Chemotherapy Protocol

RENAL CELL

EVEROLIMUS and LENVATINIB

Regimen

- Renal Cell – Everolimus-Lenvatinib

Indication

- Confirmed histological diagnosis of inoperable locally advanced or metastatic renal cell carcinoma with a clear cell component where;

  - the patient has received only one vascular endothelial growth factor (VEGF) targeted systemic therapy for advanced / metastatic renal cancer
  - the patient has progressed on previous treatment or within six months of stopping previous treatment
  - the patient has not received either everolimus or lenvatinib
  - the patient either has no brain metastases or, if the patient has brain metastases, then these have been treated and are symptomatically stable
  - no treatment breaks of more than six weeks beyond the expected cycle length are allowed (to allow any toxicity of current therapy to settle or intercurrent comorbidities to improve)

- WHO Performance status 0, 1

- Palliative intent

Toxicity

Drug	Adverse Effect
Everolimus	Diarrhoea, rash, dry skin, fatigue, non-infectious pneumonitis, increased risk of infection, hyperglycaemia, hypertriglyceridaemia
Lenvatinib	Hypertension, renal failure, hepatotoxicity, cardiac impairment, QT interval prolongation, posterior reversible encephalopathy syndrome, haemorrhage, GI perforation or fistula, thyroid abnormalities

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Monitoring

- FBC, U&Es and LFTs every 28 days

- Blood glucose levels at baseline and after 28 days of treatment. Thereafter every 4-8 weeks

- Triglycerides at baseline then every 8 weeks

- Proteinuria less than 1g/24 hours, with proteinuria measured prior to each cycle

- Thyroid function every 28 days
- Blood pressure should be monitored at baseline, after one week of lenvatinib then every two weeks for the first two months and then every 28 days thereafter.
- ECG as clinically indicated

Dose Modifications

The dose modifications listed are for haematological, liver and renal function and drug specific toxicities only. Dose adjustments may be necessary for other toxicities as well. The toxicities below should be read in conjunction with the relevant Summary of Product Characteristics (www.medicines.org.uk).

In principle all dose reductions due to adverse drug reactions should not be re-escalated in subsequent cycles without consultant approval. It is also a general rule for chemotherapy that if a third dose reduction is necessary treatment should be stopped.

Please discuss all dose reductions / delays with the relevant consultant before prescribing, if appropriate. The approach may be different depending on the clinical circumstances.

Haematological

Consider blood transfusion if patient symptomatic of anaemia or has a haemoglobin of less than 8g/dL (80mg/L).

Neutrophils (x10^9/L)	**Dose Modifications (Everolimus)**
1 or greater	Full dose
0.5 - 1	1st Occurrence Interrupt treatment until recovery to 1x10^9/L or greater then restart at the full dose 2nd Occurrence Interrupt treatment until recovery to 1x10^9/L or greater then restart at 2.5mg once a day
less than 0.5 or NCI-CTC grade 3 febrile neutropenia	1st Occurrence Interrupt treatment until the fever has resolved and the neutrophils are 1x10^9/L or greater then restart at 2.5mg once a day 2nd Occurrence Discontinue treatment permanently
NCI-CTC grade 4 febrile neutropenia	Discontinue treatment permanently
Platelets (x10^9/L)	**Dose Modifications (Everolimus)**
75 or greater	Full dose
50-75	1st Occurrence Interrupt treatment until recovery to 75x10^9/L or greater then restart at the full dose 2nd Occurrence Interrupt treatment until recovery to 75x10^9/L or greater then restart at 2.5mg once a day

less than 50	1st Occurrence Interrupt treatment until recovery to $75x10^9$/L or greater then restart at 2.5mg once a day 2nd Occurrence Discontinue treatment permanently

Hepatic Impairment

Child Pugh Class	Everolimus Dose	Lenvatinib Dose
A	7.5mg once a day	No dose adjustment
B	5mg once a day	No dose adjustment
C	If the benefit–risk assessment is considered favourable by the consultant, treat with a maximum daily dose of 2.5mg once a day	14mg once a day

Further dose reductions may be required based on tolerability

Liver-related adverse reactions most commonly reported in patients treated with lenvatinib included increases in alanine aminotransferase, increases in aspartate aminotransferase, and increases in blood bilirubin. Hepatic failure and acute hepatitis (less than 1%) have been reported in patients treated with lenvatinib. The hepatic failure cases were generally reported in patients with progressive liver metastases. Liver function tests should be monitored before initiation of treatment, then every 2 weeks for the first 2 months and monthly thereafter during treatment. In the case of hepatotoxicity, dose interruptions, adjustments, or discontinuation may be necessary. If patients have severe hepatic impairment, the initial dose of lenvatinib should be adjusted

Renal Impairment

Drug	Creatinine Clearance (ml/min)	Dose (% of original dose)
Everolimus	N/A	No dose modification required
Lenvatinib	less than 30ml/min	14mg once a day

Further dose reductions may be required based on tolerability.

Renal impairment and renal failure have been reported in patients treated with lenvatinib. The primary risk factor identified was dehydration and/or hypovolemia due to gastrointestinal toxicity. Gastrointestinal toxicity should be actively managed in order to reduce the risk of development of renal impairment or renal failure. Dose interruptions, adjustments, or discontinuation may be necessary. If patients have severe renal impairment, the initial dose of lenvatinib should be adjusted.

Other

Dose reductions or interruptions in therapy are not necessary for those toxicities that are considered unlikely to be serious or life threatening. For example, alopecia, altered taste or nail changes.

For all other non-haematological NCI-CTC grade 3 and above toxicities delay treatment until the adverse effect has resolved to NCI-CTC grade 1 or below. The dose of everolimus should then be reduced to 2.5mg once a day or discontinued as appropriate. The dose of lenvatinib is adjusted as in the table below

Dose level	Daily dose (lenvatinib)
Recommended daily dose	18 mg orally once daily
First dose reduction	14 mg orally once daily
Second dose reduction	10 mg orally once daily
Third dose reduction	8 mg orally once daily

Everolimus

Diabetes

If blood glucose is raised at baseline or the patient is a known diabetic then attempt to optimise the glycaemic control before starting everolimus.

After commencing everolimus, if the fasting glucose is between 14-27.8mmol/L or the triglycerides are in the range 5.8-11.4mmol/L then interrupt everolimus until resolved. Re-start the everolimus at 5mg once a day.

If the fasting glucose is greater than 27.8mmol/l or triglycerides are greater than 11.4mmol/L then discontinue everolimus.

Mucositis

NCI-CTC Grade	Action (everolimus)
2	Continue the everolimus without dose adjustments if the patient can tolerate it. Alternatively interrupt until symptoms have resolved to NCI-CTC grade 1 or below and then re-challenge at the same dose
3 or recurrence of grade 2 mucositis	Interrupt treatment until symptoms have resolved to NCI-CTC grade 1 or below then restart the everolimus at 2.5mg once a day
4 or recurrence of grade 3 mucositis	Discontinue everolimus

Non-infectious Pneumonitis

NCI-CTC Grade	Action (everolimus)
1	Continue everolimus without dose adjustments
2	Interrupt therapy. Consider short-term use of corticosteroids e.g. prednisolone 20mg once a day for 10-14 days. Restart everolimus at 2.5mg once a day when symptoms have resolved to NCI-CTC grade 1 or below.
3	Interrupt therapy. Prescribe corticosteroids e.g. prednisolone 40mg as indicated. Restart everolimus at 2.5mg daily once symptoms have resolved to NCI-CTC grade 1 or below or discontinue as appropriate.
4	Discontinue the everolimus. Treat appropriately.

Lenvatinib

Cardiac

Hypertension is commonly reported in association with lenvatinib and may be severe. Median time to onset is 35 days in renal cell patients patients receiving combination treatment. Blood pressure should be well controlled prior to starting treatment. Early detection and management of hypertension are important during treatment.

Blood Pressure	Recommended Action (lenvatinib)
Systolic blood pressure greater than or equal to140mmHg and up to 160mmHg or diastolic blood pressure greater than or equal to 90mmHg up to 100mmHg	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 blood pressure greater than or equal to100 mmHg despite optimal antihypertensive therapy	Withhold lenvatinib until the systolic blood pressure is less than or equal to150mmHg and diastolic blood pressure is les than or equal to 95mmHg and the patient has been on a stable dose of antihypertensive therapy for at least 48 hours, resume lenvatinib at a reduced dose level
Life-threatening consequences (malignant hypertension, neurological deficit, or hypertensive crisis)	Urgent intervention is indicated. Discontinue lenvatinib and institute appropriate medical management

Decreases in left ventricular ejection fraction (LVEF) were seen in10% of RCC patients receiving combination treatment. Patients should be monitored for signs and symptoms as dose modification may be required. Arterial thromboembolic events were reported as well, including fatal cases. Lenvatinib should be discontinued if such an arterial thromboembolic event occurs. Use lenvatinib with caution in patients who are at increased risk of cardiac events.

QT prolongation has been reported and may lead to severe ventricular arrhythmias, including Torsades de pointes. Lenvatinib is not recommended in patients with congenital long QT syndrome or those with risk factors for prolonged QT. Lenvatinib should be stopped when the QT interval is longer than 500ms. Treatment may be resumed at a reduced dose

level when the interval is 480ms or less. Electrolyte abnormalities should be corrected prior to starting treatment.

Endocrine

Lenvatinib impairs exogenous thyroid suppression. Thyroid stimulating hormone (TSH) levels should be monitored on a regular basis and thyroid hormone administration should be adjusted to reach appropriate TSH levels, according to the patient's therapeutic target.

Proteinuria

If proteinuria occurs at a level greater than 2g/24 hours interrupt treatment until it is less than this, then dose reduce down a level and resume treatment. Lenvatinib should be stopped if nephrotic syndrome occurs.

Regimen

28 day cycle continued as long as clinical benefit is observed or until unacceptable toxicity occurs (12 cycles will be set in Aria)

Drug	Dose	Days	Administration
Everolimus	5mg once a day	1-28 incl.	Oral
Lenvatinib	18mg once a day	1-28 incl.	Oral

Dose Information

- Everolimus is available as 2.5mg, 5mg and 10mg tablets.
- Everolimus will be dose rounded to the nearest 2.5mg (up if halfway).
- Lenvatinib is available as 10mg and 4mg hard capsules.

Administration Information

- Everolimus should be taken at the same time of day each day consistently with or without food. Tablets should be swallowed whole.
- Lenvatinib should be taken at the same time of day each day consistently with or without food. Capsules should be swallowed whole. If a dose is missed and cannot be taken within twelve hours then it should be missed and the next dose taken at the appropriate time.

Additional Therapy

- Routine anti-emetics are not required.
- Mouthwashes according to local or national policy on the treatment of mucositis
- Gastric protection with a proton pump inhibitor or a H_2 antagonist may be considered in patients considered at high risk of GI ulceration or bleed.

Additional Information

- The National Patient Safety Alert on oral chemotherapy (NPSA/2008/RRR001) must be followed in relation to everolimus and lenvantinib.
- It must be made clear to all staff, including those in the community, that everolimus and lenvantinib should only be prescribed under the supervision of an oncologist.
- Everolimus and lenvatinib interact with many other agents. Always check for drug interactions.
- There are several brands of both everolimus and lenvatinib. Please ensure the product you dispense is appropriate for the indication.

Coding (OPCS)

- Procurement – X71.5
- Delivery – X73.1

References
1. R Motzer, Hutson TE, Glen H et al. Lenvatinib, everolimus and the combination in patients with metastatic renal cell carcinoma: a randomised phase two open label multi-centre trial. Lancet Oncology 2015; 16 (15): 1473-1482.
2. National Institute of Health and Clinical Excellance (2018). Lenvatinib with everolimus for previously treated advanced renal cell carcinoma. Technology Appraisal 498. NICE:DOH

REGIMEN SUMMARY

Everolimus-Lenvatinib

Day 1

Take Home Medicines

1. Everolimus 5mg once a day oral
   Administration Instructions
   Oral chemotherapy.
   Please supply an original pack per 28 day cycle. There are several brands of everolimus. Please ensure the product you dispense is appropriate for the indication

2. Lenvatinib 18mg once a day oral
   Administration Instructions
   Oral chemotherapy.
   Please supply an original pack per 28 day cycle. There are several brands of lenvatinib. Please ensure the product you dispense is appropriate for the indication

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	May 2018	None	Dr Deborah Wright Pharmacist	Dr Mathew Wheater Consultant Medical Oncologist

This chemotherapy protocol has been developed as part of the chemotherapy electronic prescribing project. This was and remains a collaborative project that originated from the former CSCCN. These documents have been approved on behalf of the following Trusts;

Hampshire Hospitals NHS Foundation Trust
NHS Isle of Wight
Portsmouth Hospitals NHS Trust
Salisbury Hospitals NHS Foundation Trust
University Hospital Southampton NHS Foundation Trust
Western Sussex Hospitals NHS Foundation Trust

All actions have been taken to ensure these protocols are correct. However, no responsibility can be taken for errors that occur as a result of following these guidelines. These protocols are only one source of information. They should be read in conjunction with the latest Summary of Product Characteristics and published information.