LENVIMA®
(lenvatinib) capsules

Treatment optimisation guide

Optimising outcomes with LENVIMA® (lenvatinib) in endometrial cancer

LENVIMA® (lenvatinib) in combination with pembrolizumab is indicated for the treatment of advanced endometrial cancer (aEC) that is not MSI-H or dMMR in adults who have progressive disease after prior platinum-based therapy and for whom curative surgery or radiation is not an option.[1]

PI
LENVIMA®

INTRODUCTION

This treatment optimisation guide has been developed to support you in the management of your patients on a LENVIMA®-containing regimen.

Hopefully you will find this content useful and informative in your journey managing patients.

01
LENVIMA® in endometrial cancer: Study 309/ KEYNOTE 775 design study

02
A dosing guide

03
Your guide to managing adverse events

The information provided here does not replace the guidance of a patient's multidisciplinary team. Always seek guidance from the patient's multidisciplinary team as soon as possible.

EC: endometrial carcinoma.

PI
LENVIMA®

LENVIMA® EXPERIENCE IN ENDOMETRIAL CANCER

Study 309/ KEYNOTE-775

Phase 3 trial of patients with advanced, metastatic or recurrent endometrial carcinoma who had previously been treated with platinum-based chemotherapy, 84 % of whom had pMMR (n = 697)[2,3]

Study 309/KEYNOTE-775: A large-scale (N=827) multicenter, randomized, open-label phase 3 trial[2]

Key eligibility criteria:
- Advanced, metastatic, or recurrent endometrial cancer
- Previously treated with at least 1 prior platinum-based chemotherapy regimen (including adjuvant and neoadjuvant settings)
- ECOG PS 0–1

Key exclusion criteria:
- Endometrial sarcoma, including carcinosarcoma
- Active autoimmune disease
- A medical condition that requires immunosuppression

Randomization 1:1

(n=411) **Pembrolizimab 200 mg** IV infusion every 3 weeks
Lenvatinib 20 mg orally once daily

(n=416) **Doxorubicin 60 mg/m²** IV every 3 weeks or **Paclitaxel 80 mg/m²** IV weekly (3 weeks on, 1 week off)

Treatment with lenvatinib + pembrolizumab continued until RECIST v1.1–defined progression of disease as verified by BICR, unacceptable toxicity, or for pembrolizumab , a maximum of 24 months

Primary end points: OS and PFS, as assessed by BICR according to RECIST v1.1

Secondary end points: ORR as assessed on BICR according to RECIST v1.1; safety and side-effect profile; and health-related quality of life

Exploratory end point: Duration of response

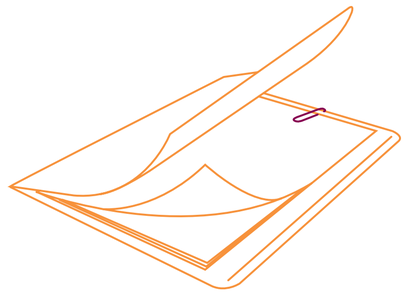
Results for the pMMR population:

Lenvatinib + pembrolizumab demonstrated a **30 % reduction in the risk of death** vs doxorubicin or paclitaxel alone[3]
- HR* = 0.70; 95 % CI, 0.58–0.83
- 5.8-month difference in median OS between LENVIMA® + pembrolizumab (18.0 months; 95 % CI, 14.9–20.5) and doxorubicin or paclitaxel (12.2 months; 95 % CI, 11.0–14.1)

Lenvatinib + pembrolizumab demonstrated a **40 % reduction in the risk of disease progression or death** vs doxorubicin or paclitaxel alone[3]
- HR* = 0.60; 95 % CI, 0.50–0.72
- 2.9-month difference in median PFS‡ between LENVIMA® + pembrolizumab (6.7 months; 95 % CI, 5.6–7.4) and doxorubicin or paclitaxel (3.8 months; 95 % CI, 3.6–5.0)

In 2022, based on these phase 3 data, lenvatinib + pembrolizumab was granted approval by Swissmedic for the treatment of adult patients with advanced endometrial cancer (aEC) that is not MSI-H or dMMR in adults who have progressive disease after prior platinum-based therapy and for whom curative surgery or radiation is not an option.[1]

The most frequent any grade adverse events (≥30 %) in the lenvatinib + pembrolizumab arm (ITT population) were hypertension (65.0 %), hypothyroidism (58.9 %), diarrhea (55.7 %), nausea (51.7 %), decreased appetite (46.6 %), vomiting (37.7 %), weight decreased (35.5 %), fatigue (34.0 %), arthralgia (32.3 %) and proteinuria (30.5 %)[3]



* Based on the stratified Cox regression model.[2]
† Based on stratified log-rank test.[2]
‡ Assessed by BICR according to RECIST v1.1.[2]
BICR: blinded independent central review, CI: confidence interval, ECOG PS: Eastern Cooperative Oncology Group performance status, HR: hazard ratio, IV: intravenous, MMR: mismatch repair, MSI: microsatellite instability, OS: overall survival, PFS: progression-free survival, RECIST: Response Evaluation Criteria In Solid Tumors.

LENVIMA® EXPERIENCE IN ENDOMETRIAL CANCER

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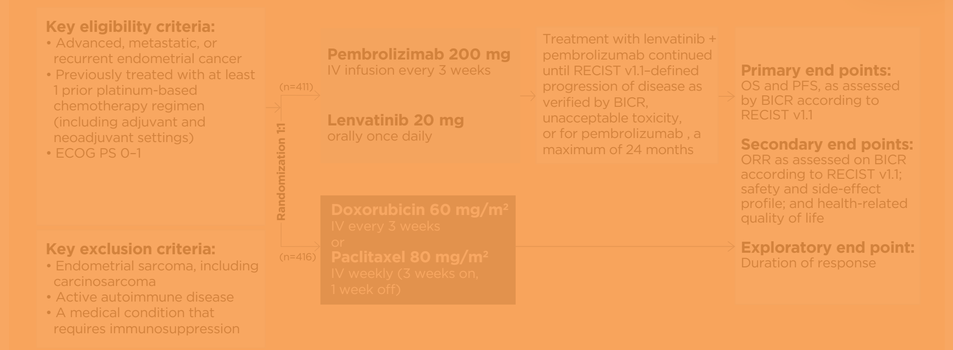

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References

1. Prescribing information LENVIMA® (lenvatinib), www.swissmedicinfo.ch.
2. Makker V, et al. Lenvatinib plus Pembrolizumab for Advanced Endometrial Cancer. N Engl J Med. 2022;386(5):437–448. With Supplementary Appendix.
3. Makker V, et al. Lenvatinib Plus Pembrolizumab in Previously Treated Advanced Endometrial Cancer: Updated Efficacy and Safety From the Randomized Phase III Study 309/ KEYNOTE-775. J Clin Oncol. 2023 Jun 1;41(16):2904–2910. With Supplementary Material.

A DOSING GUIDE

To increase the chance of achieving optimal outcomes with LENVIMA®, correct dose initiation and diligent dose management are important. This guide has been developed to inform you about the recommended starting doses and dose modifications.

1
2

THE RECOMMENDED STARTING DOSE FOR OPTIMAL OUTCOMES

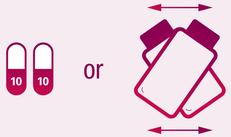
A patient's multidisciplinary team generally considers the physical and mental preparedness of patients before starting treatment.

For patients with advanced or recurrent EC treated with LENVIMA® in combination with pembrolizumab, the recommended initial dose of:

- LENVIMA® is **20 mg orally once daily**[1]
- Pembrolizumab is **200 mg intravenously once every 3 weeks**, over 30 minutes until disease progression or unacceptable toxicity

LENVIMA® 20 mg
orally **once daily**
at the same time each day

Intake with or without food



Swallow as a whole or dissolved in a tablespoon of water or apple juice

EC: endometrial carcinoma.

DOSE MODIFICATIONS TO MANAGE ANY POTENTIAL AEs

The recommended starting dose for LENVIMA® is 20 mg/day.

However, if required as part of an AE management strategy, flexible LENVIMA® dosing enables 3 dose reductions from 20 mg to 14 mg to 10 mg to 8 mg, enabling therapy to be tailored for individual patients' needs.[1]

Recommended dose	10 10	**20 mg** orally once a day
1st dose reduction	10 4	**14 mg** orally once a day
2nd dose reduction	10	**10 mg** orally once a day
3nd dose reduction	4 4	**8 mg** orally once a day

AE: adverse event.

The AEs of LENVIMA® are generally predictable and manageable, and usually occur within days of treatment initiation. The median time to first onset of the most common AEs occurred within the first 3 months of treatment initiation.[2]

A comprehensive AE management strategy can include medical management (non-pharmacological and pharmacological), dose interruptions, dose reductions and treatment discontinuation if necessary.[1-4]

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References

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2. Colombo N et al. Characterization and Management of Adverse Reactions in Patients With Advanced Endometrial Cancer Receiving Lenvatinib Plus Pembrolizumab. Oncologist. 2023 Jul 31;oyad201. doi: 10.1093/oncolo/oyad201. Online ahead of print. With supplementary material.
3. Makker V, et al. Lenvatinib plus Pembrolizumab for Advanced Endometrial Cancer. N Engl J Med. 2022;386(5):437–448.
4. Rimassa L, et al. Management of adverse events associated with tyrosine kinase inhibitors: Improving outcomes for patients with hepatocellular carcinoma Cancer Treat Rev. 2019;77:20–28.

YOUR GUIDE TO MANAGING ADVERSE EVENTS

The adverse events (AEs) of LENVIMA® are generally predictable and manageable. They may occur very early in the course of LENVIMA® treatment.[1,2] Engagement with the multidisciplinary team is important for the management of AEs.

This guide will help you to address LENVIMA®-induced AEs as early and effectively as possible, allowing patients to get the most out of the treatment. It was developed based on the LENVIMA® SmPC, supplemented with additional guidelines and recommendations for managing AEs where appropriate.

AE: adverse event.

AEs experienced in ≥25% of patients in Study 309/KEYNOTE-775 (ITT population)[1]

	LENVIMA® + pembrolizumab (n=406)		TPC (n=388)	
Median duration of treatment, days (range)	231 (1–817)		104.5 (1–785)	
Patients with any AE, n (%)	405 (99.8)		386 (99.5)	
Patients with specific AEs, n (%)	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Hypertension	264 (65.0)	159 (39.2)	20 (5.2)	10 (2.6)
Hypothyroidism	239 (58.9)	6 (1.5)	3 (0.8)	0 (0.0)
Diarrhea	226 (55.7)	33 (8.1)	79 (20.4)	8 (2.1)
Nausea	210 (51.7)	14 (3.4)	180 (46.4)	5 (1.3)
Decreased appetite	189 (46.6)	31 (7.6)	83 (21.4)	2 (0.5)
Vomiting	153 (37.7)	12 (3.0)	82 (21.1)	10 (2.6)
Weight decreased	144 (35.5)	44 (10.8)	23 (5.9)	1 (0.3)
Fatigue	138 (34.0)	22 (5.4)	107 (27.6)	12 (3.1)
Arthralgia	131 (32.3)	7 (1.7)	31 (8.0)	0 (0.0)
Proteinuria	124 (30.5)	21 (5.2)	13 (3.4)	1 (0.3)
Constipation	115 (28.3)	3 (0.7)	95 (24.5)	2 (0.5)
Anemia	114 (28.1)	28 (6.9)	189 (48.7)	60 (15.5)
Urinary tract infection	112 (27.6)	17 (4.2)	40 (10.3)	4 (1.0)
Headache	107 (26.4)	2 (0.5)	35 (9.0)	1 (0.3)
Neutropenia	37 (9.1)	8 (2.0)	132 (34.0)	101 (26.0)
Alopecia	24 (5.9)	0 (0.0)	120 (30.9)	1 (0.3)

Adapted from Makker V, et al. J Clin Oncol, 2023;41(16):2904–2910.[1]

AE: adverse event, TPC: treatment of physician's choice (doxorubicin or paclitaxel).

The median duration of treatment with LENVIMA® + pembrolizumab was more than double that of TPC, which may contribute to the difference in the occurrence of AEs between the two treatment arms.[1]

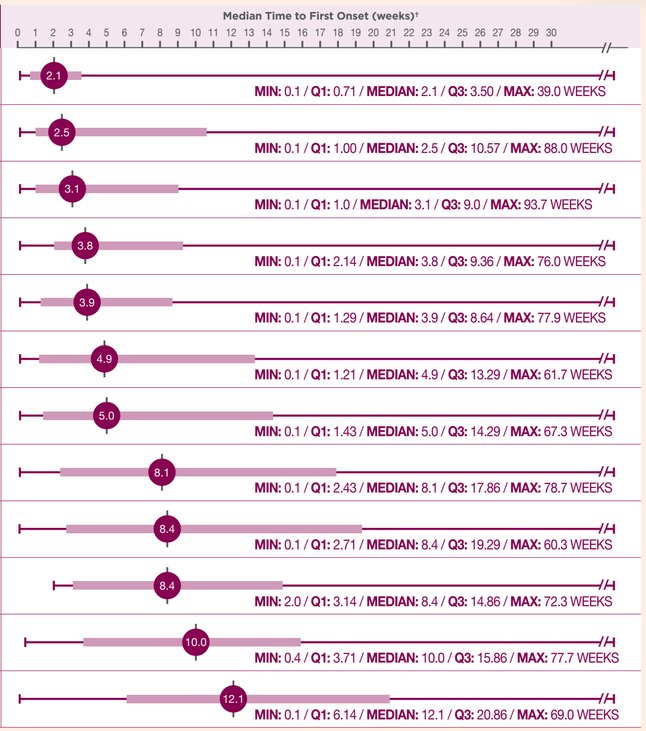
TIME TO FIRST ONSET OF COMMON AEs

During treatment with LENVIMA®, AEs may occur within days of treatment initiation.[2] **The median time to first onset of the most common AEs occurred within the first 3 months of treatment initiation.[2]**

Some of these AEs* are likely to occur within the first 5 weeks of treatment.[2]

Median times to first onset of selected common AEs from Study 309/KEYNOTE-775[2]
pMMR Population (n = 342) AEs

ADVERSE EVENTS	Incidence n	Incidence %	LENVIMA‡ Dose Interruption‡	LENVIMA‡ Dose Reduction‡	LENVIMA‡ Discontinuation‡	Pembrolizumab Dose Interruption	Pembrolizumab Dose Discontinuation	Median Time to First Onset (weeks)†
Hypertension	228	66.7%	12.3%	17.5%	2.0%	3.5%	0%	2.1 — MIN: 0.1 / Q1: 0.71 / MEDIAN: 2.1 / Q3: 3.50 / MAX: 39.0 WEEKS
Fatigue	198	57.9%	6.1%	13.2%	2.0%	4.7%	0.3%	2.5 — MIN: 0.1 / Q1: 1.00 / MEDIAN: 2.5 / Q3: 10.57 / MAX: 88.0 WEEKS
Musculoskeletal disorders	181	52.9%	4.1%	5.0%	0.6%	3.5%	0.3%	3.1 — MIN: 0.1 / Q1: 1.0 / MEDIAN: 3.1 / Q3: 9.0 / MAX: 93.7 WEEKS
Proteinuria	100	29.2%	6.7%	7.0%	1.2%	2.3%	0%	3.8 — MIN: 0.1 / Q1: 2.14 / MEDIAN: 3.8 / Q3: 9.36 / MAX: 76.0 WEEKS
Stomatitis	120	35.1%	1.8%	4.1%	0.3%	0.3%	0%	3.9 — MIN: 0.1 / Q1: 1.29 / MEDIAN: 3.9 / Q3: 8.64 / MAX: 77.9 WEEKS
Decreased Appetite	152	44.4%	6.1%	0.6%	1.5%	2.3%	0%	4.9 — MIN: 0.1 / Q1: 1.21 / MEDIAN: 4.9 / Q3: 13.29 / MAX: 61.7 WEEKS
Nausea	169	49.4%	3.5%	4.4%	0.6%	1.5%	0.9%	5.0 — MIN: 0.1 / Q1: 1.43 / MEDIAN: 5.0 / Q3: 14.29 / MAX: 67.3 WEEKS
Diarrhoea	168	55.0%	11.1%	11.7%	1.2%	8.2%	0.9%	8.1 — MIN: 0.1 / Q1: 2.43 / MEDIAN: 8.1 / Q3: 17.86 / MAX: 78.7 WEEKS
Vomiting	125	36.5%	5.0%	2.3%	1.2%	1.8%	0%	8.4 — MIN: 0.1 / Q1: 2.71 / MEDIAN: 8.4 / Q3: 19.29 / MAX: 60.3 WEEKS
Hypothyroidism	229	67.0%	2.0%	0.9%	0%	1.8%	0.3%	8.4 — MIN: 2.0 / Q1: 3.14 / MEDIAN: 8.4 / Q3: 14.86 / MAX: 72.3 WEEKS
PPES	77	22.5%	2.5%	8.8%	0.6%	2.0%	0%	10.0 — MIN: 0.4 / Q1: 3.71 / MEDIAN: 10.0 / Q3: 15.86 / MAX: 77.7 WEEKS
Weight decreased	117	34.2%	2.6%	5.0%	0.9%	1.5%	0.3%	12.1 — MIN: 0.1 / Q1: 6.14 / MEDIAN: 12.1 / Q3: 20.86 / MAX: 69.0 WEEKS



*Hypertension, fatigue, musculoskeletal disorders, proteinuria, stomatitis, decreased appetite and nausea.[2]
†Median time to first onset in patients who experienced the AE.[2]
‡Percentages of dose modifications and discontinuations were based on the safety analysis set.[2]

AE: adverse event, pMMR: mismatch repair-proficient, PPES: palmar–plantar erythrodysaesthesia syndrome.

Adapted from Colombo N, et al. Oncologist. 2023.[2]

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MANAGING AEs

General management guidelines

The following pages provide advice on when to continue or interrupt LENVIMA® treatment, based on AE severity (NCI-CTCAE grading).[1-3] The patient's multidisciplinary team can then decide to reduce the dose or permanently discontinue treatment.

CONTINUE TREATMENT with LENVIMA®* for as long as a clinical benefit is achieved or until unacceptable toxicity or disease progression occurs[4]

INTERRUPT and

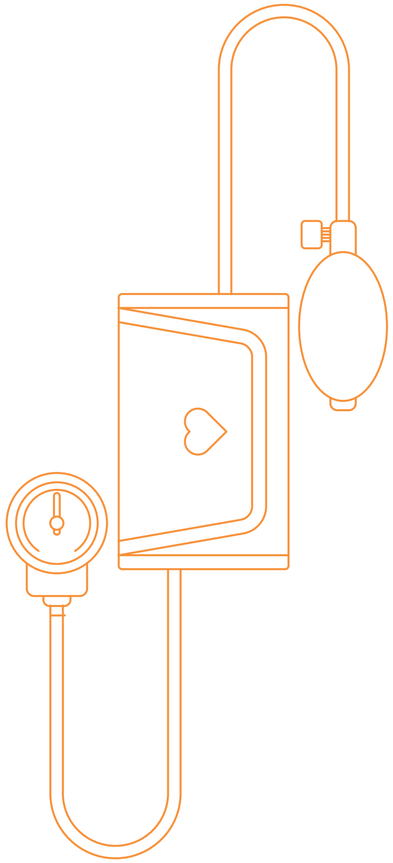
REDUCE the dose, or

DISCONTINUE LENVIMA®

However, initiate optimal medical management for the AE first.

* As part of combination treatment with pembrolizumab. For guidance on how long to continue treatment with pembrolizumab, please refer to the prescribing information.
** NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events.
AE: adverse event.

Hypertension*	**Cardiac dysfunction**	**Thrombo-embolitic events**	**QT prolongation**	**Hypothyroidism/ Thyroid dysfunction**	**Proteinuria and Nephrotic Syndrome**	**Renal failure or impairment**	**Musculoskeletal disorders**	**Fatigue**	**Diarrhoea**	**Nausea**
Anorexia (decreased appetite)	**Vomiting**	**Weight loss**	**Stomatitis (Mucositis oral)**	**Gastrointestinal perforation or Fistula**	**Hepatoxicity**	**RPLS**	**Hemorrhagic events**	**Impaired wound healing**	**PPES**	**Concomitant medications**



GRADE 1

SBP 120 to 139 mmHg or DBP 80 to 89 mmHg[3]

CONTINUE LENVIMA®[4]

GRADE 2

SBP 140 to 159 mmHg or DBP 90 to 99 mmHg if previously WNL. Change in baseline medical intervention indicated. Recurrent or persistent (≥ 24 hours). Symptomatic increase by >20 mmHg DBP or to >140/90 mmHg. Monotherapy indicated[3]

CONTINUE LENVIMA® and initiate antihypertensive therapy (if not already receiving) **or** increase dose of current antihypertensive therapy/initiate additional antihypertensive therapy[4]

GRADE 3

SBP ≥ 160 mmHg or DBP ≥ 100 mmHg. Medical intervention indicated. More than one drug or more intensive therapy than previously used indicate[3]

INTERRUPT LENVIMA® until SBP ≤ 150 mmHg, DBP ≤ 95 mmHg and patient is on a stable antihypertensive dose for ≥ 48 hours[4]

REDUCE Resume LENVIMA® at reduced dose[4]

GRADE 4

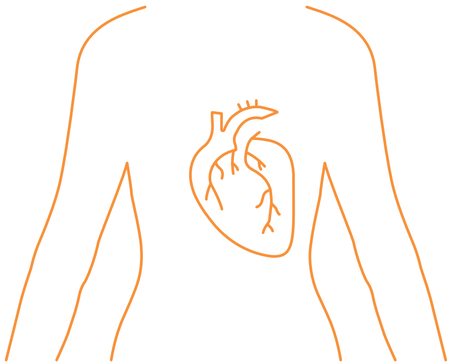
Life-threatening consequences (e.g. malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis)[3]

DISCONTINUE LENVIMA® permanently[4]

* BP should be be controlled at the start of treatment. Hypertension patients should be on a stable dose of antihypertensive therapy for ≥1 week prior to starting treatment. LVEF should be in the normal range.[2]

BP: blood pressure, DBP: diastolic blood pressure, LVEF: left ventricular ejection fraction, SBP: systolic blood pressure, WNL: within normal limits.

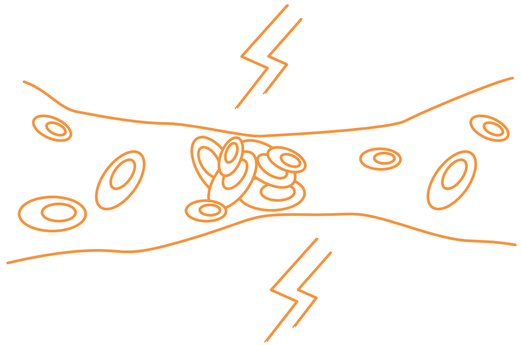
Hypertension	**Cardiac dysfunction**	Thrombo-embolitic events	QT prolongation	Hypothyroidism/ Thyroid dysfunction	Proteinuria and Nephrotic Syndrome	Renal failure or impairment	Musculoskeletal disorders	Fatigue	Diarrhoea	Nausea
Anorexia (decreased appetite)	Vomiting	Weight loss	Stomatitis (Mucositis oral)	Gastrointestinal perforation or Fistula	Hepatoxicity	RPLS	Hemorrhagic events	Impaired wound healing	PPES	Concomitant medications



GRADE 1	GRADE 2	GRADE 3	Nephrotic Syndrome
Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated[3]	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[3]	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[3]	Life-threatening consequences; urgent intervention indicated[3]
CONTINUE LENVIMA®[4]	**CONTINUE** LENVIMA® if tolerable[4]	**INTERRUPT** until improves to Grade 0 to 1 or baseline[4]	**DISCONTINUE** LENVIMA® permanently[4]
		RESUME at a reduced dose or discontinue depending on the severity and persistence of adverse reaction[4]	

ADL: activities of daily living.

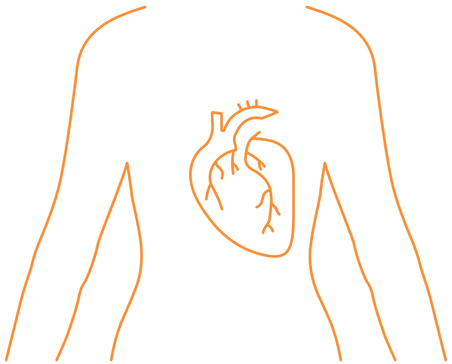
Hypertension	Cardiac dysfunction	Thrombo-embolitic events	QT prolongation	Hypothyroidism/ Thyroid dysfunction	Proteinuria and Nephrotic Syndrome	Renal failure or impairment	Musculoskeletal disorders	Fatigue	Diarrhoea	Nausea
Anorexia (decreased appetite)	Vomiting	Weight loss	Stomatitis (Mucositis oral)	Gastrointestinal perforation or Fistula	Hepatoxicity	RPLS	Hemorrhagic events	Impaired wound healing	PPES	Concomitant medications



Any grade
Arterial thromboembolic event[3]

DISCONTINUE
LENVIMA®
permanently[4]

Hypertension	Cardiac dysfunction	Thrombo-embolitic events	QT prolongation*	Hypothyroidism/ Thyroid dysfunction	Proteinuria and Nephrotic Syndrome	Renal failure or impairment	Musculoskeletal disorders	Fatigue	Diarrhoea	Nausea
Anorexia (decreased appetite)	Vomiting	Weight loss	Stomatitis (Mucositis oral)	Gastrointestinal perforation or Fistula	Hepatoxicity	RPLS	Hemorrhagic events	Impaired wound healing	PPES	Concomitant medications



QT prolongation

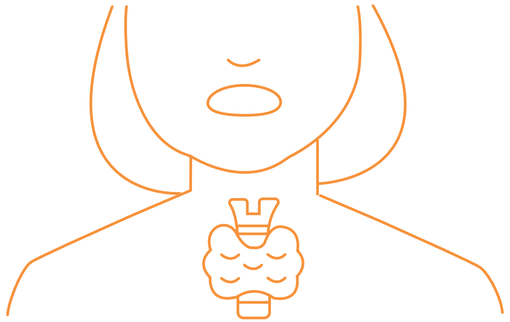
>500 ms increase from baseline

INTERRUPT
LENVIMA®
until resolves to <480 ms or baseline[4]

REDUCE
Resume LENVIMA® at a reduced dose[4]

* Electrocardiograms should be monitored at baseline and periodically during treatment in all patients with particular attention to those with congenital long QT syndrome, congestive heart failure, bradyarrhythmias, and those taking medicinal products known to prolong the QT interval, including Class Ia and III antiarrhythmics.[4]

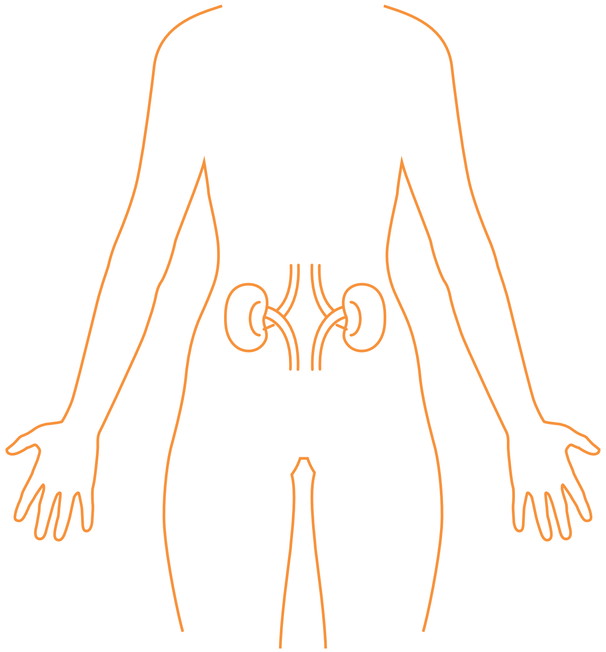
Hypertension	**Cardiac dysfunction**	**Thrombo-embolitic events**	**QT prolongation**	**Hypothyroidism/ Thyroid dysfunction***	**Proteinuria and Nephrotic Syndrome**	**Renal failure or impairment**	**Musculoskeletal disorders**	**Fatigue**	**Diarrhoea**	**Nausea**
Anorexia (decreased appetite)	**Vomiting**	**Weight loss**	**Stomatitis (Mucositis oral)**	**Gastrointestinal perforation or Fistula**	**Hepatoxicity**	**RPLS**	**Hemorrhagic events**	**Impaired wound healing**	**PPES**	**Concomitant medications**



GRADE 1	GRADE 2	GRADE 3	GRADE 4
Asymptomatic. Clinical or diagnostic observations only[3]	Symptomatic. Thyroid replacement indicated. Limiting instrumental ADL[3]	Severe symptoms. Limiting self-care ADL. Hospitalisation indicated[3]	Life-threatening consequences. Urgent intervention indicated[3]
→ **CONTINUE** LENVIMA®[2]	→ **CONTINUE** LENVIMA® if tolerable[#,2]	▯▯ **INTERRUPT** LENVIMA® if persistent or intolerable until resolution of the AE to grade ≤1 or baseline[2]	▯▯ **INTERRUPT** LENVIMA® until resolution of the AE to grade ≤1 or baseline[2]	✕ **DISCONTINUE** LENVIMA® permanently[2]
		↓	↓	
		REDUCE Resume LENVIMA® at a reduced dose[2]		

* Thyroid function of patient should be monitored (T3, T4 and TSH) prior to and during treatment. Hypotyroidism should be treated according to standard medical practice.[2]
[#] Clinical team should track all symptoms, labs, and relevant vitals; supportive measures/medications to be used, per standard medical practice.[2]
ADL: activities of daily living, AE: adverse event, TSH: thyroid-stimulating hormone.

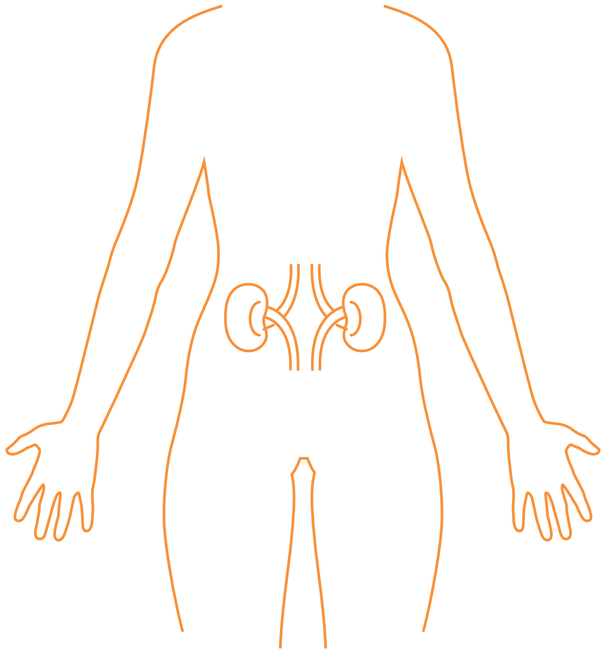
Hypertension	Cardiac dysfunction	Thrombo-embolitic events	QT prolongation	Hypothyroidism/ Thyroid dysfunction	**Proteinuria and Nephrotic Syndrome**	Renal failure or impairment	Musculoskeletal disorders	Fatigue	Diarrhoea	Nausea
Anorexia (decreased appetite)	Vomiting	Weight loss	Stomatitis (Mucositis oral)	Gastrointestinal perforation or Fistula	Hepatoxicity	RPLS	Hemorrhagic events	Impaired wound healing	PPES	Concomitant medications



GRADE 1	GRADE 2	GRADE 3	Nephrotic Syndrome
1+ proteinuria. Urinary protein ≥ULN to < 1.0 g/24 hours[3]	2+ and 3+ proteinuria. Urinary protein 1.0 to < 3.5 g/24 hours[3]	4+ proteinuria. Urinary protein ≥ 3.5 g/24 hours[3]	
	≥ 2 g/24 hours		
CONTINUE LENVIMA®[4]	**INTERRUPT** LENVIMA® until < 2 g/24 hours[4]		**DISCONTINUE** LENVIMA®
	REDUCE Resume LENVIMA® at a reduced dose[4]		

* Monitor for proteinuria prior to initiating and during treatment.[4]
ULN: upper limit of normal.

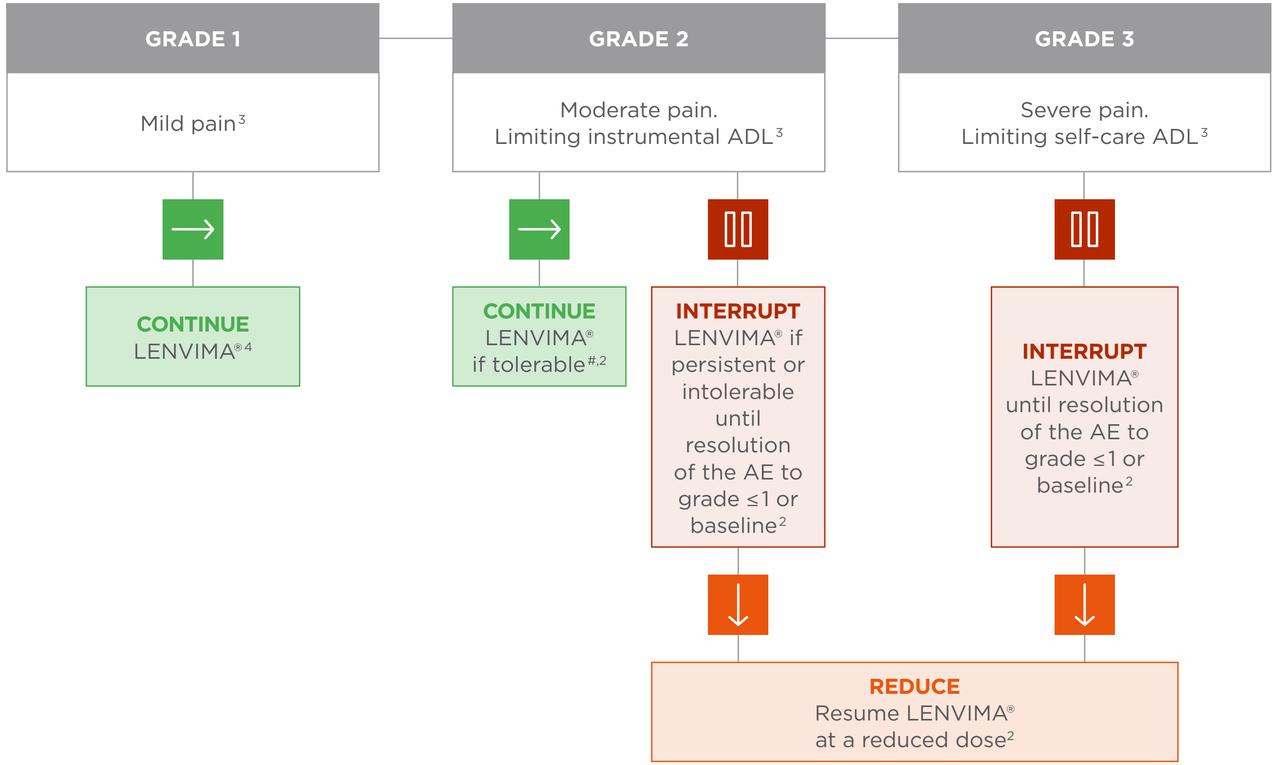
Hypertension	Cardiac dysfunction	Thrombo-embolitic events	QT prolongation	Hypothyroidism/ Thyroid dysfunction	Proteinuria and Nephrotic Syndrome	**Renal failure or impairment**	Musculoskeletal disorders	Fatigue	Diarrhoea	Nausea
Anorexia (decreased appetite)	Vomiting	Weight loss	Stomatitis (Mucositis oral)	Gastrointestinal perforation or Fistula	Hepatoxicity	RPLS	Hemorrhagic events	Impaired wound healing	PPES	Concomitant medications



GRADE 1	GRADE 2	GRADE 3	GRADE 4
Creatinine increased: >ULN–1.5× ULN[3]	Creatinine increased: >1.5–3.0× baseline; >1.5–3.0× ULN[3]	Creatinine increased: >3.0× baseline; >3.0–6.0× ULN[3]	Creatinine increased: >6.0× ULN[3]
→		⏸	✕
CONTINUE LENVIMA®[4]		**INTERRUPT** LENVIMA® until improves to Grade 0 to 1 or baseline[4]	**DISCONTINUE** LENVIMA®[4]
		↓	
		REDUCE Resume LENVIMA® at a reduced dose or discontinue depending on severity and persistence of renal impairment[4]	

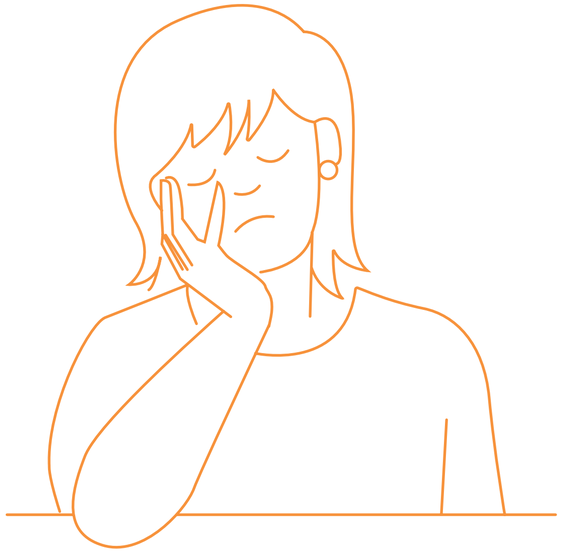
Gastrointestinal side effects must be actively managed to reduce the risk of renal failure or insufficiency.[4]
ULN: upper limit of normal.

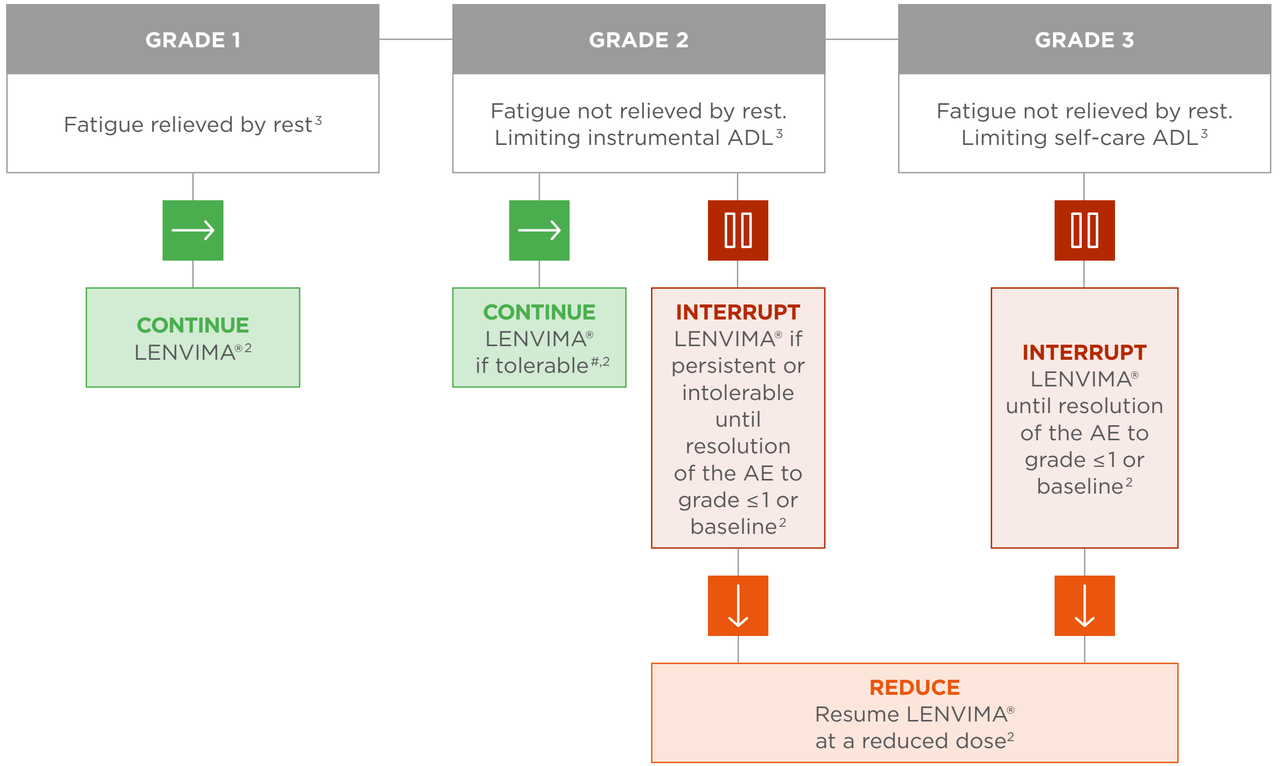
Hypertension	Cardiac dysfunction	Thrombo-embolitic events	QT prolongation	Hypothyroidism/ Thyroid dysfunction	Proteinuria and Nephrotic Syndrome	Renal failure or impairment	**Musculoskeletal disorders**	Fatigue	Diarrhoea	Nausea
Anorexia (decreased appetite)	Vomiting	Weight loss	Stomatitis (Mucositis oral)	Gastrointestinal perforation or Fistula	Hepatoxicity	RPLS	Hemorrhagic events	Impaired wound healing	PPES	Concomitant medications



Based on severity; clinical team should track all symptoms, labs, and relevant vitals; supportive measures/medications to be used, per standard medical practice.[2]
ADL: activities of daily living, AE: adverse event.

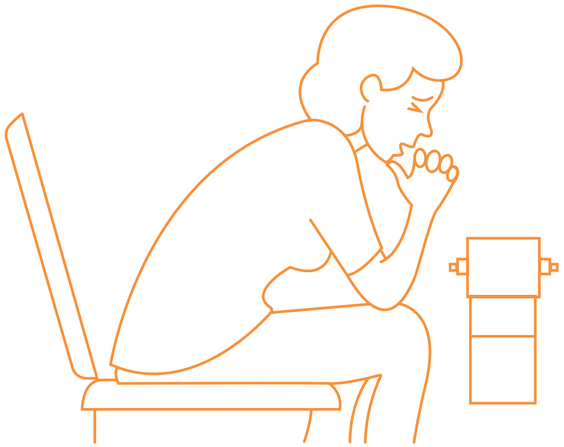
Hypertension	Cardiac dysfunction	Thrombo-embolitic events	QT prolongation	Hypothyroidism/ Thyroid dysfunction	Proteinuria and Nephrotic Syndrome	Renal failure or impairment	Musculoskeletal disorders	**Fatigue**	Diarrhoea	Nausea
Anorexia (decreased appetite)	Vomiting	Weight loss	Stomatitis (Mucositis oral)	Gastrointestinal perforation or Fistula	Hepatoxicity	RPLS	Hemorrhagic events	Impaired wound healing	PPES	Concomitant medications





Based on severity; clinical team should track all symptoms, labs, and relevant vitals; supportive measures/medications to be used, per standard medical practice.[2]
ADL: activities of daily living, AE: adverse event.

Hypertension	Cardiac dysfunction	Thrombo-embolitic events	QT prolongation	Hypothyroidism/ Thyroid dysfunction	Proteinuria and Nephrotic Syndrome	Renal failure or impairment	Musculoskeletal disorders	Fatigue	**Diarrhoea**	Nausea
Anorexia (decreased appetite)	Vomiting	Weight loss	Stomatitis (Mucositis oral)	Gastrointestinal perforation or Fistula	Hepatoxicity	RPLS	Hemorrhagic events	Impaired wound healing	PPES	Concomitant medications

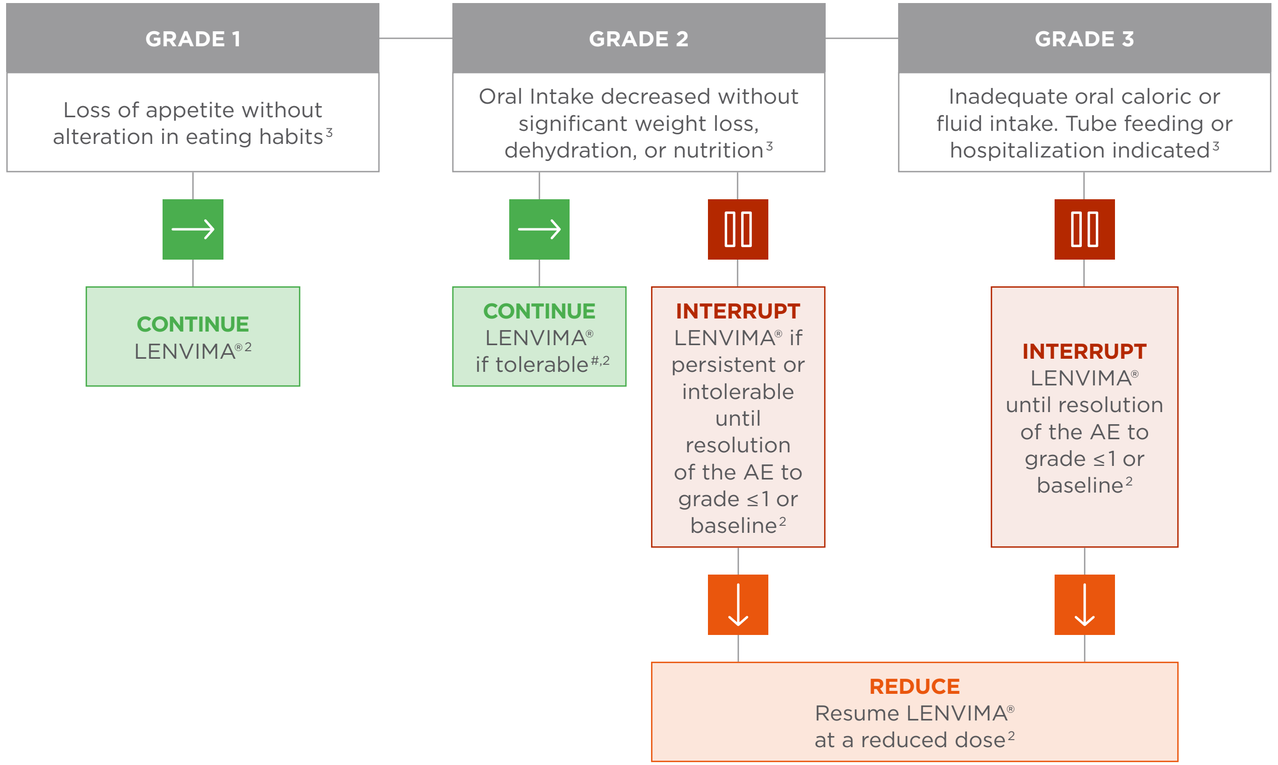


GRADE 1	GRADE 2	GRADE 3	GRADE 4
Increase of < 4 stools/ day over baseline. Mild increase in ostomy output compared with baseline[3]	Increase of 4 to 6 stools/ day over baseline. Moderate increase in ostomy output compared with baseline. Limiting instrumental ADL[3]	Increase of ≥ 7 stools/ day over baseline. Hospitalisation indicated. Severe increase in ostomy output compared with baseline. Limiting self-care ADL[3]	Life-threatening consequences. Urgent intervention indicated[3]
CONTINUE LENVIMA®[4]		**INTERRUPT** LENVIMA® until resolves to Grade 0/1 or baseline.[4,*]	**DISCONTINUE** LENVIMA® permanently[4]
		REDUCE Resume LENVIMA® at a reduced dose[4]	

* Patients should be advised to maintain adequate hydration and to be alert to the first onset of soft bowel movements.[2]
Clinicians should prescribe antidiarrheals to patients at the time of treatment initiation, to be utilized as needed.[2]
If Grade 3 for >48 hours, increase fluid intake to avoid dehydration and consider hospital admission.[5]

ADL: activities of daily living, AE: adverse event.

Hypertension	Cardiac dysfunction	Thrombo-embolitic events	QT prolongation	Hypothyroidism/ Thyroid dysfunction	Proteinuria and Nephrotic Syndrome	Renal failure or impairment	Musculoskeletal disorders	Fatigue	Diarrhoea	Nausea
Anorexia (decreased appetite)	Vomiting	Weight loss	Stomatitis (Mucositis oral)	Gastrointestinal perforation or Fistula	Hepatoxicity	RPLS	Hemorrhagic events	Impaired wound healing	PPES	Concomitant medications



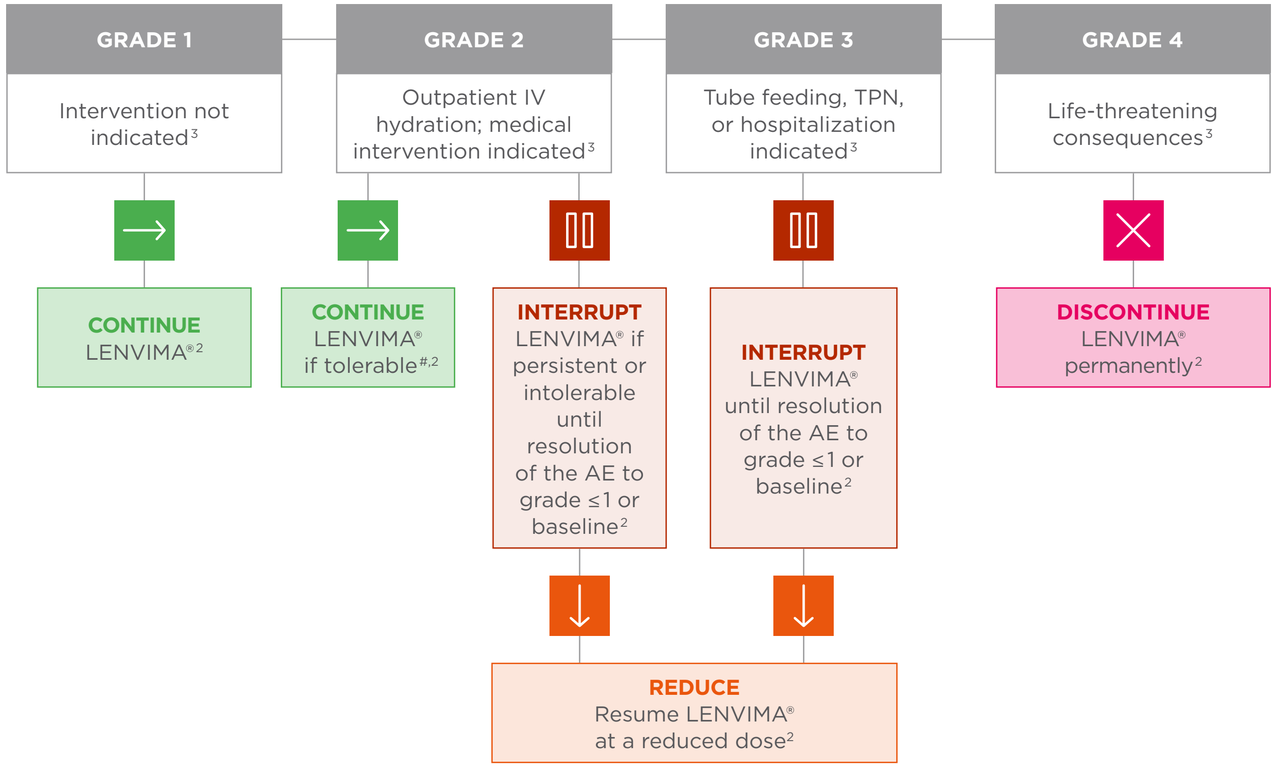
Clinicians should prescribe antiemetics at the time of treatment initiation, to be used as needed, and should treat nausea before dose-reducing lenvatinib.[2]
Based on severity; clinical team should track all symptoms, labs, and relevant vitals; supportive measures/medications to be used, per standard medical practice.[2]
AE: adverse event, TPN: total parenteral nutrition.

Hypertension	**Cardiac dysfunction**	**Thrombo-embolitic events**	**QT prolongation**	**Hypothyroidism/ Thyroid dysfunction**	**Proteinuria and Nephrotic Syndrome**	**Renal failure or impairment**	**Musculoskeletal disorders**	**Fatigue**	**Diarrhoea**	**Nausea**
Anorexia (decreased appetite)	**Vomiting**	**Weight loss**	**Stomatitis (Mucositis oral)**	**Gastrointestinal perforation or Fistula**	**Hepatoxicity**	**RPLS**	**Hemorrhagic events**	**Impaired wound healing**	**PPES**	**Concomitant medications**

GRADE 1	GRADE 2	GRADE 3	GRADE 4
Loss of appetite without alteration in eating habits[3]	Oral intake altered without significant weight loss or malnutrition. Oral nutritional supplements indicated[3]	Associated with significant weight loss or malnutrition (eg, inadequate oral caloric and/or fluid intake). Tube feeding or TPN indicated[3]	Life-threatening consequences. Urgent intervention indicated[3]
→ **CONTINUE** LENVIMA®[2]	→ **CONTINUE** LENVIMA® if tolerable[#,2]	⏸ **INTERRUPT** LENVIMA® if persistent or intolerable until resolution of the AE to grade ≤1 or baseline[2]	⏸ **INTERRUPT** LENVIMA® until resolution of the AE to grade ≤1 or baseline[2]	✕ **DISCONTINUE** LENVIMA® permanently[2]
		↓ **REDUCE** Resume LENVIMA® at a reduced dose[2]	↓ **REDUCE** Resume LENVIMA® at a reduced dose[2]	

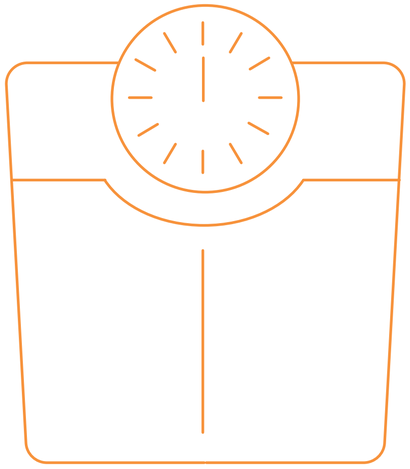
[#] Based on severity; clinical team should track all symptoms, labs, and relevant vitals; supportive measures/medications to be used, per standard medical practice.[2]
AE: adverse event, TPN: total parenteral nutrition.

Hypertension	Cardiac dysfunction	Thrombo-embolitic events	QT prolongation	Hypothyroidism/ Thyroid dysfunction	Proteinuria and Nephrotic Syndrome	Renal failure or impairment	Musculoskeletal disorders	Fatigue	Diarrhoea	Nausea
Anorexia (decreased appetite)	**Vomiting**	Weight loss	Stomatitis (Mucositis oral)	Gastrointestinal perforation or Fistula	Hepatoxicity	RPLS	Hemorrhagic events	Impaired wound healing	PPES	Concomitant medications



Clinicians should prescribe antiemetics at the time of treatment initiation, to be used as needed, and should treat vomiting before dose-reducing lenvatinib.
Based on severity; clinical team should track all symptoms, labs, and relevant vitals; supportive measures/medications to be used, per standard medical practice.[2]
AE: adverse event, TPN: total parenteral nutrition.

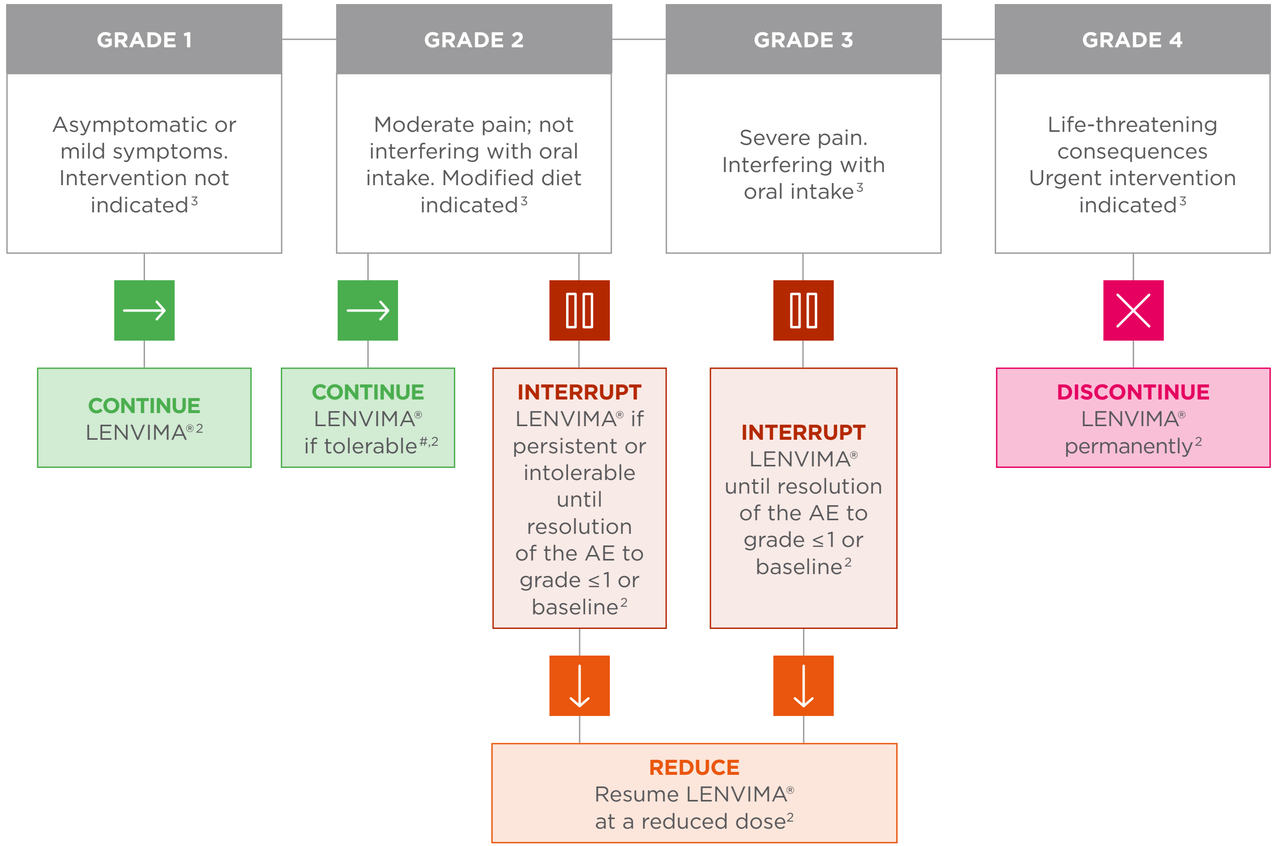
Hypertension	Cardiac dysfunction	Thrombo-embolitic events	QT prolongation	Hypothyroidism/ Thyroid dysfunction	Proteinuria and Nephrotic Syndrome	Renal failure or impairment	Musculoskeletal disorders	Fatigue	Diarrhoea	Nausea
Anorexia (decreased appetite)	Vomiting	**Weight loss**	Stomatitis (Mucositis oral)	Gastrointestinal perforation or Fistula	Hepatoxicity	RPLS	Hemorrhagic events	Impaired wound healing	PPES	Concomitant medications



GRADE 1	GRADE 2	GRADE 3
5 to <10 % loss from baseline. Intervention not indicated[3]	10 to <20 % loss from baseline. Nutritional support indicated[3]	≥20 % loss from baseline. Tube feeding or TPN indicated[3]
→ **CONTINUE** LENVIMA®[2]	→ **CONTINUE** LENVIMA® if tolerable[#,2]	⏸ **INTERRUPT** LENVIMA® if persistent or intolerable until resolution of the AE to grade ≤1 or baseline[2] → ↓	⏸ **INTERRUPT** LENVIMA® until resolution of the AE to grade ≤1 or baseline[2] → ↓
		REDUCE Resume LENVIMA® at a reduced dose[2]	

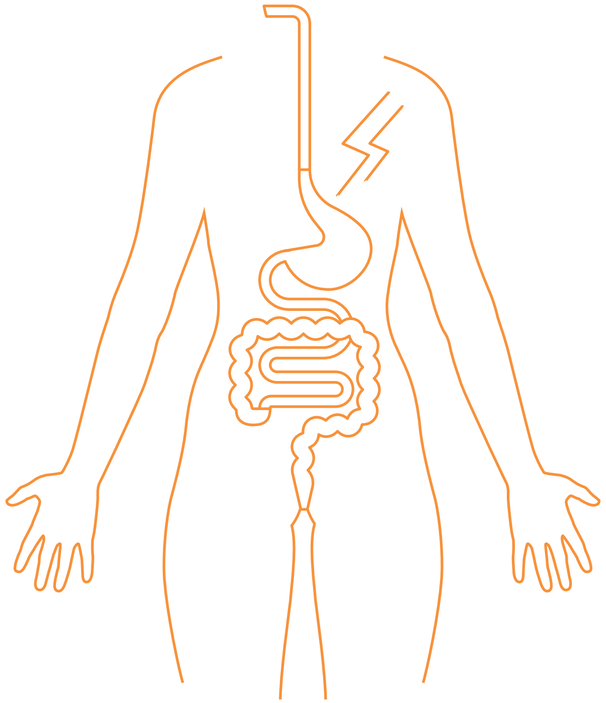
[#] Based on severity; clinical team should track all symptoms, labs, and relevant vitals; supportive measures/medications to be used, per standard medical practice.[2]
AE: adverse event, TPN: total parenteral nutrition.

Hypertension	Cardiac dysfunction	Thrombo-embolitic events	QT prolongation	Hypothyroidism/ Thyroid dysfunction	Proteinuria and Nephrotic Syndrome	Renal failure or impairment	Musculoskeletal disorders	Fatigue	Diarrhoea	Nausea
Anorexia (decreased appetite)	Vomiting	Weight loss	**Stomatitis (Mucositis oral)**	Gastrointestinal perforation or Fistula	Hepatoxicity	RPLS	Hemorrhagic events	Impaired wound healing	PPES	Concomitant medications



Based on severity; clinical team should track all symptoms, labs, and relevant vitals; supportive measures/medications to be used, per standard medical practice.[2]
AE: adverse event.

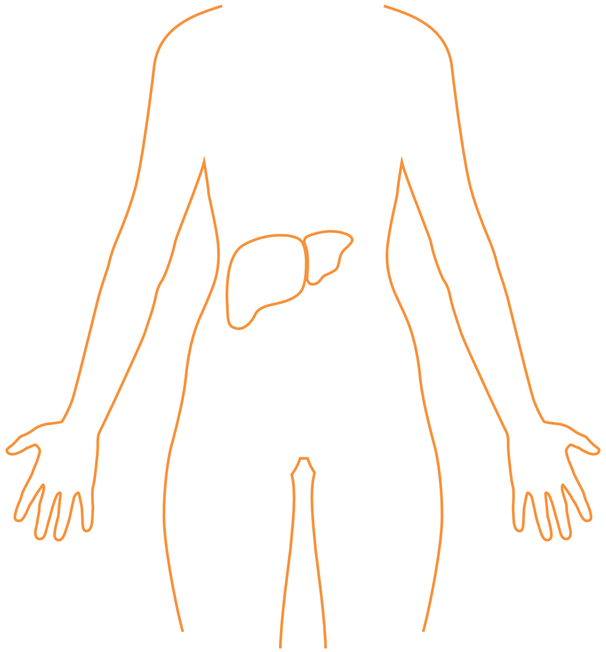
Hypertension	Cardiac dysfunction	Thrombo-embolitic events	QT prolongation	Hypothyroidism/ Thyroid dysfunction	Proteinuria and Nephrotic Syndrome	Renal failure or impairment	Musculoskeletal disorders	Fatigue	Diarrhoea	Nausea
Anorexia (decreased appetite)	Vomiting	Weight loss	Stomatitis (Mucositis oral)	Gastrointestinal perforation or Fistula	Hepatoxicity	RPLS	Hemorrhagic events	Impaired wound healing	PPES	Concomitant medications



GRADE 1	GRADE 2	GRADE 3	GRADE 4
–[3]	Invasive intervention not indicated[3]	Invasive intervention indicated[3]	Life-threatening consequences; urgent operative intervention indicated*,[3]
CONTINUE LENVIMA®[4]		**INTERRUPT** LENVIMA® until resolves to Grade 0/1 or baseline[4]	**DISCONTINUE** LENVIMA® permanently[4]
		REDUCE Resume LENVIMA® at a reduced dose[4]	

* Grade 4 Fistula formation outside gastrointestinal track: discontinue LENVIMA® permanently.[4]
GI: gastrointestinal, TPN: total parenteral nutrition.

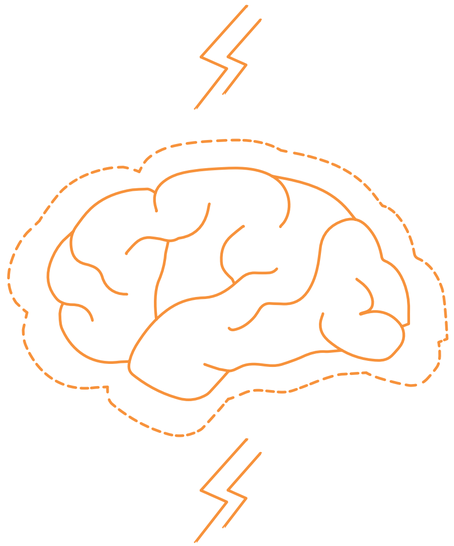
Hypertension	Cardiac dysfunction	Thrombo-embolitic events	QT prolongation	Hypothyroidism/ Thyroid dysfunction	Proteinuria and Nephrotic Syndrome	Renal failure or impairment	Musculoskeletal disorders	Fatigue	Diarrhoea	Nausea
Anorexia (decreased appetite)	Vomiting	Weight loss	Stomatitis (Mucositis oral)	Gastrointestinal perforation or Fistula	**Hepatoxicity***	RPLS	Hemorrhagic events	Impaired wound healing	PPES	Concomitant medications



GRADE 1	GRADE 2	GRADE 3	GRADE 4
Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated[3]	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[3]	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[3]	Life-threatening consequences; urgent intervention indicated[3]
CONTINUE LENVIMA®[4]		**INTERRUPT** LENVIMA® until improves to Grade 0 to 1 or baseline[4]	**DISCONTINUE** LENVIMA®[4]
		REDUCE Resume LENVIMA® at a reduced dose[4]	

* In patients treated with lenvatinib, increases in blood of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin have been reported most frequently. Liver failure and acute hepatitis (<1%) have been reported. Cases of liver failure were observed in patients with advanced liver metastases.[4]
ADL: activities of daily living.

Hypertension	Cardiac dysfunction	Thrombo-embolitic events	QT prolongation	Hypothyroidism/ Thyroid dysfunction	Proteinuria and Nephrotic Syndrome	Renal failure or impairment	Musculoskeletal disorders	Fatigue	Diarrhoea	Nausea
Anorexia (decreased appetite)	Vomiting	Weight loss	Stomatitis (Mucositis oral)	Gastrointestinal perforation or Fistula	Hepatoxicity	**RPLS**	Hemorrhagic events	Impaired wound healing	PPES	Concomitant medications



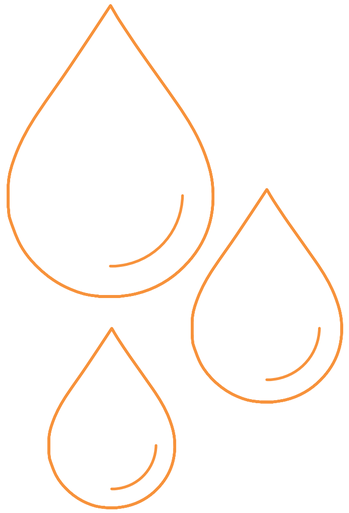
GRADE 1	GRADE 2	GRADE 3	GRADE 4
	Moderate symptoms; limiting instrumental ADL[3]	Severe symptoms; limiting self-care ADL, hospitalization[3]	Life-threatening consequences[3]

INTERRUPT
LENVIMA® until resolves to Grade 0/1 or baseline[4]

REDUCE
Consider resumption of LENVIMA® at a reduced dose[4]

ADL: activities of daily living, RPLS: reversible posterior leukoencephalopathy syndrome.

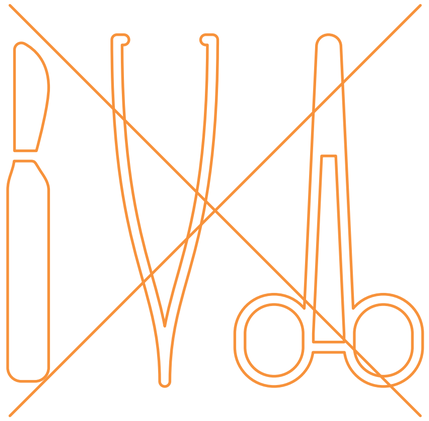
Hypertension	Cardiac dysfunction	Thrombo-embolitic events	QT prolongation	Hypothyroidism/ Thyroid dysfunction	Proteinuria and Nephrotic Syndrome	Renal failure or impairment	Musculoskeletal disorders	Fatigue	Diarrhoea	Nausea
Anorexia (decreased appetite)	Vomiting	Weight loss	Stomatitis (Mucositis oral)	Gastrointestinal perforation or Fistula	Hepatoxicity	RPLS	**Hemorrhagic events**	Impaired wound healing	PPES	Concomitant medications



GRADE 1	GRADE 2	GRADE 3	GRADE 4
Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated[3]	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[3]	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[3]	Life-threatening consequences; urgent intervention indicated[3]
CONTINUE LENVIMA®[4]		**INTERRUPT** LENVIMA® until improves to Grade 0 to 1 or baseline[4]	**DISCONTINUE** LENVIMA®[4]
		REDUCE Resume LENVIMA® at a reduced dose[4]	

ADL: activities of daily living.

Hypertension	Cardiac dysfunction	Thrombo-embolitic events	QT prolongation	Hypothyroidism/ Thyroid dysfunction	Proteinuria and Nephrotic Syndrome	Renal failure or impairment	Musculoskeletal disorders	Fatigue	Diarrhoea	Nausea
Anorexia (decreased appetite)	Vomiting	Weight loss	Stomatitis (Mucositis oral)	Gastrointestinal perforation or Fistula	Hepatoxicity	RPLS	Hemorrhagic events	**Impaired wound healing**	PPES	Concomitant medications

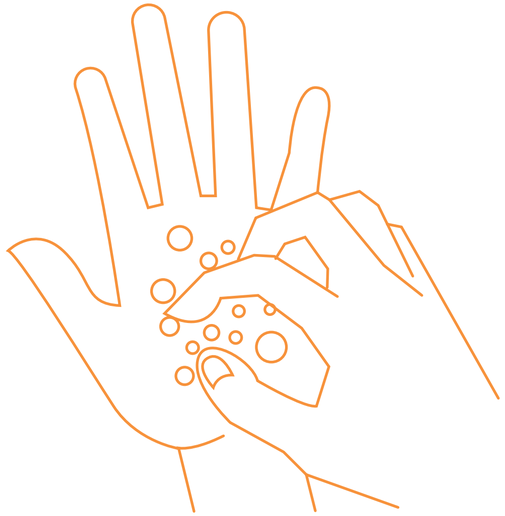


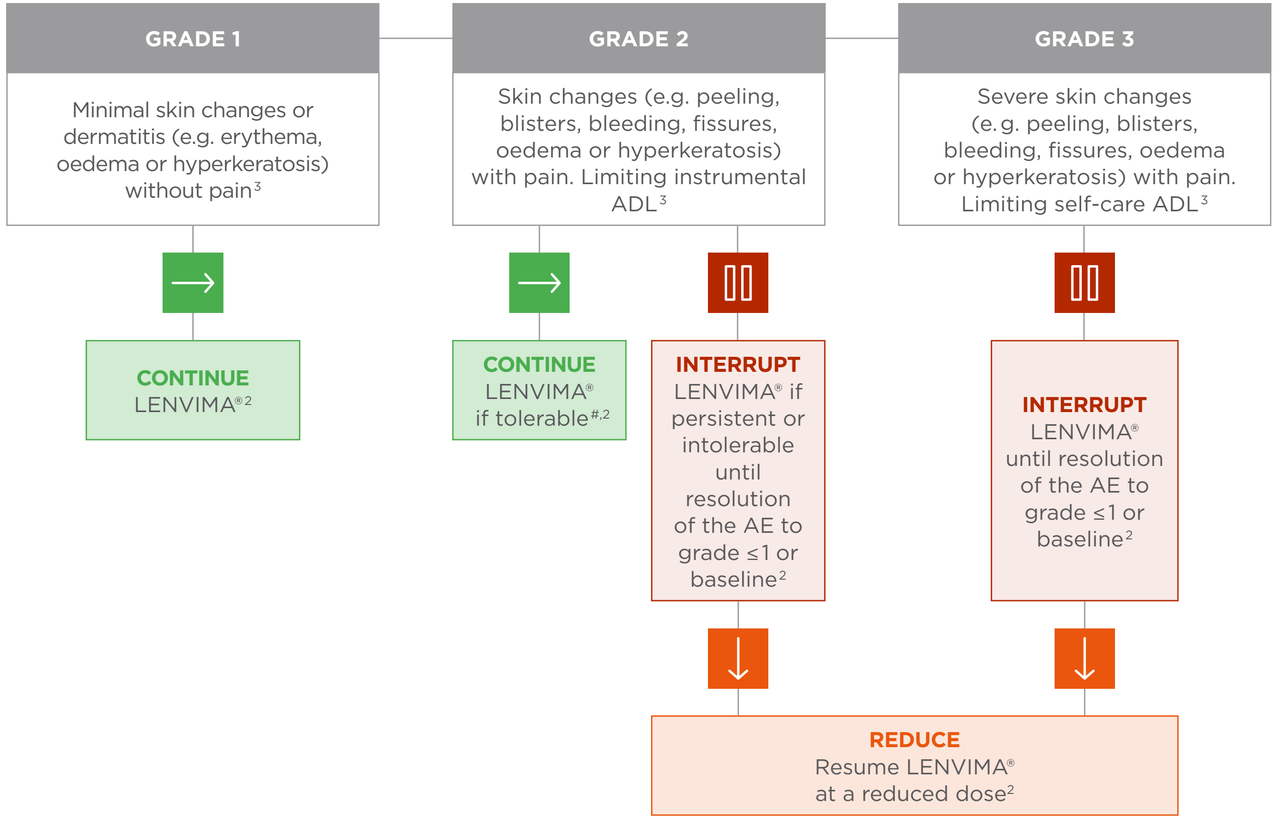
Planned surgical procedure

INTERRUPT
LENVIMA®
at least 6 days prior to elective surgery[4]

REDUCE
The decision to continue treatment with LENVIMA® should be made after clinical assessment of wound healing[4]

Hypertension	Cardiac dysfunction	Thrombo-embolitic events	QT prolongation	Hypothyroidism/ Thyroid dysfunction	Proteinuria and Nephrotic Syndrome	Renal failure or impairment	Musculoskeletal disorders	Fatigue	Diarrhoea	Nausea
Anorexia (decreased appetite)	Vomiting	Weight loss	Stomatitis (Mucositis oral)	Gastrointestinal perforation or Fistula	Hepatoxicity	RPLS	Hemorrhagic events	Impaired wound healing	**PPES**	Concomitant medications





Based on severity; clinical team should track all symptoms, labs, and relevant vitals; supportive measures/medications to be used, per standard medical practice.[2]
ADL: activities of daily living, AE: adverse event, PPES: palmar–plantar erythrodysaesthesia syndrome.

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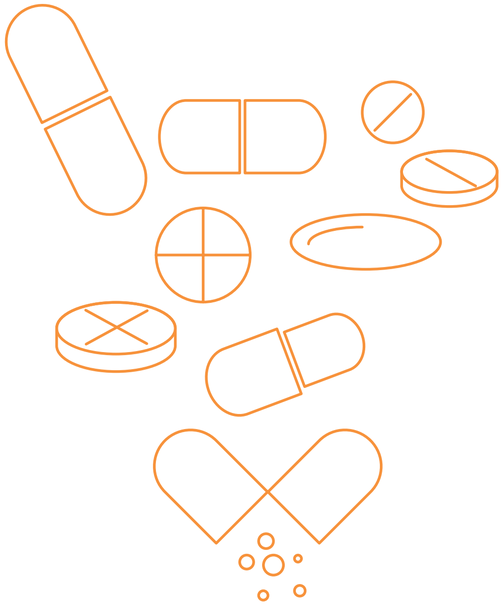

Summary of concomitant medications for the management of key AEs from Study 309/KEYNOTE-775[2] pMMR Population (n = 342)

Adverse Reaction Medications received,[a] n[b] (%)	All Patients; Lenvatinib + Pembrolizumab Group (n = 342)
Hypothyroidism – Patients with this AR	**229 (100.0)**
Patients who received ≥1 concomitant medication	**180 (78.6)**
Levothyroxine sodium	177 (77.3)
Hypertension – Patients with this AR	**228 (100.0)**
Patients who received ≥1 concomitant medication	**186 (81.6)**
Amlodipine	70 (30.7)
Amlodipine besilate	41 (18.0)
Losartan	24 (10.5)
Captopril	16 (7.0)
Ramipril	19 (8.3)
Furosemide	15 (6.6)
Nifedipine	15 (6.6)
Hydrochlorothiazide	14 (6.1)
Lisinoprol	12 (5.3)
Fatigue – Patients with this AR	**198 (100.0)**
Patients who received ≥1 concomitant medication	**10 (5.1)**
Dexamethasone	4 (2.0)
Diarrhea[c] – Patients with this AR	**188 (100.0)**
Patients who received ≥1 concomitant medication	**121 (64.4)**
Loperamide hydrochloride	51 (27.1)
Loperamide	50 (26.6)
Musculoskeletal disorders – Patients with AR	**181 (100.0)**
Patients who received ≥1 concomitant medication	**105 (58.0)**
Paracetamol	50 (27.6)
Ibuprofen	23 (12.7)
Loxoprofen sodium	12 (6.6)
Prednisone	9 (5.0)
Nausea – Patients with this AR	**169 (100.0)**
Patients who received ≥1 concomitant medication	**111 (65.7)**
Ondansetron	39 (23.1)
Metoclopramide hydrochloride	31 (18.3)
Metoclopramide	24 (14.2)
Prochlorperazine	13 (7.7)
Decreased appetite – Patients with this AR	**152 (100.0)**
Patients who received ≥1 concomitant medication	**36 (23.7)**
Megestrol acetate	8 (5.3)
Nutrients not otherwise specified	8 (5.3)

Adverse Reaction Medications received,[a] n[b] (%)	All Patients; Lenvatinib + Pembrolizumab Group (n = 342)
Vomiting – Patients with this AR	**125 (100.0)**
Patients who received ≥1 concomitant medication	**45 (36.0)**
Metoclopramide	13 (10.4)
Ondansetron	13 (10.4)
Metoclopramide hydrochloride	11 (8.8)
Vomiting – Patients with this AR	**125 (100.0)**
Patients who received ≥1 concomitant medication	**45 (36.0)**
Metoclopramide	13 (10.4)
Ondansetron	13 (10.4)
Metoclopramide hydrochloride	11 (8.8)
Stomatitis – Patients with this AR	**120 (100.0)**
Patients who received ≥1 concomitant medication	**76 (63.3)**
Nystatin	15 (12.5)
Dexamethasone	9 (7.5)
Sodium gualenate	9 (7.5)
Chlorhexidine gluconate	8 (6.7)
Lidocaine	6 (5.0)
Weight loss – Patients with this AR	**117 (100.0)**
Patients who received ≥1 concomitant medication	**12 (10.3)**
Nutrients not otherwise specified	4 (3.4)
Proteinuria – Patients with this AR	**100 (100.0)**
Patients who received ≥1 concomitant medication	**5 (5.0)**
Akritoin	1 (1.0)
Ciprofloxacin hydrochloride	1 (1.0)
Levothyroxine sodium	1 (1.0)
Losartan potassium	1 (1.0)
Olmesartan	1 (1.0)
Pantoprazole	1 (1.0)
Trimethoprim	1 (1.0)
PPES – Patients with this AR	**77 (100.0)**
Patients who received ≥1 concomitant medication	**53 (68.8)**
Clobetasol propionate	14 (18.2)
Urea	8 (10.4)
Mucopolysaccharide polysulfuric acid ester	6 (7.8)
Heparinoid	5 (6.5)
Difluprednate	4 (5.2)
Paracetamol	4 (5.2)

Adapted from Colombo N, et al. Oncologist. 2023.[2]
Concomitant medications are also part of the AE management strategy per standard medical practice. a. Medications included are those received in ≥5% of patients or the most common concomitant medication for the listed adverse reaction. b. Patients may have received more than 1 medication to treat a specific adverse reaction. c. Diarrhea encompasses only diarrhea and gastroenteritis, and not colitis, which is immune-mediated and treated with steroids and other therapies.
AE: adverse event, AR: adverse reaction, nos: not otherwise specified, pMMR: mismatch repair-proficient, PPES: palmar-plantar erythrodysesthesia syndrome.

MANAGING AEs

General management guidelines

The following pages provide advice on when to continue or interrupt LENVIMA® treatment, based on AE severity (NCI-CTCAE grading).[1–3] The patient's multidisciplinary team can then decide to reduce the dose or permanently discontinue treatment.

CONTINUE TREATMENT with LENVIMA®* for as long as a clinical benefit is achieved or until unacceptable toxicity or disease progression occurs[4]

INTERRUPT and

REDUCE the dose, or

DISCONTINUE LENVIMA®

However, initiate optimal medical management for the AE first.

* As part of combination treatment with pembrolizumab. For guidance on how long to continue treatment with pembrolizumab, please refer to the prescribing information KEYTRUDA®.
** NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events.
AE: adverse event.

References

1. Makker V, et al. Lenvatinib Plus Pembrolizumab in Previously Treated Advanced Endometrial Cancer: Updated Efficacy and Safety From the Randomized Phase III Study 309/KEYNOTE-775. J Clin Oncol. 2023;41(16):2904–2910.
2. Colombo N et al. Characterization and Management of Adverse Reactions in Patients With Advanced Endometrial Cancer Receiving Lenvatinib Plus Pembrolizumab. Oncologist. 2023 Jul 31;oyad201. doi: 10.1093/oncolo/oyad201. Online ahead of print. With supplementary material.
3. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE); v5.0, Bethesda, MD: National Cancer Institute 2017. NIH publication 09-5410.
4. Prescribing information LENVIMA® (lenvatinib), www.swissmedicinfo.ch.
5. De Wit M, et al. Prevention and management of adverse events related to regorafenib. Support Care Cancer 2014;22(3):837–846.

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