KEYTRUDA® (pembrolizumab)

LENVIMA® (lenvatinib)

i PI GB PI NI PI

Your guide to recognising and managing adverse events.

KEYTRUDA® (pembrolizumab) in combination with LENVIMA® (lenvatinib) is indicated for the treatment of adult patients with advanced or recurrent endometrial carcinoma (EC) who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and are not candidates for curative surgery or radiation.[1]

Adverse events should be reported. Reporting forms and information can be found at https://yellowcard.mhra.gov.uk/ (please note that the MHRA Yellow Card link will redirect you to an external website, for which MSD does not review or control the content) or search for MHRA Yellow Card in the Google Play or Apple App Store, or Republic of Ireland: www.hpra.ie. Adverse events should also be reported to Eisai Ltd on +44 (0)208 600 1400 or EUmedinfo@eisai.net or Merck Sharp & Dohme (UK) Limited (Tel: 020 8154 8000).

Refer to the LENVIMA® Prescribing Information and/or Summary of Product Characteristics (SmPC) for further details.

LENVIMA® and KEYTRUDA® GB and NI Prescribing Information (PI) can be accessed via the mulberry and green 'PI' buttons respectively in the top-right corner of this document throughout.

This content is intended to be viewed online, it is not intended to be printed.

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Introduction

The AEs of LENVIMA are generally manageable.[1] They may occur very early in the course of LENVIMA treatment.[2] Engagement with the multidisciplinary team is important for the management of AEs. Equally important is keeping patients and caregivers informed, and maintaining a shared decision strategy.[2]

This guide will help you to address common 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.

The advice in this section is divided into two major parts:

1 **Recognising** common AEs >

2 **Managing** common AEs >

For guidance on how to manage AEs related to KEYTRUDA, please refer to the KEYTRUDA SmPC.
For further guidance on how to manage AEs related to LENVIMA, please refer to the LENVIMA SmPC.

AE: adverse event, **SmPC:** Summary of Product Characteristics.

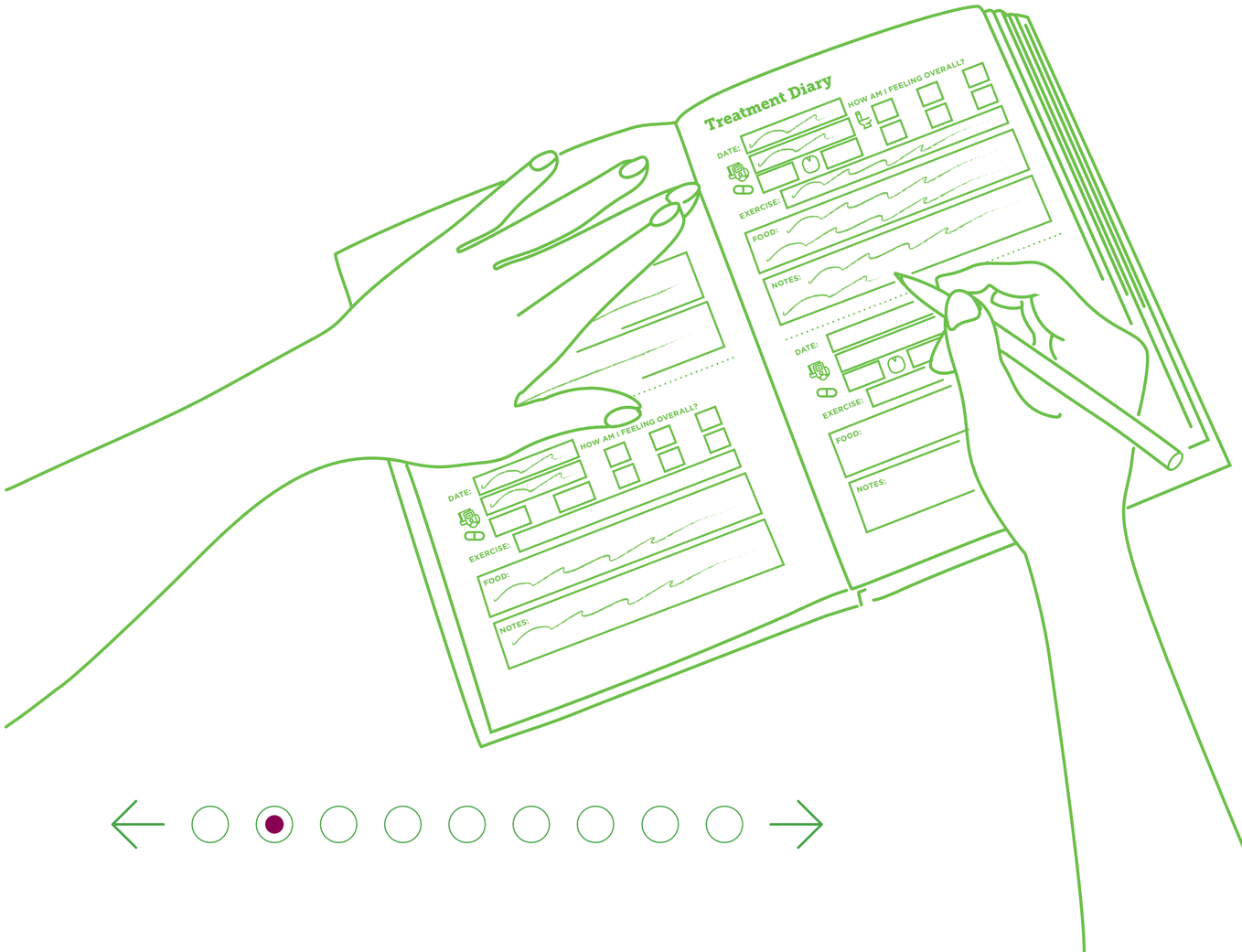
Recognising common AEs

Common AEs

There are some differences between LENVIMA-induced AEs and those that are usually managed with chemotherapy and other common cancer treatments.

It's important to be able to identify and distinguish them from the symptoms of the disease. HCPs should proactively familiarise themselves with the AE profile of LENVIMA.[2]

The ***'Keytruda/Lenvima Treatment Diary for Advanced Endometrial Cancer'*** can help to share this responsibility and ensure patients report back any AEs they experience.



AE: adverse event, **HCP**: healthcare professional.

AEs experienced in ≥25% of patients in either treatment group in KEYNOTE-775/Study 309[1]

	KEYTRUDA + LENVIMA (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†	260 (64.0)	154 (37.9)	20 (5.2)	9 (2.3)
Hypothyroidism†‡	233 (57.4)	5 (1.2)	3 (0.8)	0
Diarrhoea	220 (54.2)	31 (7.6)	78 (20.1)	8 (2.1)
Nausea	201 (49.5)	14 (3.4)	179 (46.1)	5 (1.3)
Decreased appetite	182 (44.8)	32 (7.9)	82 (21.1)	2 (0.5)
Vomiting	149 (36.7)	11 (2.7)	81 (20.9)	9 (2.3)
Weight decrease	138 (34.0)	42 (10.3)	22 (5.7)	1 (0.3)
Fatigue	134 (33.0)	21 (5.2)	107 (27.6)	12 (3.1)
Arthralgia	124 (30.5)	7 (1.7)	31 (8.0)	0
Proteinuria†	117 (28.8)	22 (5.4)	11 (2.8)	1 (0.3)
Anaemia	106 (26.1)	25 (6.2)	189 (48.7)	57 (14.7)
Constipation	105 (25.9)	3 (0.7)	96 (24.7)	2 (0.5)
Urinary tract infection	104 (25.6)	16 (3.9)	39 (10.1)	4 (1.0)
Neutropenia	30 (7.4)	7 (1.7)	131 (33.8)	100 (25.8)
Alopecia	22 (5.4)	0	120 (30.9)	2 (0.5)

Adapted from Makker V *et al. N Engl J Med* 2022.[1]

*Among the patients who received KEYTRUDA + LENVIMA, 5.7% died owing to grade 5 adverse events (gastrointestinal disorder in 1.2% of the patients, cardiac disorder in 0.5%, general disorder in 1.5%, infection in 0.7%, decreased appetite in 0.2% and neoplasms, nervous system disorder, psychiatric disorder, renal disorder, reproductive disorder, or respiratory disorder in 0.2% each). Among the patients who received doxorubicin or paclitaxel, 4.9% died owing to grade 5 adverse events (cardiac disorder in 1.0%, general disorder in 1.3%, infection in 1.5%, subdural haematoma in 0.3% and respiratory disorder in 0.8%).[1]
†This event was a clinically significant adverse event with LENVIMA therapy.[1]
‡This event was an adverse event of interest with KEYTRUDA therapy.[1]

AE: adverse event, **TPC:** treatment of physician's choice.

The median duration of treatment with KEYTRUDA + LENVIMA was more than double that of treatment of physician's choice (TPC; doxorubicin or paclitaxel), which may account for the difference in the occurrence of AEs between the two treatment arms.[1]

Time-to-first-onset of selected common AEs

During treatment with LENVIMA, AEs may occur within days of treatment initiation.[2]

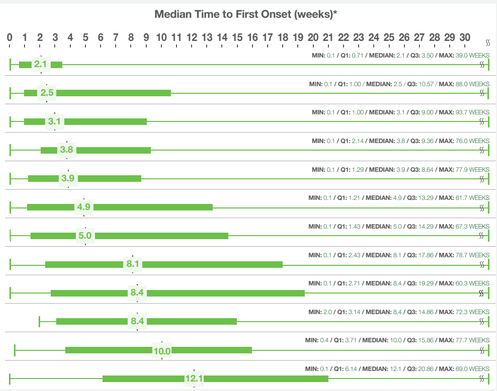
The median time-to-first-onset of selected common AEs occurred within the first 3 months of treatment initiation.[2]

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

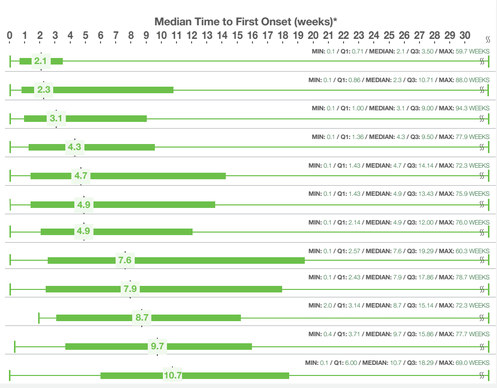
AEs were chosen regardless of causality and based on frequency of occurrence; and those leading to dose reductions, interruptions, or discontinuation of study treatment.[2]

Median times-to-first-onset of selected common AEs from KEYNOTE-775/Study 309[2]

pMMR Population (n=342) ADVERSE EVENTS	Incidence† n	Incidence† %	LENVIMA® Dose Interruption‡	LENVIMA® Dose Reduction‡	LENVIMA® Discontinuation‡	KEYTRUDA® Dose Interruption‡	KEYTRUDA® Discontinuation‡
Hypertension	228	66.7%	12.3%	17.5%	2.0%	3.5%	0%
Fatigue	198	57.9%	6.1%	13.2%	2.0%	4.7%	0.3%
Musculoskeletal disorders	181	52.9%	4.1%	5.6%	0.6%	3.5%	0.3%
Proteinuria	100	29.2%	6.7%	7.0%	1.2%	2.3%	0%
Stomatitis	120	35.1%	1.8%	4.1%	0.3%	0.3%	0%
Decreased appetite	152	44.4%	5.0%	6.1%	1.5%	2.3%	0.9%
Nausea	169	49.4%	3.5%	4.4%	0.6%	1.5%	0%
Diarrhoea	188	55.0%	11.1%	11.7%	1.2%	8.2%	0.9%
Vomiting	125	36.5%	5.0%	2.3%	1.2%	1.8%	0%
Hypothyroidism	229	67.0%	2.0%	0.9%	0%	1.8%	0.3%
PPES	77	22.5%	2.0%	8.8%	0.6%	2.0%	0%
Weight decreased	117	34.2%	2.6%	5.0%	0.9%	1.5%	0.3%



All-Comer Population (n=406) ADVERSE EVENTS	Incidence† n	Incidence† %	LENVIMA® Dose Interruption‡	LENVIMA® Dose Reduction‡	LENVIMA® Discontinuation‡	KEYTRUDA® Dose Interruption‡	KEYTRUDA® Discontinuation‡
Hypertension	264	65.0%	11.8%	17.7%	2.0%	3.4%	0%
Fatigue	238	58.6%	6.4%	11.8%	2.0%	4.2%	0.2%
Musculoskeletal disorders	213	52.5%	3.4%	4.9%	0.7%	3.4%	0.2%
Stomatitis	144	35.5%	2.2%	4.2%	0.5%	0.5%	0.2%
Nausea	201	49.5%	3.4%	4.9%	0.5%	1.7%	0%
Decreased appetite	183	45.1%	4.9%	6.2%	1.7%	2.2%	0.7%
Proteinuria	120	29.6%	6.2%	7.9%	1.2%	2.0%	0%
Vomiting	149	36.7%	5.4%	3.2%	1.0%	1.7%	0%
Diarrhoea	221	54.4%	10.8%	11.3%	1.2%	8.1%	1.0%
Hypothyroidism	279	68.7%	2.2%	0.7%	0%	1.7%	0.2%
PPES	89	21.9%	1.7%	8.1%	0.5%	1.7%	0%
Weight decreased	138	34.0%	2.5%	5.4%	1.5%	1.5%	0.2%



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

*Median time-to-first-onset patients who experienced the AE.[2]
†All grades.[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.

Definitions of grades 1 to 5 of selected common AEs* from KEYNOTE-775/ Study 309

Grading of AE severity is based on Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. The severity of some AEs, such as fatigue and diarrhoea, is based on how much the AE limits activities of daily living (ADL), which are divided into two classes: instrumental ADLs and self-care ADLs.[3]

Instrumental ADLs

- Preparing meals
- Shopping for groceries/clothes
- Using the telephone
- Managing money

Self-care ADLs

- Bathing
- Dressing and undressing
- Feeding oneself
- Using the toilet
- Taking medications

*AEs were chosen regardless of causality and based on frequency of occurrence; and those leading to dose reductions, interruptions, or discontinuation of study treatment.[2]

ADLs: activities of daily living, **AE:** adverse event.

CTCAE grades of severity of selected common AEs from KEYNOTE-775/Study 309*[3]

	Grade of severity				
	1	2	3	4	5
Hypertension (adults)	SBP 120 to 139 mmHg or DBP 80 to 89 mmHg	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 initiated	SBP ≥160 mmHg or DBP ≥100 mmHg. Medical intervention indicated. More than one drug or more intensive therapy than previously used indicated	Life-threatening consequences (e.g. malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis) Urgent intervention indicated	Death
Musculoskeletal disorders (arthralgia)	Mild pain	Moderate pain Limiting instrumental ADL	Severe pain Limiting self-care ADL	-	-
Proteinuria	1+ proteinuria Urinary protein ≥ULN to <1.0 g/24 hours	2+ and 3+ proteinuria. Urinary protein 1.0 to <3.5 g/24 hours	4+ proteinuria. Urinary protein ≥3.5 g/24 hours	-	-
Fatigue	Fatigue relieved by rest	Fatigue not relieved by rest. Limiting instrumental ADL	Fatigue not relieved by rest. Limiting self-care ADL	-	-
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake. Tube feeding, TPN or hospitalisation indicated	-	-
Diarrhoea	Increase of <4 stools/day over baseline. Mild increase in ostomy output compared with baseline	Increase of 4 to 6 stools/day over baseline. Moderate increase in ostomy output compared with baseline. Limiting instrumental ADL	Increase of ≥7 stools/day over baseline. Hospitalisation indicated. Severe increase in ostomy output compared with baseline. Limiting self-care ADL	Life-threatening consequences Urgent intervention indicated	Death

*AEs were chosen regardless of causality and based on frequency of occurrence; and those leading to dose reductions, interruptions, or discontinuation of study treatment.[2]

ADL: activities of daily living, **AE:** adverse event, **CTCAE:** Common Terminology Criteria for Adverse Events, **DBP:** diastolic blood pressure, **SBP:** systolic blood pressure, **TPN:** total parenteral nutrition, **ULN:** upper limit of normal, **WNL:** within normal limits.

CTCAE grades of severity of selected common AEs from KEYNOTE-775/Study 309*[3]

	Grade of severity				
	1	2	3	4	5
Anorexia	Loss of appetite without alteration in eating habits	Oral intake altered without significant weight loss or malnutrition. Oral nutritional supplements indicated	Associated with significant weight loss or malnutrition (e.g. inadequate oral caloric and/or fluid intake). Tube feeding or TPN indicated	Life-threatening consequences Urgent intervention indicated	Death
Stomatitis (oral mucositis)	Asymptomatic or mild symptoms Intervention not indicated	Moderate pain or ulcer that does not interfere with oral intake. Modified diet indicated	Severe pain. Interfering with oral intake	Life-threatening consequences Urgent intervention indicated	Death
Vomiting	Intervention not indicated	Outpatient intravenous hydration Medical intervention indicated	Tube feeding, TPN or hospitalisation indicated	Life-threatening consequences	Death
Hypothyroidism	Asymptomatic. Clinical or diagnostic observations only. Intervention not indicated	Symptomatic. Thyroid replacement indicated. Limiting instrumental ADL	Severe symptoms. Limiting self-care ADL. Hospitalisation indicated	Life-threatening consequences Urgent intervention indicated	Death
PPES	Minimal skin changes or dermatitis (e.g. erythema, oedema or hyperkeratosis) without pain	Skin changes (e.g. peeling, blisters, bleeding, fissures, oedema or hyperkeratosis) with pain. Limiting instrumental ADL	Severe skin changes (e.g. peeling, blisters, bleeding, fissures, oedema or hyperkeratosis) with pain Limiting self-care ADL	-	-
Weight decreased	5 to <10% from baseline. Intervention not indicated	10 to <20% from baseline Nutritional support indicated	≥20% from baseline. Tube feeding or TPN indicated	-	-

*AEs were chosen regardless of causality and based on frequency of occurrence; and those leading to dose reductions, interruptions, or discontinuation of study treatment.[2]

ADL: activities of daily living, **AE:** adverse event, **CTCAE:** Common Terminology Criteria for Adverse Events, **PPES:** palmar–plantar erythrodysaesthesia syndrome, **TPN:** total parenteral nutrition.

Managing common AEs[4]

General management guidelines

Intended to illustrate the general principles of AE management with LENVIMA. Specific AEs may require alternative management strategies - consult the flow charts on the following pages and the SmPC for detailed guidance.

The following pages provide advice on when to continue or interrupt LENVIMA treatment, based on AE severity. 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

INTERRUPT and

REDUCE the dose for severe (e.g., Grade 3) or intolerable AEs

DISCONTINUE LENVIMA in case of life-threatening reactions (e.g., Grade 4)

However, initiate optimal medical management for the AE first.

When considering whether to interrupt treatment, assess the risk-benefit ratio.[5] Dose interruptions should be avoided unless necessary.[5]

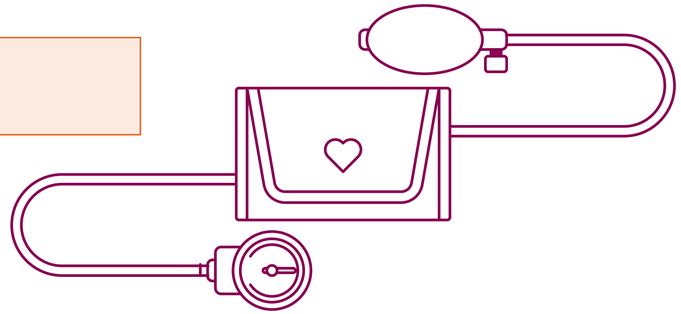
Grade 1 or 2 AEs generally do not warrant interruption of LENVIMA unless intolerable to the patient despite optimal management. Intolerable grade 1 or 2 AEs require interruption of LENVIMA until resolved to Grade 0/1 or baseline.[4]

Management strategies may involve patient education, HCP training and use of concomitant medications.[2]

*As part of combination treatment with KEYTRUDA. For guidance on how long to continue treatment with KEYTRUDA, please refer to the KEYTRUDA Summary of Product Characteristics (SmPC).

AE: adverse event.

GRADE 1	GRADE 2	GRADE 3	GRADE 4
SBP 120 to 139 mmHg or DBP 80 to 89 mmHg[3]	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 initiated[3]	SBP ≥160 mmHg or DBP ≥100 mmHg. Medical intervention indicated. More than one drug or more intensive therapy than previously used indicated[3]	Life-threatening consequences (e.g. malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis). Urgent intervention indicated[3]
→	→	⏸	✕
CONTINUE LENVIMA **NO ACTION**[4]	**CONTINUE** LENVIMA and initiate antihypertensive therapy (if not already receiving) **or CONTINUE** LENVIMA and increase the dose of the current antihypertensive therapy / initiate additional antihypertensive therapy[4]	**INTERRUPT** LENVIMA until SBP ≤150 mmHg, DBP ≤95 mmHg and patient is on a stable dose of antihypertensive therapy for ≥48 hours[4]	**URGENT** intervention required. Discontinue LENVIMA and provide appropriate medical management[4]
		↓	
		REDUCE Resume LENVIMA at a reduced dose[4]	



In KEYNOTE-775/Study 309, in patients with hypertension, 81.6% (n=186/228) in the pMMR population and 81.8% (n=216/264) in the all-comer population received at least one medication for hypertension.[2]

DBP: diastolic blood pressure, **pMMR:** mismatch repair-proficient,
SBP: systolic blood pressure, **WNL:** within normal limits.

	GRADE 1	GRADE 2	GRADE 3	GRADE 4
	Mild pain[3]	Moderate pain Limiting instrumental ADL[3]	Severe pain Limiting self-care ADL[3]	–
TOLERABLE	**CONTINUE** LENVIMA (if tolerable)[4]	**CONTINUE** LENVIMA (if tolerable)[4]	**INTERRUPT** LENVIMA until resolved to Grade 0/1 or baseline[4]	**DISCONTINUE** LENVIMA in case of life-threatening reactions[4]
INTOLERABLE	**INTERRUPT** LENVIMA (if intolerable despite optimal management) until resolved to Grade 0/1 or baseline[4]	**INTERRUPT** LENVIMA (if persistent and intolerable) until resolved to Grade 0/1 or baseline[4]		

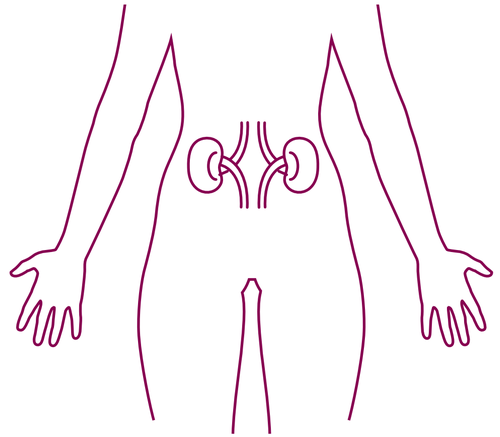
REDUCE
Resume LENVIMA at a reduced dose[4]

In KEYNOTE-775/Study 309, in patients with musculoskeletal disorders, 58.0% (n=105/181) in the pMMR population and 58.7% (n=125/213) in the all-comer population received at least one medication for musculoskeletal disorders.[2]

Consider managing patients with appropriate analgesics.[2]

ADL: activities of daily living, **pMMR:** mismatch repair-proficient.

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 **NO ACTION**[4]	**INTERRUPT** LENVIMA until resolved to <2 g/24 hours[4]		**DISCONTINUE** LENVIMA and do not resume[4]
	↓		
	REDUCE Resume LENVIMA at a reduced dose[4]		



In KEYNOTE-775/Study 309, in patients with proteinuria, 5.0% (n=5/100) in the pMMR population and 4.2% (n=5/120) in the all-comer population received at least one medication for proteinuria.[2]

Manage patients with renal dysfunction caused by diabetes or hypertension carefully.[6]

ULN: upper limit of normal, **pMMR:** mismatch repair-proficient.

	GRADE 1	GRADE 2	GRADE 3	GRADE 4
	Fatigue relieved by rest[3]	Fatigue not relieved by rest Limiting instrumental ADL[3]	Fatigue not relieved by rest Limiting self-care ADL[3]	–
TOLERABLE	**CONTINUE** LENVIMA (if tolerable)[4]	**CONTINUE** LENVIMA (if tolerable)[4]	**INTERRUPT** LENVIMA until resolved to Grade 0/1 or baseline[4]	**DISCONTINUE** LENVIMA in case of life-threatening reactions[4]
INTOLERABLE	**INTERRUPT** LENVIMA (if intolerable despite optimal management) until resolved to Grade 0/1 or baseline[4]	**INTERRUPT** LENVIMA (if persistent and intolerable) until resolved to Grade 0/1 or baseline[4]		
	REDUCE Resume LENVIMA at a reduced dose[4]			

In KEYNOTE-775/Study 309, in patients with fatigue, 5.1% (n=10/198) in the pMMR population and 5.0% (n=12/238) in the all-comer population received at least one medication for fatigue.[2]

For symptomatic treatment of fatigue in addition to dose modification, consider educating the patient on coping strategies and good sleep hygiene, light exercise if possible and a nutritious diet with proper hydration.[7]

ADL: activities of daily living, **pMMR:** mismatch repair-proficient.

Hypertension | Musculoskeletal disorders (arthralgia) | Proteinuria | Fatigue | **Nausea** | Vomiting | Diarrhoea | Decreased appetite (anorexia) | Weight Loss | Stomatitis (oral mucositis) | Hypothyroidism | PPES

GRADE 1	GRADE 2	GRADE 3	GRADE 4
Loss of appetite without alteration in eating habits[3]	Oral intake decreased without significant weight loss, dehydration or malnutrition[3]	Inadequate oral caloric or fluid intake. Tube feeding, TPN or hospitalisation indicated[3]	–

TOLERABLE

CONTINUE LENVIMA (if tolerable)[4]
MANAGE nausea with antiemetics as required[7]
ADVISE patient about dietary modifications to manage GI toxicities, such as:
- Avoiding sweet and greasy foods[8]
- Avoiding caffeine, alcohol and nicotine[9]
- Consuming simple foods (e.g. rice, noodles, skinless chicken and turkey)[9]

INTOLERABLE

INTERRUPT LENVIMA (if intolerable despite optimal management) until resolved to Grade 0/1 or baseline[4]

INTERRUPT LENVIMA (if persistent and intolerable) until resolved to Grade 0/1 or baseline[4]

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

DISCONTINUE
LENVIMA in case of life-threatening reactions[4]

REDUCE
Resume LENVIMA at a reduced dose[4]

In KEYNOTE-775/Study 309, in patients with nausea, 65.7% (n=111/169) in the pMMR population and 65.2% (n=131/201) in the all-comer population received at least one medication for nausea.[2]

GI: gastrointestinal, **pMMR:** mismatch repair-proficient,
TPN: total parenteral nutrition.

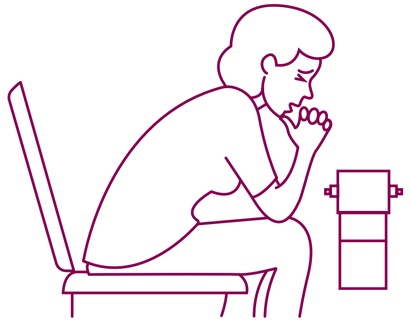
GRADE 1	GRADE 2	GRADE 3	GRADE 4
Intervention not indicated[3]	Outpatient intravenous hydration Medical intervention indicated[3]	Tube feeding, TPN or hospitalisation indicated[3]	Life-threatening consequences[3]
→	→	⏸	✕
TOLERABLE **CONTINUE** LENVIMA (if tolerable)[4] **MANAGE** vomiting with antiemetics as required[7] **ADVISE** patient about dietary modifications to manage GI toxicities, such as: • Avoiding sweet and greasy foods[8] • Avoiding caffeine, alcohol and nicotine[9] • Consuming simple foods (e.g. rice, noodles, skinless chicken and turkey)[9]	**TOLERABLE** **CONTINUE** LENVIMA (if tolerable)[4] **MANAGE** vomiting with antiemetics as required[7] **ADVISE** patient about dietary modifications to manage GI toxicities, such as: • Avoiding sweet and greasy foods[8] • Avoiding caffeine, alcohol and nicotine[9] • Consuming simple foods (e.g. rice, noodles, skinless chicken and turkey)[9]	**INTERRUPT** LENVIMA until resolved to Grade 0/1 or baseline[4]	**DISCONTINUE** LENVIMA[4]
⏸	⏸		
INTOLERABLE **INTERRUPT** LENVIMA (if intolerable despite optimal management) until resolved to Grade 0/1 or baseline[4]	**INTOLERABLE** **INTERRUPT** LENVIMA (if persistent and intolerable) until resolved to Grade 0/1 or baseline[4]		
↓	↓		

REDUCE
Resume LENVIMA at a reduced dose[4]

In KEYNOTE-775/Study 309, in patients experiencing vomiting, 36.0% (n=45/125) in the pMMR population and 34.9% (n=52/149) in the all-comer population received at least one medication for vomiting.[2]

GI: gastrointestinal, **pMMR:** mismatch repair-proficient,
TPN: total parenteral nutrition.

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]
→	→	⏸	✕
TOLERABLE **CONTINUE** LENVIMA (if tolerable)[4] • Prior to reducing or interrupting the dose, provide prompt management to prevent dehydration[4] • Ensure patients understand the importance of reporting diarrhoea as an AE so that it can be appropriately managed	**TOLERABLE** **CONTINUE** LENVIMA (if tolerable)[4] • Prior to reducing or interrupting the dose, provide prompt management to prevent dehydration[4] • Ensure patients understand the importance of reporting diarrhoea as an AE so that it can be appropriately managed	**INTERRUPT** LENVIMA until resolved to Grade 0/1 or baseline[4]	If Grade 4 for >48 hours, increase fluid intake to avoid dehydration and consider hospital admission[10] **DISCONTINUE** LENVIMA in the event of persistent Grade 4 diarrhoea (despite medical management)[4] **DO NOT RESUME** LENVIMA[4]
⏸	⏸		
INTOLERABLE **INTERRUPT** LENVIMA (if intolerable despite optimal management) until resolved to Grade 0/1 or baseline[4]	**INTOLERABLE** **INTERRUPT** LENVIMA (if persistent and intolerable) until resolved to Grade 0/1 or baseline[4]		
↓	↓	↓	
REDUCE Resume LENVIMA at a reduced dose[4]			

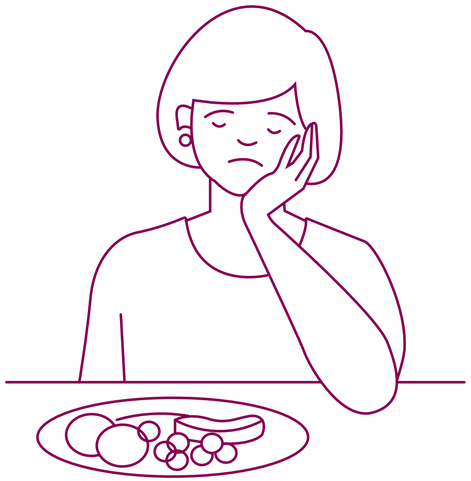


In KEYNOTE-775/Study 309, in patients with diarrhoea, 64.4% (n=121/188) in the pMMR population and 63.8% (n=141/221) in the all-comer population received at least one medication for diarrhoea.[2]

ADL: activities of daily living, **AE:** adverse event, **pMMR:** mismatch repair-proficient.

	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 (e.g. inadequate oral caloric and/or fluid intake). Tube feeding or TPN indicated[3]	Life-threatening consequences. Urgent intervention indicated[3]
TOLERABLE	**CONTINUE** LENVIMA (if tolerable)[4]	**CONTINUE** LENVIMA (if tolerable)[4]	**INTERRUPT** LENVIMA until resolved to Grade 0/1 or baseline[4]	**DISCONTINUE** LENVIMA[4]
INTOLERABLE	**INTERRUPT** LENVIMA (if intolerable despite optimal management) until resolved to Grade 0/1 or baseline[4]	**INTERRUPT** LENVIMA (if persistent and intolerable) until resolved to Grade 0/1 or baseline[4]		

REDUCE
Resume LENVIMA at a reduced dose[4]

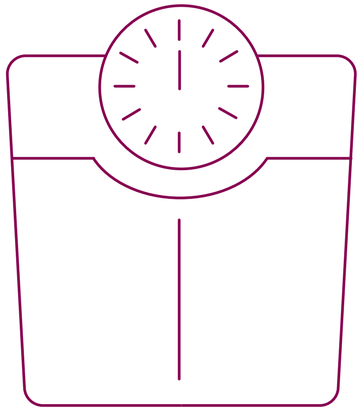


In KEYNOTE-775/Study 309, in patients with decreased appetite, 23.7% (n=36/152) in the pMMR population and 23.0% (n=42/183) in the all-comer population received at least one medication for decreased appetite.[2]

pMMR: mismatch repair-proficient, **TPN:** total parenteral nutrition.

	GRADE 1	GRADE 2	GRADE 3	GRADE 4
	5 to <10% from baseline. Intervention not indicated[3]	10 to <20% from baseline. Nutritional support indicated[3]	≥20% from baseline. Tube feeding or TPN indicated[3]	–
TOLERABLE	**CONTINUE** LENVIMA (if tolerable)[4]	**CONTINUE** LENVIMA (if tolerable)[4]	**INTERRUPT** LENVIMA until resolved to Grade 0/1 or baseline[4]	**DISCONTINUE** LENVIMA in case of life-threatening reactions[4]
INTOLERABLE	**INTERRUPT** LENVIMA (if intolerable despite optimal management) until resolved to Grade 0/1 or baseline[4]	**INTERRUPT** LENVIMA (if persistent and intolerable) until resolved to Grade 0/1 or baseline[4]		

REDUCE
Resume LENVIMA at a reduced dose[4]



In KEYNOTE-775/Study 309, in patients with weight loss, 10.3% (n=12/117) in the pMMR population and 12.3% (n=17/138) in the all-comer population received at least one medication for weight loss.[2]

pMMR: mismatch repair-proficient, **TPN:** total parenteral nutrition.

Hypertension | Musculoskeletal disorders (arthralgia) | Proteinuria | Fatigue | Nausea | Vomiting | Diarrhoea | Decreased appetite (anorexia) | Weight Loss | **Stomatitis (oral mucositis)** | Hypothyroidism | PPES

GRADE 1	GRADE 2	GRADE 3	GRADE 4
Asymptomatic or mild symptoms. Intervention not indicated[3]	Moderate pain or ulcer that does not interfere with oral intake. Modified diet indicated[3]	Severe pain. Interfering with oral intake[3]	Life-threatening consequences. Urgent intervention indicated[3]
TOLERABLE → **CONTINUE** LENVIMA (if tolerable)[4]	TOLERABLE → **CONTINUE** LENVIMA (if tolerable)[4]	**INTERRUPT** LENVIMA until resolved to Grade 0/1 or baseline[4]	**DISCONTINUE** LENVIMA[4]
INTOLERABLE → **INTERRUPT** LENVIMA (if intolerable despite optimal management) until resolved to Grade 0/1 or baseline[4]	INTOLERABLE → **INTERRUPT** LENVIMA (if persistent and intolerable) until resolved to Grade 0/1 or baseline[4]		

REDUCE
Resume LENVIMA at a reduced dose[4]

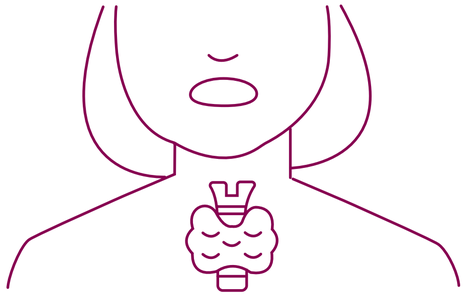
In KEYNOTE-775/Study 309, in patients with stomatitis, 63.3% (n=76/120) in the pMMR population and 63.2% (n=91/144) in the all-comer population received at least one medication for stomatitis.[2]

Consider prescribing common stomatological preparations.[11]

pMMR: mismatch repair-proficient.

	GRADE 1	GRADE 2	GRADE 3	GRADE 4
	Asymptomatic. Clinical or diagnostic observations only. Intervention not indicated[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]
TOLERABLE	**CONTINUE** LENVIMA[4]	**CONTINUE** LENVIMA (if tolerable)[4]	**INTERRUPT** LENVIMA until resolved to Grade 0/1 or baseline[4]	**DISCONTINUE** LENVIMA[4]
INTOLERABLE		**INTERRUPT** LENVIMA (if persistent and intolerable) until resolved to Grade 0/1 or baseline[4]		

REDUCE
Resume LENVIMA at a reduced dose[4]



In KEYNOTE-775/Study 309, in patients with hypothyroidism, 78.6% (n=180/229) in the pMMR population and 77.4% (n=216/279) in the all-comer population received at least one medication for hypothyroidism.[2]

If any abnormality is found, consult an endocrinologist.[12] Adjust thyroid hormone administration to reach TSH levels appropriate to the patient's therapeutic target.[4] If thyroid replacement is initiated, hypothyroidism (including Grade 4) may not require LENVIMA dose reduction or discontinuation.[2]

ADL: activities of daily living, **pMMR:** mismatch repair-proficient,
TSH: thyroid-stimulating hormone.

PPES

GRADE 1	GRADE 2	GRADE 3	GRADE 4
Minimal skin changes or dermatitis (e.g. erythema, oedema or hyperkeratosis) without pain[3]	Skin changes (e.g. peeling, blisters, bleeding, fissures, oedema or hyperkeratosis) with pain. Limiting instrumental ADL[3]	Severe skin changes (e.g. peeling, blisters, bleeding, fissures, oedema or hyperkeratosis) with pain. Limiting self-care ADL[3]	–

TOLERABLE

CONTINUE LENVIMA (if tolerable)[4]

Use moisturising cream, and consider hydrocolloid dressing for the feet[7,13]

Advise the patient on how to minimise symptoms, such as avoiding sources of heat (e.g. sitting in the sun), wear loose-fitting clothing, and gently applying skin care creams to keep their hands and feet moist[13]

INTOLERABLE

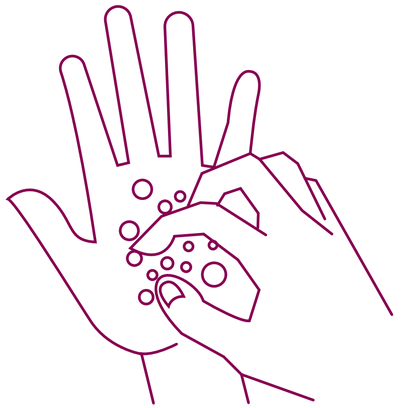
INTERRUPT LENVIMA (if intolerable despite optimal management) until resolved to Grade 0/1 or baseline[4]

INTERRUPT LENVIMA (if persistent and intolerable) until resolved to Grade 0/1 or baseline[4]

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

DISCONTINUE
LENVIMA in case of life-threatening reactions[4]

REDUCE
Resume LENVIMA at a reduced dose[4]



In KEYNOTE-775/Study 309, in patients with PPES, 68.8% (n=53/77) in the pMMR population and 69.7% (n=62/89) in the all-comer population received at least one medication for PPES.[2]

ADL: activities of daily living, **pMMR:** mismatch repair-proficient,
PPES: palmar–plantar erythrodysaesthesia syndrome.

KEYTRUDA® (pembrolizumab)

LENVIMA® (lenvatinib)

i PI GB PI NI PI

Your guide to recognising and managing adver

KEYTRUDA® (pembrolizumab) in combination with LENVIMA® (lenva
with advanced or recurrent endometrial carcinoma (EC) who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and are not candidates for curative surgery or radiation.[1]

Adverse events should be reported. Reporting forms and information can be found at https://yellowcard.mhra.gov.uk/ (please note that the MHRA Yellow Card link will redirect you to an external website, for which MSD does not review or control the content) or search for MHRA Yellow Card in the Google Play or Apple App Store, or Republic of Ireland: www.hpra.ie. Adverse events should also be reported to Eisai Ltd on +44 (0)208 600 1400 or EUmedinfo@eisai.net or Merck Sharp & Dohme (UK) Limited (Tel: 020 8154 8000).

Refer to the LENVIMA® Prescribing Information and/or Summary of Product Characteristics (SmPC) for further details.

LENVIMA® and KEYTRUDA® GB and NI Prescribing Information (PI) can be accessed via the mulberry and green 'PI' buttons respectively in the top-right corner of this document throughout.

This content is intended to be viewed online, it is not intended to be printed.

GB-KLE-00159 December 2023

MSD Eisai

Reference

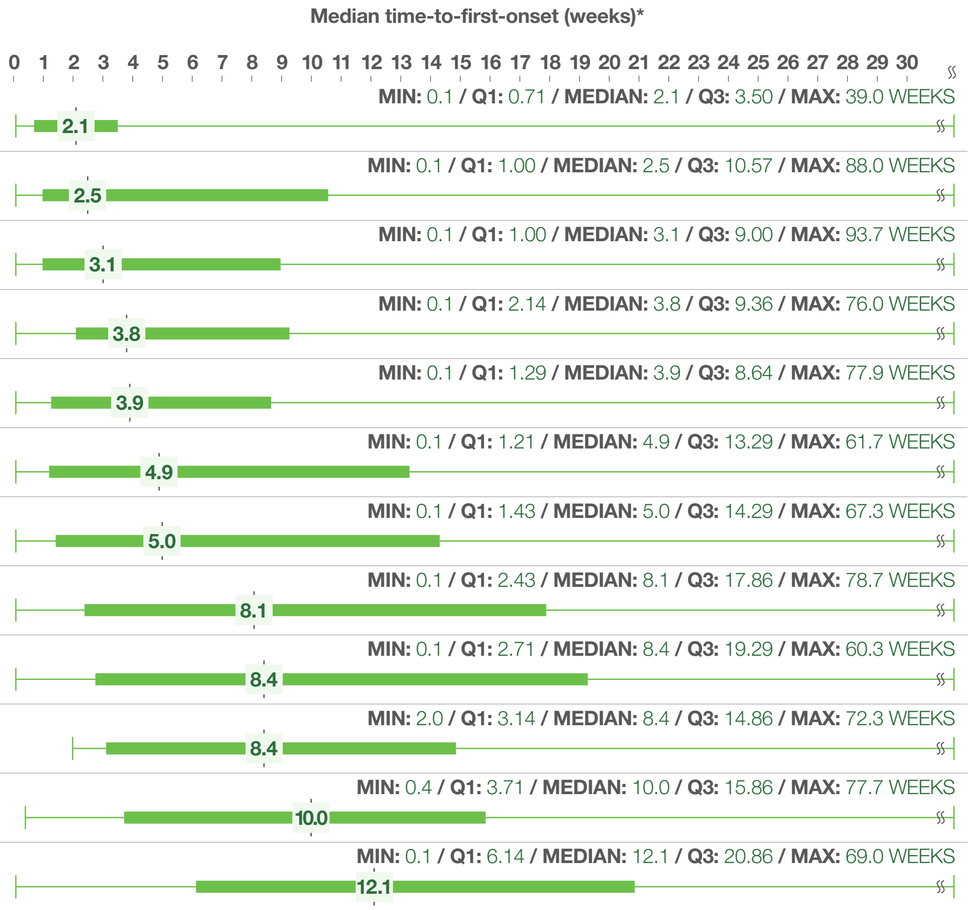
1. LENVIMA (lenvatinib) Summary of Product Characteristics.

Median times-to-first-onset of selected common AEs from KEYNOTE-775/Study 309[2]

pMMR Population (n=342) AEs

	Incidence†		LENVIMA® Dose Interruption‡	LENVIMA® Dose Reduction‡	LENVIMA® Discontinuation‡	KEYTRUDA® Dose Interruption‡	KEYTRUDA® Discontinuation‡
	n	%					
Hypertension	228	66.7	12.3%	17.5%	2.0%	3.5%	0%
Fatigue	198	57.9	6.1%	13.2%	2.0%	4.7%	0.3%
Musculoskeletal disorders	181	52.9	4.1%	5.6%	0.6%	3.5%	0.3%
Proteinuria	100	29.2	6.7%	7.0%	1.2%	2.3%	0%
Stomatitis	120	35.1	1.8%	4.1%	0.3%	0.3%	0%
Decreased appetite	152	44.4	5.0%	6.1%	1.5%	2.3%	0.9%
Nausea	169	49.4	3.5%	4.4%	0.6%	1.5%	0%
Diarrhoea	188	55.0	11.1%	11.7%	1.2%	8.2%	0.9%
Vomiting	125	36.5	5.0%	2.3%	1.2%	1.8%	0%
Hypothyroidism	229	67.0	2.0%	0.9%	0%	1.8%	0.3%
PPES	77	22.5	2.0%	8.8%	0.6%	2.0%	0%
Weight decreased	117	34.2	2.6%	5.0%	0.9%	1.5%	0.3%

All-Comer Population (n=406) AEs



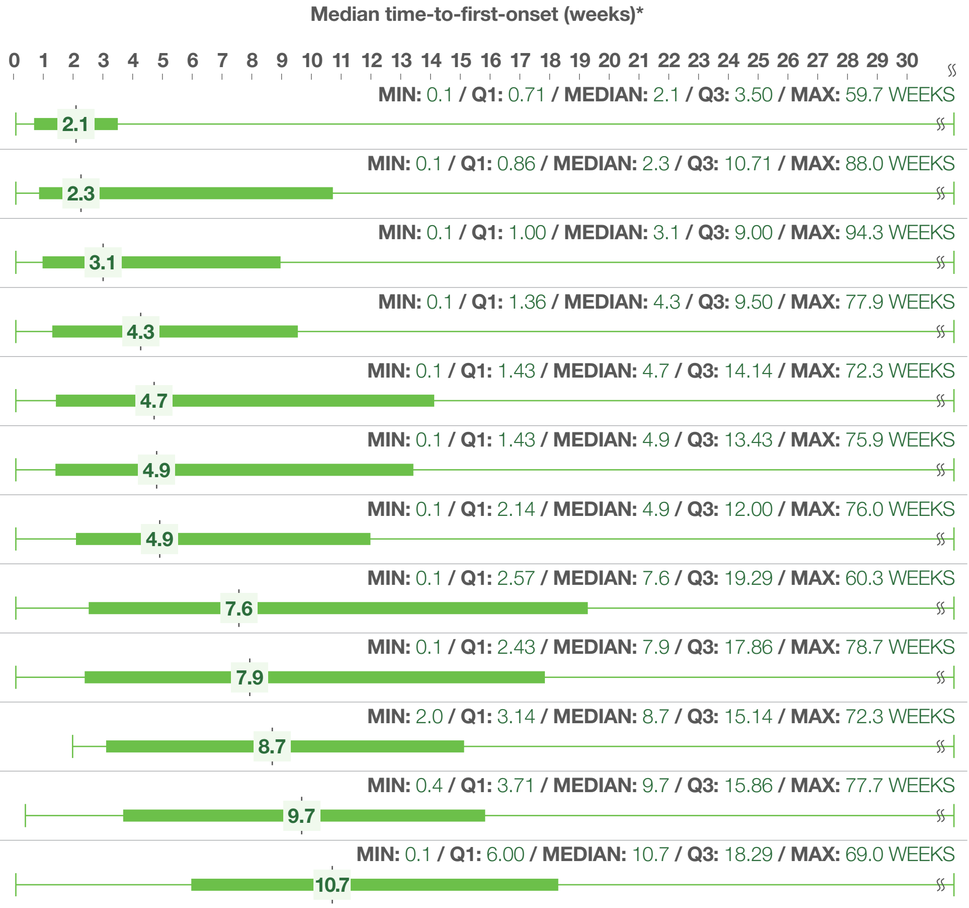
Adapted from Colombo N *et al*. *Oncologist* 2023.[2]

Median times-to-first-onset of selected common AEs from KEYNOTE-775/Study 309[2]

All-Comer Population (n=406) AEs

	Incidence†		LENVIMA® Dose Interruption‡	LENVIMA® Dose Reduction‡	LENVIMA® Discontinuation‡	KEYTRUDA® Dose Interruption‡	KEYTRUDA® Discontinuation‡
	n	%					
Hypertension	264	65.0	11.8%	17.7%	2.0%	3.4%	0%
Fatigue	238	58.6	6.4%	11.8%	2.0%	4.2%	0.2%
Musculoskeletal disorders	213	52.5	3.4%	4.9%	0.7%	3.4%	0.2%
Stomatitis	144	35.5	2.2%	4.2%	0.5%	0.5%	0.2%
Nausea	201	49.5	3.4%	4.9%	0.5%	1.7%	0%
Decreased appetite	183	45.1	4.9%	6.2%	1.7%	2.2%	0.7%
Proteinuria	120	29.6	6.2%	7.9%	1.2%	2.0%	0%
Vomiting	149	36.7	5.4%	3.2%	1.0%	1.7%	0%
Diarrhoea	221	54.4	10.8%	11.3%	1.2%	8.1%	1.0%
Hypothyroidism	279	68.7	2.2%	0.7%	0%	1.7%	0.2%
PPES	89	21.9	1.7%	8.1%	0.5%	1.7%	0%
Weight decreased	138	34.0	2.5%	5.4%	1.5%	1.5%	0.2%

pMMR Population (n=342) AEs



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

Introduction

The AEs of LENVIMA are generally manageable.[1] T
the course of LENVIMA treatment.[2] Engagement w
is important for the management of AEs. Equally i
and caregivers informed, and maintaining a share

This guide will help you to address common LENVIMA-induced AEs a
allowing patients to get the most out of the treatment. It was develop
supplemented with additional guidelines and recommendations for m

The advice in this section is divided into two major parts:

1 **Recognising** common AEs >

2 **Managing** common AEs >

For guidance on how to manage AEs related to KEYTRUDA, please refe
For further guidance on how to manage AEs related to LENVIMA, pleas

AE: adverse event, **SmPC:** Summary of Product Characteristics.

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