Focus On

KEYTRUDA (pembrolizumab) + LENVATINIB Eisai* TREATMENT OPTIMISATION

for your untreated patients with advanced RCC (aRCC) (focus on the CLEAR trial)

Start >

Prescribing Information for KEYTRUDA and LENVATINIB can be accessed via the 'PI' buttons at the top of this page and throughout

This document is not exhaustive and is not meant to replace the SmPC. Please consult the individual product Summary of Product Characteristics (SmPCs) before making any prescribing decisions.

*LENVATINIB Eisai will be referred to as LENVATINIB across this document.

KEYTRUDA in combination with LENVATINIB is indicated for the first-line (1L) treatment of adults with aRCC.[1,2]

This material has been developed and funded by Merck Sharp & Dohme and Eisai Ltd, and is intended for UK healthcare professionals only.

Adverse events should be reported. Reporting forms and information can be found at https://yellowcard.mhra.gov.uk/ or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to MSD (Tel: 0208 154 8000; E-mail: pv.uk@msd.com).

KEYTRUDA® (pembrolizumab) LENVATINIB Eisai

MSD Eisai

Please request from MSD representative the patient-targeted Risk Minimisation Materials before prescribing KEYTRUDA to minimise the risk of treatment. Patients should also receive the Risk Minimisation Materials.

1L, first-line; aRCC, advanced renal cell carcinoma; RCC, renal cell carcinoma; PI, prescribing information.

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This guide will help you to monitor and manage some key AEs that could emerge or worsen during KEYTRUDA + LENVATINIB treatment of 1L aRCC, as reported in the CLEAR trial. Addressing any AEs as early and effectively as possible could allow patients to get more out of their treatment.

Prepare · Monitor · Manage

PREPARE

your patients for treatment with KEYTRUDA + LENVATINIB

View Dosing Guide

MONITOR

your patients on the combination therapy

MANAGE

some clinically significant TEAEs for KEYTRUDA + LENVATINIB as reported in the CLEAR trial[1–3]

Go to the KEYTRUDA TEAE Management Section

Go to the LENVATINIB TEAE Management Section

AE, adverse event; aRCC, advanced renal cell carcinoma; SmPC, Summary of Product Characteristics; TEAE, treatment-emergent adverse event.

PREPARE your patients for initiating treatment

This section includes:

- How to prepare your patients for initiating treatment
- KEYTRUDA + LENVATINIB dosing and administration guide for 1L aRCC
- Some key AEs to be aware of with KEYTRUDA + LENVATINIB based on results from the CLEAR trial

1L, first-line; AE, adverse event; aRCC, advanced renal cell carcinoma; SmPC, Summary of Product Characteristics.

PREPARE Important considerations before initiating treatment[1,2]

Blood pressure (BP) check

BP should be well controlled prior to treatment with **KEYTRUDA + LENVATINIB**[2]

If a patient is known to be hypertensive, they should be on a stable dose of antihypertensive therapy for at least 1 week prior to treatment with **KEYTRUDA + LENVATINIB**[2]

Blood tests

Autoimmune disorders

Check for preexisting autoimmune disorders*[3]

Check blood glucose for signs of undiagnosed diabetes[3]

Thyroid function

Measure baseline thyroid function prior to treatment initiation, then periodically during treatment[2]

Hypothyroidism has been reported in patients treated with **KEYTRUDA + LENVATINIB**; therefore, thyroid function and hormone levels should be monitored[1,2]

Liver function

Monitor liver function prior to treatment initiation, then every 2 weeks after treatment initiation for the first 2 months and monthly thereafter during treatment[1,2]

KEYTRUDA has not been studied in patients with severe hepatic impairment*[1]

No dose adjustment for **KEYTRUDA** is needed for patients with mild or moderate hepatic impairment[1]

The **KEYTRUDA + LENVATINIB** combination should only be used in patients with severe hepatic impairment if the anticipated benefit exceeds the risk[1,2]

In patients with severe hepatic impairment (Child-Pugh C), the starting dose of **LENVATINIB** must be adjusted†[2]

Renal function

For patients with severe renal impairment, the recommended starting dose of **LENVATINIB** is 10 mg once daily (OD)[2]

No dose adjustment for **KEYTRUDA** is needed for patients with mild or moderate renal impairment[1]

KEYTRUDA has not been studied in patients with severe renal impairment*[1]

Patients with end-stage renal disease have not been studied; therefore, the use of **LENVATINIB** in these patients is not recommended[2]

Calcium levels

Hypocalcaemia has been reported in patients treated with **KEYTRUDA + LENVATINIB**[1,2]

Monitor blood calcium levels at least monthly[2]

Replace calcium as necessary during treatment[2]

BP should be monitored after 1 week of treatment with LENVATINIB, then every 2 weeks for the first 2 months, and monthly thereafter.[2]

*In patients with pre-existing autoimmune disease (AID), data from observational studies suggest that the risk of immune-mediated adverse reactions following immune-checkpoint inhibitor therapy may be increased as compared with the risk in patients without pre-existing AID. In addition, flares of the underlying AID were frequent, but the majority were mild and manageable.[1]

†Please refer to the individual product SmPCs for full details on the management of patients on **KEYTRUDA** in combination with **LENVATINIB**.

AE, adverse event; BP, blood pressure; SmPC, Summary of Product Characteristics.

AE monitoring and management >

PREPARE Important considerations before initiating the combination treatment[1,2]

Proteinuria

Urine protein should be monitored regularly during treatment[2]

If urine dipstick proteinuria ≥2+ is detected, dose interruptions, adjustments or discontinuation of **LENVATINIB** may be necessary[2]

Cardiac dysfunction

Monitor patients for clinical symptoms or signs of cardiac decompensation, as dose interruptions, adjustments or discontinuation of **LENVATINIB** may be necessary[2]

Tumour lysis syndrome (TLS)

LENVATINIB can cause Tumour lysis syndrome (TLS) which can be fatal. Risk factors for TLS include but are not limited to high tumour burden, pre-existing renal impairment and dehydration. These patients should be monitored closely and treated as clinically indicated, and prophylactic hydration should be considered.[1]

Posterior reversible encephalopathy syndrome (PRES)

In patients with signs or symptoms of PRES, dose interruptions, adjustments or discontinuation of **LENVATINIB** may be necessary[2]

Arterial thromboembolic events

LENVATINIB has not been studied in patients who have had an arterial thromboembolic event within the previous 6 months, and therefore should be used with caution in such patients[2]

A treatment decision should be made based upon an assessment of the individual patient's benefit/risk. **LENVATINIB** should be discontinued following an arterial thrombotic event[2]

Haemorrhagic events

Consider the risk of severe or fatal haemorrhagic events associated with tumour invasion or infiltration of major blood vessels (e.g. the carotid artery)[2]

In the case of bleeding, dose interruptions, adjustments or discontinuation of **LENVATINIB** may be necessary[2]

AE, adverse event; PRES, posterior reversible encephalopathy syndrome; SmPC, Summary of Product Characteristics.

AE monitoring and management >

PREPARE Important considerations before initiating the combination treatment[1,2]

QT interval prolongation

Monitor electrocardiograms in patients with congenital long QT syndrome, congestive heart failure, bradyarrhythmias and those taking drugs known to prolong the QT interval, including Class Ia and III antiarrhythmics[2]

Electrolyte abnormalities should be monitored and corrected before initiating **LENVATINIB** and periodically during treatment[2]

Diarrhoea

Ensure patients understand the importance of reporting diarrhoea as an AE so that it can be managed promptly and appropriately[2]

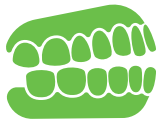
Diarrhoea has been reported frequently with **KEYTRUDA** + **LENVATINIB** and usually occurs early in the course of treatment[1,2]

Diarrhoea can be a sign of immune-mediated colitis; investigation and treatment should be considered[3]

Prompt medical management of diarrhoea should be instituted in order to prevent dehydration. Treatment should be discontinued in the event of persistence of Grade 4 diarrhoea despite medical management.

Impaired wound healing

Temporary interruption of **LENVATINIB** should be considered in patients undergoing major surgery[2]



Osteonecrosis of the jaw (ONJ)

A dental examination and appropriate preventive dentistry should be considered prior to treatment with **LENVATINIB**[2]

Invasive dental procedures are an identified risk factor for ONJ[2]

For patients who have previously received, or are receiving, intravenous bisphosphonates, invasive dental procedures should be avoided, if possible[2]

Gastrointestinal perforation and fistula formation

Gastrointestinal perforation or fistulae have been reported in patients treated with **LENVATINIB** (is a common adverse event for monotherapy and in combination). In most cases, gastrointestinal perforation and fistulae occurred in patients with risk factors such as prior surgery or radiotherapy. In the case of a gastrointestinal perforation or fistula, dose interruptions, adjustments, or discontinuation may be necessary[2]

AE, adverse event; ONJ, osteonecrosis of the jaw; SmPC, Summary of Product Characteristics.

AE monitoring and management >

PREPARE Important considerations before initiating the combination treatment[1,2]

Review concomitant medications

The use of systemic corticosteroids or immunosuppressants before starting **KEYTRUDA** should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of **KEYTRUDA***[1]

Since **KEYTRUDA** is cleared from the circulation through catabolism, no metabolic drug-drug interactions are expected[1]

Caution should be exercised when **LENVATINIB** is used either simultaneously or sequentially with antiresorptive therapy and/or other angiogenesis inhibitors because of their association with ONJ[2]

No significant drug-drug interaction is expected between **LENVATINIB** and other CYP3A/P-gp substrates[2]

It is currently unknown whether **LENVATINIB** may reduce the effectiveness of hormonal contraceptives, and therefore women of childbearing potential should avoid becoming pregnant and use highly effective contraception while on treatment with **LENVATINIB** and for at least one month after finishing treatment[2]

Provide advice on:

- Diet
- Exercise
- Home-help
- Financial support
- Mental health
- Good oral hygiene practice

Introduce and explain to the patient the multidisciplinary team that will support them

Ensure they have the contact details of key healthcare professionals

Patients treated with KEYTRUDA must be given the KEYTRUDA Patient Alert Card and be informed about the risks of KEYTRUDA before initiating therapy

*However, systemic corticosteroids or other immunosuppressants can be used after starting **KEYTRUDA** to treat immune-mediated adverse reactions. Corticosteroids may also be used as premedication when **KEYTRUDA** is used in combination with chemotherapy, as antiemetic prophylaxis, and/or to alleviate chemotherapy-related adverse reactions.[1]

AE, adverse event; CYP3A4, hepatic cytochrome P450 3A4 subtype; ONJ, osteonecrosis of the jaw; P-gp, P-glycoprotein; SmPC, Summary of Product Characteristics.

AE monitoring and management >

PREPARE The recommended starting dosage and administration for KEYTRUDA + LENVATINIB in 1L aRCC[1,2]

KEYTRUDA + LENVATINIB are administered via IV infusion and oral capsules, respectively[1,2]

The list below is not complete, please refer to the individual product SmPCs for full dosing information.

KEYTRUDA[1]

KEYTRUDA offers flexible dosing

Administered as an IV infusion

Over 30 minutes

200 mg Q3W or 400 mg Q6W

- The 200 mg Q3W (once every 3 weeks) regimen has been assessed in phase 2 and 3 registration studies across a multitude of indications of **KEYTRUDA**. An exposure-response evaluation, using modelling and simulation, led to the approval of the 400 mg Q6W (once every 6 weeks) dosing for monotherapy and combination therapy

LENVATINIB[2]

20 mg orally **OD** at the same time each day

Administered **with or without food**

Swallowed whole with water. For patients unable to swallow capsules, please refer to the SmPC for alternative methods of preparation

- **The recommended starting dose for LENVATINIB is 10 mg once daily for patients with severe renal or severe hepatic impairment.**
- Continue treatment with **LENVATINIB** for as long as there is clinical benefit or until unacceptable toxicity occurs
- For intolerable Grade 1-2 or Grade 3 AEs thought to be related to **LENVATINIB**, upon resolution/improvement of an AE to Grade 0–1 or baseline, treatment should be resumed at a reduced dose of **LENVATINIB**
  - Please refer to the **LENVATINIB** SmPC for the management of AEs
- Click the link below for information on **LENVATINIB** dose modifications in combination with **KEYTRUDA**

Dose modification >

Refer to the individual product SmPCs for full dosing information.

1L, first-line; AE, adverse event; aRCC, advanced renal cell carcinoma; IV, intravenous; OD, once daily; Q3W, every three weeks; Q6W, every six weeks; SmPC, Summary of Product Characteristics.

PREPARE

AEs of any cause that emerged or worsened during treatment in ≥25% of patients in any treatment group in the CLEAR trial*[3]

The CLEAR trial was a Phase 3, multicentre, open-label, randomised trial to determine the efficacy and safety of **KEYTRUDA + LENVATINIB** vs. sunitinib in patients with 1L aRCC[3]

The median duration of treatment with KEYTRUDA + LENVATINIB was more than double that with sunitinib (17.0 months vs. 7.8 months, respectively).[3]

The safety profile of each therapy was consistent with their known AE profiles, either alone or in combination.[3]

This list is not exhaustive. Please refer to the KEYTRUDA + LENVATINIB SmPCs for full description of AEs.

AE, n (%)	KEYTRUDA + LENVATINIB (n=352)		Sunitinib (n=340)	
	Any grade	Grade ≥3†	Any grade	Grade ≥3†
Patients with any event	351 (99.7)	290 (82.4)	335 (98.5)	244 (71.8)
Diarrhoea	216 (61.4)	34 (9.7)	168 (49.4)	18 (5.3)
Hypertension	195 (55.4)	97 (27.6)	141 (41.5)	64 (18.8)
Hypothyroidism‡	166 (47.2)	5 (1.4)	90 (26.5)	0
Decreased appetite	142 (40.3)	14 (4.0)	105 (30.9)	5 (1.5)
Fatigue	141 (40.1)	15 (4.3)	125 (36.8)	15 (4.4)
Nausea	126 (35.8)	9 (2.6)	113 (33.2)	2 (0.6)
Stomatitis	122 (34.7)	6 (1.7)	131 (38.5)	7 (2.1)
Dysphonia	105 (29.8)	0	14 (4.1)	0
Weight decrease	105 (29.8)	28 (8.0)	31 (9.1)	1 (0.3)
Proteinuria	104 (29.5)	27 (7.7)	43 (12.6)	10 (2.9)
Palmar-plantar erythrodysesthesia syndrome	101 (28.7)	14 (4.0)	127 (37.4)	13 (3.8)
Arthralgia	99 (28.1)	5 (1.4)	52 (15.3)	1 (0.3)
Rash	96 (27.3)	13 (3.7)	47 (13.8)	2 (0.6)
Vomiting	92 (26.1)	12 (3.4)	68 (20.0)	5 (1.5)
Constipation	89 (25.3)	3 (0.9)	64 (18.8)	0
Dysgeusia	43 (12.2)	1 (0.3)	95 (27.9)	1 (0.3)

Adapted from Motzer R et al. N Engl J Med. 2021;384(14);1289–1300.[3]

*Safety assessments were based on as-treated principle and consisted of monitoring and recording all AEs and serious adverse events (SAEs) with the use of the Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03, in the group of patients who received at least one dose of trial drug.[3]
†Of the 15 patients in the **KEYTRUDA + LENVATINIB** group who had Grade 5 AEs during treatment, 11 had fatal events not attributed to disease progression (acute renal failure, uncontrolled hypertension, complications from myasthenic syndrome, complications from autoimmune hepatitis, cardiac arrest and death–cause not specified in 1 patient each; haemorrhagic events in 2 patients; and sepsis in 3 patients). Among the 11 patients in the sunitinib group with Grade 5 AEs during treatment, fatal events not attributed to disease progression occurred in 2 patients (respiratory failure and acute kidney injury in 1 patient and death–cause not specified in 1 patient).[3]
‡Hypothyroidism is an AE of interest associated with **KEYTRUDA**.[3] Information regarding AEs of interest was not collected specifically as "immune-mediated", in order to preserve blinding.[3]

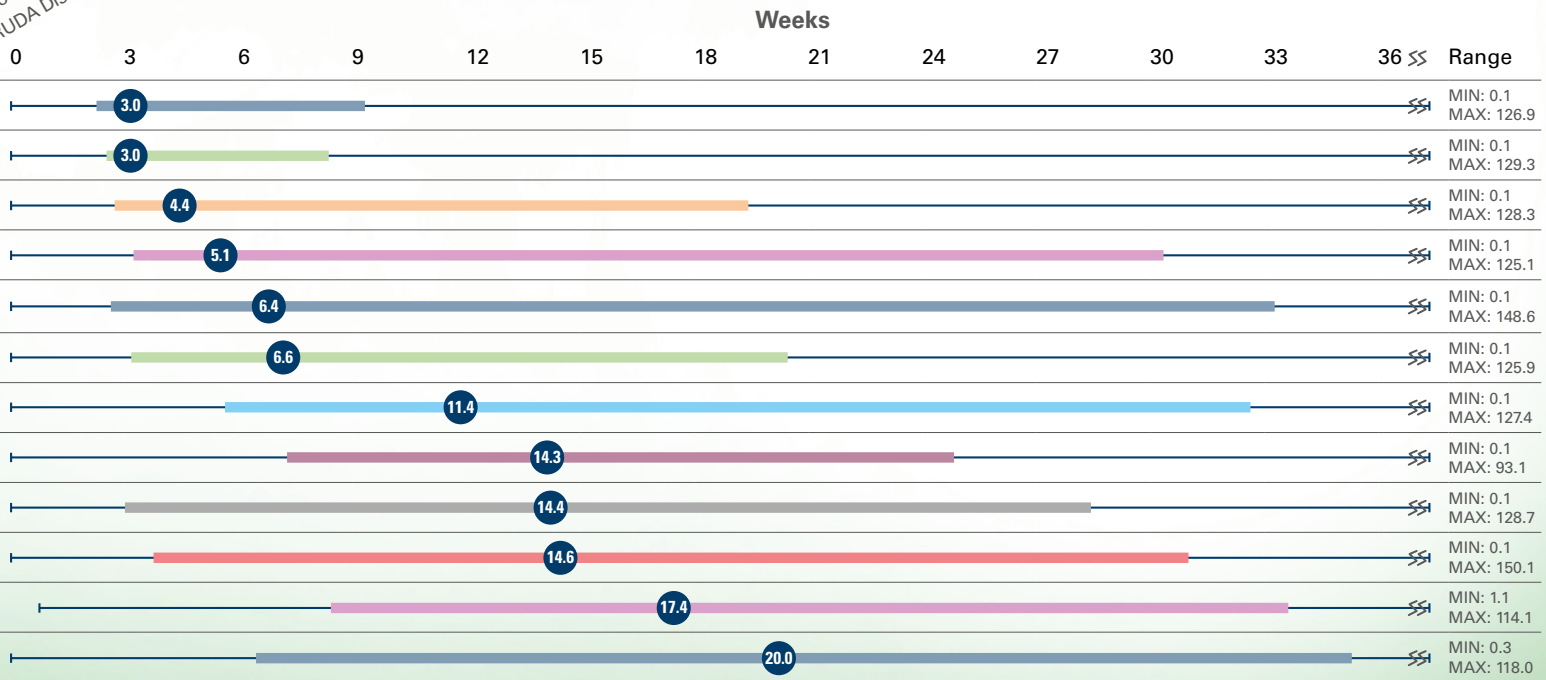
1L, first-line; AE, adverse event; aRCC, advanced renal cell carcinoma; SmPC, Summary of Product Characteristics.

PREPARE Median time to first onset of key AEs (all grades) in the CLEAR trial (exploratory analysis)[4]

During treatment with **KEYTRUDA + LENVATINIB**, AEs may occur within days of treatment initiation.[1,2]
The median time to first onset of the key AEs occurred within the first 20 weeks of treatment initiation in the CLEAR trial.[4]

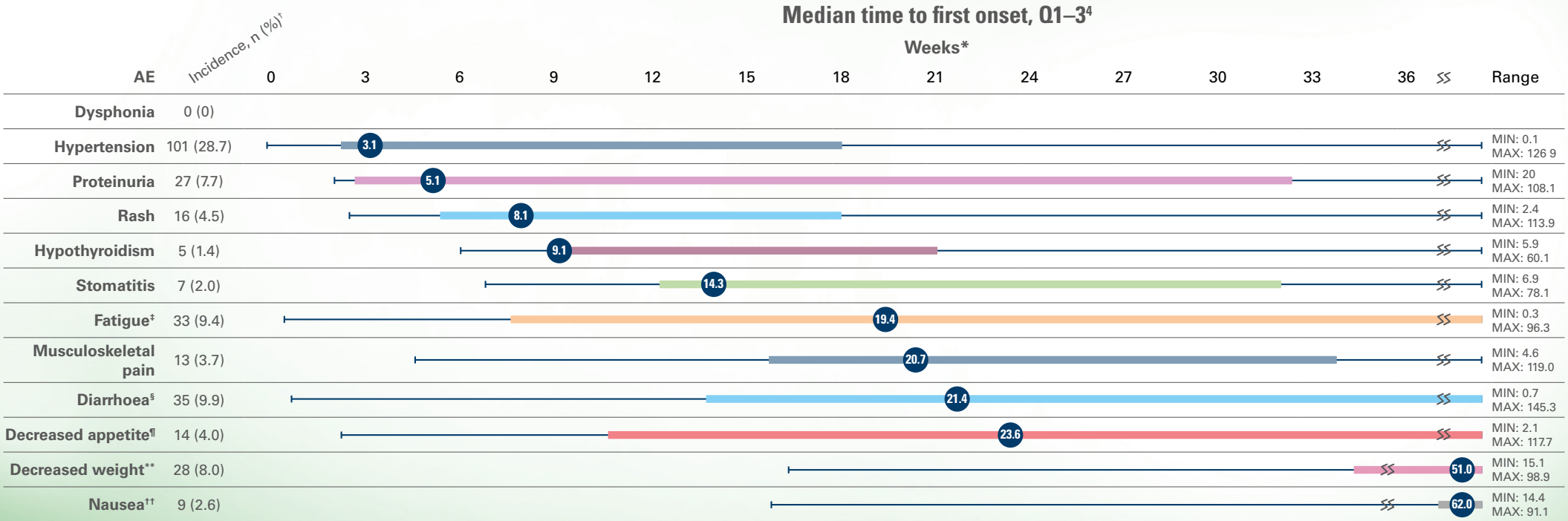
Median time to first onset of key AEs* (all grades) was between 3 and 20 weeks in the CLEAR trial[4]

AE	Incidence, n (%)	LENVATINIB Dose Interruption, n (%)	LENVATINIB Dose Reduction, n (%)	LENVATINIB Discontinuation, n (%)	KEYTRUDA Dose Interruption, n (%)	KEYTRUDA Discontinuation, n (%)	Range
Hypertension	198 (56.3)	32 (9.1)	42 (11.9)	3 (0.9)	11 (3.1)	1 (0.3)	MIN: 0.1 MAX: 126.9
Dysphonia	105 (29.8)	2 (0.6)	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	MIN: 0.1 MAX: 129.3
Fatigue	222 (63.1)	39 (11.1)	34 (9.7)	2 (0.6)	26 (7.4)	1 (0.3)	MIN: 0.1 MAX: 128.3
Proteinuria	105 (29.8)	27 (7.7)	36 (10.2)	6 (1.7)	8 (2.3)	2 (0.6)	MIN: 0.1 MAX: 125.1
Musculoskeletal pain	204 (58.0)	21 (6.0)	9 (2.6)	1 (0.3)	12 (3.4)	2 (0.6)	MIN: 0.1 MAX: 148.6
Stomatitis	152 (43.2)	18 (5.1)	16 (4.5)	1 (0.3)	4 (1.1)	0 (0.0)	MIN: 0.1 MAX: 125.9
Rash	131 (37.2)	20 (5.7)	14 (4.0)	5 (1.4)	10 (2.8)	8 (2.3)	MIN: 0.1 MAX: 127.4
Hypothyroidism	200 (56.8)	6 (1.7)	4 (1.1)	1 (0.3)	5 (1.4)	2 (0.6)	MIN: 0.1 MAX: 93.1
Nausea	126 (35.8)	15 (4.3)	18 (5.1)	1 (0.3)	5 (1.4)	1 (0.3)	MIN: 0.1 MAX: 128.7
Decreased appetite	143 (40.6)	16 (4.5)	27 (7.7)	1 (0.3)	9 (2.6)	1 (0.3)	MIN: 0.1 MAX: 150.1
Weight decreased	105 (29.8)	9 (2.6)	10 (2.8)	1 (0.3)	5 (1.4)	2 (0.6)	MIN: 1.1 MAX: 114.1
Diarrhoea	218 (61.9)	62 (17.6)	57 (16.2)	5 (1.4)	36 (10.2)	4 (1.1)	MIN: 0.3 MAX: 118.0



Adapted from Motzer R et al. Oncologist. 2023;28(6):501–509.
This was a post-hoc exploratory analysis based on data from the CLEAR trial. No formal statistical testing was planned for this analysis and, therefore, no conclusions can be drawn.[4]
*Key AEs: AEs with incidence ≥30% in the **KEYTRUDA + LENVATINIB** group that occurred either while receiving treatment or within the protocol-defined follow-up period of 30 days after the patient's last dose.[4] Coloured boxes represent Q1–Q3. Lines represent the range. Percentages are based on the safety population of the **KEYTRUDA + LENVATINIB** group (n=352). The safety population included all patients who received at least one dose of any study drug.[4]
AE, adverse event; Q, quartile; SmPC, Summary of Product Characteristics.

PREPARE Median time to first onset of Grade ≥3 AEs in the CLEAR trial (exploratory analysis)[4]



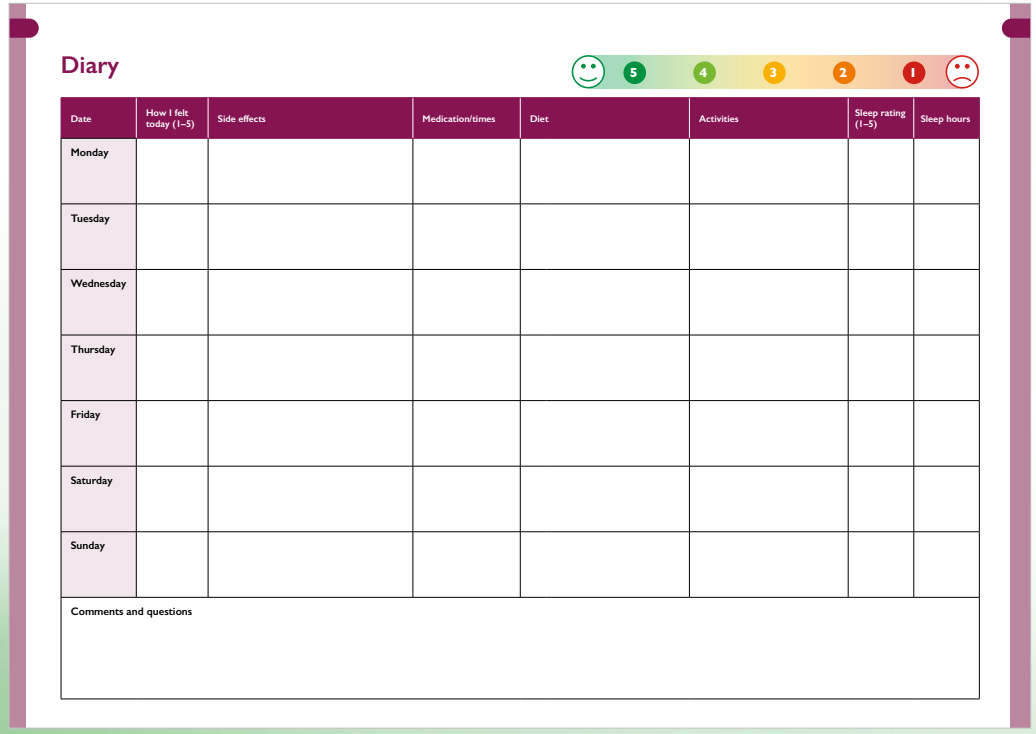
Adapted from Motzer R et al. Oncologist. 2023;28(6):501–509. **This was a post-hoc exploratory analysis based on data from the CLEAR trial. No formal statistical testing was planned for this analysis and, therefore, no conclusions can be drawn.[4]**

*Median time to first onset in patients who experienced the Grade ≥3 adverse reaction. Coloured boxes represent Q1–Q3. Lines represent the range; †Any grade. Percentages are based on the safety population of the **KEYTRUDA + LENVATINIB** group (n=352). The safety population included all patients who received at least one dose of any study drug; ‡Q1=7.86, Q3=42.29; §Q1=13.29, Q3=56.71; ¶Q1=10.14, Q3=69.14; **Q1=34.00, Q3=64.71; ††Q1=42.57, Q3=74.00.

AE, adverse event; Q, quartile; SmPC, Summary of Product Characteristics.

PREPARE Provide your patients with their KEYTRUDA + LENVATINIB Patient Treatment Guide and Diary for patients with 1L aRCC

It is important to support and encourage patients to monitor and report symptoms themselves to aid early identification and prompt management for the AEs, where appropriate.



Diary

5 4 3 2 1

Date	How I felt today (1–5)	Side effects	Medication/times	Diet	Activities	Sleep rating (1–5)	Sleep hours
Monday							
Tuesday							
Wednesday							
Thursday							
Friday							
Saturday							
Sunday							
Comments and questions							

It is important to be able to identify and distinguish TEAEs from the symptoms of aRCC. The KEYTRUDA + LENVATINIB Patient Treatment Guide and Diary for 1L aRCC can help to share this responsibility and ensure patients report back any TEAEs they experience

Ask your representative for the KEYTRUDA + LENVATINIB Treatment Guide and Diary for patients with 1L aRCC, which includes useful information on what patients can expect from their treatment and space for them to log their treatment journey and any symptoms they experience

1L, first-line; AE, adverse event; aRCC, advanced renal cell carcinoma; SmPC, Summary of Product Characteristics; TEAE, treatment-emergent adverse events.

MONITOR Recognise the AEs reported in ≥25% of patients in any treatment group in the CLEAR trial[3]

Monitor patients to aid early identification and prompt medical management of AEs.

This list of AEs is not exhaustive. Please refer to the SmPC for full safety information.

	Monitoring frequency	When to act
Diarrhoea	Regularly. Patients advised to report incidences[5]	Promptly to avoid dehydration[2]
Hypertension	• Prior to treatment initiation[2] • 1 week after **LENVATINIB** treatment initiation[2] • Then every 2 weeks for the first 2 months and monthly thereafter[2]	SBP ≥140 mmHg[2] DBP ≥90 mmHg[2]
Thyroid function	• Prior to treatment initiation[2] • Periodically during treatment[2]	Abnormal TSH levels[2]
Weight or appetite loss	Monitor weight and appetite regularly[5]	≥10% weight loss from baseline[5]
Fatigue	Prior to treatment initiation, then regularly thereafter[5]	Not relieved by rest/interrupts activities of daily living (ADL)[6–8]

	Monitoring frequency	When to act
Nausea and vomiting	Before each cycle of treatment as a minimum[9]	Oral intake decreased without significant weight loss, dehydration or malnutrition; IV fluids indicated[6]
Proteinuria	Monitor urine protein regularly[2]	If dipstick proteinuria reads ≥2+[2]
Skin reactions	Monitor skin reactions frequently[7,8]	Signs and symptoms requiring attention: • Red/blistered/peeling skin • Tingling sensations[7,8] • Discomfort, particularly in the hands and feet[7,8]
Arthralgia	Regularly. Patients advised to report pain intensity[10]	At onset of pain[10]
Dysphonia	Patients advised to report voice changes[11]	At onset of dysphonia[11]
Dysgeusia	Patients advised to report altered taste[12]	At onset of dysgeusia[12]

Patients need to be monitored for cardiac dysfunction, hepatotoxicity, QT prolongation and Tumour Lysis Syndrome. Please see the SmPC for full information.

TEAE management guide >

AE, adverse event; DBP, diastolic blood pressure; SBP, systolic blood pressure; SmPC, Summary of Product Characteristics; TEAEs, treatment-emergent adverse events; TSH, thyroid-stimulating hormone.

MONITOR Definitions of Grades 1 to 5 of selected common AEs from the CLEAR trial[3,6]

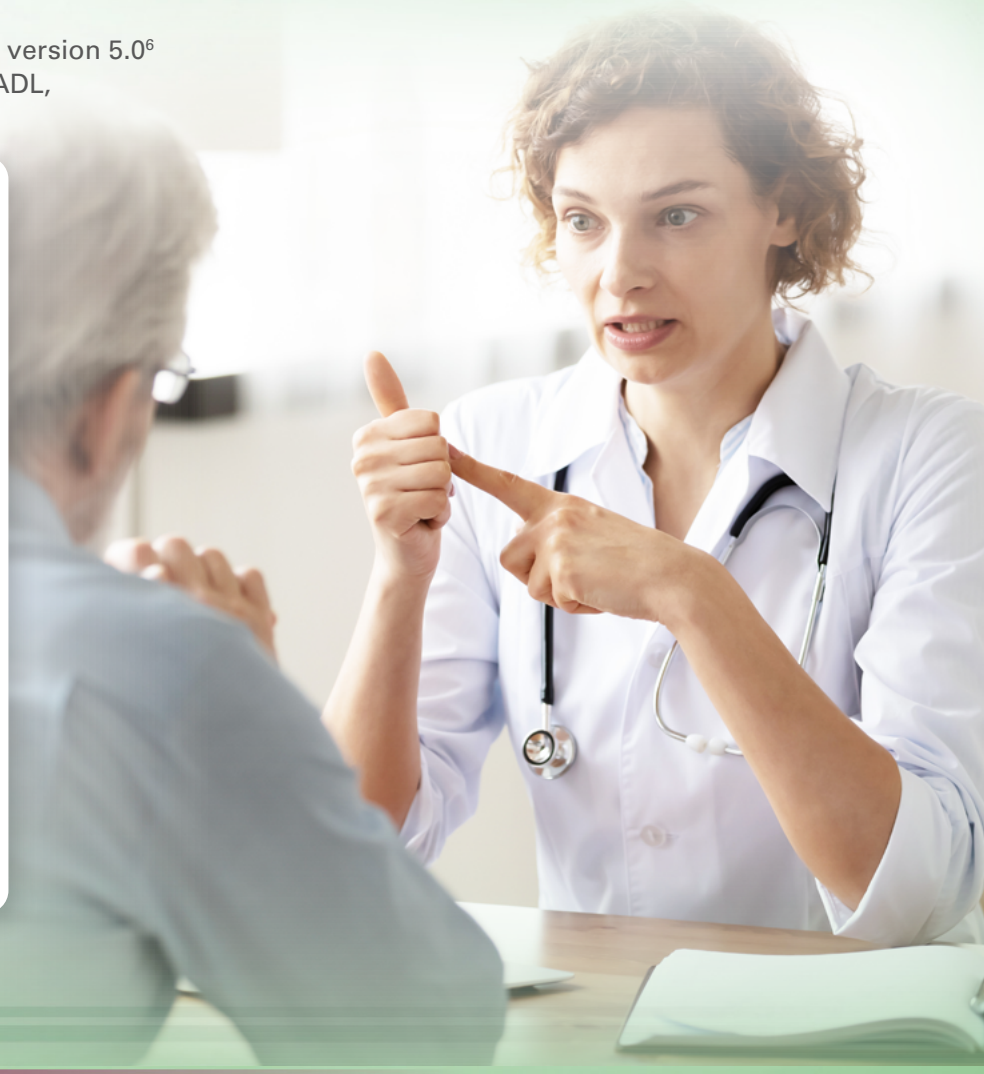
Grading of AE severity is based on Common Terminology Criteria for Adverse Events (CTCAE), version 5.0[6]
The severity of some AEs, such as fatigue and diarrhoea, is based on how much the AE limits ADL, which are divided into two classes: instrumental ADL and self-care ADL[6]

Instrumental ADL[6]

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

Self-care ADL[6]

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



ADL, activities of daily living; AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; SmPC, Summary of Product Characteristics.

MANAGE Adverse events

This section will help you to manage TEAEs with **KEYTRUDA** + **LENVATINIB** combination treatment

- The TEAEs for **KEYTRUDA** + **LENVATINIB** are generally manageable[1,2]
- In treating patients with **KEYTRUDA** + **LENVATINIB**, it is important to establish which medication is the likely cause of an AE, in order to manage the patient's symptoms accordingly. Results from the CLEAR trial have shown some AEs as a result of both **KEYTRUDA** + **LENVATINIB** in combination, however some immune-mediated AEs can be related to **KEYTRUDA** specifically.[1,2]
- When **KEYTRUDA** is used in combination with **LENVATINIB** and an AE occurs, one or both medicines should be interrupted as appropriate.[1,2] **LENVATINIB** should be withheld, dose reduced or discontinued in accordance with the instructions in the **LENVATINIB** SmPC for use in combination with **KEYTRUDA**.[1,2]
  No dose reductions are recommended for **KEYTRUDA**[1]
- Patients treated with **KEYTRUDA** must be given the Patient Alert Card and informed about the risks of **KEYTRUDA**[1]
- A comprehensive AE management strategy can include medical management (non-pharmacological and pharmacological), dose interruptions, **LENVATINIB** dose reductions and treatment discontinuation if necessary[1,2]
- **Addressing the AEs as early and effectively as possible could allow patients to get more out of their treatment**[3]

Please refer to the **KEYTRUDA** + **LENVATINIB** SmPCs for full details about managing AEs

AE, adverse event; SmPC, Summary of Product Characteristics; TEAE, treatment-emergent adverse event.

MANAGE Recommended dosing modification for KEYTRUDA + LENVATINIB in 1L aRCC[1,2]

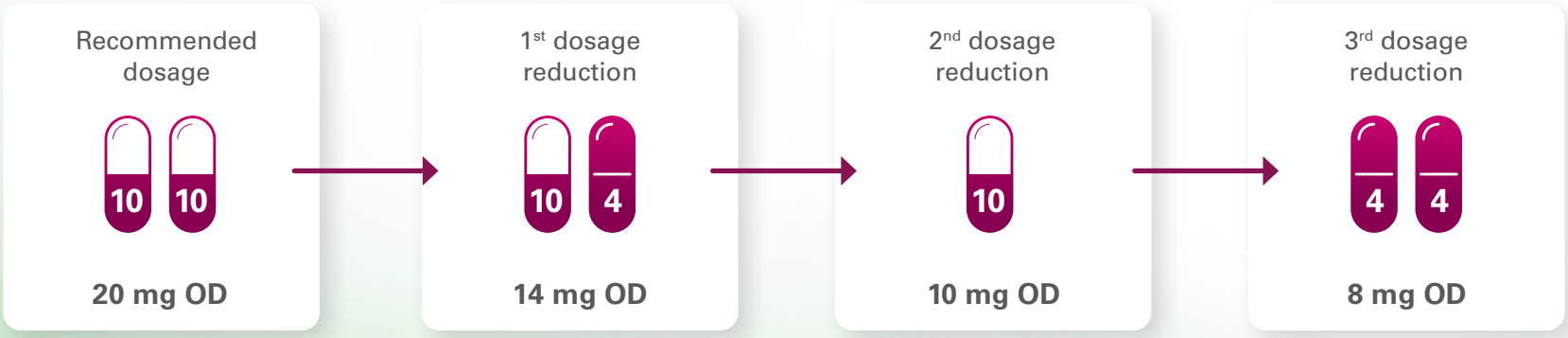
Withhold or discontinue **KEYTRUDA** in accordance with the instructions in the Prescribing Information for **KEYTRUDA**.
No dose reductions are recommended for **KEYTRUDA**[1]

KEYTRUDA must be permanently discontinued for any Grade 3 immune-mediated adverse reaction that recurs and for any Grade 4 immune-mediated toxicity, except for endocrinopathies that are controlled with replacement hormones[1]

The licensed starting dose for **LENVATINIB** when taken in combination with **KEYTRUDA** is 20 mg once daily. It is possible to gradually reduce the dose of **LENVATINIB**, when required to manage AEs[2]

The LENVATINIB starting dose for patients with severe renal or severe hepatic impairment is 10 mg.[2,13] Please refer to the SmPC for more information on these patients.

As part of the AE management strategy, the dosing of **LENVATINIB** can be altered for individual patients.[2]
Flexible **LENVATINIB** dosing enables 3 dose reductions from 20 to 14 mg, 14 to 10 mg, and 10 to 8 mg OD[2]



For intolerable Grade 1-2 or Grade 3 AEs thought to be related to **LENVATINIB**, upon resolution/improvement of an AE to Grade 0–1 or baseline, treatment with **LENVATINIB** may be resumed at a reduced dose[2]

Please refer to the individual product SmPCs for full dosing information.

1L, first-line; AE, adverse event; aRCC, advanced renal cell carcinoma; OD, once daily; SmPC, Summary of Product Characteristics.

MANAGE General management guidelines for TEAEs for KEYTRUDA + LENVATINIB in the CLEAR trial[3]

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

The patient's multidisciplinary team can then decide to reduce the dose or permanently discontinue treatment

CONTINUE TREATMENT with **KEYTRUDA** + **LENVATINIB***

INTERRUPT / WITHHOLD the treatment

RECOMMEND treatment modifications

DISCONTINUE the treatment

Go to the KEYTRUDA TEAE Management Section >

Go to the LENVATINIB TEAE Management Section >

*Continue treatment with **KEYTRUDA** for a maximum of 24 months or until disease progression or unacceptable toxicity.[1]
Withhold or discontinue **KEYTRUDA** in accordance with the instructions in the SmPC. No dose reductions are recommended for **KEYTRUDA**.[1]
LENVATINIB treatment can continue as long as clinical benefit is achieved or until disease progression/unacceptable toxicity.[2]

AE, adverse event; SmPC, Summary of Product Characteristics; TEAE, treatment-emergent adverse event.

Go to the LENVATINIB TEAE Management Section >

MANAGE

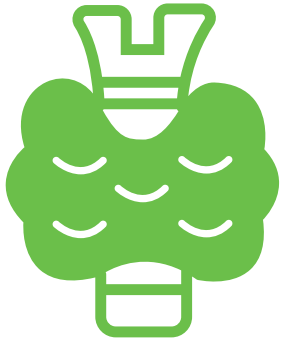
KEYTRUDA (pembrolizumab) TEAEs of interest for KEYTRUDA in the CLEAR trial[3]

Please refer to the **KEYTRUDA** SmPC for full information about AE monitoring and management.

Hypothyroidism | Hyperthyroidism | Pneumonitis | Adrenal insufficiency | Severe skin reactions | Pancreatitis | Colitis

Hepatitis | Nephritis | Infusion-related reactions | Myocarditis | Hypophysitis | Type 1 diabetes mellitus | Other TEAEs of interest for KEYTRUDA

Hypothyroidism



GRADE 1	GRADE 2	GRADE 3	GRADE 4
Asymptomatic. Clinical or diagnostic observations only. Intervention not indicated[6]	Symptomatic. Thyroid replacement indicated. Limiting instrumental ADL[6]	Severe symptoms. Limiting self-care ADL. Hospitalisation indicated[6]	Life-threatening consequences. Urgent intervention indicated[6]

Patients should be regularly monitored for changes in thyroid function[1]

Symptoms may be managed with replacement hormone therapy and treatment with KEYTRUDA may continue with monitoring[1]

Thyroid function and hormone levels should be monitored to ensure appropriate hormone replacement[1]

If Hypothyroidism thought to be related to LENVATINIB, for Grade 1-2 do not warrant LENVATINIB interruption unless intolerable despite optimal management. Grade 3 requires interruption until improvement to Grade 0-1 or baseline. If thought to be related to LENVATINIB, resume LENVATINIB at a reduced dose. LENVATINIB permanently in the event of a Grade 4 or life-threatening reaction.[2]

Long-term hormone replacement therapy may be necessary in cases of immune-mediated endocrinopathies.[1]

ADL, activities of daily living; AE, adverse event; SmPC, Summary of Product Characteristics; TEAE, treatment-emergent adverse event.

Click here to access a more comprehensive imAE management guide for KEYTRUDA >

Go to the LENVATINIB TEAE Management Section

MANAGE

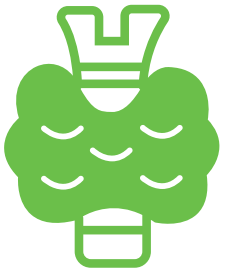
KEYTRUDA (pembrolizumab) TEAEs of interest for KEYTRUDA in the CLEAR trial[3]

Please refer to the **KEYTRUDA** SmPC for full information about AE monitoring and management.

Hypothyroidism | **Hyperthyroidism** | Pneumonitis | Adrenal insufficiency | Severe skin reactions | Pancreatitis | Colitis

Hepatitis | Nephritis | Infusion-related reactions | Myocarditis | Hypophysitis | Type 1 diabetes mellitus | Other TEAEs of interest for KEYTRUDA

Hyperthyroidism



GRADE 1	GRADE 2	GRADE 3	GRADE 4
Asymptomatic. Clinical or diagnostic observations only. Intervention not indicated[6]	Symptomatic. Thyroid suppression therapy indicated. Limiting instrumental ADL[6]	Severe symptoms. Limiting self-care ADL. Hospitalisation indicated[6]	Life-threatening consequences. Urgent intervention indicated[6]

CONTINUE

KEYTRUDA treatment and monitor[1]
Hormone replacement therapy if indicated[1]
May be managed symptomatically[1]
Thyroid function and hormone levels should be monitored to ensure appropriate hormone replacement[1]

WITHHOLD

KEYTRUDA until adverse reactions recover to Grades 0–1. For patients with Grade 3 or Grade 4 endocrinopathies that improve to Grade 2 or lower and are controlled with hormone replacement, if indicated, continuation may be considered after corticosteroid taper, if needed[1]
Thyroid function and hormone levels should be monitored to ensure appropriate hormone replacement[1]

DISCONTINUE

KEYTRUDA permanently if toxicity does not resolve to Grades 0–1 within 12 weeks after the last dose of **KEYTRUDA**, or if corticosteroid dosing cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks[1]

Patients should be monitored for changes in thyroid function.[1] Hormone levels should also be monitored.[1] Along with hypothyroidism/hyperthyroidism, thyroiditis has also been reported and can occur at any time during treatment.[1] Long-term hormone replacement therapy may be necessary in cases of immune-mediated endocrinopathies.[1]
ADL, activities of daily living; AE, adverse event; SmPC, Summary of Product Characteristics; TEAE, treatment-emergent adverse event.

Click here to access a more comprehensive imAE management guide for KEYTRUDA

Go to the LENVATINIB TEAE Management Section

MANAGE

KEYTRUDA (pembrolizumab) TEAEs of interest for KEYTRUDA in the CLEAR trial[3]

Please refer to the **KEYTRUDA** SmPC for full information about AE monitoring and management.

Hypothyroidism | Hyperthyroidism | **Pneumonitis** | Adrenal insufficiency | Severe skin reactions | Pancreatitis | Colitis

Hepatitis | Nephritis | Infusion-related reactions | Myocarditis | Hypophysitis | Type 1 diabetes mellitus | Other TEAEs of interest for KEYTRUDA

Pneumonitis

GRADE 1	GRADE 2	GRADE 3	GRADE 4
Asymptomatic. Clinical or diagnostic observations only. Intervention not indicated[6]	Symptomatic. Medical intervention indicated. Limiting instrumental ADL[6]	Severe symptoms. Limiting self-care ADL. Oxygen indicated[6]	Life-threatening respiratory compromise. Urgent intervention indicated (e.g. tracheotomy or intubation)[6]
→	⏸	✕	✕
CONTINUE	**WITHHOLD**	**DISCONTINUE**	
KEYTRUDA treatment and monitor[1]	**KEYTRUDA** until reactions recover to Grades 0–1[1] Corticosteroids should be administered for Grade ≥2 events (initial dose of 1–2 mg/kg/day prednisone or equivalent followed by a taper)[1]	**KEYTRUDA** permanently[1]	

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DISCONTINUE

KEYTRUDA permanently if treatment-related toxicity does not resolve to Grades 0–1 within 12 weeks after the last dose of **KEYTRUDA**, or if corticosteroid dosing cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks, or if Grade 2 pneumonitis recurs[1]

Patients should be monitored for signs and symptoms of pneumonitis.[1] Suspected pneumonitis should be confirmed with radiographic imaging and other causes excluded.[1] Fatal cases of pneumonitis have been reported in patients receiving **KEYTRUDA**.[1]

ADL, activities of daily living; AE, adverse event; SmPC, Summary of Product Characteristics; TEAE, treatment-emergent adverse event.

Click here to access a more comprehensive imAE management guide for KEYTRUDA

Go to the LENVATINIB TEAE Management Section

MANAGE

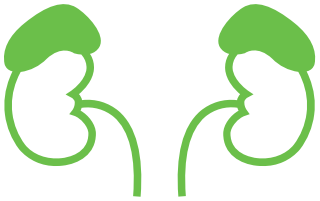
KEYTRUDA® (pembrolizumab) TEAEs of interest for KEYTRUDA in the CLEAR trial[3]

Please refer to the **KEYTRUDA** SmPC for full information about AE monitoring and management.

Hypothyroidism | Hyperthyroidism | Pneumonitis | **Adrenal insufficiency** | Severe skin reactions | Pancreatitis | Colitis

Hepatitis | Nephritis | Infusion-related reactions | Myocarditis | Hypophysitis | Type 1 diabetes mellitus | Other TEAEs of interest for KEYTRUDA

Adrenal insufficiency



GRADE 1	GRADE 2	GRADE 3	GRADE 4
Asymptomatic. Clinical or diagnostic observations only. Intervention not indicated[6]	Moderate symptoms. Medical intervention indicated[6]	Severe symptoms. Hospitalisation indicated[6]	Life-threatening consequences. Urgent intervention indicated[6]
→	⏸	⏸	⏸
CONTINUE	**WITHHOLD**	**WITHHOLD**	
KEYTRUDA treatment[1]	**KEYTRUDA** until controlled by hormone replacement[1]	**KEYTRUDA** until adverse reactions recover to Grades 0–1. For patients with Grade 3 or Grade 4 endocrinopathies that improve to Grade 2 or lower and are controlled with hormone replacement, if indicated, continuation of **KEYTRUDA** may be considered after corticosteroid taper, if needed[1]	

✕

DISCONTINUE

KEYTRUDA permanently if treatment-related toxicity does not resolve to Grades 0–1 within 12 weeks after the last dose of **KEYTRUDA**, or if corticosteroid dosing cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks[1]

Patients should be monitored for signs and symptoms of adrenal insufficiency and other causes excluded.[1] Long-term hormone replacement therapy may be necessary in cases of immune-mediated endocrinopathies.[1] Corticosteroids to treat adrenal insufficiency and other hormone replacement should be administered as clinically indicated.[1]
AE, adverse event; SmPC, Summary of Product Characteristics;
TEAE, treatment-emergent adverse event.

Click here to access a more comprehensive imAE management guide for KEYTRUDA

Go to the LENVATINIB TEAE Management Section

MANAGE

KEYTRUDA (pembrolizumab) TEAEs of interest for KEYTRUDA in the CLEAR trial[3]

Please refer to the **KEYTRUDA** SmPC for full information about AE monitoring and management.

Hypothyroidism	Hyperthyroidism	Pneumonitis	Adrenal insufficiency	**Severe skin reactions**	Pancreatitis	Colitis
Hepatitis	Nephritis	Infusion-related reactions	Myocarditis	Hypophysitis	Type 1 diabetes mellitus	Other TEAEs of interest for KEYTRUDA

Skin reactions (SJS/TEN)
Terms cover multiple AEs

Patients should be monitored for suspected severe skin reactions and other causes should be excluded. For suspected SJS or TEN, the patient should be referred to a specialised unit for assessment and treatment[1]

CONTINUE

For Grade 1 or 2 events treatment may continue, with monitoring[1]
May be managed symptomatically[8]

WITHHOLD

KEYTRUDA for Grade 3 skin reaction or suspected SJS or TEN, until adverse reactions recover to Grades 0–1.[1]
Corticosteroids should be administered[1]

DISCONTINUE

KEYTRUDA permanently for Grade 4 or confirmed SJS or TEN[1]

DISCONTINUE

KEYTRUDA permanently if treatment-related toxicity does not resolve to Grades 0–1 within 12 weeks after the last dose of **KEYTRUDA**, or if corticosteroid dosing cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks[1]

Patients should be monitored for suspected skin reactions.[1] Other causes should be excluded.[1] Caution should be used when considering the use of **KEYTRUDA** in a patient who has previously experienced a severe or life-threatening skin adverse reaction on prior treatment with other immune-stimulatory anticancer agents.[1]
AE, adverse event; SJS, Stevens-Johnson syndrome; SmPC, Summary of Product Characteristics; TEAE, treatment-emergent adverse event; TEN, toxic epidermal necrolysis.

Click here to access a more comprehensive imAE management guide for KEYTRUDA

Go to the LENVATINIB TEAE Management Section >

MANAGE

KEYTRUDA® (pembrolizumab) TEAEs of interest for KEYTRUDA in the CLEAR trial[3]

Please refer to the **KEYTRUDA** SmPC for full information about AE monitoring and management.

Hypothyroidism | Hyperthyroidism | Pneumonitis | Adrenal insufficiency | Severe skin reactions | **Pancreatitis** | Colitis

Hepatitis | Nephritis | Infusion-related reactions | Myocarditis | Hypophysitis | Type 1 diabetes mellitus | Other TEAEs of interest for KEYTRUDA

Pancreatitis

GRADE 1	GRADE 2	GRADE 3	GRADE 4
	Enzyme elevation. Radiologic findings only[6]	Severe pain. Vomiting. Medical intervention indicated (e.g. analgesia, nutritional support)[6]	Life-threatening consequences. Urgent intervention indicated[6]
→	⏸	⏸	✕
CONTINUE	**WITHHOLD**	**WITHHOLD**	**DISCONTINUE**
KEYTRUDA treatment[1]	**KEYTRUDA** until adverse reactions recover to Grades 0–1[1] Administer corticosteroids for Grade ≥2 events (initial dose of 1–2 mg/kg/day prednisone or equivalent followed by a taper)[1]		**KEYTRUDA** permanently for recurrent Grade 3 or Grade 4 pancreatitis[1]

✕

DISCONTINUE

KEYTRUDA permanently if treatment-related toxicity does not resolve to Grades 0–1 within 12 weeks after the last dose of **KEYTRUDA**, or if corticosteroid dosing cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks[1]

AE, adverse event; SmPC, Summary of Product Characteristics; TEAE, treatment-emergent adverse event.

Click here to access a more comprehensive imAE management guide for KEYTRUDA >

MANAGE

KEYTRUDA (pembrolizumab) TEAEs of interest for KEYTRUDA in the CLEAR trial[3]

Go to the LENVATINIB TEAE Management Section >

Please refer to the **KEYTRUDA** SmPC for full information about AE monitoring and management.

Hypothyroidism	Hyperthyroidism	Pneumonitis	Adrenal insufficiency	Severe skin reactions	Pancreatitis	**Colitis**
Hepatitis	Nephritis	Infusion-related reactions	Myocarditis	Hypophysitis	Type 1 diabetes mellitus	Other TEAEs of interest for KEYTRUDA

Colitis

GRADE 1	GRADE 2	GRADE 3	GRADE 4
Asymptomatic. Clinical or diagnostic observations only. Intervention not indicated[6]	Abdominal pain. Mucus or blood in stool[6]	Severe abdominal pain. Peritoneal signs[6]	Life-threatening consequences. Urgent intervention indicated[6]
→	⏸	⏸	✕
CONTINUE	**WITHHOLD**	**WITHHOLD**	**DISCONTINUE**
KEYTRUDA treatment[1]	**KEYTRUDA** until adverse reactions recover to Grades 0–1[1] Administer corticosteroids for Grade ≥2 events (initial dose of 1–2 mg/kg/day prednisone or equivalent followed by a taper)[1]		**KEYTRUDA** permanently[1]

✕

DISCONTINUE

KEYTRUDA permanently if treatment-related toxicity does not resolve to Grades 0–1 within 12 weeks after the last dose of **KEYTRUDA**, if corticosteroid dosing cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks, or if recurrent Grade 3 colitis occurs[1]

Diarrhoea has been reported frequently with **KEYTRUDA + LENVATINIB**.[1,2] It usually occurs early in the course of treatment and might be related to **LENVATINIB**.[2]
Diarrhoea can be as a sign of immune-mediated colitis; patients should be monitored for signs and symptoms of colitis and other causes excluded.[1]
AE, adverse event; SmPC, Summary of Product Characteristics; TEAE, treatment-emergent adverse event.

Click here to access a more comprehensive imAE management guide for KEYTRUDA >

Go to the LENVATINIB TEAE Management Section

MANAGE

KEYTRUDA (pembrolizumab) TEAEs of interest for KEYTRUDA in the CLEAR trial[3]

Please refer to the **KEYTRUDA** SmPC for full information about AE monitoring and management.

Hypothyroidism | Hyperthyroidism | Pneumonitis | Adrenal insufficiency | Severe skin reactions | Pancreatitis | Colitis

Hepatitis | Nephritis | Infusion-related reactions | Myocarditis | Hypophysitis | Type 1 diabetes mellitus | Other TEAEs of interest for KEYTRUDA

Hepatitis

GRADE 1	GRADE 2	GRADE ≥3
AST or ALT <3.0 x ULN or total bilirubin <1.5 times the ULN[1]	AST or ALT >3.0–5.0 x ULN or total bilirubin >1.5–3 times the ULN[1]	AST or ALT >5 x ULN or total bilirubin >3 x ULN[1]
→	⏸	✕
CONTINUE	**WITHHOLD**	**DISCONTINUE**
KEYTRUDA and monitor[1]	**KEYTRUDA** until adverse reactions recover to Grades 0–1[1] Administer an initial dose of 0.5–1 mg/kg/day prednisone or equivalent followed by a taper[1]	**KEYTRUDA** permanently[1] Administer 1–2 mg/kg/day prednisone or equivalent followed by a taper[1]

✕

DISCONTINUE

KEYTRUDA permanently if treatment-related toxicity does not resolve to Grades 0–1 within 12 weeks after the last dose of **KEYTRUDA**, or if corticosteroid dosing cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks[1]
In the case of liver metastasis with baseline Grade 2 elevation of AST or ALT, hepatitis with AST or ALT increases ≥50% and lasting ≥1 week, permanently discontinue **KEYTRUDA**[1]

For information on how to manage LENVATINIB on patients with hepatic impairment please consult with the product's SmPC.

Patients should be monitored for changes in liver function (at the start of treatment, periodically during treatment and as indicated based on clinical evaluation) and symptoms of hepatitis, and other causes excluded.[1]

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SmPC, Summary of Product Characteristics; TEAE, treatment-emergent adverse event; ULN, upper limit of normal.

Click here to access a more comprehensive imAE management guide for KEYTRUDA

MANAGE

KEYTRUDA (pembrolizumab) TEAEs of interest for KEYTRUDA in the CLEAR trial[3]

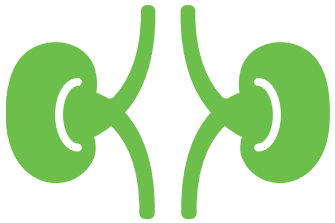
Go to the LENVATINIB TEAE Management Section >

Please refer to the **KEYTRUDA** SmPC for full information about AE monitoring and management.

Hypothyroidism | Hyperthyroidism | Pneumonitis | Adrenal insufficiency | Severe skin reactions | Pancreatitis | Colitis

Hepatitis | **Nephritis** | Infusion-related reactions | Myocarditis | Hypophysitis | Type 1 diabetes mellitus | Other TEAEs of interest for KEYTRUDA

Nephritis



GRADE 1	GRADE 2	GRADE ≥3
Creatinine within normal limits[1]	Creatinine >1.5–≤3 x ULN[1]	Creatinine >3 x ULN[1]
→	⏸	✕
CONTINUE	**WITHHOLD**	**DISCONTINUE**
KEYTRUDA treatment and monitor[1]	**KEYTRUDA** until adverse reactions recover to Grades 0–1[1] Corticosteroids should be administered for Grade ≥2 events (initial dose of 1–2 mg/kg/day prednisone or equivalent followed by a taper)[1]	**KEYTRUDA** permanently[1]

✕

DISCONTINUE

KEYTRUDA permanently if toxicity does not resolve to Grades 0–1 within 12 weeks after the last dose of **KEYTRUDA**, or if corticosteroid dosing cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks[1]

Patients should be monitored for changes in renal function (at the start of treatment, periodically during treatment and as indicated based on clinical evaluation) and symptoms of nephritis, and other causes excluded.[1]
AE, adverse event; SmPC, Summary of Product Characteristics;
TEAE, treatment-emergent adverse event; ULN, upper limit of normal.

Click here to access a more comprehensive imAE management guide for KEYTRUDA >

MANAGE

KEYTRUDA (pembrolizumab) TEAEs of interest for KEYTRUDA in the CLEAR trial[3]

Go to the LENVATINIB TEAE Management Section >

Please refer to the **KEYTRUDA** SmPC for full information about AE monitoring and management.

Hypothyroidism | Hyperthyroidism | Pneumonitis | Adrenal insufficiency | Severe skin reactions | Pancreatitis | Colitis

Hepatitis | Nephritis | **Infusion-related reactions** | Myocarditis | Hypophysitis | Type 1 diabetes mellitus | Other TEAEs of interest for KEYTRUDA

Infusion-related reactions

GRADE 1	GRADE 2	GRADE 3	GRADE 4
Mild transient reaction. Infusion interruption not indicated. Intervention not indicated[6]	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g. antihistamines, NSAIDS, narcotics, IV fluids). Prophylactic medications indicated for ≤24 hours[6]	Prolonged (e.g. not rapidly responsive to symptomatic medication and/or brief interruption of infusion). Recurrence of symptoms following initial improvement. Hospitalisation indicated for clinical sequelae[6]	Life-threatening consequences. Urgent intervention indicated[6]
→	→	✕	✕
CONTINUE	**CONTINUE**	**DISCONTINUE**	**DISCONTINUE**
KEYTRUDA treatment and monitor closely[1] Consider premedication with antipyretic and antihistamine therapy[1]		Stop infusion[1] Permanently discontinue **KEYTRUDA**[1]	

Patients should be monitored for severe infusion-related reactions including hypersensitivity and anaphylaxis.[1] Severe infusion-related reactions have been reported with patients receiving **KEYTRUDA**; these include drug hypersensitivity, anaphylactic reaction, anaphylactoid reaction, hypersensitivity, infusion-related hypersensitivity reaction, cytokine release syndrome and serum sickness.[1] Patients should be monitored during infusion.[1]

AE, adverse event; IV, intravenous; NSAID, non-steroid anti-inflammatory drug; SmPC, Summary of Product Characteristics; TEAE, treatment-emergent adverse event.

Click here to access a more comprehensive imAE management guide for KEYTRUDA >

Go to the LENVATINIB TEAE Management Section

MANAGE

KEYTRUDA® (pembrolizumab) TEAEs of interest for KEYTRUDA in the CLEAR trial[3]

Please refer to the **KEYTRUDA** SmPC for full information about AE monitoring and management.

Hypothyroidism | Hyperthyroidism | Pneumonitis | Adrenal insufficiency | Severe skin reactions | Pancreatitis | Colitis

Hepatitis | Nephritis | Infusion-related reactions | **Myocarditis** | Hypophysitis | Type 1 diabetes mellitus | Other TEAEs of interest for KEYTRUDA

Myocarditis

GRADE 1	GRADE 2	GRADE 3	GRADE 4
	Symptoms with moderate activity or exertion[6]	Severe with symptoms at rest or with minimal activity or exertion. Intervention indicated. New onset of symptoms[6]	Life-threatening consequences. Urgent intervention indicated (e.g. continuous IV therapy or mechanical haemodynamic support)[6]
CONTINUE KEYTRUDA treatment[1]	**WITHHOLD** KEYTRUDA until adverse reactions recover to Grades 0–1[1]	**DISCONTINUE** KEYTRUDA permanently for Grade 3 or Grade 4 myocarditis[1]	

DISCONTINUE

KEYTRUDA permanently if treatment-related toxicity does not resolve to Grades 0–1 within 12 weeks after the last dose of KEYTRUDA, or if corticosteroid dosing cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks[1]

The safety of re-initiating KEYTRUDA therapy in patients previously experiencing immune-mediated myocarditis is not known.[1]

AE, adverse event; IV, intravenous; SmPC, Summary of Product Characteristics; TEAE, treatment-emergent adverse event.

Click here to access a more comprehensive imAE management guide for KEYTRUDA

Go to the LENVATINIB TEAE Management Section

MANAGE

KEYTRUDA (pembrolizumab) TEAEs of interest for KEYTRUDA in the CLEAR trial[3]

Please refer to the **KEYTRUDA** SmPC for full information about AE monitoring and management.

Hypothyroidism | Hyperthyroidism | Pneumonitis | Adrenal insufficiency | Severe skin reactions | Pancreatitis | Colitis

Hepatitis | Nephritis | Infusion-related reactions | Myocarditis | **Hypophysitis** | Type 1 diabetes mellitus | Other TEAEs of interest for KEYTRUDA

Hypophysitis

GRADE 1	GRADE 2	GRADE 3	GRADE 4
Asymptomatic or mild symptoms. Clinical or diagnostic observations only. Intervention not indicated[6]	Moderate. Minimal, local or non-invasive intervention indicated. Limiting age-appropriate instrumental ADL[6]	Severe or medically significant but not immediately life-threatening. Hospitalisation or prolongation of existing hospitalisation indicated. Limiting self-care ADL[6]	Life-threatening consequences. Urgent intervention indicated[6]
→	⏸	⏸	
CONTINUE	**WITHHOLD**	**WITHHOLD**	
KEYTRUDA treatment[1]	**KEYTRUDA** until controlled by hormone replacement[1]	**KEYTRUDA** until adverse reactions recover to Grades 0–1. For patients with Grade 3 or Grade 4 endocrinopathies that improve to Grade 2 or lower and are controlled with hormone replacement, if indicated, continuation of **KEYTRUDA** may be considered after corticosteroid taper, if needed[1]	
		✕ **DISCONTINUE**	
		KEYTRUDA permanently if treatment-related toxicity does not resolve to Grades 0–1 within 12 weeks after the last dose of **KEYTRUDA**, or if corticosteroid dosing cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks[1]	

Patients should be monitored for signs and symptoms of hypophysitis (including hypopituitarism) and other causes excluded. Pituitary function and hormone levels should be monitored to ensure appropriate hormone replacement.[1] Long-term hormone replacement therapy may be necessary in cases of immune-mediated endocrinopathies.[1]
ADL, activities of daily living; AE, adverse event; SmPC, Summary of Product Characteristics; TEAE, treatment-emergent adverse event.

Click here to access a more comprehensive imAE management guide for KEYTRUDA

Go to the LENVATINIB TEAE Management Section

MANAGE

KEYTRUDA (pembrolizumab) TEAEs of interest for KEYTRUDA in the CLEAR trial[3]

Please refer to the **KEYTRUDA** SmPC for full information about AE monitoring and management.

Hypothyroidism | Hyperthyroidism | Pneumonitis | Adrenal insufficiency | Severe skin reactions | Pancreatitis | Colitis

Hepatitis | Nephritis | Infusion-related reactions | Myocarditis | Hypophysitis | **Type 1 diabetes mellitus** | Other TEAEs of interest for KEYTRUDA

Type 1 diabetes mellitus

GRADE 1	GRADE 2	GRADE 3	GRADE 4
Abnormal glucose above baseline with no medical intervention[6]	Change in daily management from baseline for a diabetic. Oral antiglycaemic agent initiated. Workup for diabetes[6]	Insulin therapy initiated. Hospitalisation indicated[6]	Life-threatening consequences. Urgent intervention indicated[6]

CONTINUE

KEYTRUDA treatment with insulin*[1]

WITHHOLD

KEYTRUDA until metabolic control is achieved with administration of insulin and symptoms improve to Grade 2 or lower[1]
Withhold **KEYTRUDA** in the event of Grade ≥3 hyperglycaemia or associated ketoacidosis. Treatment may be restarted if metabolic control is achieved[1]

DISCONTINUE

KEYTRUDA permanently if metabolic control is not achieved: if treatment-related toxicity does not resolve to Grades 0–1 within 12 weeks after the last dose of **KEYTRUDA**, or if corticosteroid dosing cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks[1]

Patients should be monitored for hyperglycaemia or other signs and symptoms of diabetes.[1]
Insulin should be administered for type 1 diabetes.[1]
*Long-term hormone replacement therapy may be necessary in cases of immune-mediated endocrinopathies.[1]
AE, adverse event; SmPC, Summary of Product Characteristics;
TEAE, treatment-emergent adverse event.

Click here to access a more comprehensive imAE management guide for KEYTRUDA

MANAGE

KEYTRUDA (pembrolizumab) TEAEs of interest for KEYTRUDA in the CLEAR trial[3]

Go to the LENVATINIB TEAE Management Section >

Please refer to the **KEYTRUDA** SmPC for full information about AE monitoring and management.

Hypothyroidism | Hyperthyroidism | Pneumonitis | Adrenal insufficiency | Severe skin reactions | Pancreatitis | Colitis

Hepatitis | Nephritis | Infusion-related reactions | Myocarditis | Hypophysitis | Type 1 diabetes mellitus | Other TEAEs of interest for KEYTRUDA

Other TEAEs of interest for KEYTRUDA from the CLEAR trial

Other TEAEs of interest for **KEYTRUDA** that occurred in the CLEAR trial include encephalitis, myasthenic syndrome, myositis, thyroiditis and uveitis[3]

WITHHOLD

KEYTRUDA for immune-mediated AEs based on the severity and type of reaction (Grade 2 or 3) until adverse reactions recover to 0–1[1]

DISCONTINUE

KEYTRUDA permanently if treatment-related toxicity does not resolve to Grades 0–1 within 12 weeks after the last dose of **KEYTRUDA**, or if corticosteroid dosing cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks[1]

DISCONTINUE

KEYTRUDA permanently for any recurrent Grade 3 immune-mediated toxicity and for any Grade 4 immune-mediated toxicity[1]

Discontinue **KEYTRUDA** permanently in the case of Grade 3 or 4 encephalitis[1]

Based on limited data from clinical studies in patients whose immune-mediated adverse reactions could not be controlled with corticosteroid use, consider administration of other systemic immunosuppressants[1]

AE, adverse event; SmPC, Summary of Product Characteristics; TEAE, treatment-emergent adverse event.

Click here to access a more comprehensive imAE management guide for KEYTRUDA >

Go to the KEYTRUDA TEAE Management Section >

MANAGE

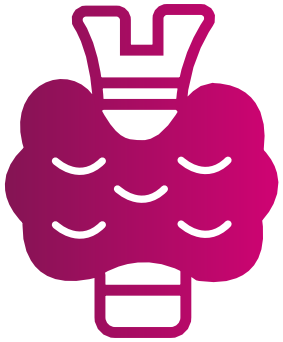
Clinically significant TEAEs for LENVATINIB in the CLEAR trial[3]

Please refer to the **LENVATINIB** SmPC for further information.

Hypothyroidism | Hypertension | PPES | Proteinuria | Haemorrhage | Hepatotoxicity | Renal impairment

QT prolongation | Arterial thromboembolism | Cardiac dysfunction | GI perforation or fistula | Hypocalcaemia | Non-GI fistula | PRES/RPLS

Hypothyroidism



If hypothyroidism is thought to be related to an immune-mediated AE, please refer to the **KEYTRUDA** SmPC.

ADL, activities of daily living; AE, adverse event; SmPC, Summary of Product Characteristics; TEAE, treatment-emergent adverse event; TSH, thyroid-stimulating hormone.

Please refer to the individual product SmPCs for further information.

GRADE 1	GRADE 2	GRADE 3	GRADE 4
Asymptomatic. Clinical or diagnostic observations only. Intervention not indicated[6]	Symptomatic. Thyroid replacement indicated. Limiting instrumental ADL[6]	Severe symptoms. Limiting self-care ADL. Hospitalisation indicated[6]	Life-threatening consequences. Urgent intervention indicated[6]

Thyroid function should be monitored before treatment initiation, then periodically during treatment with KEYTRUDA + LENVATINIB and as indicated based on clinical evaluation.[1,2]

If any abnormality in thyroid function is found, consult an endocrinologist.[5]

Hypothyroidism should be treated according to standard medical practice to maintain euthyroid state.[2]

Adjust thyroid hormone administration to reach TSH levels appropriate to the patient's therapeutic target.[2]

If intolerable despite optimal management, interrupt **LENVATINIB** until resolves to Grade 0–1 or baseline. If thought to be related to **LENVATINIB**, resume **LENVATINIB** at a reduced dose[2]

DISCONTINUE

LENVATINIB permanently in the event of a Grade 4 or life-threatening reaction[2]

Go to the KEYTRUDA TEAE Management Section >

MANAGE

Clinically significant TEAEs for LENVATINIB in the CLEAR trial[3]

Please refer to the **LENVATINIB** SmPC for further information.

Hypothyroidism | **Hypertension** | PPES | Proteinuria | Haemorrhage | Hepatotoxicity | Renal impairment

QT prolongation | Arterial thromboembolism | Cardiac dysfunction | GI perforation or fistula | Hypocalcaemia | Non-GI fistula | PRES/RPLS

Hypertension

BP should be monitored after 1 week of treatment with **LENVATINIB**, then every 2 weeks for the first 2 months, and monthly thereafter.[2]

In the CLEAR trial, patients with baseline hypertension had a higher incidence of proteinuria than patients without baseline hypertension.[2]

AE, adverse event; BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure; SmPC, Summary of Product Characteristics; TEAE, treatment-emergent adverse event; WNL, within normal limits.

GRADE 1	GRADE 2	GRADE 3	GRADE 4
SBP 120 to 139 mmHg or DBP 80 to 89 mmHg[6]	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[6]	SBP ≥160 mmHg or DBP ≥100 mmHg. Medical intervention indicated. More than one drug or more intensive therapy than previously used indicated[6]	Life-threatening consequences (e.g. malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis) Urgent intervention indicated[6]
→	→	⏸	✕
CONTINUE	**CONTINUE**	**INTERRUPT**	**DISCONTINUE**
LENVATINIB treatment[2]	**LENVATINIB** and initiate antihypertensive therapy (if not already receiving) or increase dose of current antihypertensive therapy/initiate additional antihypertensive therapy[2]	**LENVATINIB** if AE occurred despite optimal antihypertensive treatment[2]	**LENVATINIB** permanently and provide appropriate medical management[2]
		↓	
		REDUCE	
		Resume **LENVATINIB** at a reduced dose when SBP ≤150 mmHg, DBP ≤95 mmHg and patient has been on a stable antihypertensive dose for at least 48 hours[2]	

If intolerable despite optimal management, interrupt **LENVATINIB** until resolves to Grade 0–1 or baseline. If thought to be related to **LENVATINIB**, resume **LENVATINIB** at a reduced dose[2]

Go to the KEYTRUDA TEAE Management Section >

MANAGE

Clinically significant TEAEs for LENVATINIB in the CLEAR trial[3]

Please refer to the **LENVATINIB** SmPC for further information.

Hypothyroidism	Hypertension	**PPES**	Proteinuria	Haemorrhage	Hepatotoxicity	Renal impairment
QT prolongation	Arterial thromboembolism	Cardiac dysfunction	GI perforation or fistula	Hypocalcaemia	Non-GI fistula	PRES/RPLS

PPES

GRADE 1	GRADE 2	GRADE 3	Grade 4
Minimal skin changes or dermatitis (e.g. erythema, oedema, or hyperkeratosis) without pain[6]	Skin changes (e.g. peeling, blisters, bleeding, fissures, oedema, or hyperkeratosis) with pain. Limiting instrumental ADL[6]	Severe skin changes (e.g. peeling, blisters, bleeding, fissures, oedema, or hyperkeratosis) with pain. Limiting self-care ADL[6]	
→		⏸	✕
CONTINUE		**INTERRUPT**	**DISCONTINUE**
LENVATINIB (if tolerable)[2] Use moisturising cream, and consider hydrocolloid dressing for the feet[11,12] 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[12]		**LENVATINIB** until resolves to Grade 0–1 or baseline[2]	**LENVATINIB** permanently in the event of a Grade 4 or life-threatening reaction[2]
If intolerable despite optimal management, interrupt **LENVATINIB** until resolves to Grade 0–1 or baseline. If thought to be related to **LENVATINIB**, resume **LENVATINIB** at a reduced dose[2]		↓	
		REDUCE	
		Resume **LENVATINIB** at a reduced dose[2]	

ADL, activities of daily living; AE, adverse event; PPES, palmar–plantar erythrodysaesthesia syndrome; SmPC, Summary of Product Characteristics; TEAE, treatment-emergent adverse event.

Go to the KEYTRUDA TEAE Management Section

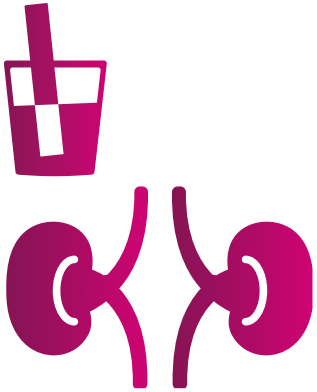
MANAGE

Clinically significant TEAEs for LENVATINIB in the CLEAR trial[3]

Please refer to the **LENVATINIB** SmPC for further information.

Hypothyroidism	Hypertension	PPES	**Proteinuria**	Haemorrhage	Hepatotoxicity	Renal impairment
QT prolongation	Arterial thromboembolism	Cardiac dysfunction	GI perforation or fistula	Hypocalcaemia	Non-GI fistula	PRES/RPLS

Proteinuria



Manage patients with renal dysfunction caused by diabetes or hypertension carefully.[16]

In the CLEAR trial, patients with baseline hypertension had a higher incidence of proteinuria than patients without baseline hypertension[2]

AE, adverse event; SmPC, Summary of Product Characteristics; TEAE, treatment-emergent adverse event; ULN, upper limit of normal.

GRADE 1	GRADE 2	GRADE 3	Nephrotic Syndrome
1+ proteinuria. Urinary protein ≥ULN to <1.0 g/24 hours[6]	2+ and 3+ proteinuria. Urinary protein 1.0 to <3.5 g/24 hours[6]	4+ proteinuria. Urinary protein ≥3.5 g/24 hours[6]	
→	⏸		✕
CONTINUE	**INTERRUPT**		**DISCONTINUE**
LENVATINIB treatment[2]	**LENVATINIB** until resolves to <2 g/24 hours[2]		**LENVATINIB** treatment[2]
If intolerable despite optimal management, interrupt **LENVATINIB** until resolves to Grade 0–1 or baseline. If thought to be related to **LENVATINIB**, resume **LENVATINIB** at a reduced dose[2]	↓		
	REDUCE		
	Resume **LENVATINIB** at a reduced dose[2]		

Go to the KEYTRUDA TEAE Management Section >

MANAGE

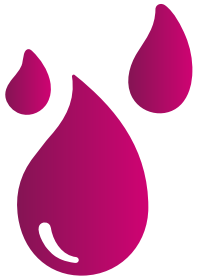
Clinically significant TEAEs for LENVATINIB in the CLEAR trial[3]

Please refer to the **LENVATINIB** SmPC for further information.

Hypothyroidism | Hypertension | PPES | Proteinuria | **Haemorrhage** | Hepatotoxicity | Renal impairment

QT prolongation | Arterial thromboembolism | Cardiac dysfunction | GI perforation or fistula | Hypocalcaemia | Non-GI fistula | PRES/RPLS

Haemorrhage



GRADE 1	GRADE 2	GRADE 3	GRADE 4
Mild symptoms, intervention not indicated[6]	Moderate symptoms, transfusion indicated[6]	Transfusion indicated. Invasive intervention indicated. Hospitalisation indicated[6]	Life-threatening consequences. Urgent intervention indicated[6]
→	→	⏸	✕
CONTINUE	**CONTINUE**	**INTERRUPT**	**DISCONTINUE**
LENVATINIB treatment[2]	**LENVATINIB** treatment[2]	**LENVATINIB** until resolves to Grade 0–1 or baseline[2]	**LENVATINIB** permanently in the event of a Grade 4 or life-threatening reaction[2]
If intolerable despite optimal management, interrupt **LENVATINIB** until resolves to Grade 0–1 or baseline. If thought to be related to **LENVATINIB**, resume **LENVATINIB** at a reduced dose[2]		↓	
		REDUCE	
		Resume **LENVATINIB** at a reduced dose[2]	

Please refer to the CTCAE guide for the Grade definitions specific to the bleeding type of your patient.[6]

AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; SmPC, Summary of Product Characteristics; TEAE, treatment-emergent adverse event.

Go to the KEYTRUDA TEAE Management Section >

MANAGE

Clinically significant TEAEs for LENVATINIB in the CLEAR trial[3]

Please refer to the **LENVATINIB** SmPC for further information.

Hypothyroidism | Hypertension | PPES | Proteinuria | Haemorrhage | **Hepatotoxicity** | Renal impairment

QT prolongation | Arterial thromboembolism | Cardiac dysfunction | GI perforation or fistula | Hypocalcaemia | Non-GI fistula | PRES/RPLS

Hepatotoxicity

The LENVATINIB starting dose for patients with severe renal or severe hepatic impairment is 10 mg.[2] Please refer to the SmPC for more information on these patients.

KEYTRUDA + LENVATINIB should be used in patients with severe hepatic impairment only if the anticipated benefit exceeds the risk.[2]

AE, adverse event; ALT, alanine transaminase; AST, aspartate transaminase; SmPC, Summary of Product Characteristics; TEAE, treatment-emergent adverse event; ULN, upper limit of normal.

Please refer to the individual product SmPCs for further information.

GRADE 1	GRADE 2	GRADE 3	GRADE 4
ALT increase: >ULN – 3.0 x ULN if baseline was normal; 1.5 – 3.0 x baseline if baseline was abnormal. AST increase: >ULN – 3.0 x ULN if baseline was normal; 1.5 – 3.0 x baseline if baseline was abnormal. Bilirubin increase: >ULN – 1.5 x ULN if baseline was normal; > 1.0 – 1.5 x baseline if baseline was abnormal[6]	ALT increase: >3.0 – 5.0 x ULN if baseline was normal; >3.0 – 5.0 x baseline if baseline was abnormal. AST increase: >3.0 – 5.0 x ULN if baseline was normal; >3.0 – 5.0 x baseline if baseline was abnormal. Bilirubin increase: >1.5 – 3.0 x ULN if baseline was normal; >1.5 – 3.0 x baseline if baseline was abnormal[6]	ALT increase: >5.0 – 20.0 x ULN if baseline was normal; >5.0 – 20.0 x baseline if baseline was abnormal. AST increase: >5.0 – 20.0 x ULN if baseline was normal; >5.0 – 20.0 x baseline if baseline was abnormal. Bilirubin increase: >3.0 – 10.0 x ULN if baseline was normal; >3.0 – 10.0 x baseline if baseline was abnormal[6]	ALT increase: >20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal. AST increase: >20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal. Bilirubin increase: >10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal[6]
→		⏸	✕
CONTINUE		**INTERRUPT**	**DISCONTINUE**
LENVATINIB treatment[2]		**LENVATINIB** until resolves to Grade 0–1 or baseline[2]	**LENVATINIB** in the event of a Grade 4 reaction[2]
If intolerable despite optimal management, interrupt **LENVATINIB** until resolves to Grade 0–1 or baseline. If thought to be related to **LENVATINIB**, resume **LENVATINIB** at a reduced dose[2] Further dose adjustments may be necessary based on individual tolerability[2]		↓	
		REDUCE	
		Resume **LENVATINIB** at a reduced dose[2]	

Go to the KEYTRUDA TEAE Management Section >

MANAGE

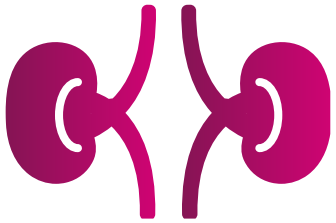
Clinically significant TEAEs for LENVATINIB in the CLEAR trial[3]

Please refer to the **LENVATINIB** SmPC for further information.

Hypothyroidism | Hypertension | PPES | Proteinuria | Haemorrhage | Hepatotoxicity | **Renal impairment**

QT prolongation | Arterial thromboembolism | Cardiac dysfunction | GI perforation or fistula | Hypocalcaemia | Non-GI fistula | PRES/RPLS

Renal impairment



The LENVATINIB starting dose for patients with severe renal or severe hepatic impairment is 10 mg.[2] Please refer to the SmPC for more information on these patients.

Manage patients with renal dysfunction caused by diabetes or hypertension carefully.[16]

AE, adverse event; CrCL, creatinine clearance; eGFR, estimated glomerular filtration rate; LLN, lower limit of normal; SmPC, Summary of Product Characteristics; TEAE, treatment-emergent adverse event.

GRADE 1	GRADE 2	GRADE 3	Nephrotic Syndrome
eGFR or CrCl <LLN–60 mL/min/1.73 m² or proteinuria 2+ present; urine protein/creatinine >0.5[6]	eGFR or CrCl 59–30 ml/min/1.73 m² [6]	eGFR or CrCl 29–15 mL/min/1.73 m² [6]	eGFR or CrCl <15 mL/min/1.73 m². Dialysis or renal transplant indicated[6]
→	→	⏸	✕
CONTINUE		**INTERRUPT**	**DISCONTINUE**
LENVATINIB treatment[2]		**LENVATINIB** until eGFR or CrCL resolves to Grade 0–1 or baseline[2]	Patients with end-stage renal disease have not been studied, therefore the use of **LENVATINIB** in these patients is not recommended[2]
If intolerable despite optimal management, interrupt **LENVATINIB** until resolves to Grade 0–1 or baseline. If thought to be related to **LENVATINIB**, resume **LENVATINIB** at a reduced dose[2] Further dose adjustments may be necessary based on individual tolerability[2]		↓	
		REDUCE	
		Resume **LENVATINIB** at a reduced dose[2]	

Go to the KEYTRUDA TEAE Management Section

MANAGE

Clinically significant TEAEs for LENVATINIB in the CLEAR trial[3]

Please refer to the **LENVATINIB** SmPC for further information.

Hypothyroidism | Hypertension | PPES | Proteinuria | Haemorrhage | Hepatotoxicity | Renal impairment

QT prolongation | Arterial thromboembolism | Cardiac dysfunction | GI perforation or fistula | Hypocalcaemia | Non-GI fistula | PRES/RPLS

QT prolongation

GRADE 1	GRADE 2	GRADE 3	GRADE 4
Average QTc 450–480 ms[6]	Average QTc 481–500 ms[6]	Average QTc ≥501 ms. >60 ms change from baseline[6]	Torsade de pointes. Polymorphic ventricular tachycardia; signs/ symptoms of serious arrhythmia[6]

→

CONTINUE

LENVATINIB treatment[2]

If intolerable despite optimal management, interrupt **LENVATINIB** until resolves to Grade 0–1 or baseline. If thought to be related to **LENVATINIB**, resume **LENVATINIB** at a reduced dose[2]

>500 ms[2]

⏸

INTERRUPT

LENVATINIB until resolves to <480 ms or baseline[2]

↓

REDUCE

Resume **LENVATINIB** at a reduced dose[2]

✕

DISCONTINUE

LENVATINIB should be permanently discontinued if medical management is not successful[2]

AE, adverse event; QTc, corrected QT interval; SmPC, Summary of Product Characteristics; TEAE, treatment-emergent adverse event.

Go to the KEYTRUDA TEAE Management Section >

MANAGE

Clinically significant TEAEs for LENVATINIB in the CLEAR trial[3]

Please refer to the **LENVATINIB** SmPC for further information.

Hypothyroidism | Hypertension | PPES | Proteinuria | Haemorrhage | Hepatotoxicity | Renal impairment

QT prolongation | **Arterial thromboembolism** | Cardiac dysfunction | GI perforation or fistula | Hypocalcaemia | Non-GI fistula | PRES/RPLS

Arterial thromboembolism

The most commonly reported arterial thromboembolic event in the **KEYTRUDA** + **LENVATINIB**-treated group in the CLEAR trial was myocardial infarction (3.4%). The median time to onset of arterial thromboembolic events was 10.4 months in the **KEYTRUDA** + **LENVATINIB**-treated group[2]

LENVATINIB has not been studied in patients who have had an arterial thromboembolism within the previous 6 months, and therefore should be used with caution in such patients. A treatment decision should be made based upon an assessment of the individual patient's benefit/risk. **LENVATINIB** should be discontinued following an arterial thrombotic event[2]

DISCONTINUE

LENVATINIB permanently if an arterial thromboembolism event of any Grade occurs[2]

AE, adverse event; SmPC, Summary of Product Characteristics; TEAE, treatment-emergent adverse event.

Please refer to the individual product SmPCs for further information.

Go to the KEYTRUDA TEAE Management Section

MANAGE

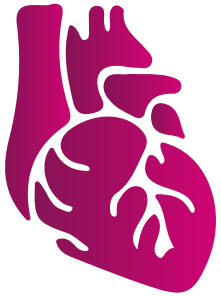
Clinically significant TEAEs for LENVATINIB in the CLEAR trial[3]

Please refer to the **LENVATINIB** SmPC for further information.

Hypothyroidism | Hypertension | PPES | Proteinuria | Haemorrhage | Hepatotoxicity | Renal impairment

QT prolongation | Arterial thromboembolism | **Cardiac dysfunction** | GI perforation or fistula | Hypocalcaemia | Non-GI fistula | PRES/RPLS

Cardiac dysfunction*



GRADE 2	GRADE 3	GRADE 4
Resting ejection fraction 50–40%. 10–19% drop from baseline[6]	Resting ejection fraction 39–20%. ≥20% drop from baseline[6]	Resting ejection fraction <20%[6]
→	⏸	✕
CONTINUE	**INTERRUPT**	**DISCONTINUE**
LENVATINIB treatment[2]	**LENVATINIB** until resolves to Grade 0–1 or baseline[2]	**LENVATINIB** permanently in the event of a Grade 4 reaction[2]
If intolerable despite optimal management, interrupt **LENVATINIB** until resolves to Grade 0–1 or baseline. If thought to be related to **LENVATINIB**, resume **LENVATINIB** at a reduced dose[2]	↓	
	REDUCE	
	Resume **LENVATINIB** at a reduced dose[2]	

Patients should be monitored for clinical symptoms or signs of cardiac decompensation, as dose interruptions, adjustments, or discontinuation may be necessary.

*Cardiac dysfunction characterised by reduced ejection fraction.[6]

AE, adverse event; SmPC, Summary of Product Characteristics; TEAE, treatment-emergent adverse event.

Go to the KEYTRUDA TEAE Management Section >

MANAGE

Clinically significant TEAEs for LENVATINIB in the CLEAR trial[3]

Please refer to the **LENVATINIB** SmPC for further information.

Hypothyroidism | Hypertension | PPES | Proteinuria | Haemorrhage | Hepatotoxicity | Renal impairment

QT prolongation | Arterial thromboembolism | Cardiac dysfunction | **GI perforation or fistula** | Hypocalcaemia | Non-GI fistula | PRES/RPLS

GI perforation or fistula

Gastrointestinal perforation or fistulae have been reported in patients treated with LENVATINIB (is a common adverse event for monotherapy and in combination). In most cases, gastrointestinal perforation and fistulae occurred in patients with risk factors such as prior surgery or radiotherapy. In the case of a gastrointestinal perforation or fistula, dose interruptions, adjustments, or discontinuation may be necessary.[2]

AE, adverse event; GI, gastrointestinal; SmPC, Summary of Product Characteristics; TEAE, treatment-emergent adverse event.

GRADE 1	GRADE 2	GRADE 3	GRADE 4
Asymptomatic[6]	Symptomatic. Invasive intervention not indicated[6]	Invasive intervention indicated[6]	Life-threatening consequences. Urgent intervention indicated[6]
→	→	⏸	✕
CONTINUE	**CONTINUE**	**INTERRUPT**	**DISCONTINUE**
LENVATINIB treatment[2]	**LENVATINIB** treatment[2]	**LENVATINIB** until resolves to Grade 0–1 or baseline[2]	**LENVATINIB** permanently in the event of a Grade 4 or life-threatening reaction[2]
If intolerable despite optimal management, interrupt **LENVATINIB** until resolves to Grade 0–1 or baseline. If thought to be related to **LENVATINIB**, resume **LENVATINIB** at a reduced dose[2]		↓	
		REDUCE	
		Resume **LENVATINIB** at a reduced dose[2]	

Go to the KEYTRUDA TEAE Management Section

MANAGE

Clinically significant TEAEs for LENVATINIB in the CLEAR trial[3]

Please refer to the **LENVATINIB** SmPC for further information.

Hypothyroidism | Hypertension | PPES | Proteinuria | Haemorrhage | Hepatotoxicity | Renal impairment

QT prolongation | Arterial thromboembolism | Cardiac dysfunction | GI perforation or fistula | **Hypocalcaemia** | Non-GI fistula | PRES/RPLS

Hypocalcaemia

GRADE 1	GRADE 2	GRADE 3	GRADE 4
Corrected serum calcium of <LLN–8.0 mg/dL; <LLN–2.0 mmol/L. Ionised calcium <LLN–1.0 mmol/L[6]	Corrected serum calcium of <8.0–7.0 mg/dL; <2.0–1.75 mmol/L. Ionised calcium <1.0–0.9 mmol/L. Symptomatic[6]	Corrected serum calcium of <7.0–6.0 mg/dL; <1.75–1.5 mmol/L. Ionised calcium <0.9–0.8 mmol/L. Hospitalisation indicated[6]	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L. Ionised calcium <0.8 mmol/L. Life-threatening consequences[6]
→	→	⏸	✕
CONTINUE		**INTERRUPT**	**DISCONTINUE**
LENVATINIB treatment[2]		**LENVATINIB** until resolves to Grade 0–1 or baseline[2]	**LENVATINIB** in the event of a life-threatening, Grade 4 reaction[2]
If intolerable despite optimal management, interrupt **LENVATINIB** until resolves to Grade 0–1 or baseline. If thought to be related to **LENVATINIB**, resume **LENVATINIB** at a reduced dose[2]		↓	
		REDUCE	
		Resume **LENVATINIB** at a reduced dose[2]	

AE, adverse event; LLN, lower limit of normal; SmPC, Summary of Product Characteristics; TEAE, treatment-emergent adverse event.

Go to the KEYTRUDA TEAE Management Section >

MANAGE

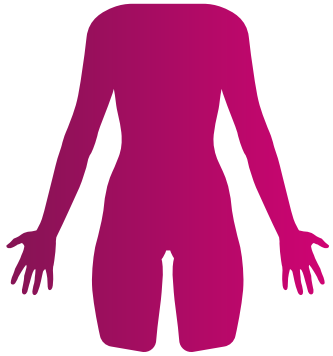
Clinically significant TEAEs for LENVATINIB in the CLEAR trial[3]

Please refer to the **LENVATINIB** SmPC for further information.

Hypothyroidism | Hypertension | PPES | Proteinuria | Haemorrhage | Hepatotoxicity | Renal impairment

QT prolongation | Arterial thromboembolism | Cardiac dysfunction | GI perforation or fistula | Hypocalcaemia | **Non-GI fistula** | PRES/RPLS

Non-GI fistula



Patients may be at increased risk for the development of fistulae when treated with **LENVATINIB**.[2]
Cases of fistula formation or enlargement that involved areas of the body other than the stomach or intestines were observed in clinical trials and in post-marketing experience, including:[2]

- Tracheal fistulae
- Tracheo-oesophageal fistulae
- Oesophageal fistulae
- Cutaneous fistulae
- Female genital tract fistulae

DISCONTINUE

LENVATINIB should not be started in patients with fistulae to avoid worsening and **LENVATINIB** should be permanently discontinued in patients with oesophageal or tracheobronchial tract involvement and any Grade 4 fistula[2]

Limited information is available on the use of dose interruption or reduction in the management of other events, but worsening was observed in some cases and caution should be taken[2]

AE, adverse event; GI, gastrointestinal; SmPC, Summary of Product Characteristics; TEAE, treatment-emergent adverse event.

Go to the KEYTRUDA TEAE Management Section

MANAGE

Clinically significant TEAEs for LENVATINIB in the CLEAR trial[3]

Please refer to the **LENVATINIB** SmPC for further information.

Hypothyroidism	Hypertension	PPES	Proteinuria	Haemorrhage	Hepatotoxicity	Renal impairment
QT prolongation	Arterial thromboembolism	Cardiac dysfunction	GI perforation or fistula	Hypocalcaemia	Non-GI fistula	**PRES/RPLS**

PRES/RPLS

INTERRUPT

LENVATINIB if PRES/RPLS of any Grade occurs[2]

↓

REDUCE

Considering resuming **LENVATINIB** at a reduced dose if resolves to Grade 0–1[2]

Mild to severe hypertension may be present[2] and appropriate measures should be taken to control blood pressure – see hypertension tab for details.

AE, adverse event; PRES, posterior reversible encephalopathy syndrome; RPLS, reversible posterior leukoencephalopathy syndrome; SmPC, Summary of Product Characteristics; TEAE, treatment-emergent adverse event.

REFERENCES

1. KEYTRUDA® (pembrolizumab) Summary of Product Characteristics.
2. LENVATINIB Eisai Summary of Product Characteristics.
3. Motzer R et al. N Engl J Med. 2021;384(14):1289–1300. Including supplementary appendices.
4. Motzer R et al. Oncologist. 2023;28(6):501–509.
5. Ikeda M et al. Expert Opin Drug Saf. 2018;17(11):1095–1105.
6. US Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0; 27 November 2017.
7. Roe H, Lennan E. Nursing: Research and Reviews. 2014;4: 103–115.
8. UKONS. Acute Oncology Initial Management Guidelines Version 2.0; 2018.
9. NCCN. Antiemesis guidelines v2.2023. Available at: https:// www.nccn.org/professionals/physician_gls/pdf/antiemesis.pdf. Accessed November 2023.
10. Giusti et al. Ann Oncol. 2018; 29 (Suppl 4):iv166–iv191.
11. Stachler RJ et al. Otolaryngol Head Neck Surg. 2018;158(Suppl 1):S1–S42.
12. Cancer Care Ontorio. Dysgeusia In Adults With Cancer Symptom Management Algorithm. Available at: https://www.cancercareontario.ca/en/system/files_force/symptoms/DysguesiaAlgorithm.pdf?download=1. Accessed: November 2023.
13. Makker V et al. Oncologist. 2021;26(9):e1599–e1608.
14. Rimassa L et al. Cancer Treat Rev. 2019;77:20–28.
15. Cancer.net (ASCO). Hand-foot syndrome or palmarplantarerythrodysesthesia. Available at: https://www.cancer.net/coping-with-cancer/physical-emotional-and-socialeffectscancer/managing-physical-side-effects/hand-footsyndrome-orpalmar-plantar-erythrodysesthesia. Accessed November 2023.
16. Takahashi S et al. Cancers Head Neck. 2017;2:7.

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