Regimen Monograph

A - Regimen Name

LENV Regimen

lenvatinib

Disease Site	Genitourinary - Renal Cell / Kidney
Intent	Palliative
Regimen Category	**Evidence-informed :** Regimen is considered appropriate as part of the standard care of patients; meaningfully improves outcomes (survival, quality of life), tolerability or costs compared to alternatives (recommended by the Disease Site Team and national consensus body e.g. pan-Canadian Oncology Drug Review, pCODR). Recommendation is based on an appropriately conducted phase III clinical trial relevant to the Canadian context OR (where phase III trials are not feasible) an appropriately sized phase II trial. Regimens where one or more drugs are not approved by Health Canada for any indication will be identified under Rationale and Use. This **Regimen Abstract** is an **abbreviated** version of a Regimen Monograph and contains only top level information on usage, dosing, schedule, cycle length and special notes (if available). Information in regimen abstracts is accurate to the extent of the ST-QBP regimen master listings, and has not undergone the full review process of a regimen monograph. Full regimen monographs will be published for each ST-QBP regimen as they are developed.
Rationale and Uses	For second-line treatment of metastatic renal cell carcinoma.

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B - Drug Regimen

lenvatinib	24 mg	PO	Daily

(This drug is not currently publicly funded for this regimen and intent)

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C - Cycle Frequency

CONTINUOUS TREATMENT

Until disease progression or unacceptable toxicity.

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D - Premedication and Supportive Measures

Antiemetic Regimen: Moderate – Consider prophylaxis daily

Other Supportive Care:

Also refer to CCO Antiemetic Recommendations.

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E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated.

Blood pressure should be well controlled and electrolyte abnormalities should be corrected prior to starting treatment.

Adequate washout period is required between lenvatinib and other systemic anticancer treatments such as sorafenib (in RCC studies, minimum washout period was 3 weeks).

Dosage with toxicity

Reduced doses should not be increased.

Dose Levels:

Dose level	Lenvatinib Dose (mg daily)
0	24
-1	20
-2	14
-3	10
-4	Discontinue

No recommendations are available for resuming lenvatinib in patients with grade 4 adverse reactions that resolve.

Toxicity	Severity	Action
Hypertension	≥ 140/90	Treat with anti-hypertensives
	Grade 3 that persists despite optimal antihypertensive therapy	Hold until recovery to ≤ grade 2; resume at 1 dose level ↓.*
	Grade 4, life-threatening	Discontinue
Cardiotoxicity or hemorrhage	Grade 3	Hold until recovery to ≤ grade 1 or baseline; resume at 1 dose level ↓* or discontinue depending on severity and persistence.
	Grade 4	Discontinue
Nephrotoxicity or hepatotoxicity	Grade 3	Hold until recovery to ≤ grade 1 or baseline; resume at 1 dose level ↓* or discontinue depending on severity and persistence.
	Grade 4	Discontinue
Hepatic failure	Grade 3 or 4	Discontinue
Proteinuria	≥ 2 g proteinuria / 24 h (≥ 2+ on urine dipstick)	Hold until proteinuria < 2 g / 24 h; resume at 1 dose level ↓.*
	Nephrotic syndrome	Discontinue
Nausea, vomiting, diarrhea**	Persistent and intolerable Grade 2	Hold until recovery to ≤ grade 1 or baseline; resume at 1 dose level ↓.

	or Grade 3	
	Grade 4 despite medical management	Discontinue
QT prolongation	Grade 3 or 4	Hold until recovery to ≤ grade 1 or baseline; resume at 1 dose level ↓.*
PRES	Any	Hold until resolved; resume at 1 dose level ↓* or discontinue depending on the severity and persistence of neurologic symptoms.
Arterial thromboembolism		Discontinue
GI perforation or fistula		
Wound healing complications		
Other treatment-related toxicity	Persistent and intolerable Grade 2 Or Grade 3 Or Grade 4 lab abnormalities considered non-life-threatening	Medically manage. Hold until recovery to ≤ grade 1 or baseline; resume at 1 dose level ↓.*
	Grade 4 (except lab abnormalities considered non-life-threatening)	Discontinue
Major surgery		Hold at least 6 days prior to scheduled surgery, resume after adequate wound healing.

*For each occurrence of toxicity, reduce dose in succession based on the previous dose level (see dose levels table).

**Initiate prompt medical management in order to reduce the risk of development of renal impairment or failure.

Hepatic Impairment

Lenvatinib exposure increases in severe hepatic impairment.

Childs classification of hepatic impairment	Lenvatinib Starting dose (mg daily)
A	24
B	24
C	14

Renal Impairment

Lenvatinib exposure increases with severe renal impairment.

Creatinine clearance (ml/min)	Lenvatinib Starting dose (mg daily)
50-80	24
30-49	24
< 30	14
End stage renal failure	No data: not recommended for use

Dosage in the Elderly

No dosage adjustment is recommended. Use with caution and monitor patients closely.

Patients aged 75 and older had a higher incidence of toxicity, including severe and fatal adverse events compared to younger patients leading to treatment discontinuation (21% vs. 14%). Patients 75 years or older were more likely to experience grade 3-4 hypertension, proteinuria, decreased appetite, and dehydration as compared to patients < 65 years old.

Body weight

No adjustment of starting dose is required based on body weight.

Patients with body weight <60 kg had a higher incidence of PPE, proteinuria, severe electrolyte abnormalities and a trend towards severe anorexia.

Dosage based on gender

No adjustment of starting dose is required based on gender.

Females had a higher incidence of hypertension, including severe hypertension, proteinuria and PPE, while males had a higher incidence of cardiotoxicity, GI perforation and fistulas.

Dosage based on ethnicity

No adjustment of starting dose is required based on race.

Asian patients had a higher incidence of peripheral edema, hypertension, fatigue, hand-foot syndrome, proteinuria, thrombocytopenia and elevated TSH levels compared to Caucasian patients.

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F - Adverse Effects

Refer to lenvatinib drug monograph(s) for additional details of adverse effects

Very common (≥ 50%)	**Common (25-49%)**	**Less common (10-24%)**	**Uncommon (< 10%), but may be severe or life-threatening**
• Increased creatinine (may be severe) • Hypertension (may be severe) • Diarrhea (may be severe) • Anorexia, weight loss • Increased LFTs (may be severe)	• Hypoalbuminemia • Nausea, vomiting • Fatigue • Mucositis • Abnormal electrolytes • Headache • Hypothyroidism • Bleeding (may be severe) • Proteinuria (may be severe) • Hand-foot syndrome • Abdominal pain • Dysphonia	• Cough, dyspnea (may be severe) • Peripheral edema • Rash • Hypoglycemia • Dysgeusia • Dry mouth • Increased triglycerides • Dizziness • Myelosuppression • Dyspepsia • Prolonged QT interval • Alopecia • Increased	• Arterial / venous thromboembolism • Cardiotoxicity • Arrhythmia • Artery dissection/ aneurysm • Fracture • GI obstruction, perforation • Fistula • hepatotoxicity • Hypersensitivity • Retinal vein thrombosis • Rhabdomyolysis • PRES, seizure

	• Constipation • Musculoskeletal pain	amylase/lipase • Infection • Insomnia • Bradycardia	• Wound dehiscence • Cholecystitis • Pancreatitis • Secondary malignancy • Pneumonitis • Hyperglycemia

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G - Interactions

Refer to lenvatinib drug monograph(s) for additional details

- Lenvatinib may be an inducer of CYP3A4 and PgP in the GI tract that could lead to decreased exposure to oral CYP3A4/PgP substrates. Use with caution with substrates that have a narrow therapeutic index.
- Drugs that decrease heart rate, prolong the PR or QT interval, or disrupt electrolyte levels may increase the risk of arrhythmias. Avoid if possible; monitor closely if used together.
- Adequate washout period is required between lenvatinib and other systemic anticancer treatments such as sorafenib.

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H - Drug Administration and Special Precautions

Refer to lenvatinib drug monograph(s) for additional details

Administration

- Lenvatinib should be taken at the same time daily, with or without food.
- Capsules should be swallowed whole with water.
- If the patient has difficulty swallowing, capsule(s) may be added (without breaking or crushing) to a tablespoon of water or apple juice in a small glass. Capsule(s) should be left in the liquid for at least 10 minutes and stirred for at least 3 minutes to allow the capsule shell(s) to

dissolve. The entire suspension should then be swallowed. After drinking, the glass should be filled with the same amount of water or apple juice, swirled a few times, then additional liquid should be swallowed.

- If a dose is missed and it cannot be taken within 12 hours, then that dose should be skipped and the next dose should be taken at the usual time.
- Lenvatinib should be stored between 15-30^{o}C.

Contraindications

- Patients who have a hypersensitivity to this drug or to any ingredient in the formulation or component of the container.

Warning/Precautions

- The degree of tumour invasion of major blood vessels should be considered prior to treatment given the potential risk of hemorrhage associated with tumour shrinkage.
- Lenvatinib is not recommended in patients with congenital long QT syndrome or those who are taking medications known to prolong the QT interval.
- Use with caution in patients at risk of prolonged QT, including females, aged ≥ 65 years, family history of sudden cardiac death at < 50 years of age, pre-existing cardiac disease, history of arrhythmias, electrolyte disturbances or conditions leading to electrolyte disturbances, bradycardia, acute neurological events, diabetes mellitus and autonomic neuropathy.
- Use lenvatinib with caution in patients who are at risk for, or have a history of cardiac events or arterial thromboembolism. The drug has not been studied in patients who have had an arterial thromboembolic event within the previous 6 months.
- Patients with prior surgery or radiotherapy are at increased risk of GI perforation or fistulas.

Pregnancy/Lactation

- Lenvatinib is not recommended for use in pregnancy as it's likely to cause fetal harm. Highly effective contraception (including barrier method) should be used by both sexes during treatment, and for at least **1 month** after the last dose.
- Breastfeeding is not recommended.
- Reduced male and female fertility is likely.

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

- Blood pressure; Baseline, after 1 week, then every 2 weeks for the first 2 months, monthly thereafter while on treatment
- CBC; Baseline and at each visit
- ECG ; Baseline and as clinically indicated
- Liver function tests; Baseline, every 2 weeks for the first 2 months, then monthly during treatment
- Renal function tests; Baseline and at each visit
- Serum calcium and electrolytes; Baseline, at least monthly and as clinically indicated
- Thyroid function tests; Baseline and monthly during treatment, or as clinically indicated
- Urine protein; Baseline and at each visit
- Clinical toxicity assessment for GI effects, infection, wound healing complications, bleeding, hypertension, thromboembolism, cardiac and neurologic effects; At each visit
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - Administrative Information

Outpatient prescription for home administration

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K - References

Lenvatinib drug monograph, Cancer Care Ontario.

Motzer RJ, Hutson TE, Gle H et al. Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial.Lancet Oncol 2015;16:1473-82.

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M - Disclaimer

Regimen Abstracts

A Regimen Abstract is an abbreviated version of a Regimen Monograph and contains only top level information on usage, dosing, schedule, cycle length and special notes (if available). It is intended for healthcare providers and is to be used for informational purposes only. It is not intended to constitute or be a substitute for medical advice, and all uses of the Regimen Abstract are subject to clinical judgment. Such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information's quality, accuracy, currency, completeness, or reliability, and Cancer Care Ontario disclaims all liability for the use of this information, and for any claims, actions, demands or suits that arise from such use.

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Regimen Monographs

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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