Adverse reaction management in advanced or metastatic renal cell carcinoma (RCC)

# Handbook for adverse reaction management

KEYTRUDA®, in combination with LENVIMA®, is indicated for the treatment of adult patients with advanced (not amenable to curative surgery or radiation) or metastatic RCC with no prior systemic therapy for metastatic RCC.[1,2]

# Contents

This book is a guide to managing adverse events in patients with advanced or metastatic renal cell carcinoma on KEYTRUDA® + LENVIMA® combination therapy. Adverse events can be serious, and it's important to understand the appropriate monitoring and the actions to take if an event occurs.

It's also important that patients are aware of serious side effects and how to respond to them. You can use this guide to help understand how to manage adverse events that may occur on their KEYTRUDA® + LENVIMA® journey.

# Dosage and administration for your patients

## KEYTRUDA® + LENVIMA®

Recommended dosing for adult patients with advanced or metastatic RCC with no prior systemic therapy for metastatic RCC[1,2]

> Management of adverse reactions may require interruption of LENVIMA® treatment. Upon resolution/improvement of an adverse reaction, treatment should be resumed at a reduced dose. Refer to the recommended treatment modifications on Table 1 and Table 3 of the LENVIMA® Product Monograph.
>
> No dose reductions are recommended for KEYTRUDA®. Withhold or discontinue KEYTRUDA® to manage immune-related adverse events in accordance with the instructions in the KEYTRUDA® Product Monograph.

Please refer to the Product Monographs for complete information on dosing, administration and dosage adjustments.

### KEYTRUDA®


Administered as an intravenous (IV) infusion over 30 minutes


200 mg

OR


400 mg

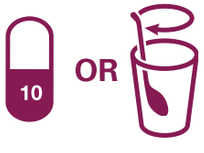
**Continue treatment until unacceptable toxicity, disease progression or for up to 24 months or 35 doses for 200 mg or 18 doses for 400 mg, whichever is longer.**

***in combination with***

### LENVIMA®


20 mg orally once daily at the same time each day

Taken with or without food




Swallowed whole or dissolved in a glass of liquid

**Continue treatment until unacceptable toxicity or disease progression.**

# KEYTRUDA®:


Administered as an intravenous (IV) infusion over 30 minutes


200 mg

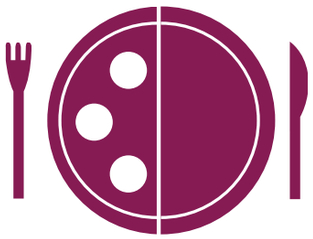
OR


400 mg

**Continue treatment until unacceptable toxicity, disease progression or for up to 24 months or 35 doses for 200 mg or 18 doses for 400 mg, whichever is longer.**

# LENVIMA®


20 mg orally once daily at the same time each day



Taken with or without food


Swallowed whole or dissolved in a glass of liquid

**Continue treatment until unacceptable toxicity or disease progression.**

# Dosage and administration for your patients (cont'd)

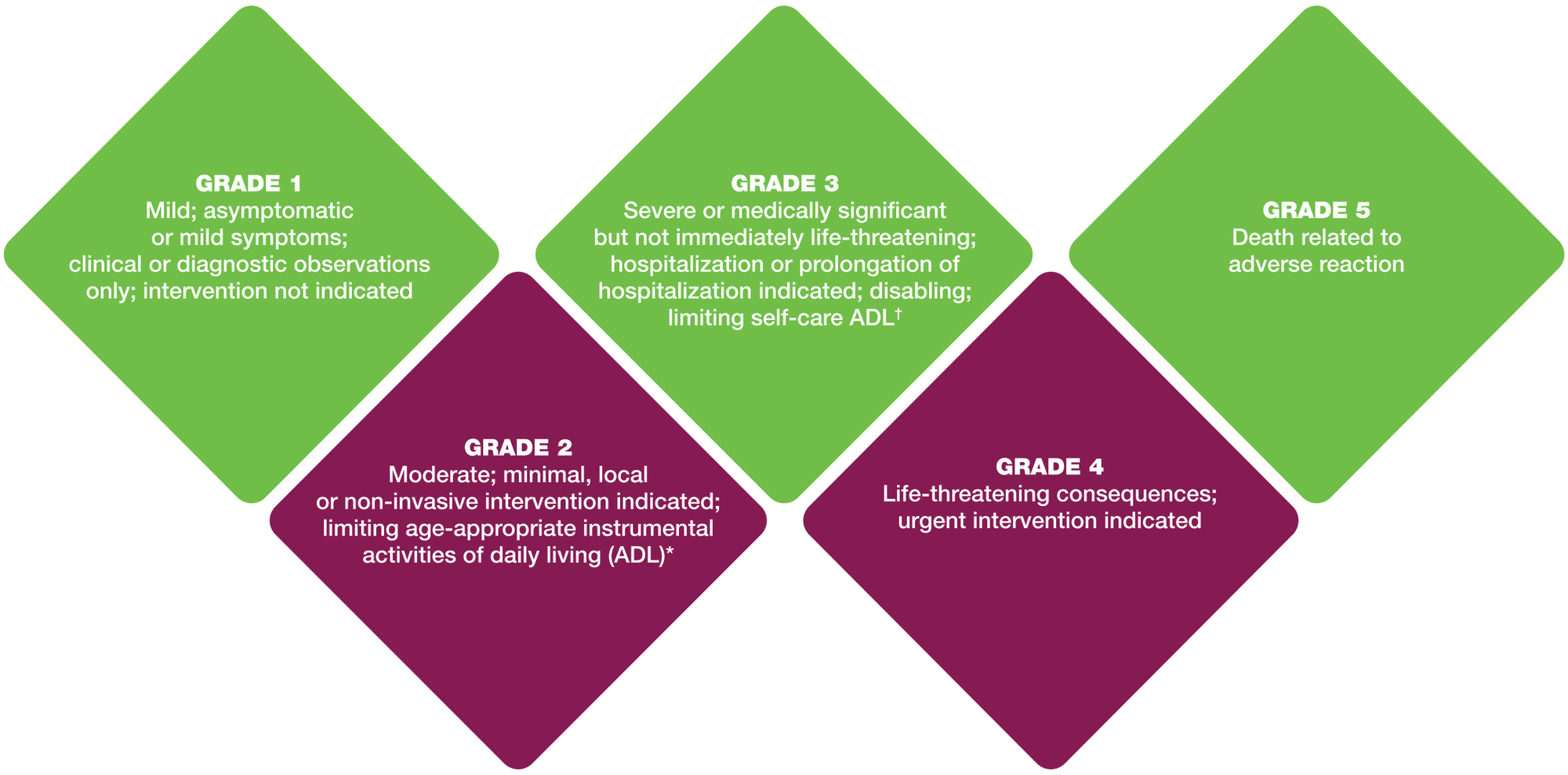
## LENVIMA® administration[2]

- LENVIMA® capsules should be swallowed whole or dissolved in a small glass of liquid. To dissolve in liquid, put capsules into 1 tablespoon of water or apple juice without breaking or crushing the capsules. Leave the capsules in the water or apple juice for at least 10 minutes. Stir for at least 3 minutes. After drinking the mixture, add 1 tablespoon of water or apple juice to the glass, swirl the contents a few times and swallow the water or apple juice.
- If a dose is missed and cannot be taken within 12 hours, skip that dose and take the next dose at the usual time of administration.
- The recommended dosage of LENVIMA® for patients with RCC and severe renal impairment (creatinine clearance less than 30 mL/min) is 10 mg orally once daily.
- The recommended dosage of LENVIMA® for patients with RCC and severe hepatic impairment (Child-Pugh C) is 10 mg orally once daily.

Please refer to the Product Monographs for complete information on dosing, administration and dosage adjustments.

# Grading adverse events

Grading refers to the severity of the adverse event. The general grading scheme is provided below:[3]




For more information on grading specific adverse events, visit the U.S. Department of Health and Human Services Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 published November 27, 2017. The CTCAE is available at: ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf.

* Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
† Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Safety profile in advanced or metastatic RCC with no prior systemic therapy

# Pivotal trial: KEYNOTE-581/CLEAR STUDY

The safety of KEYTRUDA® administered in combination with LENVIMA® was evaluated in KEYNOTE-581/CLEAR STUDY, a multicentre, open-label, randomized, Phase III trial in 1,047 patients with advanced or metastatic RCC with clear cell component and no prior systemic therapy for metastatic RCC.[1,2]

**KEYTRUDA®** + **LENVIMA®**: Median duration of study treatment: 17.0 months (range: 0.1 to 39.1).[1,2]

**KEYTRUDA®** : Median duration of study treatment: 15.1 months (range: 0.03 to 29.6).[1]

**Sunitinib:** Median duration of study treatment: 7.8 months (range: 0.1 to 37.0).[1,2]

Patients received:

| | |
|---|---|
| KEYTRUDA® 200 mg IV every 3 weeks in combination with LENVIMA® 20 mg orally QD (n=355)<br>OR<br>Sunitinib 50 mg orally QD for 4 weeks, then off treatment for 2 weeks (n=357)<br>OR<br>LENVIMA® 18 mg orally QD in combination with everolimus 5 mg orally QD* (n=357) | Until unacceptable toxicity or disease progression as determined by the investigator and confirmed by BIRC using RECIST 1.1 |

- Administration of KEYTRUDA® and LENVIMA® was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered by the investigator to be deriving clinical benefit*
- KEYTRUDA® was continued for a maximum of 24 months or 35 administrations, whichever was longer; LENVIMA® could be continued beyond 24 months
- Assessment of tumour status was performed at baseline and then every 8 weeks

* Use of LENVIMA® in combination with everolimus for previously treated patients with RCC is off-label for adult patients with advanced (not amenable to curative surgery or radiation) or metastatic RCC with no prior systemic therapy for metastatic RCC.

† Administration of LENVIMA® with pembrolizumab beyond RECIST-defined disease progression is off-label; the recommended dosing states that treatment should be stopped when disease progression occurs.

BICR=blinded independent central review; IV=intravenous; QD=once-daily; RECIST=response evaluation criteria in solid tumour.

# KEYNOTE-581/CLEAR study safety profile: KEYTRUDA® combination therapy with LENVIMA®[1,2]

For more information ▶

## Adverse events in ≥20% of patients with advanced or metastatic RCC

The frequencies below are based on all reported adverse events, regardless of the investigator assessment of causality.

| Adverse events | KEYTRUDA® + LENVIMA® (N=352) | | Sunitinib (N=340) | |
|---|---|---|---|---|
| | All Grades (%) | Grades 3–4 (%) | All Grades (%) | Grades 3–4 (%) |
| Hypothyroidism* | 57 | 1 | 32 | 0 |
| Diarrhea† | 62 | 10 | 50 | 6 |
| Stomatitis‡ | 43 | 2 | 43 | 2 |
| Nausea | 36 | 3 | 33 | 1 |
| Abdominal pain§ | 27 | 2 | 18 | 1 |
| Vomiting | 26 | 3 | 20 | 1 |
| Constipation | 25 | 1 | 19 | 0 |
| Fatigue¶ | 63 | 9 | 56 | 8 |
| Hepatotoxicity** | 25 | 9 | 21 | 5 |
| Decreased weight | 30 | 8 | 9 | 0 |
| Decreased appetite†† | 41 | 4 | 31 | 1 |
| Musculoskeletal pain‡‡ | 58 | 4 | 41 | 3 |
| Headache | 23 | 1 | 16 | 1 |
| Proteinuria§§ | 30 | 8 | 13 | 3 |
| Acute kidney injury¶¶ | 21 | 5 | 16 | 2 |
| Dysphonia | 30 | 0 | 4 | 0 |
| Rash*** | 37 | 5 | 17 | 1 |
| Palmar-plantar erythrodysesthesia syndrome††† | 29 | 4 | 38 | 4 |
| Hypertension‡‡‡ | 56 | 29 | 43 | 20 |
| Hemorrhagic events§§§ | 27 | 5 | 26 | 4 |

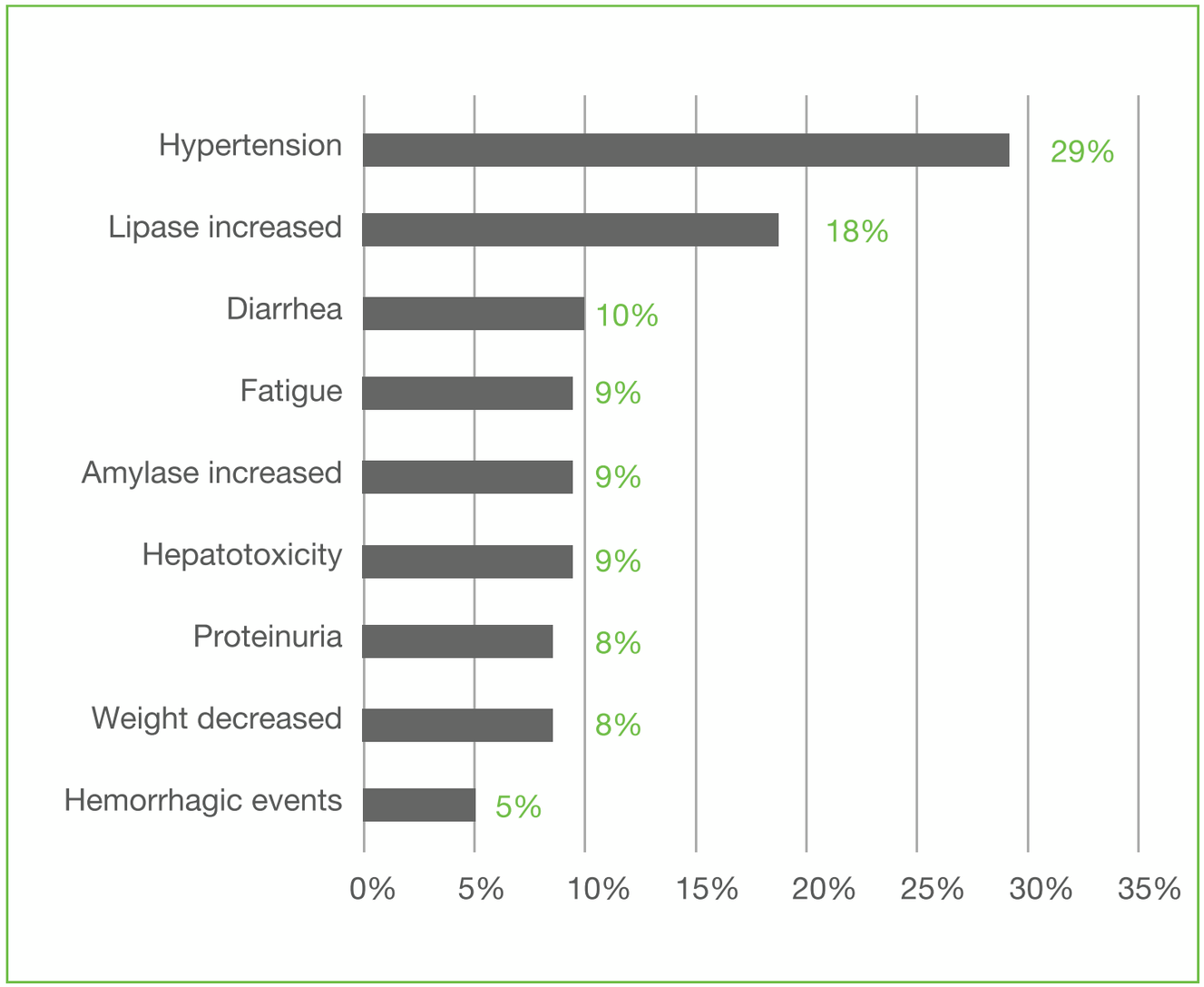
* Includes hypothyroidism, increased blood thyroid stimulating hormone, secondary hypothyroidism.
† Includes diarrhea, gastroenteritis.
‡ Includes aphthous ulcer, gingival pain, glossitis, glossodynia, mouth ulceration, mucosal inflammation, oral discomfort, oral mucosal blistering, oral pain, oropharyngeal pain, pharyngeal inflammation, stomatitis.
§ Includes abdominal discomfort, abdominal pain, abdominal rigidity, abdominal tenderness, epigastric discomfort, lower abdominal pain, upper abdominal pain.
¶ Includes asthenia, fatigue, lethargy, malaise.
** Includes alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, drug-induced liver injury, hepatic enzyme increased, hepatic failure, hepatic function abnormal, hepatocellular injury, hepatotoxicity, hyperbilirubinemia, hypertransaminasemia, immune-mediated hepatitis, liver function test increased, liver injury, transaminases increased, gamma-glutamyltransferase increased.
†† Includes decreased appetite, early satiety.
‡‡ Includes arthralgia, arthritis, back pain, bone pain, breast pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, musculoskeletal stiffness, myalgia, neck pain, non-cardiac chest pain, pain in extremity, pain in jaw.
§§ Includes hemoglobinuria, nephrotic syndrome, proteinuria.
¶¶ Includes acute kidney injury, azotemia, blood creatinine increased, creatinine renal clearance decreased, hypercreatininemia, renal failure, renal impairment, oliguria, glomerular filtration rate decreased, nephropathy toxic.
*** Includes genital rash, infusion site rash, penile rash, perineal rash, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular.
††† Includes palmar erythema, palmar-plantar erythrodysesthesia syndrome, plantar erythema.
‡‡‡ Includes essential hypertension, increased blood pressure, increased diastolic blood pressure, hypertension, hypertensive crisis, hypertensive retinopathy, labile blood pressure.
§§§ Includes all hemorrhage terms. Hemorrhage terms that occurred in 1 or more subjects in either treatment group include: anal hemorrhage, aneurysm ruptured, blood blister, blood loss anemia, blood urine present, catheter site hematoma, cerebral microhemorrhage, conjunctival hemorrhage, contusion, diarrhea hemorrhagic, disseminated intravascular coagulation, ecchymosis, epistaxis, eye hemorrhage, gastric hemorrhage, gastritis hemorrhagic, gingival bleeding, hemorrhage urinary tract, hemothorax, hematemesis, hematoma, hematochezia, hematuria, hemoptysis, hemorrhoidal hemorrhage, increased tendency to bruise, injection site hematoma, injection site hemorrhage, intra-abdominal hemorrhage, lower gastrointestinal hemorrhage, Mallory-Weiss syndrome, melaena, petechiae, rectal hemorrhage, renal hemorrhage, retroperitoneal hemorrhage, small intestinal hemorrhage, splinter hemorrhages, subcutaneous hematoma, subdural hematoma, subarachnoid hemorrhage, thrombotic thrombocytopenic purpura, tumour hemorrhage, traumatic hematoma, upper gastrointestinal hemorrhage.

Adapted from the KEYTRUDA® and LENVIMA® Product Monographs.

# KEYNOTE-581/CLEAR study safety profile: **KEYTRUDA®** combination therapy with **LENVIMA®** (cont'd)

Eighty-two percent of patients had ≥Grade 3 adverse reactions.

## Most common ≥Grade 3 adverse reactions (≥5%)[1,2]



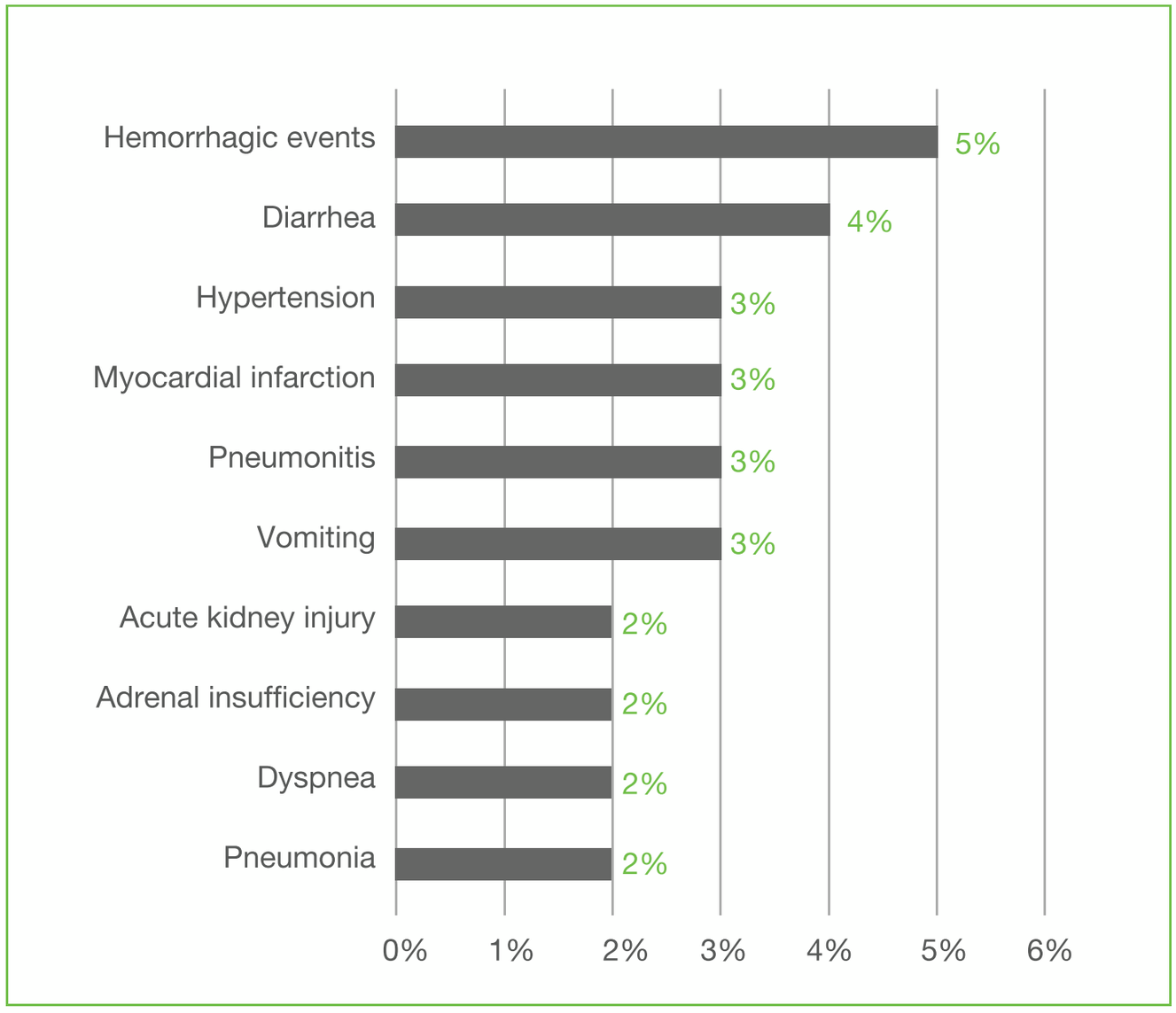
# KEYNOTE-581/CLEAR study safety profile: **KEYTRUDA®** combination therapy with **LENVIMA®** (cont'd)

Fatal adverse events occurred in 4.3% of patients treated with KEYTRUDA® + LENVIMA®, including:[1,2]

- Cardio-respiratory arrest (0.9%)
- Sepsis (0.9%)
- One case (0.3%) each of:
  - Arrhythmia
  - Autoimmune hepatitis
  - Dyspnea
  - Hypertensive crisis
  - Increased blood creatinine
  - Multiple organ dysfunction syndrome
  - Myasthenic syndrome
  - Myocarditis
  - Nephritis
  - Pneumonitis
  - Ruptured aneurysm
  - Subarachnoid hemorrhage

Serious adverse reactions occurred in 51% of patients receiving KEYTRUDA® + LENVIMA®.

## Serious adverse reactions in ≥2% of patients[1,2]

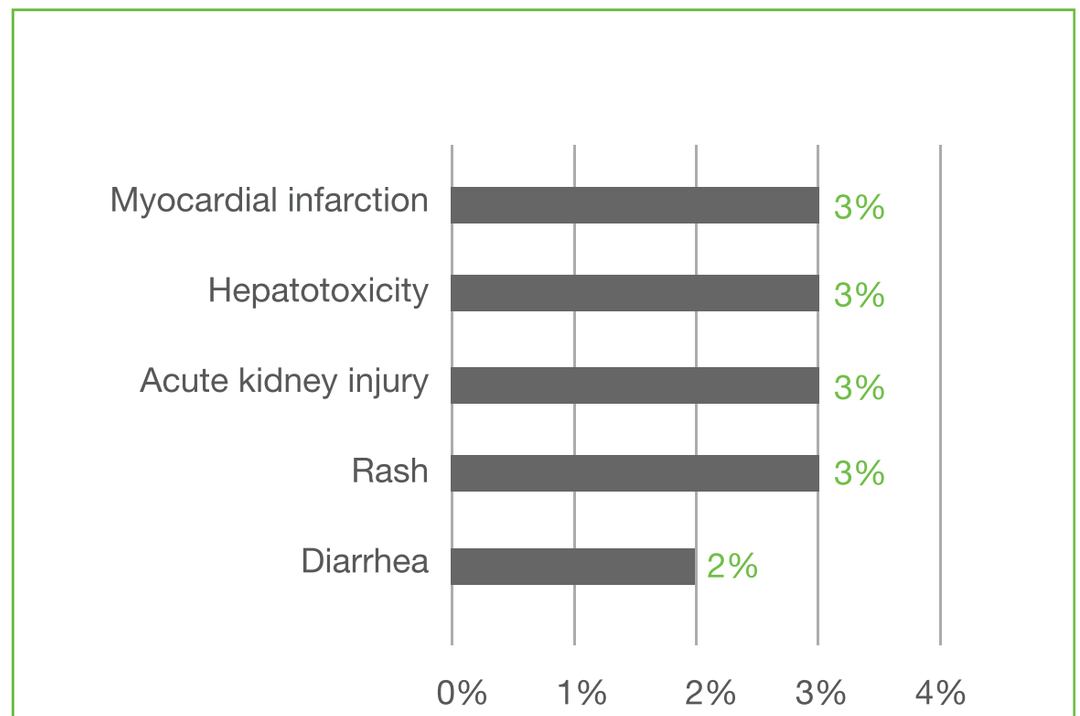


# KEYNOTE-581/CLEAR study safety profile: **KEYTRUDA®** combination therapy with **LENVIMA®** (cont'd)

## Discontinuations

37% of patients receiving KEYTRUDA® + LENVIMA® permanently discontinued either KEYTRUDA®, LENVIMA® or both due to an adverse event (29% KEYTRUDA® only, 26% LENVIMA® only, 13% both).

## Most common adverse events (≥2%) resulting in permanent discontinuation of KEYTRUDA®, LENVIMA® or both[1,2]

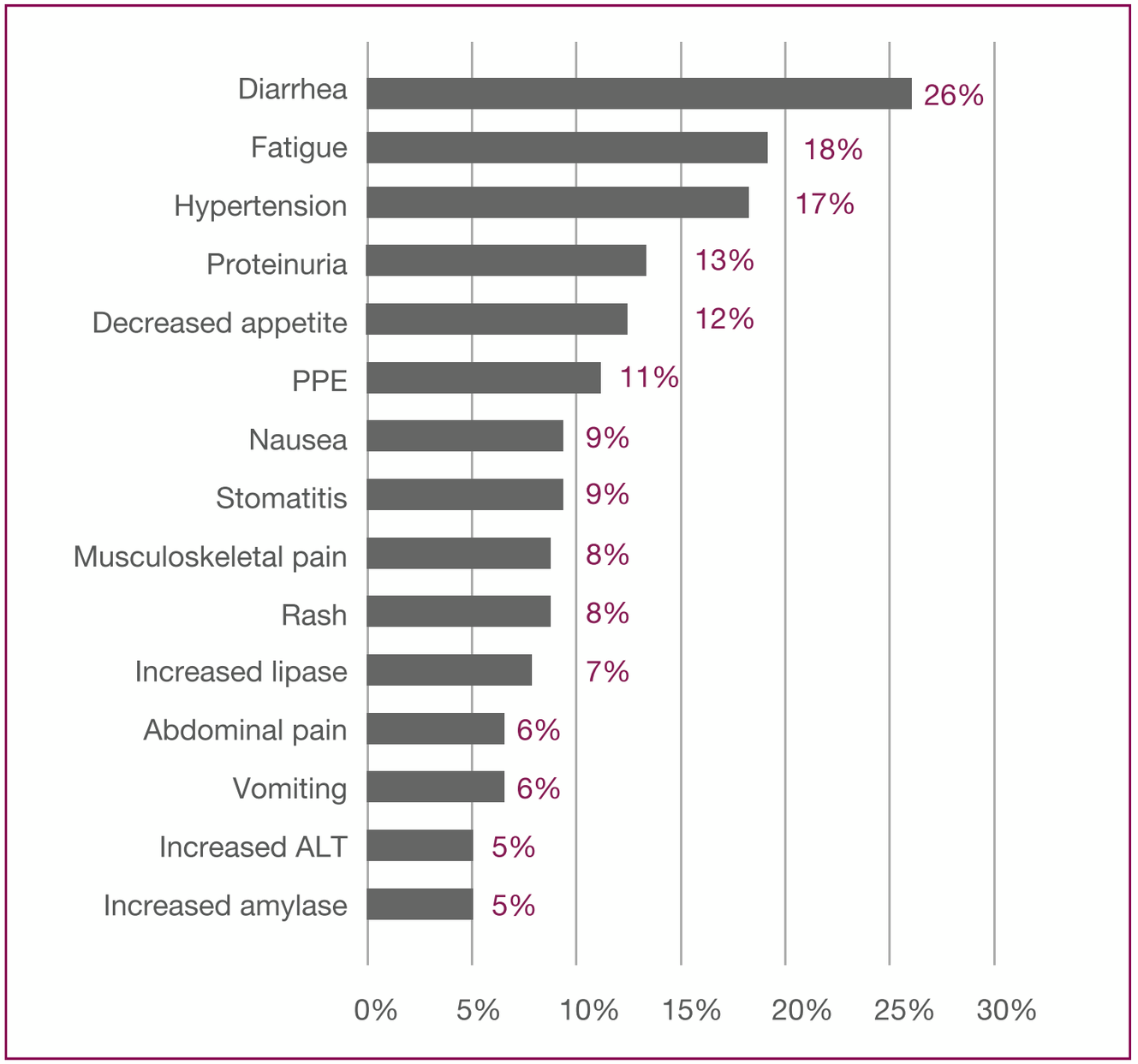


# KEYNOTE-581/CLEAR study safety profile: KEYTRUDA® combination therapy with LENVIMA® (cont'd)

## Dose interruptions

**LENVIMA®**: Median time to first dose reduction: 1.9 months; median average daily dose: 14 mg.[1]

**LENVIMA®: Most common adverse events (≥5%) resulting in dose reduction or interruption of LENVIMA®** [2]



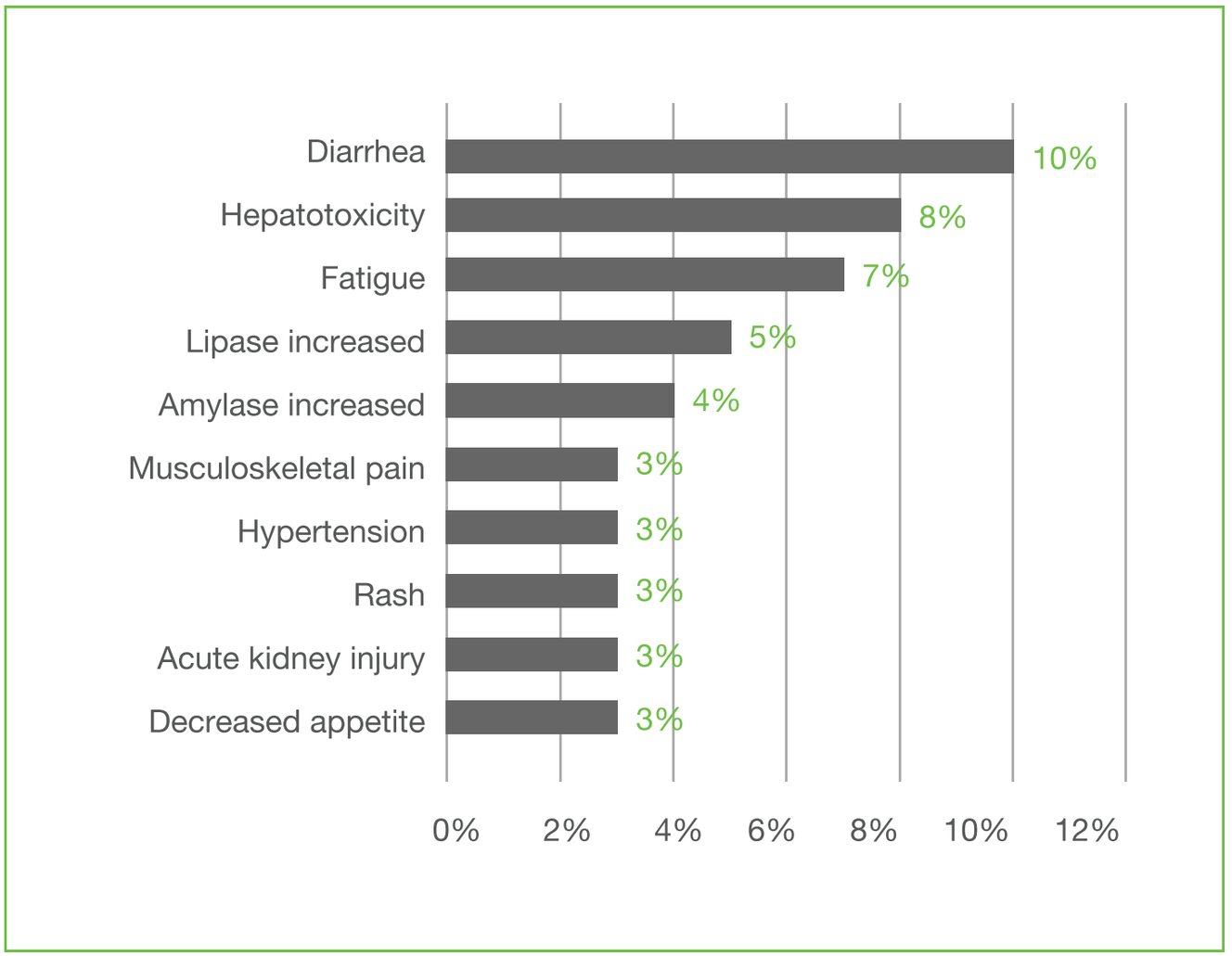

ALT=alanine aminotransferase; PPE=palmar-plantar erythrodysesthesia.

# KEYNOTE-581/CLEAR study safety profile: **KEYTRUDA®** combination therapy with **LENVIMA®** (cont'd)

## Dose interruptions

78% of patients receiving KEYTRUDA® + LENVIMA® interrupted dosing for either KEYTRUDA®, LENVIMA® or both due to an adverse event (55% KEYTRUDA® only, 73% LENVIMA® only, 39% both). LENVIMA® was dose reduced in 69% of patients.[1,2]

## **KEYTRUDA:** Most common adverse events (≥3%) resulting in interruption of KEYTRUDA®[1]




ALT=alanine aminotransferase; PPE=palmar-plantar erythrodysesthesia.

# Monitoring and management of adverse events

No dose reductions are recommended for KEYTRUDA®.

- Withhold or discontinue KEYTRUDA® to manage immune-mediated adverse events in accordance with the instructions in the KEYTRUDA® Product Monograph

When administering KEYTRUDA® + LENVIMA®, interrupt one or both drugs, dose reduce or discontinue LENVIMA®, as appropriate. Based on the absence of clinical experience, there are no recommendations on resumption of dosing for LENVIMA® in patients with Grade 4 clinical adverse reactions that resolve.[2]

Treatment should be discontinued in case of life-threatening reactions (e.g., Grade 4), except for non-life-threatening laboratory abnormalities, which should be managed as severe reactions (e.g., Grade 3).[2]

Recommended dose modifications for LENVIMA® for persistent and intolerable Grade 2 or Grade 3 adverse events or Grade 4 laboratory abnormalities in RCC[2*]

| Adverse events | Interruption | Adjusted dose† |
|---|---|---|
| 1st occurrence | Interrupt until resolved to Grade 0–1 or baseline | **14 mg** orally once daily |
| 2nd occurrence‡ | | **10 mg** orally once daily |
| 3rd occurrence‡ | | **8 mg** orally once daily |

Adapted from the LENVIMA® Product Monograph.

* Initiate medical management for nausea, vomiting, or diarrhea prior to interruption or dose reduction of LENVIMA®.
† Reduce dose in succession based on the previous dose level (20 or 18 mg, 14 mg, 10 mg or 8 mg per day). Dose increases should not occur after reductions have been made.
‡ Refers to the same or a different adverse reaction that requires dose modification.

# Treatment modifications for LENVIMA®

Adverse reactions requiring dose modification[2]

| Adverse reaction | CTCAE guide | Action | Dose modification |
|---|---|---|---|
| Hypertension | Grade 3* | Hold | Resolves to Grade 0, 1 or 2 |
| | Grade 4 | Discontinue | Do not resume |
| Cardiac dysfunction | Grade 3 | Hold | Resolves to Grade 0, 1 or baseline |
| | Grade 4 | Discontinue | Do not resume |
| Arterial thrombotic event | Any Grade | Discontinue | Do not resume |
| Hepatotoxicity | Grade 3 | Hold | Consider resuming at reduced dose if resolves to Grade 0–1 or baseline |
| | Grade 4‡ | Discontinue | Do not resume |
| Hepatic failure | Grade 3 or 4 | Discontinue | Do not resume |
| Proteinuria | >2g/24 hours | Hold | Resolves to <2 g/24 hours |
| Nephrotic syndrome | – | Discontinue | Do not resume |
| Nausea, vomiting, and diarrhea† | Grade 3 | Hold | Resolves to Grade 0, 1 or baseline |
| | Grade 4 | Discontinue | Do not resume |
| Renal failure or impairment | Grade 3 | Hold | Consider resuming at reduced dose if resolves to Grade 0–1 or baseline |
| | Grade 4 | Discontinue | Do not resume |
| GI perforation | Any Grade | Discontinue | Do not resume |
| Fistula | Grade 3 or 4 | Discontinue | Do not resume |
| QTc prolongation | >500 ms | Hold | Resolves to <480 ms or baseline |
| PRES/RPLS | Grade 2–3 | Hold | Consider resuming at reduced dose if resolves to Grade 0–1 or permanently discontinue depending on severity and persistence of neurologic symptoms |
| | Grade 4 | Discontinue | Do not resume |
| Hemorrhage | Grade 3 | Hold | Resolves to Grade 0–1 |
| | Grade 4 | Discontinue | Do not resume |

Adapted from the LENVIMA® Product Monograph.

GI=gastrointestinal, PRES/RPLS=Posterior Reversible Encephalopathy Syndrome or Reversible Posterior Leukoencephalopathy Syndrome, QTc=corrected QT interval.
* Grade 3 despite optimal anti-hypertensive therapy.
† Initiate prompt medical management for nausea, vomiting or diarrhea. Permanently discontinue for Grade 4 vomiting and diarrhea despite medical management.
‡ Grade 4 laboratory abnormalities judged to be non-life-threatening, may be managed as severe reactions (e.g., Grade 3).

# Patient counselling

Counsel your patients to watch for these serious side effects and talk to their healthcare professional in all cases if they experience:[1,2]

**KEYTRUDA® :**

**COMMON**

- **Inflammation of the lungs** (pneumonitis), which can cause shortness of breath, chest pain, or coughing
- **Inflammation of the intestines** (colitis), which can cause diarrhea or more bowel movements than usual, black, tarry, sticky stools or stools with blood or mucus, severe stomach pain or tenderness, nausea, vomiting
- **Inflammation of the pituitary or thyroid gland** (hypophysitis, hypopituitarism, including secondary adrenal insufficiency; hyperthyroidism, hypothyroidism), which can cause rapid heartbeat, weight loss, increased sweating, weight gain, hair loss, feeling cold, constipation, voice getting deeper, muscle aches, dizziness or fainting, headaches that will not go away or unusual headache, feeling more hungry or thirsty, urinating more often than usual
- **Skin problems**, which can cause rash, itching; skin blistering, peeling, or sores; ulcers in mouth or in lining of nose, throat, or genital area

**UNCOMMON**

- **Inflammation of the liver** (hepatitis), which can cause nausea or vomiting, feeling less hungry, pain on the right side of stomach, yellowing of skin or whites of eyes, dark urine, bleeding or bruising more easily than normal
- **Inflammation of the kidneys** (nephritis), which can cause changes in the amount or colour of urine
- **Muscle problems**, which can cause muscle pain or weakness, severe or persistent muscle or joint pains (myositis)
- **Muscle problems**, which can cause weakness and rapid fatigue of muscles or weakness and tingling in arms and legs (myasthenia gravis or Guillain-Barré syndrome)
- **Low red blood cell count** (anemia/hemolytic anemia)
- **Eye problems**, which can cause changes in eyesight
- **Shortness of breath, irregular heartbeat, feeling tired, or chest pain** (myocarditis)
- **Blood sugar problems** (type 1 diabetes mellitus) which can cause hunger or thirst, a need to urinate more often, or weight loss
- **Confusion, fever, memory problems, or seizures** (encephalitis)
- **Swollen lymph nodes, rash or tender lumps on skin, cough, or eye pain** (sarcoidosis)
- **Inflammation of the pancreas** (pancreatitis), which can cause abdominal pain, nausea, and vomiting
- **Reactions related to the infusion** such as shortness of breath, itching or rash, dizziness, or fever, wheezing, flushing, feeling like passing out
- **Pain, numbness, tingling, or weakness in the arms or legs; bladder or bowel problems including needing to urinate more frequently, urinary incontinence, difficulty urinating and constipation** (myelitis)
- **Inflammation of blood vessels** (vasculitis), symptoms include red skin lesions, numbness and weakness
- **Decreased function of the parathyroid gland**, which may include muscle cramps or spasms, fatigue and weakness (hypoparathyroidism)
- **Pain in the upper right part of the stomach, swelling of the liver or spleen, fatigue, itching, or yellowing of the skin or the whites of eyes** (sclerosing cholangitis)

**For more information ▶**

# Patient counselling

Counsel your patients to watch for these serious side effects and talk to their healthcare professional in all cases if they experience:[1,2]

**LENVIMA®:**

**VERY COMMON**

- Diarrhea: passing loose or more frequent stools (bowel movements) than normal

**COMMON**

- **Hypothyroidism** (low level of thyroid hormone in the blood): changes in heart rate, appetite or weight; tiredness; feeling cold; swelling at front of the neck, abnormal levels of thyroid stimulating hormone in the blood
- **Wound complications** (a wound that does not heal)
- **Dehydration** (dry mouth, excessive thirst): thirst, headache, loss of appetite, feel tired and weak, lack of sweating, decreased blood pressure and urine, dark yellow urine
- **Urinary tract infection** (infection in urinary system including kidneys, ureters, bladder and urethra): pain or burning sensation while urinating, frequent urination, blood in urine, pain in the pelvis, strong smelling urine, cloudy urine
- **Inflammation of the pancreas** (pancreatitis): upper abdominal pain, fever, rapid pulse, nausea, vomiting, tenderness when touching the abdomen

**UNCOMMON**

- **Osteonecrosis** (severe jaw bone problems): pain in the mouth, teeth and/or jaw, swelling or sores inside the mouth, numbness or a feeling of heaviness in the jaw, or loosening of a tooth

Counsel your patients to **stop taking LENVIMA® immediately and get immediate help** if they experience:[2]

**VERY COMMON**

- **High blood pressure** (hypertension): headaches, vision disorders, nausea, and vomiting
- **Bleeding**: black, tarry, or bloody stools, or coughing up of blood, sudden and severe headache with nausea, vomiting and loss of consciousness

**COMMON**

- **Liver problems**: yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite, bleeding or bruising more easily than normal, itchiness, or feeling very tired
- **Hypocalcemia** (low level of calcium in the blood): muscle aches, cramps or stiffness; tingling in lips, fingers and feet; fast heartrate
- **Blood clots**: chest pain or pressure; pain in the arms, back, neck or jaw; shortness of breath; numbness or weakness on one side of the body; trouble talking; sudden severe headache; or sudden vision changes
- **Perforation** (tear in your stomach or intestinal wall) or fistula (an abnormal connection between two or more body parts): severe abdominal pain, chills, fever, nausea, vomiting, or a leak of air from the lung into the chest causing sudden chest pain and/or difficulty breathing
- **Ascites** (an abnormal build-up of fluid in the abdomen): sudden weight gain, swollen belly, belly pain, nausea, vomiting, heartburn
- **Kidney problems**: nausea, vomiting, swelling (hands, feet, or around the eyes), foamy urine and fatigue
- **QT prolongation** (an abnormal heart signal): fainting, seizures or fits
- **Infections** (including pneumonia and sepsis): fever, chills, shivering, fast heartrate, rapid breathing
- **Myocardial infarction** (heart attack): chest pain; feeling of pressure, heaviness or squeezing across the chest; occasionally pain in other parts of the body, pain may feel like it is spreading from the chest to the arms, back, neck or jaw

**RARE**

- **Heart failure** (heart does not pump as well as it should): shortness of breath; swelling of ankles and feet
- **Posterior Reversible Encephalopathy Syndrome (PRES)**: headache, seizures, weakness, confusion, high blood pressure, blindness or change in vision, or problems thinking

**VERY RARE**

- **Artery dissection** sudden severe pain in the back, chest or abdomen
- **Artery aneurysm** (a bulge in the wall of any artery including in the chest, arms, legs, heart, and brain): symptoms will differ by the site, and can include: cough, coughing up blood; strong pain high in the neck or back; problems swallowing; hoarse voice; unusual pulsing in the chest or abdomen
- **Cholecystitis** (Inflammation of the gallbladder): fever, nausea, pain that radiates to the shoulder or back, severe pain in the upper right abdomen, vomiting

Advise patients that taking LENVIMA® with pembrolizumab can cause serious immune-mediated side effects, including:

- **Adrenal insufficiency** (decreased release of hormones from the adrenal glands): weakness, fatigue, dizziness upon standing, loss of appetite, nausea, vomiting, diarrhea
- **Myocarditis** (inflammation of the heart muscle): abnormal heartbeat, chest pain, fatigue, fever and other signs of infection like muscle aches, sore throat and diarrhea
- **Pneumonitis** (inflammation of the lungs): shortness of breath, chest pain, cough
- **Myasthenic syndrome** (muscle problems): weakness and fatigue of the muscles

Patients should consult with their healthcare professional if they experience immune-mediated adverse reactions.

Monitor complete blood cell counts, electrocardiogram and electrolytes in LENVIMA® patients regularly.

# Important safety information for LENVIMA®

Clinical use:

- The safety and efficacy of LENVIMA® has not been established in patients <18 years of ages. LENVIMA® should not be used in children <2 years of age.
- For first-line treatment of metastatic RCC with LENVIMA® and pembrolizumab, no overall differences in effectiveness were observed between elderly vs. younger patients. In patients ≥65 years of age, adverse events Grade 3 or higher and discontinuations were higher than in patients <65 years of age.

Most serious warnings & precautions:

- **Hypertension and its complications, including fatal artery dissection**: Serious cases of artery dissection, some fatal, have been reported with or without hypertension. Blood pressure should be well controlled prior to treatment. Monitor blood pressure while on treatment. Blood pressure should be monitored after 1 week of treatment with LENVIMA®, then every 2 weeks for the first 2 months and then monthly thereafter while on treatment. If a patient develops systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg active management is recommended. Early detection and management of hypertension are important to minimize dose interruptions and reductions. Withhold LENVIMA® for Grade 3 hypertension that persists despite optimal antihypertensive therapy; discontinue for life-threatening hypertension.
- **Cardiac failure, including fatal cases**: Cardiac failure, including fatal cases, have been reported. Monitor for symptoms or signs of cardiac decompensation. Withhold LENVIMA® for Grade 3 cardiac dysfunction until improvement to ≤Grade 1 or baseline; discontinue for Grade 4 cardiac dysfunction.
- **Arterial thromboembolism (ATE), including fatal cases**: ATE events have been reported. Exercise caution in patients at risk for, or with a history of ATE; discontinue LENVIMA® following an event. Base treatment decisions upon patient benefit/risk.
- **Gastrointestinal perforation and fistula formation**: Serious events and their sequelae have been commonly reported in clinical trials, including fatal events; discontinue LENVIMA® if these events occur.
- **Hepatotoxicity/hepatic failure, including fatal cases**: Events including hepatic encephalopathy and fatal reactions have been reported. LENVIMA® is not recommended for use in patients with Child-Pugh C impairment. Conduct liver function tests before LENVIMA® initiation, every 2 weeks for 2 months, then monthly. Withhold LENVIMA® for development of Grade 3 or greater liver impairment until resolved; discontinue for hepatic failure.
- **Renal failure and impairment, including fatal cases**: The risk was primarily due to dehydration/hypovolemia because of diarrhea and vomiting. Withhold LENVIMA® if Grade 3 or 4 renal failure/impairment until resolved. LENVIMA® is not recommended in patients with end-stage renal disease.
- **Hemorrhage, including fatal cases**: Hemorrhagic events have been reported, some fatal. Withhold LENVIMA® in patients with Grade 3 hemorrhage until resolved; discontinue for Grade 4.
- **Posterior Reversible Encephalopathy Syndrome (PRES)**: Confirm the diagnosis of PRES with MRI; symptoms include headache, seizure, lethargy, confusion, altered mental function, blindness, visual or neurological disturbances with/without hypertension. Control blood pressure. Withhold LENVIMA® if Grade 1–3 signs/symptoms of PRES are present until recovery. Discontinue for Grade 4.

Other relevant warnings and precautions:

- Prior anticancer treatments
- Osteonecrosis of the jaw (ONJ): Consider a dental examination and preventative dentistry prior to initiating LENVIMA®. If possible, avoid invasive dental procedures. Caution is advised with agents associated with ONJ such as bisphosphonates and denosumab
- Wound healing complications: Withhold LENVIMA® for at least 6 days prior to surgery. Resume LENVIMA® following adequate wound healing. Permanently discontinue in the case of wound healing complications
- Use with drugs that can disrupt electrolyte levels should be avoided
- Concomitant use with QT/QTc interval-prolonging drugs should be avoided
- Hypocalcemia
- Impairment of thyroid stimulating hormone suppression/thyroid dysfunction
- Diarrhea: Initiate prompt medical management
- Proteinuria
- Fertility
- Men and women of reproductive potential should use contraception
- Pregnancy: LENVIMA® should not be used during pregnancy unless necessary and based on a benefit/risk assessment of the mother and fetus
- Breastfeeding: LENVIMA® should not be used during breastfeeding
- Electrolyte-disrupting drugs: When possible, avoid the use of LENVIMA® with drugs that can disrupt electrolyte levels
- Caution in Asian and Caucasian patients
- Body weight <60 kg
- Use of drugs that lower heart rate and/or prolong the PR interval
- Monitor complete blood cell count (CBC)

For more information:

Consult the LENVIMA® Product Monograph at https://ca.eisai.com/-/media/Files/CanadaEisai/LENVIMA-Product Monograph-EN.pdf for important information relating to adverse reactions, drug interactions, and dosing not discussed in this piece. The Product Monograph is also available by calling Eisai Limited at 1-888-551-0547.

GO TO REFERENCES

# Important safety information for KEYTRUDA®

**Clinical use:**

**Pediatrics (<18 years of age):** Safety and efficacy of KEYTRUDA® in pediatric patients have not been established for renal cell carcinoma.

**Geriatrics (≥65 years of age):** No overall differences in safety or efficacy were reported between elderly patients (65 years and over) and younger patients (less than 65 years).

**Relevant warnings and precautions:**

- Immune-mediated adverse reactions, including severe and fatal cases:
  - Pneumonitis
  - Colitis
  - Hepatitis
  - Nephritis and renal dysfunction
  - Endocrinopathies including adrenal insufficiency, hypophysitis, type 1 diabetes mellitus and thyroid disorders
  - Severe skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis
- Other immune-mediated adverse events including uveitis, arthritis, myositis, encephalitis, sarcoidosis, myasthenic syndrome/myasthenia gravis, vasculitis, Guillain-Barré syndrome, hemolytic anemia, pancreatitis, myelitis, hypoparathyroidism, myocarditis, sclerosing cholangitis
- Solid organ transplant rejection
- Elevated liver enzymes in combination with axitinib for RCC
- Allogeneic stem cell transplant after and before treatment
- Severe infusion-related reactions
- Teratogenic toxicity
- Women of childbearing potential should use highly effective contraception and take active measure to avoid pregnancy during treatment with KEYTRUDA® and for at least 4 months after the last dose
- Advise women not to breastfeed during treatment and for at least 4 months after the last dose of KEYTRUDA®
- Patients with hepatic or renal impairment
- Driving and operating machinery
- Monitoring requirements

For more information:

Please consult the Product Monograph at www.merck.ca/static/pdf/KEYTRUDA-PM_E.pdf for important information regarding adverse reactions, drug interactions, and dosing information which have not been discussed in this piece.

The Product Monograph is also available by calling us at 1-800-567-2594 or by email at medinfocanada@merck.com.

# References

References:
1. KEYTRUDA® Product Monograph. Merck Canada Inc. October 19th, 2023.
2. LENVIMA® Product Monograph. Eisai Limited. July 19th, 2023.
3. U.S. Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE): Version 5.0. Available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf. Accessed October 19, 2022.



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