A PRACTICAL GUIDE FOR HCPS

Optimising early identification of adverse events in patients receiving KEYTRUDA® (pembrolizumab) and enfortumab vedotin▼

KEYTRUDA, in combination with enfortumab vedotin, is indicated for the first-line treatment of unresectable or metastatic urothelial carcinoma in adults.[1]

Disclaimers:

This promotional booklet is intended for UK HCPs only and was developed by MSD based on various sources of current published data, including the KEYTRUDA SmPC, and does not constitute part of any official guidelines. The full list of sources used can be found in the reference list on page 14 of this document.

HCPs should always refer to the SmPC and Risk Minimisation Materials for further information and apply their own clinical judgement based on the individual patient's circumstances to minimise the risks associated with the use of medicines mentioned in this booklet before making any prescribing decisions.

The KEYTRUDA Prescribing Information can be accessed by clicking the link here or on page 15 of this PDF.

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 Merck Sharp & Dohme (UK) Limited (Tel: 0208 154 8000).

MSD

HCP, healthcare professional; SmPC, Summary of Product Characteristics.

KEYTRUDA® (pembrolizumab)

GB-PDO-03706; October 2025.

CONTENTS

AE, adverse event.

INTRODUCTION

This booklet is designed to support HCPs in the early identification of AEs which may arise in patients receiving KEYTRUDA and EV. For each AE, screening questions are also included for HCPs to use during consultations with patients to aid in the early detection of treatment-related AEs. This booklet is not intended to provide guidance on the management of these AEs; for information on AE management, please refer to the SmPC.

The seven AEs highlighted in this booklet (skin reactions, peripheral neuropathy, hyperglycaemia, gastrointestinal events, fatigue, pneumonitis, and ocular disorders) reflect those identified by Brower B, et al., as key AEs of clinical interest for KEYTRUDA and EV, based on pooled safety data from the KEYNOTE-A39/EV-302 trial and dose escalation cohorts A and K from the EV-103 trial.[2] This selection is based on the assessment of Brower B, et al., and does not necessarily represent the opinions of MSD.

For each AE detailed, key information is provided on potential risk factors, as well as signs and symptoms, to facilitate timely recognition of AEs to support patient safety and treatment continuity. For a comprehensive overview of AEs associated with KEYTRUDA and EV, please consult their respective SmPCs.

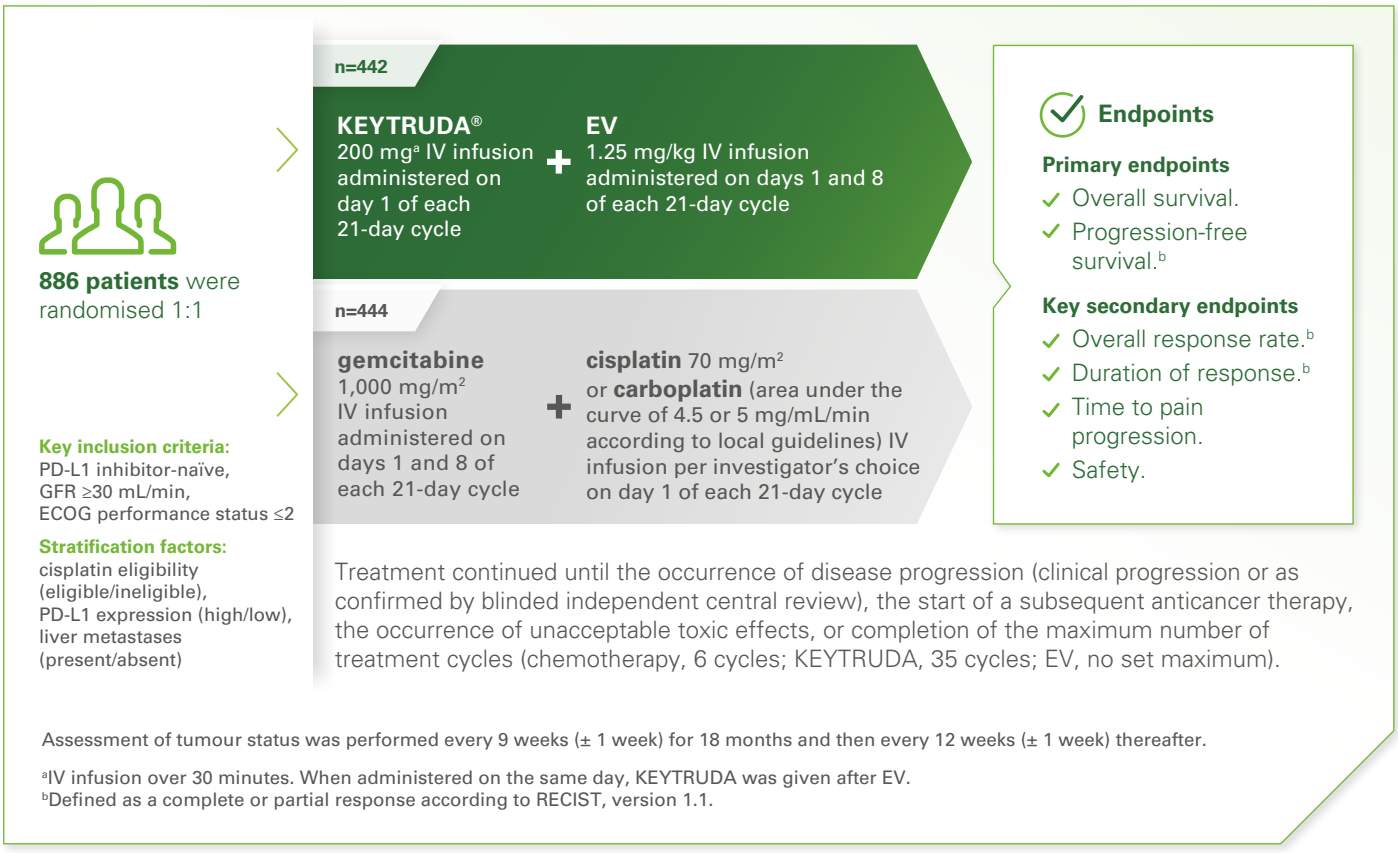
KEYNOTE-A39/EV-302

STUDY OVERVIEW

For full information on KEYNOTE-A39 please refer to reference cited below.[3]

KEYTRUDA, a PD-1 immune checkpoint inhibitor, and EV, an ADC, have been evaluated in the KEYNOTE-A39 trial as a combination treatment for patients with la/mUC.[2,3] The pivotal KEYNOTE-A39 study was a Phase III, global, open-label, randomised trial comparing the efficacy and safety of KEYTRUDA and EV with that of platinum-based chemotherapy in patients with previously untreated la/mUC (**Figure 1**).[2,3]

Figure 1. KEYNOTE-A39 study design[3,4]



Adapted from Powles T, et al. *N Engl J Med.* 2024;390(10):875–888.[3]

ADC, antibody–drug conjugate; AE, adverse event; BICR, blinded independent centralised review; ECOG, Eastern Cooperative Oncology Group; EV, enfortumab vedotin; GFR, glomerular filtration rate; HCP, healthcare professional; IV, intravenous; la/mUC, locally advanced metastatic urothelial cancer; PD-1, programmed cell death protein 1; PD-L1, programmed cell death-ligand 1; RECIST, Response Evaluation Criteria in Solid Tumours; SmPC, Summary of Product Characteristics.

KEYNOTE-A39/EV-302 (continued)

EFFICACY OVERVIEW

The KEYNOTE-A39 clinical trial demonstrated statistically significant and clinically meaningful improvement in overall and progression-free survival in patients receiving KEYTRUDA and EV compared with those receiving chemotherapy (**Table 1**).[2,3]

Table 1: Progression-free and overall survival in patients receiving KEYTRUDA and EV or chemotherapy[3]

Median follow-up: 17.2 months	Progression-free survival			Overall survival		
	Median (95% CI)	Events, n	HR (95% CI)	Median (95% CI)	Events, n	HR (95% CI)
KEYTRUDA + EV	12.5 months (10.4–16.6)	223	0.45 (0.38–0.54); P<0.001	31.5 months (25.4–NR)	133	0.47 (0.38–0.58); P<0.001
Chemotherapy	6.3 months (6.2–6.5)	307		16.1 months (13.9–18.3)	226	

CI, confidence interval; HR, hazard ratio; NR, not reached.
Adapted from Powles T, et al. *N Engl J Med.* 2024;390(10):875–888.[3]

SAFETY OVERVIEW

The safety profile of KEYTRUDA and EV was manageable and consistent with what has been reported previously for this combination, with no new safety signals identified.[3,5] Overall, the incidence of AEs in patients receiving KEYTRUDA and EV was observed to be higher than for KEYTRUDA alone.[1] Adverse reactions were generally similar to those observed in patients receiving KEYTRUDA and EV as monotherapy.[1] Treatment-related AEs of grade ≥3 occurred in 55.9% of the patients receiving KEYTRUDA and EV and in 69.5% of those in the chemotherapy group.[3] The most common treatment-related AEs of any grade in patients treated with KEYTRUDA and EV included peripheral sensory neuropathy (50.0%), pruritus (39.8%) and alopecia (33.2%) (**Table 2**).[3]

As monotherapies, KEYTRUDA and EV are associated with some of the AEs observed with the combination, which may complicate attributing any one AE to a specific agent.[2] However, with vigilant monitoring, early detection, and prompt intervention for treatment-emergent AEs, it is the opinion of Brower B, et al., that most AEs can be managed, allowing patients to continue with their treatment.[2]

TREATMENT-RELATED AEs

Treatment-related AEs of any grade occurred in 427 patients (97.0%) receiving KEYTRUDA and EV and in 414 patients (95.6%) in the chemotherapy group (**Table 2**).[3]

Table 2. Treatment-related AEs in patients receiving KEYTRUDA and EV or chemotherapy[3]

AE,[a] n, (%)	KEYTRUDA and EV (N=440)		Chemotherapy (N=433)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any AE	427 (97.0)	246 (55.9)	414 (95.6)	301 (69.5)
Peripheral sensory neuropathy	220 (50.0)	16 (3.6)	43 (9.9)	0
Pruritus	175 (39.8)	5 (1.1)	21 (4.8)	0
Alopecia	146 (33.2)	2 (0.5)	34 (7.9)	1 (0.2)
Maculopapular rash	144 (32.7)	34 (7.7)	14 (3.2)	0
Fatigue	129 (29.3)	13 (3.0)	156 (36.0)	18 (4.2)
Diarrhoea	121 (27.5)	16 (3.6)	48 (11.1)	3 (0.7)

AE, adverse event; EV, enfortumab vedotin.

Adverse event,[a] n, (%)	KEYTRUDA and EV (N=440)		Chemotherapy (N=433)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Decreased appetite	118 (26.8)	5 (1.1)	98 (22.6)	6 (1.4)
Nausea	89 (20.2)	5 (1.1)	168 (38.8)	12 (2.8)
Anaemia	61 (13.9)	15 (3.4)	245 (56.6)	136 (31.4)
Hyperglycaemia	48 (10.9)	22 (5.0)	3 (0.7)	0
Neutropenia	40 (9.1)	21 (4.8)	180 (41.6)	130 (30.0)
Neutrophil count decreased	16 (3.6)	11 (2.5)	54 (12.5)	39 (9.0)
Thrombocytopenia	15 (3.4)	2 (0.5)	148 (34.2)	84 (19.4)
Platelet count decreased	3 (0.7)	0	63 (14.5)	28 (6.5)

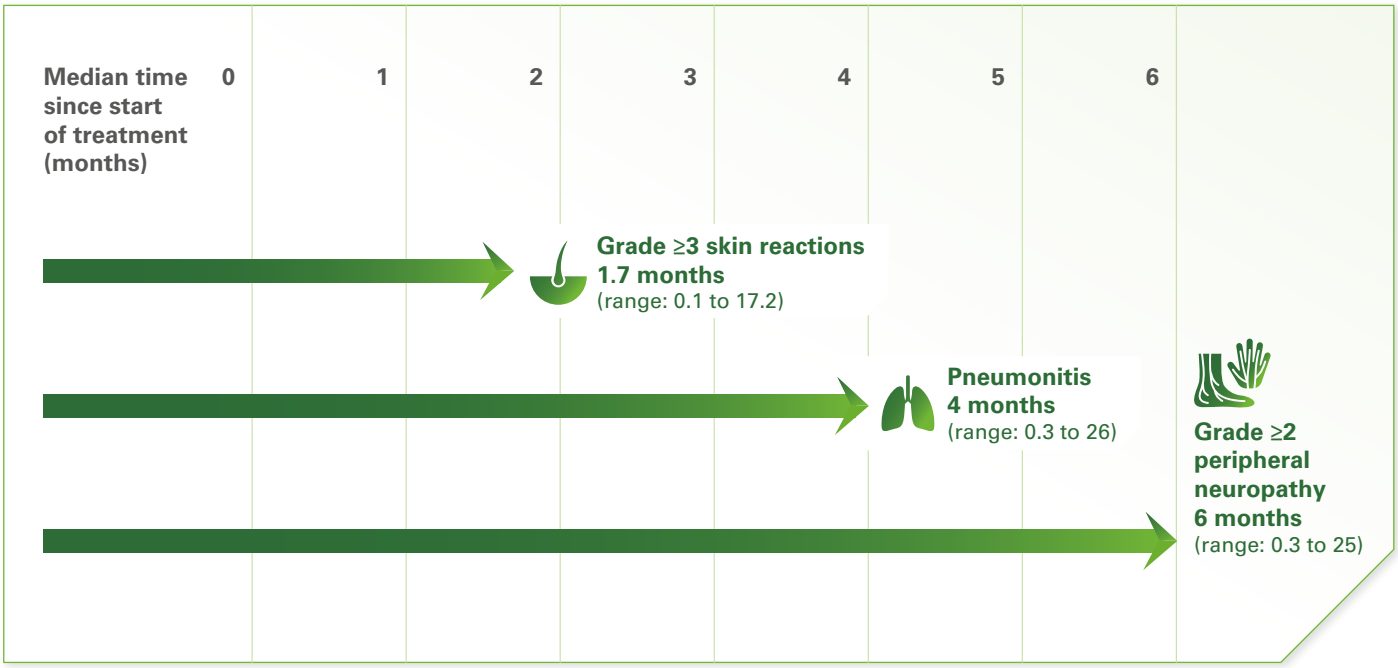
Adapted from Powles T, et al. *N Engl J Med.* 2024;390(10):875–888.[3]

[a]Included are treatment-related AEs of any grade that occurred in ≥20% of patients and those events grade ≥3 that occurred in ≥5% in either treatment group. Treatment-related AEs were defined as those events for which there is a reasonable possibility that they were caused by the trial treatment, as assessed by the investigator.[3]

Treatment-related AEs can occur early in treatment, but the onset can be delayed, and the duration may be prolonged, with the median time to onset for select AEs occurring at different times for different AEs (**Figure 2**).[2]

MEDIAN TIME TO AE ONSET

Figure 2. Median time to onset for select AEs in patients receiving KEYTRUDA and EV in the KEYNOTE-A39 and EV-103 trials (dose escalation cohorts A and K)[2]



Adapted from Brower B, et al. *Front Oncol.* 2024;14:1326715.[2]

Patients should be counselled to report any new or worsening symptoms that can be associated with KEYTRUDA and EV to their care team to determine if prompt intervention is necessary.[6] For each AE described within this booklet, key information is provided on potential risk factors, signs and symptoms, and screening questions to help you support your patients.

AE, adverse event; EV, enfortumab vedotin.

SKIN REACTIONS

The incidence of any-grade or grade ≥3 treatment-related pruritus in patients receiving KEYTRUDA and EV was 39.8% and 1.1%, respectively.[3] For any-grade and grade ≥3 maculopapular rash, the incidence was 32.7% and 7.7%, respectively,[3] which is higher than observed with KEYTRUDA monotherapy.[1]

RISK FACTORS

Select risk factors for the development of skin reactions include[2]:

- A prior history of a dermatological condition (including immune-related skin disorders such as psoriasis or lupus)
- Rash/pruritus
- Allergies
- Dry skin
- High sun exposure
- Prior cutaneous reactions to previous lines of anticancer therapies
- Immunosuppression
- Skin damage due to therapeutic radiation

SIGNS AND SYMPTOMS

Potential signs and symptoms for skin reactions associated with KEYTRUDA and EV treatment include warning signs for severe skin-related AEs, including SJS/TEN, such as malaise, fever (≥100.4°F or ≥38°C), ocular and mucosal involvement and dermatodynia.[6,7]

SCREENING QUESTIONS

Possible screening questions to support the identification of skin reactions during patient consultations include[6]:

- Have you noticed any new or worsening rashes?
- Have you experienced fever or other generalised symptoms?
- Have you noticed any blistering in/around your mouth, eyes and/or genitals?

AE, adverse event; EV, enfortumab vedotin; SJS/TEN, Stevens–Johnson syndrome/toxic epidermal necrolysis.

PERIPHERAL NEUROPATHY

The incidence of any-grade and grade ≥3 treatment-related peripheral sensory neuropathy in patients receiving KEYTRUDA and EV was 50.0% and 3.6%, respectively.[3]

RISK FACTORS

Select risk factors for the development of peripheral neuropathy include[2]:

- Certain anticancer therapies, including monomethyl auristatin E–containing ADCs
- Comorbidities such as diabetes mellitus
- Older age
- Spinal involvement of mUC
- Non-malignant spinal disease

SIGNS AND SYMPTOMS

Potential signs and symptoms of peripheral neuropathy that may be associated with KEYTRUDA and EV treatment[6,8]:

- Peripheral sensory neuropathy: Pain/burning, numbness, tingling or loss of sensation
- Peripheral motor neuropathy: Loss of coordination or muscle weakness

SCREENING QUESTIONS

Possible screening questions to support the identification of peripheral sensory neuropathy during patient consultations include[6]:

- Have you noticed sensations such as pain, burning, numbness or tingling anywhere on your body?
- Have you had trouble walking or performing daily tasks?
- Ask the patient to pick up a coin, pen or other object, or to button or unbutton a shirt. Difficulty with these tasks may indicate onset of peripheral neuropathy

ADC, antibody–drug conjugate; EV, enfortumab vedotin; mUC, metastatic urothelial cancer.

HYPERGLYCAEMIA

The incidence of any-grade and grade ≥3 treatment-related hyperglycaemia in patients receiving KEYTRUDA and EV was 10.9% and 5.0%, respectively.[3]

RISK FACTORS

Select risk factors for the development of hyperglycaemia include[2]:

- History of or ongoing diabetes mellitus and/or hyperglycaemia
- A BMI ≥30 kg/m^2
- Illness/infection
- Use of systemic steroids
- Underlying fatty liver disease

SIGNS AND SYMPTOMS

Potential signs and symptoms of hyperglycaemia associated with KEYTRUDA and EV treatment include[6,9]:

- Increased urination, increased thirst, weight loss, lethargy, confusion, drowsiness, blurred vision, focal neurological deficits or altered mental status. Patients with diabetic ketoacidosis can present with nausea, vomiting, abdominal pain, hyperventilation and a fruity breath odour

SCREENING QUESTIONS

Possible screening questions to support the identification of hyperglycaemia during patient consultations include[6]:

- Have you noticed increased urination or thirst?
- Have you experienced periods of confusion or drowsiness?

BMI, body mass index; EV, enfortumab vedotin.

GASTROINTESTINAL EVENTS

The incidence of any-grade and grade ≥3 treatment-related diarrhoea in patients receiving KEYTRUDA and EV was 27.5% and 3.6%, respectively.[3]

RISK FACTORS

Administration of immunotherapies is the main risk factor for the development of gastrointestinal events.[2]

SIGNS AND SYMPTOMS

Potential signs and symptoms of gastrointestinal events associated with KEYTRUDA and EV treatment include[6]:

- Abdominal pain, nausea, cramping, blood or mucus in stool, changes in bowel habits, fever, abdominal distention, obstipation or constipation

SCREENING QUESTIONS

Possible screening questions to support the identification of gastrointestinal events during patient consultations include[6]:

- Have you noticed any changes in your bowel movements from what is normal for you, such as a change in appearance or consistency?
- Have you experienced any recent pain in your abdomen? Can you describe the pain and how frequently it occurs?

EV, enfortumab vedotin.

FATIGUE

The incidence of any-grade and grade ≥3 treatment-related fatigue in patients receiving KEYTRUDA and EV was 29.3% and 3.0%, respectively.[3]

RISK FACTORS

Select risk factors for the development of fatigue include[2]:

- Comorbidities (disease-related or treatment-related fatigue)
- Anaemia
- Anorexia
- Weight loss
- Endocrinopathies

SIGNS AND SYMPTOMS

Potential signs and symptoms associated with fatigue include[6]:

- Weight gain, hair loss, cold intolerance, constipation, depression, mood changes or loss of libido, limiting ADL

SCREENING QUESTIONS

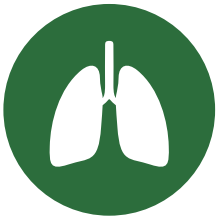
Possible screening questions to support the identification of fatigue during patient consultations include[6]:

- Have you noticed any changes in being able to complete normal activities?
- Have you experienced periods of low mood or energy?
- Have you noticed changes in your weight or appetite?

ADL, activities of daily living; EV, enfortumab vedotin.

PNEUMONITIS

The incidence of any grade and grade ≥3 pneumonitis in patients receiving KEYTRUDA and EV was 10% and 4%, respectively.[2]



RISK FACTORS

Select risk factors for the development of pneumonitis include[1,10,11]:

- Prior thoracic radiation (immune-mediated pneumonitis)
- Certain types of cancer
- Baseline lung conditions
- A history of smoking or asthma
- Prior curative-intent radiotherapy and squamous tumour histology

SIGNS AND SYMPTOMS

Potential signs and symptoms that are common with pneumonitis associated with KEYTRUDA and EV treatment include[10,11]:

- Persistent cough, decreased activity tolerance, fever, chest pain, shortness of breath or trouble breathing

SCREENING QUESTIONS

Possible screening questions to support the identification of pneumonitis during patient consultations include[6]:

- Have you been coughing or had any chest pain?
- Are you able to do all the activities you normally do without difficulty breathing?

EV, enfortumab vedotin.

OCULAR DISORDERS

The incidence of the most common ocular disorder, dry eye, was 24% in patients receiving KEYTRUDA and EV; there were no instances of grade ≥3 dry eye.[2]

RISK FACTORS

Select risk factors for the development of ocular disorders include[2,12,13]:

- For dry eyes: Older age
- For keratitis and corneal complications: Anticancer therapy administration, such as ADCs
- For keratitis: Contact lens use

SIGNS AND SYMPTOMS

Potential signs and symptoms of ocular disorders associated with KEYTRUDA and EV treatment include[6]:

- Dry eye
- Increased tear production
- Conjunctivitis
- Blurred/distorted vision
- Blind spots
- Change in colour vision
- Photophobia
- Tenderness/pain
- Eyelid swelling
- Proptosis

SCREENING QUESTIONS

Possible screening questions to support the identification of ocular disorders during patient consultations include[6]:

- Have you noticed any changes in your vision, including blurred vision, or does light cause discomfort to your eyes?
- Have you had any pain or dryness in/around your eyes?

ADC, antibody–drug conjugate; EV, enfortumab vedotin.

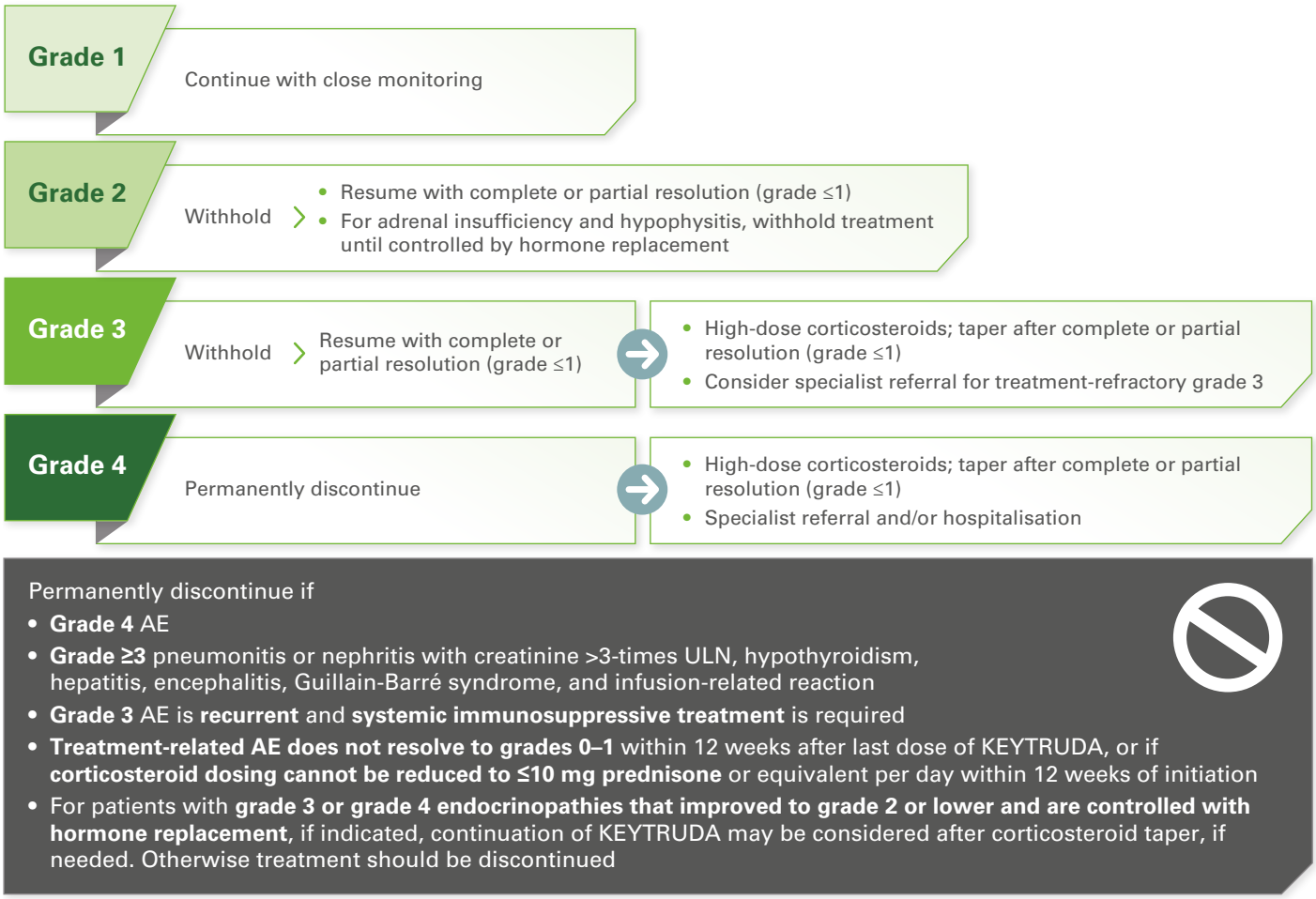
SEVERITY GRADING OF AEs

The general severity grading of an AE is based on the general National Cancer Institute Common Terminology Criteria for Adverse Events guideline (v6.0) and contains unique clinical descriptions of severity for each AE.[6,14]

- **Grade 1:** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- **Grade 2:** Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL
  - Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc
- **Grade 3:** Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care ADL
  - Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications and not being bedridden
- **Grade 4:** Life-threatening consequences; urgent intervention indicated
- **Grade 5:** Death related to AE

The AEs included in this booklet may be associated with treatment using KEYTRUDA and EV. Where AEs are linked to KEYTRUDA, please refer to the general management guidance below, which is dependent on the severity grading of the AE (**Figure 3**). The AEs included in this booklet are not exhaustive and reflect those identified by Brower B, et al., as key AEs of clinical interest for KEYTRUDA and EV, based on pooled safety data from the KEYNOTE-A39 trial and dose escalation cohorts A and K from the EV-103 trial.[2] This selection is based on the assessment of Brower B, et al., and does not necessarily represent the opinions of MSD. HCPs should refer to the SmPC for KEYTRUDA and for EV for the full list of potential AEs and for more detailed guidance on their monitoring and management.

Figure 3. The general management of immune-related AEs associated with KEYTRUDA[1,6]



Adapted from Brower B, et al. *Front Oncol.* 2024;14(suppl):1326715.[6]

ADL, activities of daily living; AE, adverse event; EV, enfortumab vedotin; HCP, healthcare professional; SmPC, Summary of Product Characteristics; ULN, upper limit of normal.

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KEYTRUDA®
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