Everolimus and Lenvatinib

Indication

Treatment of advanced renal cell carcinoma in patients following treatment with one prior vascular endothelial growth factor (VEGF) targeted therapy.

ECOG performance score 0-1.

(NICE TA498)

ICD-10 codes

Codes with a prefix C64

Regimen details

Day	Drug	Dose	Route
1-28	Everolimus	5mg OD	PO
1-28	Lenvatinib	18mg OD	PO

Cycle frequency

28 days - continuous

Number of cycles

Continue until disease progression or unacceptable toxicity.

Administration

Everolimus

Everolimus is available as 2.5mg, 5mg.

The tablets should be swallowed whole with a glass of water at the same time each day either with or without food, but not after a high fat meal.

If a dose is missed or the patient vomits after taking their dose, the patient should not take an additional dose. The patient should take the usual prescribed dose on the following day.

Grapefruit and grapefruit juice should be **avoided** whilst taking everolimus.

Lenvatinib

Lenvatinib (Kisplyx®) is available as 4mg and 10mg capsules. The dose is made up of 1 x 10mg capsule and 2 x 4mg capsules.

The tablets should be swallowed whole with a glass of water at the same time each day, either with or without food. Alternatively, the capsules may be added (without breaking or crushing them) to a tablespoon of water or apple juice in a small glass to produce a suspension. The capsules must be left in the liquid for at least 10 minutes and stirred for at least 3 minutes to dissolve the capsule shells. The suspension should then be swallowed. After drinking, the same amount of water or apple juice (one tablespoon) must be added to the glass and swirled a few times. The additional liquid must also be swallowed.

If a dose is missed and it is more than 12 hours from the time the dose was due, the dose should be missed. The patient should take the usual prescribed dose on the following day.

NOTE: The **Kisplyx®** brand is the only product licensed for the treatment of renal cell carcinoma.

Pre-medication
Nil

Emetogenicity
This regimen has mild emetic potential (although nausea is common).

Additional supportive medication
Antiemetics as required.
Loperamide if required.
Emollients

Extravasation
N/A

Investigations – pre first cycle

Investigation	Validity period
FBC	7 days
U+E (including creatinine)	7 days
LFTs	7 days
Calcium	7 days
Magnesium	7 days
Fasting glucose	7 days
Lipids	7 days
Thyroid function tests	Baseline
Blood pressure	Baseline. Must be controlled before initiating treatment.
Urinalysis	Baseline
ECG	Baseline

Electrolyte abnormalities should be corrected prior to commencing treatment.

Investigations – pre subsequent cycles

Investigation	Validity period
FBC	Every 2 weeks for the first 2 months then every 4 weeks
U+E (including creatinine)	Every 2 weeks for the first 2 months then every 4 weeks
LFTs	Every 2 weeks for the first 2 months then every 4 weeks
Calcium	Every 4 weeks
Magnesium	Every 4 weeks
Fasting glucose	Every 6-8 weeks then as clinically indicated
Lipids	Every 6-8 weeks then as clinically indicated
Thyroid function tests	Every 6-8 weeks then as clinically indicated
Blood pressure	After week 1 then every 2 weeks for the first 2 months then every 4 weeks.
ECG	As clinically indicated

CXR every 8 weeks or as per symptoms at consultants discretion.

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	Limit
Neutrophils	≥ 1.0 x 10^9/L
Platelets	≥ 75 x 10^9/L
CrCl	> 30mL/min
Bilirubin	≤ ULN
ALT/AST	≤ ULN

Dose modifications

Lenvatinib dose modifications:

Dose level	Lenvatinib dose
Full dose	18mg OD
First dose reduction	14mg OD
Second dose reduction	10mg OD
Third dose reduction	8mg OD

There is limited data of dosing below 8mg OD.

The dose of everolimus may be reduced to alternate days or 2.5mg OD. Dose modifications lower than this are not recommended.

- **Haematological toxicity**

Toxicity	Definition	Dose adjustment
Neutropenia	Neutrophils 0.5 - < 1.0 x 10^9/L	1st occurrence: Delay until ≥ 1.0 x 10^9/L then continue both drugs at same dose 2nd occurrence: Delay until ≥ 1.0 x 10^9/L then continue with reduced dose of everolimus. 3rd occurrence: Discontinue everolimus
	Neutrophils <0.5 x 10^9/L	1st occurrence: Delay until ≥ 1.0 x 10^9/L then continue with reduced dose of everolimus 2nd occurrence: Discontinue everolimus
Febrile neutropenia	Grade 3	Delay until neutrophils ≥ 1.25 x 10^9/L and no fever then continue with reduced dose of everolimus
	Grade 4	Discontinue everolimus
Thrombocytopenia	Platelets 50-75 x 10^9/L	1st occurrence: Delay until recovery then continue at same dose 2nd occurrence: Delay until recovery then continue with reduced dose of everolimus 3rd occurrence: Discontinue everolimus
	Platelets 25-49 x 10^9/L	1st occurrence: Delay until recovery then continue reduced dose everolimus 2nd occurrence: Discontinue everolimus
	Platelets <25 x 10^9/L	Discontinue everolimus

- **Renal impairment**

No adjustment of starting dose for either agent 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 OD lenvatinib with 5 mg OD of everolimus. Further dose adjustments may be necessary based on individual tolerability. Treatment is not recommended in patients with end-stage renal disease.

Cases of renal failure have been reported in patients receiving everolimus. Renal function should be monitored. Patients with acute renal failure should stop treatment until the cause has been investigated and treated.

- **Hepatic impairment**

Everolimus is mainly excreted via hepatic elimination. Doses adjustments should be made as per table below:

Degree of hepatic impairment	**Everolimus dose**	**Lenvatinib dose**
Mild (Child Pugh A)	5mg OD	18mg OD
Moderate (Child Pugh B)	5mg OD	18mg OD
Severe (Child Pugh C)	Not recommended – if used dose must not exceed 2.5mg OD	Not recommended – if used 10mg OD

Child Pugh Classification:

Score	1	2	3
Bilirubin (µmol/L)	<34	34-50	>50
Albumin (g/L)	>35	28-35	<28
PT (s prolonged)	<4	4-6	>6
Encephalopathy	none	mild	marked
Ascites	none	mild	marked

The individual scores are summed and then grouped as:

- <7 = A
- 7-9 = B
- >9 = C

Further dose adjustments may be necessary on the basis of individual tolerability.

- **Other toxicities**

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

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. For toxicities thought to be related to everolimus, treatment should be interrupted, reduced to alternate days or 2.5mg OD, or discontinued. For toxicities thought to be related to both lenvatinib and everolimus, lenvatinib should be reduced prior to reducing everolimus.

Treatment should be discontinued in case of life-threatening reactions (Grade 4) with the exception of laboratory abnormalities judged to be non-life-threatening, in which case they should be managed as severe reactions (Grade 3).

Everolimus

Toxicity	Definition	Dose adjustment
Non-infectious pneumonitis	Grade 1	100%
	Grade 2	If symptomatic withhold treatment until to ≤ Grade 1. Resume at reduced dose when symptoms resolve Discontinue if symptoms do not resolve within 4 weeks.
	Grade 3	Withhold treatment until ≤ Grade 1 May resume at reduced dose if evidence of clinical benefit. If grade 3 toxicity recurs discontinue.
	Grade 4	Discontinue
Stomatitis	Grade 1	100%
	Grade 2	Withhold treatment until ≤ Grade 1 Resume at same dose If recurs at Grade 2, withhold treatment until ≤ Grade 1 and resume at reduced dose.
	Grade 3	Withhold treatment until ≤ Grade 1 Resume at reduced dose
	Grade 4	Discontinue
Other non-haematological toxicity (except alopecia and metabolic events)	Grade 1	100%
	Grade 2	If toxicity is tolerable, no dose modification required. If intolerable withhold treatment until ≤ Grade 1 and then resume at same dose If recurs at Grade 2, withhold treatment until ≤ Grade 1 and resume at reduced dose.
	Grade 3	Withhold treatment until ≤ Grade 1 Resume at reduced dose. If grade 3 toxicity recurs discontinue.
	Grade 4	Discontinue
Metabolic events (hyperglycaemia, dyslipidaemia)	Grade 1 or 2	100%
	Grade 3	Withhold treatment and resume at reduced dose
	Grade 4	Discontinue

Lenvatinib:

Hypertension

Blood pressure	Action
Systolic ≥140 - <160 mmHg **or** Diastolic ≥90 - <100 mmHg	Initiate or increase antihypertensive medication Continue lenvatinib
Systolic ≥160 mmHg **or** Diastolic ≥100 mmHg	Withhold lenvatinib When systolic ≤150 mmHg and diastolic ≤95 mmHg and patient has been stable on antihypertensive therapy for at least 48 hours, resume lenvatinib at reduced dose.
Malignant hypertension **or** Neurological deficit **or** Hypertensive crisis	Discontinue lenvatinib and commence urgent appropriate medical management.

Low body weight

There is limited data for lenvatinib patients with body weight <60 kg in renal cell carcinoma. However in thyroid cancer, patients with low body weight (<60 kg) had a higher incidence of PPE, proteinuria, of Grade 3 or 4 hypocalcaemia and hyponatraemia, and a trend towards a higher incidence of Grade 3 or 4 decreased appetite.

QT interval prolongation

QT interval prolongation has been reported in patients treated with lenvatinib. Electrocardiograms should be monitored in all patients particularly those with congenital long QT syndrome, congestive heart failure, bradyarrhythmics, and those taking medicinal products known to prolong the QT interval, including Class Ia and III antiarrhythmics. Lenvatinib should be withheld in the event of development of QT interval prolongation greater than 500 ms. Lenvatinib should be resumed at a reduced dose when QTc prolongation is resolved to < 480 ms or baseline.

Electrolyte disturbances such as hypokalaemia, hypocalcaemia, or hypomagnesaemia increase the risk of QT prolongation. Any electrolyte abnormalities should be corrected before starting treatment. Periodic monitoring of ECG and electrolytes (magnesium, potassium and calcium) should be considered during treatment. Blood calcium levels should be monitored at least monthly and calcium should be replaced as necessary during lenvatinib treatment. Lenvatinib dose should be interrupted or dose adjusted as necessary depending on severity, presence of ECG changes, and persistence of hypocalcaemia.

If any of the following occur interrupt lenvatinib treatment until grade 0-1 or baseline:

- Proteinuria (≥ 2g/24 hours)
- Grade 3 renal impairment
- Grade 3 cardiac dysfunction
- PRES/RPLS
- Grade 3 hepatotoxicity
- Grade 3 haemorrhage
- Grade 3 GI perforation
- Grade 3 diarrhoea

If any of the following occur discontinue lenvatinib treatment:

- Grade 4 hypertension
- Nephrotic syndrome
- Grade 4 renal impairment
- Grade 4 cardiac dysfunction
- Grade 4 hepatotoxicity
- Arterial thromboembolisms
- Grade 4 haemorrhage
- Grade 4 GI perforation
- Grade 4 non GI fistula
- Grade 4 diarrhoea

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Myelosuppression
Cardiotoxicity
Venous thromboembolism
Impaired wound healing
Teratogenicity
Hepatotoxicity
Infertility (males)
ARDS

- **Frequently occurring side effects**

Diarrhoea
Nausea and vomiting
Hyperlipidaemia
Hyperglycaemia
Hypertension
Hypothyroidism
Oedema
Myelosuppression
Rash
Pneumonitis (patients should report any new or worsening respiratory symptoms)
Stomatitis/Mucositis

- **Other side effects**

Taste disturbances
Fatigue
Headache
Insomnia
Weight loss

Significant drug interactions – for full details consult product literature/ reference texts

Everolimus:

Potent CYP3A4 and PgP inhibitors (e.g. ketoconazole, voriconazole, clarithromycin, ritonavir): avoid co-administration - may increase plasma concentrations of everolimus. Risk of toxicity.

Moderate CYP3A4 and PgP inhibitors (e.g. erythromycin, imatinib, ciclosporin, verapamil, diltiazem, grapefruit juice): co administration with caution and close monitoring/consider dose reduction of everolimus.

Grapefruit and grapefruit juice: avoid as an inhibitor of CYP3A4 and may increase plasma concentrations of everolimus.

Inducers of CYP3A4 (e.g. rifampicin, phenytoin, carbamazepine, dexamethasone, St Johns Wort): avoid co-administration - may reduce exposure to everolimus. Risk of therapeutic failure.

ACE inhibitors: caution, increased risk of angioedema.

Lenvatinib:

As lenvatinib may **prolong the QT interval** avoid concomitant use of other medications which can lead to QT prolongation (including amiodarone, quinidine, sotolol, chloroquine, clarithromycin). Use with caution in patients taking **medications which may cause electrolyte disturbances**.

Oral contraceptives: it is not known if lenvatinib may reduce the effectiveness of hormonal contraceptives and so women should also use a barrier method.

Agents acting on the renin-angiotensin aldosterone system: use with caution due to potentially higher risk for acute renal failure.

Additional comments

Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take everolimus.

Women of childbearing potential should avoid becoming pregnant and use highly effective contraception while on treatment with lenvatinib and for at least one month after finishing treatment. 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.

References

- Motzer, R et al; Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial Lancet Oncology 2015; 16 (15): 1473 - 1482
- National Institute for Clinical Excellence (TA498) accessed 20 December 2018 via www.nice.org.uk
- Summary of Product Characteristics Everolimus - Afinitor®(Novartis) accessed 20 December 2018 at www.medicines.org.uk
- Summary of Product Characteristics Lenvatinib - Kisplyx®(Eisai) accessed 20 December 2018 at www.medicines.org.uk

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Date: December 2018