plus two 4 mg capsules
First dose reduction	14 mg orally once daily	One 10 mg capsule plus one 4 mg capsule
Second dose reduction	10 mg orally once daily	One 10 mg capsule
Third dose reduction	8 mg orally once daily	Two 4 mg capsules
Limited data are available for doses below 8 mg		

Haematological toxicity

Proceed on day 1 if:-

ANC ≥ 1.0 x 10^9/L	Platelets ≥ 100 x 10^9/L*

Discuss with consultant if:-

ANC ≤ 0.99 x 10^9/L	Platelets ≤ 100 x 10^9/L*

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, the recommended starting dose is 10 mg of lenvatinib with 5 mg of everolimus taken once daily. Further dose adjustments may be necessary based on individual tolerability. Patients with end-stage renal disease were not studied, therefore the use of lenvatinib in these patients is not recommended.

Elevations of serum creatinine, usually mild, and proteinuria have been reported. Monitoring of renal function, including measurement of blood urea nitrogen (BUN), urinary protein or serum creatinine, is recommended prior to the start of therapy and periodically thereafter.

Hepatic impairment

No data with the combination is available in patients with hepatic impairment. No adjustment of starting dose of the combination 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, the recommended starting dose of lenvatinib is 10 mg taken once daily in combination with the dose of everolimus recommended for patients with severe hepatic impairment in the everolimus SPC. Further dose adjustments may be necessary on the basis of individual tolerability. The combination should be used in patients with severe hepatic impairment only if the anticipated benefit exceeds the risk.

References:

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