EVEROLIMUS LENVATINIB (Kisplyx)

INDICATION (ICD10) C64
Check the most recent Blueteq eligibility criteria before prescribing. Blueteq registration required (www.england.nhs.uk/publication/national-cancer-drugs-fund-list/)
The treatment of previously treated advanced renal cell carcinoma
2. Confirmed histological diagnosis of renal cell carcinoma with a clear cell component Note: papillary, chromophobe and Xp11 translocation sub types can be treated as per clear cell pathway
3. Either metastatic disease or inoperable locally advanced disease
4. Previously received only 1 vascular endothelial growth factor (VEGF)-targeted systemic therapy for advanced/metastatic renal cancer*
5. Progressed on previous treatment or within 6 months of discontinuing previous treatment
6. ECOG performance status of either 0 or 1. Patients with a performance status of 2 or more are not eligible for lenvatinib with everolimus
7. No previous treatment with either lenvatinib or everolimus
9. Lenvatinib with everolimus will be continued until loss of clinical benefit or unacceptable toxicity or patient choice to stop treatment
10. If unacceptable toxicity occurs, the daily doses of lenvatinib and, if necessary, everolimus are to be modified as needed according to the dose/management plan as set out in section 4.2 of the Summary of Product Characteristics for lenvatinib (Kisplyx)
11. No treatment breaks of more than 6 weeks beyond the expected cycle length are allowed (to allow any toxicity of current therapy to settle or intercurrent comorbidities to improve)
12.Lenvatinib (Kisplyx) and everolimus are to be otherwise used as set out in their Summaries of Product Characteristics

REGIMEN
EVEROLIMUS 5mg orally daily
LENVATINIB 18mg orally daily

CYCLE FREQUENCY AND NUMBER OF CYCLES
Daily for 28 days continuously until progression or toxicity

ADMINISTRATION
Everolimus
Available as 2.5mg, 5mg and 10mg tablets
Swallow whole with or without food.

Lenvatinib
Available as 4mg and 10mg capsules

ANTI-EMETICS
Minimal risk all days

CONCURRENT MEDICATION REQUIRED
Mouth care eg difflam, gelclair

EXTRAVASATION AND TYPE OF LINE / FILTERS
Not applicable

INVESTIGATIONS

Blood results required before SACT administration
FBC, U&E and LFTs minimum monthly for first 3 months then alternate months
Neutrophils x 10^9/L ≥1.5
Platelets x 10^9/L ≥100
Random blood sugar, lipid profile each cycle; if elevated to repeat on fasting blood minimum monthly for 1st 3 months then alternate months
Blood pressure, after 1st week, then every 2 weeks for first 2 months, then monthly

MAIN TOXICITES AND ADVERSE REACTIONS

Everolimus	Increased glucose, lipids and triglycerides Decreased haemoglobin, lymphocytes, neutrophils and platelets Hypersensitivity reactions Pneumonitis, Infections Oral ulceration, mucositis
Lenvatinib	Hypertension, cardiac dysfunction, QT prolongation Proteinurea, diarrhoea Nephrotic syndrome Hepatotoxicity Haemorrhage, arterial thromboembolisms, GI perforation

INTERACTIONS WHICH MAY REQUIRE DOSE MODIFICATIONS
(not exhaustive list check SPC/BNF/Stockleys)

Everolimus	Strong CYP3A4 inhibitors (eg clarithromycin, itraconazole, posaconazole, voriconazole) should be avoided. CYP3A4 inducers (eg carbamazepine, phenytoin) should be avoided. ACE inhibitors increase risk of angioedema Grapefruit and grapefruit juice should be avoided
Lenvatinib	Check interactions carefully, interacts with a huge number of drugs.

DOSE MODIFICATIONS

Lenvatinib

Recommended dose	18mg once daily
First dose reduction	14mg once daily
Second dose reduction	10mg once daily
Third dose reduction	8mg once daily

Haematological

Everolimus

Thrombocytopenia grade 2 (platelets <75, ≥50x10^9/l)	Temporary dose interruption until recovery to grade ≤1 (platelets ≥75x10^9/l). Re-initiate treatment at same dose.
Thrombocytopenia grade 3 & 4 (platelets <50x10^9/l	Temporary dose interruption until recovery to grade ≤1 (platelets ≥75x10^9/l). Re-initiate treatment at 5mg daily.
Neutropenia grade 2 (ANC ≥1x10^9/l)	No dose adjustment required.
Neutropenia grade 3 (ANC <1, ≥0.5x10^9/l)	Temporary dose interruption until recovery to grade ≤2 (ANC ≥1x10^9/l). Re-initiate treatment at same dose.
Neutropenia grade 4 (ANC <0.5x10^9/l)	Temporary dose interruption until recovery to grade ≤2 (≥1x10^9/l). Re-initiate treatment at 5mg daily.
Febrile neutropenia grade 3	Temporary dose interruption until recovery to grade ≤2 (≥1.25x10^9/l) and no fever. Re-initiate treatment at 5mg daily.
Febrile neutropenia grade 4	Discontinue treatment.

Non-haematogical

Everolimus

Metabolic events (e.g. hyperglycaemia, dyslipidaemia) grade 2	No dose adjustment required.
Metabolic events (e.g. hyperglycaemia, dyslipidaemia) grade 3	Temporary dose interruption. Re-initiate treatment at 5mg daily.
Metabolic events (e.g. hyperglycaemia, dyslipidaemia) grade 4	Discontinue treatment.
Non-infectious pneumonitis grade 2	Consider interruption of therapy until symptoms improve to Grade ≤1. Re-initiate treatment at 5mg daily. Discontinue treatment if failure to recover within 4 weeks.
Non-infectious pneumonitis grade 3	Interrupt treatment until symptoms resolve to grade ≤1. Consider re-initiating treatment at 5mg daily. If toxicity recurs at Grade 3, consider discontinuation.
Non-infectious pneumonitis 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. Re-initiate treatment at 5mg daily.
Stomatitis grade 3	Temporary dose interruption until recovery to grade ≤1. Re-initiate treatment at 5mg daily.
Stomatitis 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. Re-initiate treatment

	at 5mg daily.
Other non-haematological toxicities (excluding metabolic events) grade 3	Temporary dose interruption until recovery to grade ≤1. Consider re-initiating treatment at 5mg daily. If toxicity recurs at grade 3, consider discontinuation.
Other non-haematological toxicities (excluding metabolic events) grade 4	Discontinue treatment.

Lenvatinib

Arterial thromboembolisms – any grade	Discontinue. Do not resume
Cardiac dysfunction – grade 3	Interrupt. Resolves to grade 0-1 or baseline
Cardiac dysfunction – grade 4	Discontinue. Do not resume
Diarrhoea – grade 3	Interrupt. Resolves to grade 0-1 or baseline
Diarrhoea – grade 4 (despite medical management)	Discontinue. Do not resume
GI perforation or fistula – grade 3	Interrupt. Resolves to grade 0-1 or baseline
GI perforation or fistula – grade 4	Discontinue. Do not resume
Non-GI fistula – grade 4	Discontinue. Do not resume
Hemorrhage – grade 3	Interrupt. Resolves to grade 0-1
Hemorrhage – grade 4	Discontinue. Do not resume
Hepatotoxicity – grade 3	Interrupt. Resolves to grade 0-1 or baseline
Hepatotoxicity – grade 4	Discontinue. Do not resume
Hypertension - grade 3 (despite optimal antihypertensive therapy) Systolic BP ≥140mmHg up to <160mmHg or diastolic BP ≥90mmHg up to <100mmHg Systolic BP ≥160mmHg or diastolic BP ≥100mmHg despite optimal antihypertensive therapy Life-threatening consequences (malignant hypertension, neurological deficit, or hypertensive crisis)	Interrupt. Resolves to grade 0-1 or baseline 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. 1. Withhold lenvatinib 2. When systolic BP ≤150mmHg, diastolic BP ≤95mmHg, and patient has been on a stable dose of antihypertensive therapy for at least 48 hours, resume lenvatinib at a reduced dose. Urgent intervention is indicated. Discontinue lenvatinib and institute appropriate medical management.
Hypertension - grade 4	Discontinue. Do not resume
Nephrotic syndrome	Discontinue. Do not resume
PRES/RPLS – any grade	Interrupt. Consider resuming at reduced dose if resolves to grade 0-1
Proteinurea ≥2g/24 hours	Interrupt. Resolves to <2g/24 hours
QT prolongation >500ms	Interrupt. Resolves to <480ms or baseline
Renal impairment or failure – grade 3	Interrupt. Resolves to grade 0-1 or baseline
Renal impairment or failure – grade 4	Discontinue. Do not resume

Hepatic impairment
Child-Pugh scores are based on ascites, encephalopathy, INR, albumin, total bilirubin

Everolimus

Moderate hepatic impairment (Child-Pugh class B)	Reduce to 5mg daily.
Severe hepatic impairment (Child-Pugh class C)	Everolimus has not been evaluated and is not recommended for use in this patient population.

Lenvatinib

Mild (Child-Pugh A) or moderate (Child-Pugh B)	no adjustment of starting dose is required
Severe (Child-Pugh class C)	the recommended starting dose is 10mg once daily. Further dose adjustments may be necessary on the basis of individual tolerability.

Renal impairment
Everolimus
No dose adjustment is required

Lenvatinib
Mild or moderate renal impairment no adjustment of starting dose is required.
Severe renal impairment, the recommended starting dose is 10mg of lenvatinib with 5 mg of everolimus taken once daily. Further dose adjustments may be necessary based on individual tolerability.
End-stage renal disease were not studied, therefore the use of lenvatinib in these patients is not recommended.

REFERENCES
1. Everolimus SPC April 2019
2. Lenvatinib SPC October 2019