A Guide to KEYTRUDA® (pembrolizumab) and How to Manage Immune-Mediated Adverse Events

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NI prescribing information can be found at: https://www.emcpi.com/pi/ni/378
A detailed list of all adverse events can be found in the KEYTRUDA SmPC.

MSD

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KEYTRUDA® (pembrolizumab)

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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 1548000). **By clicking this link, you will be redirected to the MHRA website.**

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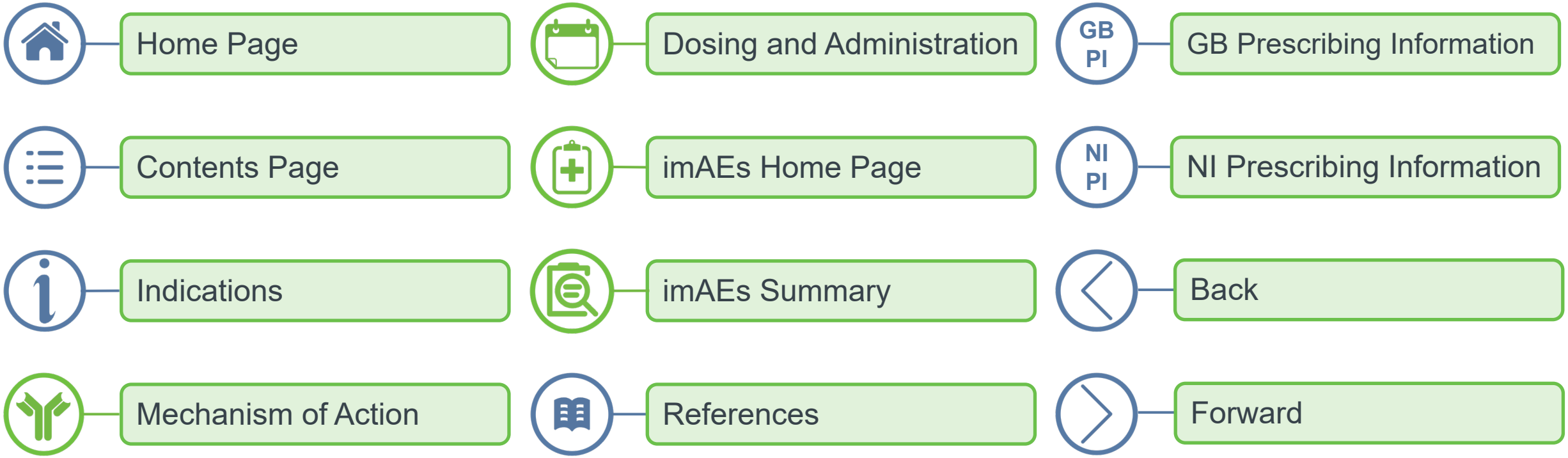
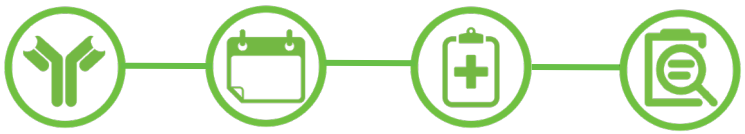
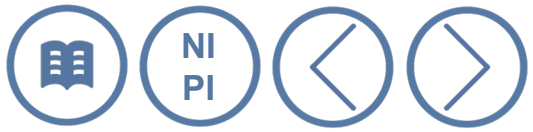
How to use this immune-mediated adverse events guide

- This is an interactive PDF developed as a guide to KEYTRUDA® (pembrolizumab) and how to manage immune-mediated adverse events (imAEs)
- Please use the below icons to navigate around this guide:







Links, abbreviations and references

Links to external sites

- The URL links in this slide deck will redirect you to third-party websites. Please note that:
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References and abbreviations

- References, and definitions of all abbreviations used in this deck can be found at the end of the presentation

KEYTRUDA® (pembrolizumab) indications[1]

Melanoma

- **KEYTRUDA** as monotherapy is indicated for the treatment of adults and adolescents aged 12 years and older with advanced (unresectable or metastatic) melanoma.
- **KEYTRUDA** as monotherapy is indicated for the adjuvant treatment of adults and adolescents aged 12 years and older with Stage IIB, IIC or III melanoma and who have undergone complete resection.

Non-small cell lung carcinoma (NSCLC)

- **KEYTRUDA** as monotherapy is indicated for the adjuvant treatment of adults with non-small cell lung carcinoma who are at high risk of recurrence following complete resection and platinum-based chemotherapy.
- **KEYTRUDA** as monotherapy is indicated for the first-line treatment of metastatic non-small cell lung carcinoma in adults whose tumours express PD-L1 with a ≥ 50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations.
- **KEYTRUDA**, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of metastatic non-squamous non-small cell lung carcinoma in adults whose tumours have no EGFR or ALK positive mutations.
- **KEYTRUDA**, in combination with carboplatin and either paclitaxel or nab-paclitaxel, is indicated for the first-line treatment of metastatic squamous non-small cell lung carcinoma in adults.
- **KEYTRUDA** as monotherapy is indicated for the treatment of locally advanced or metastatic non-small cell lung carcinoma in adults whose tumours express PD-L1 with a ≥ 1% TPS and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should also have received targeted therapy before receiving KEYTRUDA.

Classical Hodgkin lymphoma (cHL)

- **KEYTRUDA** as monotherapy is indicated for the treatment of adult and paediatric patients aged 3 years and older with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option.

Urothelial carcinoma

- **KEYTRUDA** as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy.
- **KEYTRUDA** as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10.

Head and neck squamous cell carcinoma (HNSCC)

- **KEYTRUDA**, as monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, is indicated for the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1.
- **KEYTRUDA** as monotherapy is indicated for the treatment of recurrent or metastatic head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a ≥ 50% TPS and progressing on or after platinum-containing chemotherapy.

KEYTRUDA® (pembrolizumab) indications[1]

Renal cell carcinoma (RCC)

- **KEYTRUDA**, in combination with axitinib, is indicated for the first-line treatment of advanced renal cell carcinoma in adults.
- **KEYTRUDA**, in combination with lenvatinib, is indicated for the first-line treatment of advanced renal cell carcinoma in adults.
- **KEYTRUDA** as monotherapy is indicated for the adjuvant treatment of adults with renal cell carcinoma at increased risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions (for selection criteria, please see section 5.1).

Colorectal cancer (CRC)

- **KEYTRUDA** as monotherapy is indicated for the first-line treatment of metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer in adults.

Microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) cancers

KEYTRUDA as monotherapy is indicated for the treatment of the following MSI-H or dMMR tumours in adults with:

- first-line treatment of metastatic colorectal cancer;
- unresectable or metastatic colorectal cancer after previous fluoropyrimidine-based combination therapy
- advanced or recurrent endometrial carcinoma, who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation;
- unresectable or metastatic gastric, small intestine, or biliary cancer, who have disease progression on or following at least one prior therapy.

Oesophageal carcinoma

- **KEYTRUDA**, in combination with platinum and fluoropyrimidine-based chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic carcinoma of the oesophagus in adults whose tumours express PD-L1 with a CPS ≥ 10.

Triple-negative breast cancer (TNBC)

- **KEYTRUDA**, in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery, is indicated for the treatment of adults with locally advanced, or early-stage triple-negative breast cancer at high risk of recurrence.
- **KEYTRUDA**, in combination with chemotherapy, is indicated for the treatment of locally recurrent unresectable or metastatic triple-negative breast cancer in adults whose tumours express PD-L1 with a CPS ≥ 10 and who have not received prior chemotherapy for metastatic disease.

Endometrial carcinoma (EC)

- **KEYTRUDA,** in combination with lenvatinib, is indicated for the treatment of advanced or recurrent endometrial carcinoma in adults who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation.

KEYTRUDA® (pembrolizumab) indications[1]

Cervical cancer (CC)

- **KEYTRUDA**, in combination with chemotherapy with or without bevacizumab, is indicated for the treatment of persistent, recurrent, or metastatic cervical cancer in adults whose tumours express PD-L1 with a CPS ≥ 1.

Gastric or gastro-oesophageal junction (GEJ) adenocarcinoma

- **KEYTRUDA**, in combination with trastuzumab, fluoropyrimidine and platinum-containing chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1.
- **KEYTRUDA**, in combination with fluoropyrimidine and platinum-containing chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1

Biliary tract carcinoma (BTC)

- **KEYTRUDA,** in combination with gemcitabine and cisplatin, is indicated for the first-line treatment of locally advanced unresectable or metastatic biliary tract carcinoma in adults.

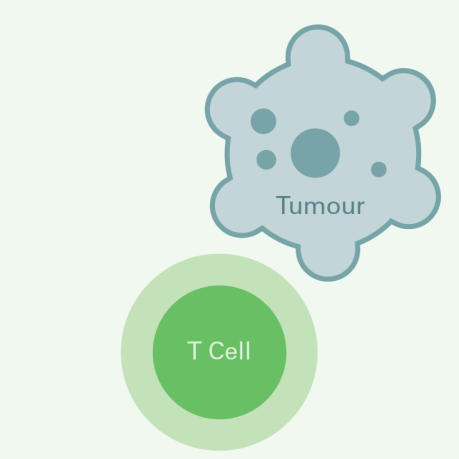
Contents

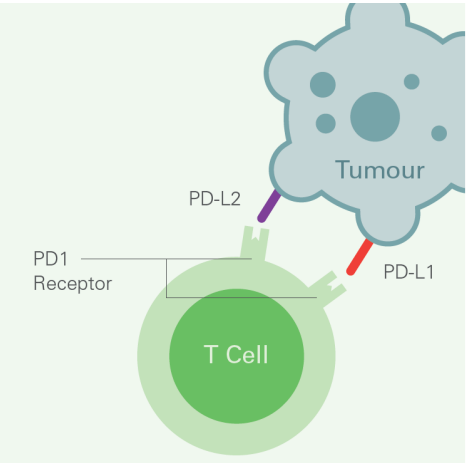
Mechanism of Action

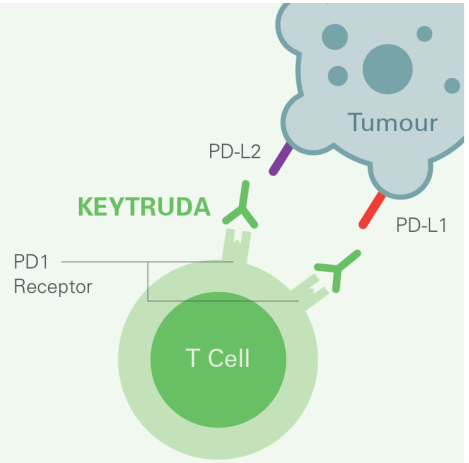
KEYTRUDA®
(pembrolizumab)

KEYTRUDA monotherapy mechanism of action[1,2]

- **KEYTRUDA** is a humanised monoclonal antibody which binds to the programmed cell death-1 (PD-1) receptor, blocking both immune-suppressing ligands, PD-L1 and PD-L2, from interacting with PD-1 to help potentiate T-cell response and immune response[1,2]







Normal immune response

When interacting with most aberrant or cancerous cells, T cells are activated and can attack tumour cells.

Tumour evasion and T cell deactivation

A proportion of tumours can evade the immune system through the PD-1 pathway. The PD-L1 and PD-L2 ligands on tumours can bind with PD-1 receptors on T cells to inactivate the T cells.

T cell reactivation with KEYTRUDA

KEYTRUDA binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, which helps potentiate the immune response. While having an effect on the tumour, this could also affect the immune system's interaction with normal healthy cells throughout the body.

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KEYTRUDA and cytotoxic chemotherapy mechanism of action[3,4]

Cytotoxic chemotherapy can increase the rate of cancer cell death, activating a broader range of T cells.

Combining **KEYTRUDA** and cytotoxic chemotherapy may enhance the immune response, increasing tumour cell death.

In combination with

KEYTRUDA

Chemotherapy

KEYTRUDA and TKI mechanisms of action[1,5]

KEYTRUDA and TKIs, such as **axitinib**, inhibit two distinct disease pathways in advanced RCC.[1,5]

KEYTRUDA

Tumour evasion of immune responses[1]

KEYTRUDA binds to the PD-1 receptor potentiating T-cell responses, including anti-tumour response.

Axitinib

Tumour angiogenesis[5]

Axitinib is a potent inhibitor of VEGFR-1/2/3, receptors that have been implicated in pathologic angiogenesis, tumour growth, and metastatic progression of cancer.

KEYTRUDA and multi-TKI mechanisms of action[1]

KEYTRUDA and multi-TKIs, such as **lenvatinib**, combine to help overcome resistance to immunotherapy.[1]

KEYTRUDA

Tumour evasion of immune responses[1]

KEYTRUDA binds to the PD-1 receptor potentiating T-cell responses, including anti-tumour response.

Lenvatinib

Greater T-cell activation

Lenvatinib in combination with **KEYTRUDA** results in a tumour microenvironment with greater T-cell activation to help overcome primary and acquired resistance to immunotherapy. This may improve tumour responses compared to either treatment alone.[1]

Dosing and Administration

Please refer to KEYTRUDA SmPC and Risk Minimisation Materials (RMM), axitinib SmPC and relevant chemotherapy SmPCs before prescribing

KEYTRUDA®
(pembrolizumab)

KEYTRUDA as monotherapy or combination therapy is available across adult indications as:[1,6]

Every **3 weeks** 200 mg **OR** Every **6 weeks** 400 mg

400 mg Q6W dosing schedule for KEYTRUDA was based on an exposure-response (E-R) evaluation using modelling and simulation[1,6]

Over **30 minutes**

The recommended dose of **KEYTRUDA** in adults is either **200 mg Q3W** or **400 mg Q6W administered intravenously over 30 minutes** using a sterile, nonpyrogenic, low-protein binding 0.2 to 5 µm in-line or add-on filter[1]

Patients should be treated with **KEYTRUDA** until disease progression or unacceptable toxicity (and up to maximum duration of therapy if specified for an indication)
Refer to the SmPC for further details before prescribing[1]

When administering **KEYTRUDA** as part of a combination with chemotherapy, **KEYTRUDA** should be administered first[1]

KEYTRUDA as a monotherapy is available for paediatric patients with cHL as:[1]

The recommended dose of **KEYTRUDA** as **monotherapy** in paediatric patients aged 3 years and older with cHL or patients aged 12 years and older with melanoma is **2 mg/kg bodyweight (up to a maximum of 200 mg), Q3W administered intravenously over 30 minutes** using a sterile, nonpyrogenic, low-protein binding 0.2 to 5 µm in-line or add-on filter[1]

Patients should be treated with **KEYTRUDA** until disease progression or unacceptable toxicity (and up to maximum duration of therapy if specified for an indication)

Refer to the SmPC for further details before prescribing[1]

Dosing and administration of KEYTRUDA and axitinib (RCC)[1,5]

KEYTRUDA[1]

Every 3 weeks

200 mg

- The recommended dose for **KEYTRUDA** as part of combination therapy in adults is **200 mg every 3 weeks** as an **intravenous infusion over 30 minutes**
- **KEYTRUDA** is administered using a sterile, low-protein binding 0.2 to 5 µm in-line or add-on filter
- Patients should be treated with **KEYTRUDA** until disease progression or unacceptable toxicity
- Other medicinal products should not be co-administered through the same infusion line

Axitinib[5]

Twice daily

2 mg ❮ 3 mg ❮ 5 mg ❯ 7 mg ❯ 10 mg

Recommended starting dose

- Dose increase of **axitinib** (to 7 mg or 10 mg BID) or reduction (to 3 mg or 2 mg BID) is recommended based on individual safety and tolerability
- Dose escalation of **axitinib** above the initial 5 mg dose may be considered at intervals of six weeks or longer
- **Prescribers should refer to the axitinib SmPC before use**

Dosing and administration of KEYTRUDA and lenvatinib (RCC)[1,7]

KEYTRUDA[1]

Every 3 weeks

200 mg

- The recommended dose for **KEYTRUDA** as part of combination therapy in adults is **200 mg every 3 weeks** as an **intravenous infusion over 30 minutes**
- **KEYTRUDA** is administered using a sterile, low-protein binding 0.2 to 5 µm in-line or add-on filter
- Patients should be treated with **KEYTRUDA** until disease progression or unacceptable toxicity
- Other medicinal products should not be co-administered through the same infusion line

Lenvatinib[7]

Once daily

20 mg

Recommended starting dose

- Recommended dose is 20mg (2 x 10 mg capsules) orally once daily in combination with KEYTRUDA (either 200mg every 3 weeks or 400mg every 6 weeks, via IV infusion over 30 minutes)
- Daily dose of Lenvatinib to be modified as needed according to dose/toxicity management plan
- **Prescribers should refer to the lenvatinib SmPC before use**

Immune-Mediated Adverse Events (imAEs)

KEYTRUDA is associated with imAEs and these slides focus on the treatment modifications for imAEs only. A full list of undesirable effects can be found in the KEYTRUDA SmPC.

Consider all adverse events (AEs) and refer to the KEYTRUDA SmPC and Risk Minimisation Materials (RMM) for full information on all AEs before prescribing KEYTRUDA.

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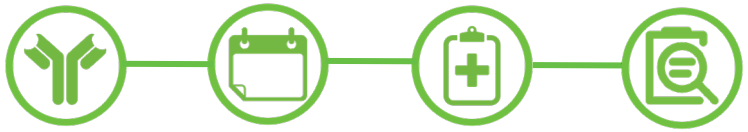
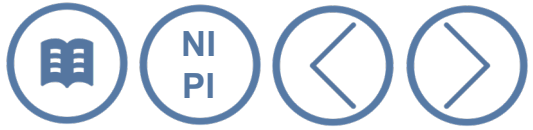

KEYTRUDA safety in a studied population[1]

KEYTRUDA safety data studied populations based on Q3W administration

Pooled safety population of KEYTRUDA[1]

- The safety of pembrolizumab as monotherapy has been evaluated in 7,631 patients with advanced melanoma, resected Stage III melanoma (adjuvant therapy), NSCLC, cHL, urothelial carcinoma, HNSCC, CRC, endometrial, gastric, small intestine, biliary, pancreatic cancer or adjuvant therapy of RCC across four doses (2 mg/kg bw every 3 weeks, 200 mg every 3 weeks, or 10 mg/kg bw every 2 or 3 weeks) in clinical studies.
- The safety of KEYTRUDA in combination with chemotherapy has been evaluated in 4,787 patients across tumour types receiving 200 mg, 2 mg/kg bw or 10 mg/kg bw KEYTRUDA every 3 weeks, in clinical studies.
- When KEYTRUDA is administered in combination with chemotherapy, refer to the SmPC for the respective combination therapy components prior to initiation of treatment.

KEYTRUDA safety in a studied population[1]

KEYTRUDA safety data studied populations based on Q3W administration

KEYTRUDA in combination with TKIs[1]

- The safety of KEYTRUDA in combination with axitinib or lenvatinib in advanced RCC, and in combination with lenvatinib in advanced EC has been evaluated in a total of 1,456 patients with advanced RCC or advanced EC receiving 200 mg KEYTRUDA every 3 weeks with either axitinib 5mg twice daily or lenvatinib 20 mg once daily in clinical studies, as appropriate.
- When pembrolizumab is administered in combination with axitinib or lenvatinib, refer to the SmPC for axitinib or lenvatinib prior to initiation of treatment. For additional lenvatinib safety information related to advanced RCC see the SmPC for Kisplyx and for advanced EC see the SmPC for Lenvima.

Urothelial carcinoma - specific precaution[1]

Use of Keytruda in urothelial carcinoma patients who have received prior platinum-containing chemotherapy[1]

- Physicians should consider the delayed onset of KEYTRUDA effect before initiating treatment in patients with poorer prognostic features and/or aggressive disease. In urothelial carcinoma, a higher number of deaths within 2 months was observed in KEYTRUDA compared to chemotherapy. Factors associated with early deaths were fast progressive disease on prior platinum therapy and liver metastases.

KEYTRUDA safety in a studied population[1]

Certain groups were excluded from clinical trials

Patients with the following conditions were excluded from clinical studies[1]:

- Active CNS metastases; ECOG PS ≥ 2 (except for urothelial carcinoma and RCC); HIV infection, hepatitis B or hepatitis C infection; active systemic autoimmune disease; interstitial lung disease; prior pneumonitis requiring systemic corticosteroid therapy; a history of severe hypersensitivity to another monoclonal antibody; receiving immunosuppressive therapy and a history of severe immune-mediated adverse reactions from treatment with ipilimumab, defined as any Grade 4 toxicity or Grade 3 toxicity requiring corticosteroid treatment (> 10 mg/day prednisone or equivalent) for greater than 12 weeks.
- Patients with active infections were excluded from clinical studies and were required to have their infection treated prior to receiving KEYTRUDA. Patients with active infections occurring during treatment with KEYTRUDA were managed with appropriate medical therapy. Patients with clinically significant renal (creatinine > 1.5 x ULN) or hepatic (bilirubin > 1.5 x ULN, ALT, AST > 2.5 x ULN in the absence of liver metastases) abnormalities at baseline were excluded from clinical studies, therefore information is limited in patients with severe renal and moderate to severe hepatic impairment.

KEYTRUDA immune-mediated adverse event overview[1]

KEYTRUDA is associated with immune-mediated adverse events.[1]

Recommended treatment modifications for KEYTRUDA are dependent on type and Grade. Specific immune-mediated adverse events can be found in the SmPC and later in this document.

- Immune-mediated adverse reactions, including severe and fatal cases, have occurred in patients receiving KEYTRUDA
- Most immune-mediated adverse events are reversible and may be managed with interruptions of KEYTRUDA, administration of corticosteroids and/or supportive care
- Immune-mediated adverse events have also occurred after the last dose of KEYTRUDA. Immune-mediated adverse reactions affecting more than one body system can occur simultaneously

KEYTRUDA Grade 3–4 immune-mediated adverse events.[1,6]

Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI-CTCAE v.4). A table of the grades for individual immune-mediated adverse events can be found HERE and at the end of this presentation

- KEYTRUDA must be permanently discontinued for any Grade 3 immune-mediated adverse reaction that recurs and for any Grade 4 immune-mediated adverse reaction toxicity, except for endocrinopathies that are controlled with replacement hormones
- For more details please refer to the SmPC for managing individual immune-mediated adverse reactions

Please refer to the KEYTRUDA Summary of Product Characteristics and Risk Minimisation Materials before prescribing KEYTRUDA.

Treatment Modifications for Immune-Mediated Adverse Events (imAEs)[1,6]


Hyperthyroidism


Hypothyroidism


Colitis


Hepatitis

Elevated liver enzymes


Adrenal insufficiency


Hypophysitis


Pneumonitis


Diabetes


Nephritis


Other imAEs


Infusion related reactions


Skin reactions

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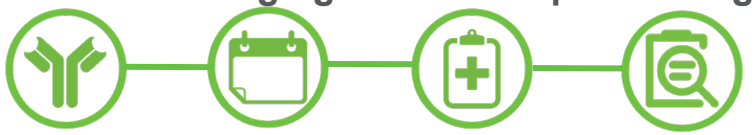
Please refer to the KEYTRUDA SmPC and Risk Minimisation Materials (RMM) for full information on managing AEs before prescribing KEYTRUDA.



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Hyperthyroidism

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Hyperthyroidism[1]

Treatment modifications for hyperthyroidism in patients prescribed KEYTRUDA

	Grade 1	Grade 2	Grade 3–4
KEYTRUDA treatment	May continue treatment and monitor	May continue treatment and monitor	Withhold until recovery to Grade ≤1. If toxicity does not resolve to Grade 0–1 within 12 weeks after last dose of KEYTRUDA, or corticosteroid dosing cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks, permanently discontinue KEYTRUDA
Corticosteroid treatment	-	-	Consider administration of corticosteroids and taper as required Please refer to the SmPC for further information
Additional management	May be managed symptomatically Thyroid function and hormone levels should be monitored to ensure appropriate replacement		For patients with Grade 3 or Grade 4 endocrinopathies that improved to Grade 2 or lower and are controlled with hormone replacement, if indicated, continuation of KEYTRUDA may be considered after corticosteroid taper, if needed. Otherwise treatment should be discontinued.

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

Hyperthyroidism[1]

Prevalence in clinical trials

Pooled safety population of KEYTRUDA[1]

- Hyperthyroidism occurred in 394 (5.2%) patients, including Grade 2 or 3 cases in 108 (1.4%) and 9 (0.1% patients, respectively, receiving pembrolizumab. The median time to onset of hyperthyroidism was 1.4 months (range 1 day to 23.2 months). The median duration was 1.6 months (range 4 days to 43.1+ months). Hyperthyroidism led to discontinuation of pembrolizumab in 4 (0.1%) patients. Hyperthyroidism resolved in 326 (82.77%) patients, 11 with sequelae.

Monitoring hyperthyroidism in patients prescribed KEYTRUDA[1]

- Patients should be monitored for the changes in thyroid function (at the start of treatment, periodically throughout and when indicated by clinical evaluation) as well as clinical signs and symptoms of thyroid disorders. Hormone levels should also be monitored.
- Along with hypothyroidism/hyperthyroidism, thyroiditis has also been reported and can occur at any time during treatment.

Hypothyroidism

KEYTRUDA®
(pembrolizumab)

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Hypothyroidism[1]

Treatment modifications for hypothyroidism in patients prescribed KEYTRUDA

KEYTRUDA treatment	May continue treatment and monitor
Additional management	May be managed with replacement hormone therapy without treatment interruption and corticosteroids Thyroid function and hormone levels should be monitored to ensure appropriate replacement

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

Hypothyroidism[1]

Prevalence in clinical trials

Pooled safety population of KEYTRUDA[1]

- Hypothyroidism occurred in 939 (12.3%) patients, including Grade 2 or 3 cases in 687 (9.0%) and 8 (0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of hypothyroidism was 3.4 months (range 1 day to 25.9 months). The median duration was not reached (range 2 days to 63.0+ months). Hypothyroidism led to discontinuation of pembrolizumab in 6 (0.1%) patients. Hypothyroidism resolved in 216 (23.0%) patients, 16 with sequelae.
- In patients with cHL (n=389) the incidence of hypothyroidism was 17%, all of which were Grade 1 or 2. In patients with HNSCC treated with pembrolizumab as monotherapy (n=909), the incidence of hypothyroidism was 16.1% (all Grades) with 0.3% Grade 3. In patients with HNSCC treated with pembrolizumab in combination with platinum and 5-FU chemotherapy (n=276), the incidence of hypothyroidism was 15.2%, all of which were Grade 1 or 2. In patients treated with pembrolizumab in combination with axitinib or lenvatinib (n=1,456), the incidence of hypothyroidism was 46.2% (all Grades) with 0.8% Grade 3 or 4.

Monitoring hypothyroidism in patients prescribed KEYTRUDA[1]

- Patients should be monitored for the changes in thyroid function (at the start of treatment, periodically throughout and when indicated by clinical evaluation) as well as clinical signs and symptoms of thyroid disorders. Hormone levels should also be monitored.
- Along with hypothyroidism/hyperthyroidism, thyroiditis has also been reported and can occur at any time during treatment.
- Hypothyroidism is more frequently reported in patients with HNSCC with prior radiation therapy.

Colitis

KEYTRUDA®
(pembrolizumab)

Colitis[1]

Treatment modifications for colitis in patients prescribed KEYTRUDA

	Grade 1	Grade 2–3	Grade 4
KEYTRUDA treatment	May continue treatment and monitor	Withhold until adverse event recovers to Grade 0–1. If toxicity does not resolve to Grade 0–1 within 12 weeks after last dose of KEYTRUDA, or corticosteroid dosing cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks, permanently discontinue KEYTRUDA For recurrent Grade 3, permanently discontinue	Permanently discontinue
Corticosteroid treatment	-	Initial dose of 1–2 mg/kg per day prednisone or equivalent followed by a taper	
Additional management	The potential risk of gastrointestinal perforation should be taken into consideration		

Colitis[1]

Prevalence in clinical trials

Pooled safety population of KEYTRUDA[1]

- Colitis occurred in 158 (2.1%) patients, including Grade 2, 3 or 4 cases in 49 (0.6%), 82 (1.1%) and 6 (0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of colitis was 4.3 months (range 2 days to 24.3 months). The median duration was 1.1 month (range 1 day to 45.2 months). Colitis led to discontinuation of pembrolizumab in 48 (0.6%) patients. Colitis resolved in 132 patients, 2 with sequelae.
- In patients with CRC treated with KEYTRUDA as monotherapy (n=153), the incidence of colitis was 6.5% (all Grades) with 2.0% Grade 3 and 1.3% Grade 4.

Monitoring colitis in patients prescribed KEYTRUDA[1]

- Patients should be monitored for the signs and symptoms of colitis and other causes excluded.

Hepatitis

KEYTRUDA®
(pembrolizumab)

Hepatitis[1]

Treatment modifications for hepatitis in patients prescribed KEYTRUDA

	Grade 1	Grade 2 (AST or ALT >3x to 5x ULN or total bilirubin >1.5x to 3x ULN)	Grade 3–4 (AST or ALT >5x ULN or total bilirubin >3x ULN)
KEYTRUDA treatment	May continue treatment and monitor	Withhold until adverse event recovers to Grade 0–1. If toxicity does not resolve to Grade 0–1 within 12 weeks after last dose of KEYTRUDA, or corticosteroid dosing cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks, permanently discontinue KEYTRUDA	Permanently discontinue
Corticosteroid treatment	-	Initial dose of 0.5–1 mg/kg per day prednisone or equivalent followed by a taper	Dose of 1–2 mg/kg per day prednisone or equivalent followed by a taper
Additional management	In the case of liver metastasis with baseline Grade 2 elevation of AST or ALT, hepatitis with AST or ALT increases ≥50% and last ≥1 week, **permanently discontinue** KEYTRUDA		

Hepatitis[1]

Prevalence in clinical trials

Patients with clinically significant renal (creatinine > 1.5 x ULN) or hepatic (bilirubin > 1.5 x ULN, ALT, AST > 2.5 x ULN in the absence of liver metastases) abnormalities at baseline were excluded from clinical trials, therefore information is limited in patients with severe renal and moderate to severe hepatic impairment.

Pooled safety population of KEYTRUDA[1]

- Hepatitis occurred in 80 (1.0%) patients, including Grade 2, 3 or 4 cases in 12 (0.2%), 55 (0.7%) and 8 (0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of hepatitis was 3.5 months (range 8 days to 26.3 months). The median duration was 1.3 months (range 1 day to 29.0+ months). Hepatitis led to discontinuation of pembrolizumab in 37 (0.45%) patients. Hepatitis resolved in 60 patients.

Monitoring hepatitis in patients prescribed KEYTRUDA[1]

- Patients should be monitored for changes in liver function (at the start of treatment, periodically throughout and when indicated by clinical evaluation) and for symptoms of hepatitis. When hepatitis is suspected, exclude other causes of liver dysfunction.
  - Please refer to the KEYTRUDA SmPC for full information on managing elevation in liver enzymes before prescribing KEYTRUDA.

Liver enzyme elevations

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Liver enzyme elevations[1]

Treatment modifications for liver enzyme elevations in patients with RCC prescribed KEYTRUDA in combination with axitinib

	AST or ALT <3x ULN	AST or ALT ≥3x ULN but <10x ULN without concurrent total bilirubin ≥2x ULN	AST or ALT >5 x ULN or total bilirubin >3 x ULN
KEYTRUDA treatment	May continue treatment and monitor enzymes as long as below limits detailed here	Withhold until adverse event recovers to Grade 0–1	Permanently discontinue
Corticosteroid treatment	-	Consider administration of corticosteroids and taper as required.	Consider administration of corticosteroids and taper as required.
Additional management	If treatment is withheld following AST or ALT ≥3 times ULN but <10 times ULN without concurrent total bilirubin ≥2 times ULN, rechallenge with a single medicine or sequential rechallenge with both medicines after recovery. If rechallenging with axitinib, consider dose reduction as per axitinib SmPC.		

Liver enzyme elevations[1]

Prevalence in clinical trials

Patients with clinically significant renal (creatinine > 1.5 x ULN) or hepatic (bilirubin > 1.5 x ULN, ALT, AST > 2.5 x ULN in the absence of liver metastases) abnormalities at baseline were excluded from clinical trials, therefore information is limited in patients with severe renal and moderate to severe hepatic impairment.

Pooled safety population of KEYTRUDA[1]

- In a clinical study of previously untreated patients with RCC receiving pembrolizumab in combination with axitinib, a higher than expected incidence of Grades 3 and 4 ALT increased (20%) and AST increased (13%) were observed. The median time to onset of ALT increased was 2.3 months (range: 7 days to 19.8 months). In patients with ALT ≥ 3 times ULN (Grades 2-4, n=116), ALT resolved to Grades 0-1 in 94%. Fifty-nine percent of the patients with increased ALT received systemic corticosteroids. Of the patients who recovered, 92 (84%) were rechallenged with either pembrolizumab (3%) or axitinib (31%) monotherapy or with both (50%). Of these patients, 55% had no recurrence of ALT > 3 times ULN, and of those patients with recurrence of ALT > 3 times ULN, all recovered. There were no Grade 5 hepatic events.

Monitoring liver enzyme elevations in patients prescribed KEYTRUDA[1]

- Patients should be monitored for changes in liver enzymes before initiation of and periodically throughout treatment. More frequent monitoring of liver enzymes may be considered when not used as a monotherapy.
- Please refer to the KEYTRUDA SmPC for full information on managing elevation in liver enzymes before prescribing KEYTRUDA.

Adrenal insufficiency

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Adrenal insufficiency[1]

Treatment modifications for adrenal insufficiency in patients prescribed KEYTRUDA

	Grade 1	Grade 2	Grade 3–4
KEYTRUDA treatment	May continue treatment and monitor	Withhold treatment until controlled by hormone replacement	Withhold until recovery to Grade ≤1. If toxicity does not resolve to Grade 0–1 within 12 weeks after last dose of KEYTRUDA, or corticosteroid dosing cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks, permanently discontinue KEYTRUDA
Corticosteroid treatment	Administer corticosteroids to treat adrenal insufficiency, followed by corticosteroid taper if indicated		
Additional management	Hormone replacement therapy if indicated May be managed symptomatically		For patients with Grade 3 or Grade 4 endocrinopathies that improved to Grade 2 or lower and are controlled with hormone replacement, if indicated, continuation of KEYTRUDA may be considered after corticosteroid taper, if needed. Otherwise treatment should be discontinued.

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

Adrenal insufficiency[1]

Prevalence in clinical trials

Pooled safety population of KEYTRUDA[1]

- Adrenal insufficiency occurred in 74 (1.0%) patients, including Grade 2, 3 or 4 cases in 34 (0.4%), 27 (0.4%) and 4 (0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of adrenal insufficiency was 5.4 months (range 1 day to 23.7 months). The median duration was not reached (range 3 days to 40.1+ months). Adrenal insufficiency led to discontinuation of pembrolizumab in 13 (0.2%) patients. Adrenal insufficiency resolved in 28 patients, 11 with sequelae.

Monitoring adrenal insufficiency in patients prescribed KEYTRUDA[1]

- Patients should be monitored for the signs and symptoms of adrenal insufficiency and exclude other causes.
- Pituitary function and hormone levels should be monitored to ensure appropriate hormone replacement.

Hypophysitis

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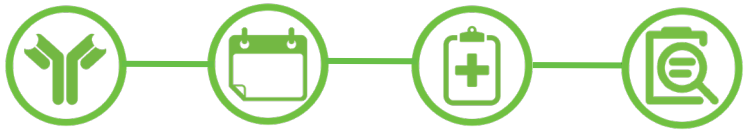

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Hypophysitis[1]

Treatment modifications for hypophysitis in patients prescribed KEYTRUDA

	Grade 1	Grade 2	Grade 3–4 or symptomatic hypophysitis
KEYTRUDA treatment	May continue treatment and monitor	Withhold treatment until controlled by hormone replacement	Withhold until recovery to Grade ≤1. If toxicity does not resolve to Grade 0–1 within 12 weeks after last dose of KEYTRUDA, or corticosteroid dosing cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks, permanently discontinue KEYTRUDA
Corticosteroid treatment	Administer corticosteroids to treat hypophysitis, followed by corticosteroid taper if needed		
Additional management	Hormone replacement therapy if indicated May be managed symptomatically		For patients with Grade 3 or Grade 4 endocrinopathies that improved to Grade 2 or lower and are controlled with hormone replacement, if indicated, continuation of KEYTRUDA may be considered after corticosteroid taper, if needed. Otherwise treatment should be discontinued.

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

Hypophysitis[1]

Prevalence in clinical trials

Pooled safety population of KEYTRUDA[1]

- Hypophysitis occurred in 52 (0.7%) patients, including Grade 2, 3 or 4 cases in 23 (0.3%), 24 (0.3%) and 1 (< 0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of hypophysitis was 5.9 months (range 1 day to 17.7 months). The median duration was 3.6 months (range 3 days to 48.1+ months). Hypophysitis led to discontinuation of pembrolizumab in 14 (0.2%) patients. Hypophysitis resolved in 23 patients, 8 with sequelae.

Monitoring hypophysitis in patients prescribed KEYTRUDA[1]

- Patients should be monitored for the signs and symptoms of hypophysitis (including hypopituitarism) and exclude other causes.
- Pituitary function and hormone levels should be monitored to ensure appropriate hormone replacement.

Pneumonitis

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Pneumonitis[1]

Treatment modifications for pneumonitis in patients prescribed KEYTRUDA

	Grade 1	Grade 2	Grade 3–4
KEYTRUDA treatment	May continue treatment and monitor	Withhold until adverse event recovers to Grade 0–1. If toxicity does not resolve to Grade 0–1 within 12 weeks after last dose of KEYTRUDA, or corticosteroid dosing cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks, permanently discontinue KEYTRUDA For recurrent Grade 2, permanently discontinue	Permanently discontinue
Corticosteroid treatment	-	Dose of 1–2 mg/kg per day prednisone or equivalent followed by a taper	
Additional management	Note: Fatal cases of pneumonitis have been reported in patients receiving KEYTRUDA **KEYTRUDA should be permanently discontinued for Grade 3-4 or recurrent Grade 2 pneumonitis**		

Pneumonitis[1]

Prevalence in clinical trials

Pooled safety population of KEYTRUDA[1]

- Pneumonitis occurred in 324 (4.42%) patients, including Grade 2, 3, 4 or 5 cases in 143 (1.9%), 81 (1.1%), 19 (0.2%) and 9 (0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of pneumonitis was 3.7 months (range 2 days to 27.2 months). The median duration was 2.0 months (range 1 day to 51.0+ months). Pneumonitis occurred more frequently in patients with a history of prior thoracic radiation (8.1%) than in patients who did not receive prior thoracic radiation (3.9%). Pneumonitis led to discontinuation of pembrolizumab in 131 (1.7%) patients. Pneumonitis resolved in 196 patients, 6 with sequelae.
- In patients with NSCLC, pneumonitis occurred in 160 (5.7%), including Grade 2, 3, 4 or 5 cases in 62 (2.2%), 47 (1.7%), 14 (0.5%) and 10 (0.4%), respectively. In patients with NSCLC, pneumonitis occurred in 8.9% with a history of prior thoracic radiation.
- In patients with cHL, the incidence of pneumonitis (all Grades) ranged from 5.2% to 10.8% for cHL patients in KEYNOTE-087 (n=210) and KEYNOTE-204 (n=148), respectively.

Monitoring pneumonitis in patients prescribed KEYTRUDA[1]

- Patients should be monitored for signs and symptoms of pneumonitis. When pneumonitis is suspected, evaluate with radiographic imaging to exclude other causes.

Type 1 Diabetes Mellitus (Hyperglycaemia/Diabetic Ketoacidosis)

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Type 1 diabetes mellitus[1] (Hyperglycaemia/Diabetic ketoacidosis)

Treatment modifications for Type 1 diabetes in patients prescribed KEYTRUDA

	Type 1 diabetes	Type 1 diabetes associated with Grade ≥3 hyperglycaemia (glucose >250 mg/dL or >13.9 mmol/L) or ketoacidosis
KEYTRUDA treatment	May continue treatment and monitor	KEYTRUDA should be withheld until metabolic control is achieved
Additional management	Administer insulin	Administer insulin

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

Type 1 diabetes mellitus[1] (Hyperglycaemia/Diabetic ketoacidosis)

Prevalence in clinical trials

Pooled safety population of KEYTRUDA[1]

- Severe endocrinopathies, including type 1 diabetes mellitus, have been observed with KEYTRUDA treatment.
- In patients treated with KEYTRUDA monotherapy, the proportion of patients who experienced a shift from baseline to a Grade 3 or 4 laboratory abnormality for increased glucose (potentially indicating hyperglycaemia) was 5.3% for KEYTRUDA monotherapy, 5.6% for KEYTRUDA in combination with chemotherapy and 7.8% for KEYTRUDA in combination with axitinib.

Monitoring hyperglycaemia in patients prescribed KEYTRUDA[1]

- Patients should be monitored for hyperglycaemia or other signs and symptoms of Type 1 diabetes.

Nephritis

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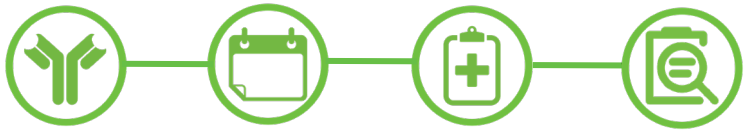

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Nephritis[1]

Treatment modifications for nephritis in patients prescribed KEYTRUDA

	Grade 1	Grade 2 (creatinine >1.5 to 3x ULN)	Grade 3–4 (creatinine >3 x ULN)
KEYTRUDA treatment	May continue treatment and monitor	Withhold based on the severity of creatinine elevations and until adverse events recover to Grade 0–1. If toxicity does not resolve to Grade 0–1 within 12 weeks after last dose of KEYTRUDA, or corticosteroid dosing cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks, permanently discontinue KEYTRUDA	Permanently discontinue
Corticosteroid treatment	-	Initial dose of 1–2 mg/kg per day prednisone or equivalent followed by a taper	
Additional management	Management depends on the severity of creatinine elevations		

Nephritis[1]

Prevalence in clinical trials

Pooled safety population of KEYTRUDA[1]

- Nephritis occurred in 37 (0.45%) patients, including Grade 2, 3 or 4 cases in 11 (0.1%), 19 (0.2%) and 2 (< 0.1%) patients, respectively, receiving pembrolizumab as monotherapy. The median time to onset of nephritis was 4.2 months (range 12 days to 21.4 months). The median duration was 3.3 months (range 6 days to 28.2+ months). Nephritis led to discontinuation of pembrolizumab in 17 (0.2%) patients. Nephritis resolved in 25 patients, 5 with sequelae.
- In patients with non-squamous NSCLC treated with pembrolizumab in combination with pemetrexed and platinum chemotherapy (n=488), the incidence of nephritis was 1.4% (all Grades) with 0.8% Grade 3 and 0.4% Grade 4.

Monitoring nephritis in patients prescribed KEYTRUDA[1]

- Patients should be monitored for changes in renal function. When nephritis is suspected, exclude other causes of renal dysfunction.

Other Immune-Mediated Adverse Events (imAEs)

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Other immune-mediated adverse events[1]

Treatment modifications for other imAEs in patients prescribed KEYTRUDA

	Grade 2-3*	Grade 4 and recurrent Grade 3
KEYTRUDA treatment	• Based on the severity and type of the reaction, withhold treatment until adverse reactions recover to Grade 0–1. • **Permanently discontinue** if a Grade 3 event occurs more than once • First occurrence of Grade 3 myocarditis or encephalitis or Guillain-Barre syndrome – **permanently discontinue**	Permanently discontinue
Corticosteroid treatment	Administer corticosteroids followed by corticosteroid taper if indicated	
Additional management	***In the case of Grade 2 and first occurrence of Grade 3 adverse events:** If treatment related toxicity is not resolved within 12 weeks after last dose of KEYTRUDA or if corticosteroid dose cannot be reduced less or equal to 10mg/day prednisolone or equivalent per day within 12 weeks, KEYTRUDA should be permanently discontinued	

Other immune-mediated adverse events[1]

Monitoring other immune-mediated adverse events in patients prescribed KEYTRUDA[1]

- Patients should be monitored for the signs and symptoms of other immune-mediated adverse events. Other causes should be excluded.
- The following additional clinically significant, immune-mediated adverse reactions have been reported in clinical studies or in post-marketing experience: uveitis, arthritis, myositis, myocarditis, pancreatitis, Guillain-Barré syndrome, myasthenic syndrome, haemolytic anaemia, sarcoidosis, encephalitis, myelitis, vasculitis, cholangitis sclerosing, gastritis, cystitis noninfective and hypoparathyroidism.
- Immune-mediated adverse reactions affecting more than one body system can occur simultaneously.
- Severe and fatal cases have been reported in clinical trials or in post-marketing experience.

Transplant-related adverse reactions[1]

Solid organ transplant rejection[1]

- Solid organ transplant rejection has been reported in the post-marketing setting in patients treated with PD-1 inhibitors. Treatment with KEYTRUDA may increase the risk of rejection in solid organ transplant recipients.
- The benefit of treatment with KEYTRUDA vs the risk of possible organ rejection should be considered in these patients.

Transplant-related adverse reactions[1]

Complications of allogenic Haematopoietic Stem Cell Transplant (HSCT)[1]

- **Allogeneic HSCT after treatment with KEYTRUDA**
  - Cases of graft-versus-host-disease (GVHD) and hepatic veno-occlusive disease (VOD) have been observed in patients with cHL undergoing allogeneic HSCT after previous exposure to KEYTRUDA
  - Until further data become available, careful consideration to the potential benefits of HSCT and the possible increased risk of transplant-related complications should be made case by case
- **Allogeneic HSCT prior to treatment with KEYTRUDA**
  - In patients with a history of allogeneic HSCT, acute GVHD, including fatal GVHD, has been reported after treatment with KEYTRUDA. Patients who experienced GVHD after their transplant procedure may be at an increased risk for GVHD after treatment with KEYTRUDA
  - Consider the benefit of treatment with KEYTRUDA vs the risk of possible GVHD in patients with a history of allogeneic HSCT
- **Allogenic HSCT in classical Hodgkin lymphoma (cHL)**
  - Of 14 patients in KEYNOTE-013 who proceeded to allogeneic HSCT after treatment with KEYTRUDA, 6 patients reported GVHD and 1 patient reported chronic GVHD, none of which were fatal. Two patients experienced hepatic VOD, one of which was fatal. One patient experienced engraftment syndrome post-transplant
  - Of 32 patients in KEYNOTE-087 who proceeded to allogeneic HSCT after treatment with KEYTRUDA, 16 patients reported acute GVHD and 7 patients reported chronic GVHD, two of which were fatal. No patients experienced hepatic VOD. No patients experienced engraftment syndrome post-transplant
  - Of 14 patients in KEYNOTE-204 who proceeded to allogeneic HSCT after treatment with KEYTRUDA, 8 patients reported acute GVHD and 3 patients reported chronic GVHD, none of which were fatal. No patients experienced hepatic VOD. One patient experienced engraftment syndrome post-transplant

Infusion-Related Reactions

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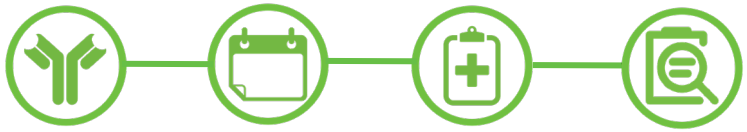

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Infusion-related reactions[1]

Treatment modifications for infusion-related reactions in patients prescribed KEYTRUDA

	Mild to moderate reactions (Grade 1–2)	Severe reactions (Grade 3–4)
KEYTRUDA treatment	May continue treatment and monitor	Stop infusion. Permanently discontinue
Additional management	Monitor closely and consider premedication with antipyretic and antihistamine therapy	-

KEYTRUDA, when used as monotherapy or in combination, must be administered by intravenous infusion over 30 minutes

Infusion-related reactions[1]

Prevalence in clinical trials

Pooled safety population of KEYTRUDA[1]

- Severe infusion-related reactions, including hypersensitivity and anaphylaxis, have been reported in patients receiving KEYTRUDA.

Monitoring infusion-related reactions in patients prescribed KEYTRUDA[1]

- Severe infusion-related reactions including hypersensitivity and anaphylaxis have been reported with patients receiving KEYTRUDA. These included drug hypersensitivity, anaphylactic reaction, anaphylactoid reaction, hypersensitivity and cytokine release syndrome.
- Patients should be monitored during infusion.

Use of KEYTRUDA in combination with chemotherapy[1]

- KEYTRUDA in combination with chemotherapy should be used with caution in patients ≥ 75 years after careful consideration of the potential benefit/risk on an individual basis.

Skin Reactions

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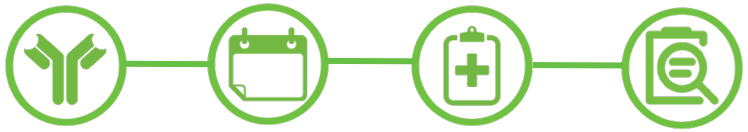

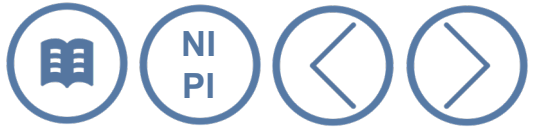

Skin reactions[1]

Treatment modifications for skin reactions in patients prescribed KEYTRUDA

	Grade 1–2	Grade 3 or suspected SJS or TEN	Grade 4 or confirmed SJS or TEN
KEYTRUDA treatment	May continue treatment and monitor	Withhold until adverse reactions recover to Grades 0–1. If toxicity does not resolve to Grade 0–1 within 12 weeks after last dose of KEYTRUDA, or corticosteroid dosing cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks, permanently discontinue KEYTRUDA	Permanently discontinue
Additional management	May be managed symptomatically	For signs or symptoms of SJS or TEN, the patient should be referred to a specialised unit for assessment and treatment	

Skin reactions[1]

Prevalence in clinical trials

Pooled safety population of KEYTRUDA[1]

- Immune-mediated severe skin reactions occurred in 130 (1.7%) patients, including Grade 2, 3, 4 or 5 cases in 11 (0.1%), 103 (1.3%), 1 (< 0.1%) and 1 (< 0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of severe skin reactions was 2.8 months (range 2 days to 25.5 months). The median duration was 1.9 months (range 1 day to 47.1+ months). Severe skin reactions led to discontinuation of pembrolizumab in 18 (0.2%) patients. Severe skin reactions resolved in 95 patients, 2 with sequelae.
- Rare cases of SJS and TEN, some of them with fatal outcome, have been reported in patients receiving KEYTRUDA.

Monitoring skin reactions in patients prescribed KEYTRUDA[1]

- Patients should be monitored for suspected skin reactions. Other causes should be excluded.
- 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.

Immune-Mediated Adverse Events Summary

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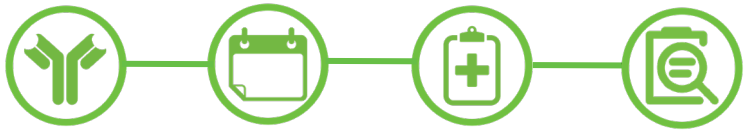
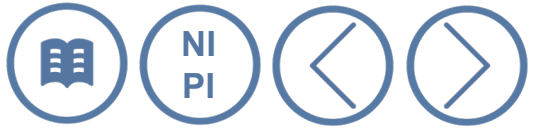

Immune-mediated Adverse Event Summary[1]

Hyperthyroidism	• For changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and clinical signs and symptoms of thyroid disorders	• For Grade 2 hyperthyroidism. Treatment with KEYTRUDA may continue with monitoring. • For patients with Grade 3 or Grade 4 hyperthyroidism that improved to Grade 2 or lower, continuation may be considered, after corticosteroid taper, if needed. Thyroid function and hormone levels should be monitored to ensure appropriate hormone replacement • For Grade ≥3 withhold until recovery to Grade ≤1.* For patients with Grade 3–4 endocrinopathies that improved to Grade 2 or lower and is controlled with hormone replacement, if indicated, continuation of KEYTRUDA may be considered after corticosteroid taper, if needed
Hypothyroidism	• For changes in thyroid function	• Symptoms may be managed with replacement hormone therapy and treatment with KEYTRUDA may continue with monitoring • Thyroid function and hormone levels should be monitored to ensure appropriate replacement
Immune-mediated colitis	• For signs and symptoms of colitis; exclude other causes	• Withhold KEYTRUDA for Grade 2 or Grade 3 colitis until adverse reactions recover to Grades 0–1* • Administer corticosteroids for Grade ≥2 events (initial dose of 1–2 mg/kg per day prednisone or equivalent followed by a taper) • Permanently discontinue KEYTRUDA for recurrent Grade 3 or Grade 4 colitis
Immune-mediated hepatitis	• For changes in liver function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and symptoms of hepatitis; exclude other causes	• For Grade 2 hepatitis, withhold until adverse event recovers to Grade 0–1.* Administer an initial dose of 0.5–1 mg/kg per day prednisone or equivalent followed by a taper • For Grade ≥3 hepatitis, permanently discontinue KEYTRUDA. Administer 1–2 mg/kg per day prednisone or equivalent followed by a taper

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

Immune-mediated Adverse Event Summary[1]

Immune-mediated Endocrinopathies: Adrenal insufficiency and hypophysitis	• For signs and symptoms of adrenal insufficiency and hypophysitis (including hypopituitarism) and other causes excluded	• For Grade 2 adrenal insufficiency, and hypophysitis, withhold KEYTRUDA until controlled by hormone replacement • For Grade ≥3 adrenal insufficiency and hypophysitis withhold KEYTRUDA until adverse reactions recover to Grades 0-1* • For patients with Grade 3 or Grade 4 endocrinopathies that improved to Grade 2 or lower and are controlled with hormone replacement, if indicated, continuation of KEYTRUDA may be considered after corticosteroid taper, if needed. Otherwise treatment should be discontinued.
Type-1 Diabetes	• For hyperglycaemia or other signs and symptoms of diabetes • Insulin should be administered for type 1 diabetes	• For Type 1 diabetes, KEYTRUDA may continue with insulin* • For Type 1 diabetes associated with Grade ≥3 hyperglycaemia or associated ketoacidosis, withhold KEYTRUDA. Treatment may be restarted if metabolic control is achieved
Immune-mediated pneumonitis	• For signs and symptoms of pneumonitis • Suspected pneumonitis should be confirmed with radiographic imaging and other causes excluded	• Administer corticosteroids for Grade ≥2 events (initial dose of 1–2 mg/kg per day prednisone or equivalent followed by a taper) • Withhold KEYTRUDA for Grade 2 pneumonitis until adverse reactions recover to Grades 0-1.* • Permanently discontinue KEYTRUDA for Grade 3, Grade 4, or recurrent Grade 2 pneumonitis
Immune-mediated nephritis	• For changes in renal function; exclude other causes	• Administer corticosteroids for Grade ≥2 events (initial dose of 1–2 mg/kg per day prednisone or equivalent followed by a taper) • Based on severity of creatinine elevations: ▪ Withhold KEYTRUDA for Grade 2 with creatinine > 1.5 to ≤ 3 times upper limit of normal (ULN) until adverse reactions recover to Grades 0–1.* ▪ Permanently discontinue KEYTRUDA for Grade ≥ 3 nephritis with creatinine > 3 times ULN

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

Immune-mediated Adverse Event Summary[1]

Other immune-mediated adverse reactions	• Monitor for signs and symptoms of: uveitis, arthritis, myositis, myocarditis, pancreatitis, Guillain-Barré syndrome, myasthenic syndrome, haemolytic anaemia, sarcoidosis, encephalitis, myelitis, vasculitis, cholangitis sclerosing, gastritis, cystitis noninfective, hypoparathyroidism, and solid organ transplant rejection following KEYTRUDA treatment in donor organ recipients	• For Grade 2–3, withhold KEYTRUDA until adverse reactions recover to Grade 0–1* • KEYTRUDA should be permanently discontinued in the case of Grade 3 or 4 myocarditis, encephalitis and Guillain Barré syndrome • Permanently discontinue drug if any Grade 3 immune-mediated toxicity occurs a second time and for any Grade 4 immune-mediated toxicity • 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
Infusion related reactions	• Severe infusion-related reactions, including hypersensitivity and anaphylaxis, have been reported in patients receiving KEYTRUDA	• For Grade 1–2 (mild to moderate) infusion-related reactions, KEYTRUDA treatment may continue with monitoring. • Monitor closely and consider premedication with antipyretic and antihistamine therapy • For Grade 3–4 (severe) reactions, infusion should be stopped and KEYTRUDA permanently discontinued
Skin reactions	• For signs and symptoms of skin reactions (Including SJS and TEN), exclude other causes	• Withhold KEYTRUDA for Grade 3 or suspected SJS or TEN, until adverse reactions recover to Grades 0–1.* • Permanently discontinue KEYTRUDA for Grade 4 or confirmed SJS or TEN • For signs or symptoms of SJS or TEN, the patient should be referred to a specialised unit for assessment and treatment
Elevated liver enzymes	• For liver enzyme elevations, in patients with RCC being treated with KEYTRUDA in combination with axitinib	• If ALT or AST ≥3x ULN but <10x ULN without concurrent total bilirubin ≥2x ULN, both KEYTRUDA and axitinib should be withheld until these adverse reactions recover to Grades 0–1. Corticosteroid therapy may be considered • If ALT or AST ≥10x ULN or >3x ULN with concurrent total bilirubin ≥2x ULN, both KEYTRUDA and axitinib should be permanently discontinued and corticosteroid therapy may be considered

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

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Abbreviations

Abbreviation	Definition
5-FU	fluorouracil
AE	adverse event
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BID	twice a day
cHL	classical Hodgkin lymphoma
CPS	combined positive score
EGFR	epidermal growth factor receptor
GVHD	graft-versus-host-disease
HSCT	haematopoietic stem cell transplant
HNSCC	head and neck squamous cell carcinoma
imAE	immune-mediated adverse event
IV	intravenous

Abbreviation	Definition
NSAIDS	non-steroidal anti-inflammatory drugs
NSCLC	non-small cell lung carcinoma
PD-1	programmed death-1
PD-L1	programmed death ligand-1
PD-L2	programmed death ligand-2
QxW	every x weeks
RCC	renal cell carcinoma
SJS	Stevens-Johnson syndrome
TEN	toxic epidermal necrolysis
TNBC	triple-negative breast cancer
TPS	tumour proportion score
ULN	upper limit of normal
VOD	veno-occlusive disease

CTCAE Grading Criteria[8]

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4
Adrenal insufficiency	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; hospitalisation indicated	Life-threatening consequences; urgent intervention indicated
ALT increase	>ULN–3.0 x ULN	>3.0–5.0 x ULN	>5.0–20.0 x ULN	>20.0 x ULN
AST increase	>ULN–3.0 x ULN	>3.0–5.0 x ULN	>5.0–20.0 x ULN	>20.0 x ULN
Colitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Abdominal pain; mucus or blood in stool	Severe abdominal pain; change in bowel habits; medical intervention indicated; peritoneal signs	Life-threatening consequences; urgent intervention indicated
Hyperthyroidism	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thyroid suppression therapy indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; hospitalisation indicated	Life-threatening consequences; urgent intervention indicated
Hyperglycaemia	Fasting glucose value >ULN–160 mg/dL; Fasting glucose value >ULN–8.9 mmol/L	Fasting glucose value >160–250 mg/dL; Fasting glucose value >8.9–13.9 mmol/L	>250–500 mg/dL; >13.9–27.8 mmol/L; hospitalisation indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences
Hypothyroidism	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thyroid replacement therapy indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; hospitalisation indicated	Life-threatening consequences; urgent intervention indicated

CTCAE Grading Criteria[8]

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4
Blood and lymphatic system disorders	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of existing hospitalisation indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated
Infusion related reaction	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	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	Life-threatening consequences; urgent intervention indicated
Nephritis (acute kidney injury)	Creatinine level increase of >0.3 mg/dL; creatinine 1.5–2.0 x above baseline	Creatinine 2–3 x above baseline	Creatinine >3 x baseline or >4.0 mg/dL; hospitalisation indicated	Life-threatening consequences; dialysis indicated
Pneumonitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; oxygen indicated	Life-threatening respiratory compromise; urgent intervention indicated (e.g. tracheotomy or intubation)
Skin reactions	Term covers multiple adverse events			

KEYTRUDA® (pembrolizumab)

NI prescribing information can be found at: https://www.emcpi.com/pi/ni/378

Pooled safety data of KEYTRUDA across all indications and AE management can be found in the Summary of Product Characteristics (SmPC):
Northern Ireland - https://www.emcpi.com/pi/ni/378

Refer to KEYTRUDA SmPC and Risk Minimisation Materials (RMM) before prescribing.

Adverse events should be reported. Reporting forms and information can be found at https://yellowcard.mhra.gov.uk/ (**This links to an external site**) or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to MSD, UK (Tel: 0208 154 8000).

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