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This document has been developed and funded by MSD.

KEYTRUDA® (pembrolizumab)

KEYTRUDA SC® (pembrolizumab) subcutaneous injection | 395 mg/2.4 mL 790 mg/4.8 mL

Actor portrayal

KEYTRUDA SC (pembrolizumab) subcutaneous injection: Protocol support fact sheet

For further information please contact Merck Sharp & Dohme (UK) Limited:
Email: medicalinformationuk@msd.com
Tel: 0208 154 8000

Adverse events should be reported. Reporting forms and information can be found at https://yellowcard.mhra.gov.uk/ or search for the MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to Merck Sharp & Dohme (UK) Limited (Tel: 020 8154 8000; email: pv.uk@msd.com).

Prescribing Information for KEYTRUDA 395 mg solution for injection can be found here.
Prescribing Information for KEYTRUDA 790 mg solution for injection can be found here.
Prescribing Information for KEYTRUDA 25 mg/mL concentrate for solution for infusion can be found here.

Please consult the SmPCs and Risk Management Materials for further information before making any prescribing decisions.

GB-PDS-00104 | May 2026

MSD

Purpose of this document

This document is to support NHS healthcare professionals in updating existing Trust protocols to include the subcutaneous formulation of pembrolizumab alongside the established intravenous formulation, supporting the effective integration across all adult licensed indications.

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Indications and reimbursement

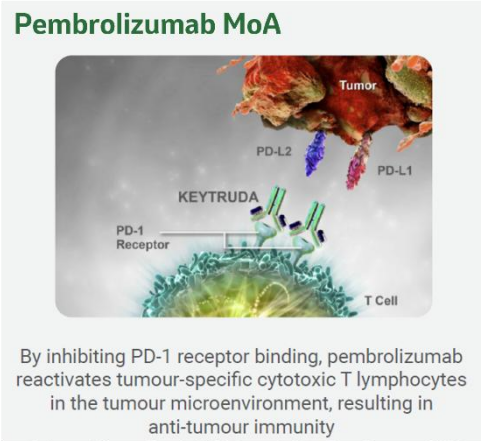
KEYTRUDA SC is licensed for use in adult patients across most KEYTRUDA IV indications, whether alone or in combination with other therapies.[1-3] Please see Appendix 1 for the full list of indications.

One such indication is KEYTRUDA IV and KEYTRUDA SC, in combination with pemetrexed and platinum chemotherapy, are each indicated for the first-line treatment of metastatic non-small cell lung carcinoma (mNSCLC) in adults whose tumours have no *EGFR* or *ALK* positive mutations.[1-3]

KEYTRUDA SC is reimbursed for all approved adult indications currently reimbursed for KEYTRUDA IV.

KEYTRUDA SC mechanism of action

KEYTRUDA SC is pembrolizumab with recombinant berahyaluronidase alfa.[1] Pembrolizumab is a selective, humanised monoclonal antibody designed to block the interaction between PD-1 and both PD-L1 and PD-L2.[1,4] Berahyaluronidase alfa, an excipient in KEYTRUDA SC, is a variant of human hyaluronidase, an enzyme that temporarily breaks down hyaluronan, a polysaccharide found in the extracellular matrix of the subcutaneous tissue.[1,5,6] This results in enhanced drug dispersion and permeation, facilitating delivery of pembrolizumab.[1,5,6]



Adapted from Pardoll DM, et al. Nat Rev Cancer 2012.

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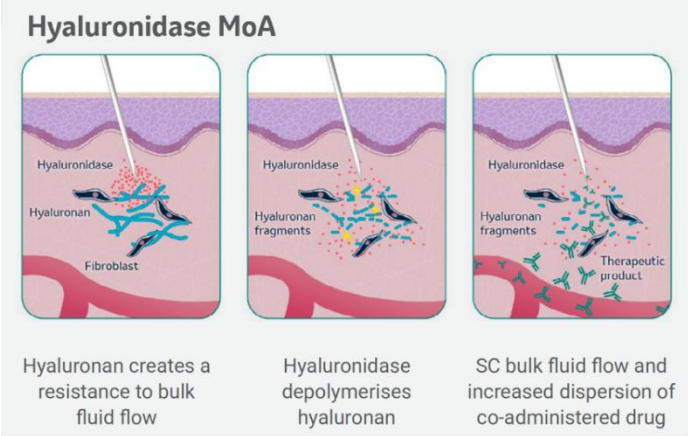


Adapted from Connor RJ, et al. J Pharmacol Toxicol Methods 2020.

Considerations for subcutaneous administration

Cancer prevalence is rising, with increases among younger adults.[7] As a result, demand for systemic anti-cancer therapies continues to grow at an estimated rate of 6-8% each year, placing additional pressure on services.[8] Additionally, cancer wait times remain longer than expected. Only 69% of people in England received their diagnosis and started their first treatment within 62 days of an urgent referral in October 2025, compared to a target of 85%.[9] These challenges are further compounded by ongoing NHS workforce shortages, which continue to limit capacity across the system.[10]

Against this backdrop of rising demand, constrained capacity, and workforce pressures, there is an increased need to optimise treatment delivery models in order to relieve pressure across oncology services.

Subcutaneous formulations can reduce preparation and administration time when compared to IV formulations, as well as reduce patient chair time, potentially resulting in important time and resource efficiencies.[11-13] Alongside flexibility in the anatomical sites of administration with subcutaneous formulations, there is also the potential for patients to receive subcutaneous treatment outside the infusion centre or infusion suite.[11]

KEYTRUDA SC dosing

KEYTRUDA SC provides two dosing options in a ready-to-use vial which does not require dilution (each with a disctinct colour and ordering code).[1,2]

Composition and contents

Q3W dose[1]	Q6W dose[2]
395 mg pembrolizumab per 2.4 mL	**790 mg pembrolizumab per 4.8 mL**
(165 mg units per mL)	(165 mg units per mL)
	
Vial shown to scale, not actual size.	Vial shown to scale, not actual size.
GTIN: 00366582512479 **Marketing authorisation number:** PL 53095/0112 **Carton:** x1 vial, 50 mm x 50 mm x 90 mm	**GTIN:** 00366582512486 **Marketing authorisation number:** PL 53095/0113 **Carton:** x1 vial, 50 mm x 50 mm x 90 mm

Type I glass vials containing clear to slightly opalescent, colourless to slightly yellow solution, pH 5.3–5.9.[1,2]

Each carton contains one vial.[1,2]

The recommended dose of KEYTRUDA solution for injection in adults is either:[1]

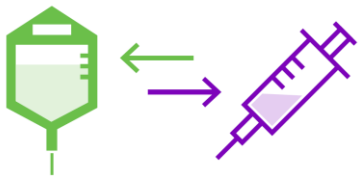
- 395 mg every 3 weeks administered as a subcutaneous injection over 1 minute or
- 790 mg every 6 weeks administered as a subcutaneous injection over 2 minutes

Patients should be treated with KEYTRUDA solution for injection until disease progression or unacceptable toxicity (and up to the maximum duration of therapy if specified for an indication).[1]

Dosing for select indications and in combination[1]

Indication-specific dosing and dosing in combination for KEYTRUDA SC are the same as for KEYTRUDA IV. Please see Appendix 2.

Switching between KEYTRUDA IV and KEYTRUDA SC[1]



Patients receiving KEYTRUDA IV can switch to KEYTRUDA SC at their next scheduled dose. Patients receiving KEYTRUDA SC can switch to KEYTRUDA IV at their next scheduled dose.

Summary of KEYTRUDA SC data

MK-3475A-D77 non-inferiority PK bridging study (for full study details, please see Appendix 3)[14]

MK-3475A-D77 was a randomised, multi-centre, open-label, active-controlled Phase III non-inferiority study. The dual primary endpoints were non-inferiority of KEYTRUDA SC vs KEYTRUDA IV based on Cycle 1 $AUC_{0\text{-}6wks}$ and Steady state (cycle 3) C_{trough}, and the study demonstrated that pembrolizumab overall drug exposure for KEYTRUDA SC was non-inferior to that of KEYTRUDA IV, $p<0.0001$. Secondary endpoints of PFS, ORR, and OS were based on descriptive analysis and were comparable for KEYTRUDA SC and KEYTRUDA IV.

The immunogenicity profile of KEYTRUDA SC was also consistent with the known immunogenicity profile of KEYTRUDA IV — 1.4% (3/211) of patients in the KEYTRUDA SC plus chemotherapy arm developed treatment-emergent anti-pembrolizumab antibodies, and 0.5% (1/211) developed neutralising antibodies against pembrolizumab, compared to 0.9% (1/114) of patients in the KEYTRUDA IV plus chemotherapy arm who developed treatment-emergent anti-pembrolizumab antibodies and 0% (0/114) who developed neutralising antibodies.

The incidence of treatment-emergent anti-recombinant berahyaluronidase alfa antibodies was 1.5% (3/194) with low titer values reported for all three subjects and no detectable systemic concentration of recombinant berahyaluronidase alfa.

The safety profile of KEYTRUDA SC was generally consistent with the known safety profile of KEYTRUDA IV, with the addition of injection-site reactions, which were infrequent (occurring in 2.4% (6/251) of patients) and were all Grade 1.

Time & Motion study (for full study details, please see Appendix 4)[13]

An observational Time & Motion study at 17 sites participating in the MK-3475A-D77 study demonstrated a:

- 44.3% reduction in active HCP time for the preparation process of KEYTRUDA SC vs KEYTRUDA IV (5.1 minutes vs 9.1 minutes, respectively)
- 46.3% reduction in active HCP time for the administration process with KEYTRUDA SC vs KEYTRUDA IV (8.9 minutes vs 16.7 minutes, respectively)
- 49.6% reduction in patient chair time with KEYTRUDA SC vs KEYTRUDA IV (59.0 minutes vs 117.2 minutes, respectively)

Whilst the study may not be representative of individual processes at a local level, the study suggests that KEYTRUDA SC may lead to important time and resource efficiencies.

MK-3475A-F11 study (for full study details, please see Appendix 5)[15]

In MK-3475A-F11, a Phase II crossover study of participant-reported preference for KEYTRUDA SC or KEYTRUDA IV, approximately two-thirds of patients and HCPs preferred KEYTRUDA SC over KEYTRUDA IV, and more patients chose to continue with KEYTRUDA SC than KEYTRUDA IV (68% vs 32%) after Cycle 6 in the treatment continuation period. Safety findings were comparable within arms pre- and post-switching, indicating the safety of switching from one route of administration to the other.

Preparation of the KEYTRUDA SC injection syringe[1]

The KEYTRUDA SC syringe can be prepared for injection in four steps:

1 Check the vial

Check the vial label to ensure the correct formulation is prepared and administered to the patient as prescribed.

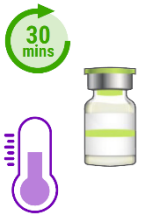
Visually inspect the vial for particulate matter and discolouration. The solution should be clear to slightly opalescent, colourless to slightly yellow.

Discard the vial if visible particles or discolouration are observed.

2 Bring the vial to room temperature

Allow the refrigerated vial to come to room temperature for at least 30 minutes.

- Prior to the preparation for administration, if needed, the **unpunctured vial may be stored at room temperature for up to 24 hours**



Do not dilute. Do not shake the vial.

3 Withdraw the required volume

Withdraw either 2.4 mL (395 mg) or 4.8 mL (790 mg) using a sterile syringe and a **transfer needle (18–21G recommended)**.

- KEYTRUDA SC is compatible with polypropylene and polycarbonate syringe material and stainless steel transfer and injection needles

KEYTRUDA SC vial is for single use only. Discard the empty vial or any unused portion left in the vial. Dispose in accordance with local requirements.

4 Change to injection needle before use

To avoid needle clogging, change the needle to a 25–30G, 13 mm hypodermic injection needle immediately prior to subcutaneous injection.

Do not attach the hypodermic needle until immediately prior to subcutaneous injection to avoid clogging.

Storage of KEYTRUDA SC[1]

Storage of unopened vial

The storage requirements of KEYTRUDA SC vials are the same as that for KEYTRUDA IV.[1,3]

- Store in a refrigerator (2°C–8°C)
- Do not freeze
- Do not shake
- Store in the original carton to protect from light
- If removed from refrigeration, vials can remain at room temperature (≤25°C) for up to 24 hours prior to preparation for administration

The shelf life of unopened vials of KEYTRUDA SC is 3 years.

Storage of the prepared syringe[1]

This product does not contain preservative and should be used immediately after withdrawing from the vial.

If not used immediately, store the syringe containing KEYTRUDA SC solution for injection with the transfer needle and cap in place for:

- Up to 8 hours at room temperature (≤25°C) or
- Up to 24 hours at 2°C–8°C. The 24-hour period may include up to 8 hours at room temperature (≤25°C)

In-use storage times and conditions are the responsibility of the user. Do not attach the hypodermic injection needle until immediately prior to administration to avoid clogging. Discard if storage time exceeds these limits.

Administration of KEYTRUDA SC[1]

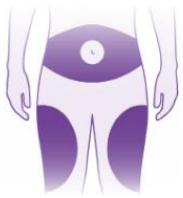
Key considerations for administration

KEYTRUDA SC should be administered by a HCP only.

KEYTRUDA SC is for subcutaneous use only. Do not administer KEYTRUDA SC intravenously.

KEYTRUDA SC should not be substituted for or with KEYTRUDA IV because they have different recommended dosages and routes of administration.

Administration techniques



- Inject KEYTRUDA SC into the subcutaneous tissue of the thigh or abdomen, avoiding the 5 cm area around the navel
- Do not inject into skin that is damaged, sore, bruised, scarred, scaly, or has red patches
- Rotate injection sites for subsequent injections (ensure the injection site is at least 2.5 cm from the previous injection site)
- During treatment with KEYTRUDA SC, do not administer other medicinal products for subcutaneous use at the same site as KEYTRUDA SC

Inject one 2.4 mL dose of KEYTRUDA SC (395 mg) subcutaneously every 3 weeks over 1 minute or inject one 4.8 mL dose of KEYTRUDA SC (790 mg) subcutaneously every 6 weeks over 2 minutes.

When administering KEYTRUDA SC in combination with intravenous chemotherapy, KEYTRUDA SC should be administered first. When administering as part of a combination with enfortumab vedotin, KEYTRUDA SC should be administered after enfortumab vedotin when given on the same day.

Contraindications[1]

KEYTRUDA SC is contraindicated in any patients with hypersensitivity to the active substance or to any of the following excipients:

- Recombinant berahyaluronidase alfa
- L-histidine
- L-histidine hydrochloride monohydrate
- L-methionine
- Sucrose
- Polysorbate 80 (E433)
    - There are 0.2 mg of polysorbate 80 in each mL of solution
- Water for injections

Interactions[1]

Consistent with KEYTRUDA IV, no formal pharmacokinetic drug interaction studies have been conducted with KEYTRUDA SC. Since KEYTRUDA is cleared from the circulation through catabolism, no metabolic drug-drug interactions are expected.

The use of systemic corticosteroids or immunosuppressants before starting KEYTRUDA should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of KEYTRUDA. However, systemic corticosteroids or other immunosuppressants can be used after starting KEYTRUDA to treat immune-mediated adverse reactions. Corticosteroids can also be used as premedication, when KEYTRUDA is used in combination with chemotherapy, as antiemetic prophylaxis and/or to alleviate chemotherapy-related adverse reactions.

Special populations[1]

All recommendations for special populations are the same for KEYTRUDA SC as for KEYTRUDA IV.

Consistent with KEYTRUDA IV, no dose adjustments are necessary with KEYTRUDA SC for the elderly (≥ 65 years), those with mild or moderate renal impairment, and those with mild or moderate hepatic impairment. KEYTRUDA has not been studied in patients with severe renal impairment or severe hepatic impairment.

Use of KEYTRUDA in combination with chemotherapy

Consistent with KEYTRUDA IV, KEYTRUDA SC 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.

Paediatric population[1]

The safety and efficacy of KEYTRUDA SC in children below 18 years of age has not been established.

Fertility, pregnancy and lactation[1]

For women of childbearing potential, who are pregnant or are breast-feeding, the same precautions apply to KEYTRUDA SC as KEYTRUDA IV. See Appendix 6.

Special warnings and precautions for use[1]

The special warnings and precautions for use of KEYTRUDA SC, including immune-mediated adverse reactions, transplant-related adverse reactions, infusion-related reactions, use of KEYTRUDA in combination with chemotherapy, and disease-specific precautions are the same as those for KEYTRUDA IV. See Appendix 7.

Safety and tolerability of KEYTRUDA SC

The safety profile of KEYTRUDA SC in combination with platinum doublet chemotherapy was evaluated in the MK-3475A-D77 Phase III study which included 126 and 251 patients treated with the intravenous and subcutaneous formulations respectively. The safety profile of KEYTRUDA SC was overall consistent with the known safety profile of KEYTRUDA IV in combination with chemotherapy, with an additional adverse reaction of injection-site reactions (2.4% (6/251) in the KEYTRUDA SC arm), which were all Grade 1.[1]

In the MK-3475A-D77 study, the reported injection-site reactions included terms of injection-site reaction (0.8%), injection-site erythema (0.4%), injection-site haemorrhage (0.4%), injection-site induration (0.4%) and injection-site pain (0.4%). The median time to onset of the first injection-site reaction from the most recent dose administration was 2.0 days (range 1–2 days). The median duration of the first event of injection-site reaction was 5.5 days (range 2–20 days). No participant discontinued treatment in the KEYTRUDA SC arm due to injection-site AEs.[14]

Summary of the KEYTRUDA safety profile[1]

KEYTRUDA IV and KEYTRUDA SC are most commonly associated with immune-mediated adverse reactions. Most, of these, including severe reactions, can be resolved following the initiation of appropriate medical therapy or withdrawal of KEYTRUDA. Consistent with KEYTRUDA IV, no dose reductions of KEYTRUDA SC are recommended.

For more details on the safety profile for KEYTRUDA as monotherapy and as combination therapy, see Appendix 8. This is the same for KEYTRUDA SC as it is for KEYTRUDA IV.

Data for selected adverse reactions are the same for KEYTRUDA SC as they are for KEYTRUDA IV. Please consult the relevant SmPCs.

The management of adverse reactions for KEYTRUDA SC, either as monotherapy or in combination, is the same as that for KEYTRUDA IV. See Appendix 9.

Appendix 1: KEYTRUDA SC 395 mg (Q3W) and KEYTRUDA SC 790 mg (Q6W) therapeutic indications[1]

Melanoma

KEYTRUDA as monotherapy is indicated for the treatment of adults with advanced (unresectable or metastatic) melanoma.

KEYTRUDA as monotherapy is indicated for the adjuvant treatment of adults with Stage IIB, IIC or III melanoma and who have undergone complete resection.

NSCLC

KEYTRUDA, in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment, is indicated for the treatment of resectable non-small cell lung carcinoma at high risk of recurrence in adults.

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

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 CPS ≥ 10.

Head and neck squamous cell carcinoma (HNSCC)

KEYTRUDA as monotherapy is indicated for the treatment of resectable locally advanced head and neck squamous cell carcinoma as neoadjuvant treatment, continued as adjuvant treatment in combination with radiation therapy with or without concomitant cisplatin and then as monotherapy inadults whose tumours express PD-L1 with a CPS ≥ 1.

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.

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.

MSI-H or dMMR cancers

CRC

KEYTRUDA as monotherapy is indicated for adults with MSI-H or dMMR colorectal cancer in the following settings:

- first-line treatment of metastatic colorectal cancer;
- treatment of unresectable or metastatic colorectal cancer after previous fluoropyrimidine-based combination therapy.

Non-colorectal cancers

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

- 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 carboplatin and paclitaxel, is indicated for the first-line treatment of primary advanced or recurrent endometrial carcinoma in adults.

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.

Cervical cancer

KEYTRUDA, in combination with chemoradiotherapy (external beam radiation therapy followed by brachytherapy), is indicated for the treatment of FIGO 2014 Stage III - IVA locally advanced cervical cancer in adults who have not received prior definitive therapy.

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.

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.

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.

Appendix 2: Dosing for select indications and in combination[1]

For the adjuvant treatment of melanoma, NSCLC, or RCC, KEYTRUDA should be administered until disease recurrence, unacceptable toxicity, or for a duration of up to one year.

For the neoadjuvant and adjuvant treatment of resectable NSCLC, patients should be treated with neoadjuvant KEYTRUDA in combination with chemotherapy for 4 doses of 395 mg every 3 weeks or 2 doses of 790 mg every 6 weeks or until disease progression that precludes definitive surgery or unacceptable toxicity, followed by adjuvant treatment with KEYTRUDA as monotherapy for 13 doses of 395 mg every 3 weeks or 7 doses of 790 mg every 6 weeks or until disease recurrence or unacceptable toxicity. Patients who experience disease progression that precludes definitive surgery or unacceptable toxicity related to KEYTRUDA as neoadjuvant treatment in combination with chemotherapy should not receive KEYTRUDA monotherapy as adjuvant treatment.

For the neoadjuvant and adjuvant treatment of resectable locally advanced HNSCC, patients should be treated with neoadjuvant KEYTRUDA as monotherapy for 2 doses of 395 mg every 3 weeks or 1 dose of 790 mg or until disease progression that precludes definitive surgery or unacceptable toxicity, followed by adjuvant treatment with KEYTRUDA in combination with radiation with or without concomitant cisplatin for 3 doses of 395 mg every 3 weeks or 2 doses of 790 mg every 6 weeks followed by KEYTRUDA as monotherapy for 12 doses of 395 mg every 3 weeks or 6 doses of 790 mg every 6 weeks or until disease recurrence or unacceptable toxicity. Patients who experience disease progression that precludes definitive surgery or unacceptable toxicity related to KEYTRUDA monotherapy as neoadjuvant treatment should not receive KEYTRUDA in combination with radiation with or without concomitant cisplatin as adjuvant treatment.

For the neoadjuvant and adjuvant treatment of TNBC, patients should be treated with neoadjuvant KEYTRUDA in combination with chemotherapy for 8 doses of 395 mg every 3 weeks or 4 doses of 790 mg every 6 weeks or until disease progression that precludes definitive surgery or unacceptable toxicity, followed by adjuvant treatment with KEYTRUDA as monotherapy for 9 doses of 395 mg every 3 weeks or 5 doses of 790 mg every 6 weeks or until disease recurrence or unacceptable toxicity. Patients who experience disease progression that precludes definitive surgery or unacceptable toxicity related to KEYTRUDA as neoadjuvant treatment in combination with chemotherapy should not receive KEYTRUDA monotherapy as adjuvant treatment.
For first-line treatment of primary advanced or recurrent EC, the recommended dose of KEYTRUDA is 395 mg every 3 weeks for 6 cycles in combination with chemotherapy, followed by KEYTRUDA 790 mg every 6 weeks for up to 14 cycles as monotherapy.

For locally advanced cervical cancer, patients should be treated with KEYTRUDA concurrent with chemoradiotherapy, followed by KEYTRUDA as monotherapy. KEYTRUDA can be administered as either 395 mg every 3 weeks or 790 mg every 6 weeks until disease progression, unacceptable toxicity or up to 24 months.

When administering KEYTRUDA as part of a combination with enfortumab vedotin, KEYTRUDA should be administered after enfortumab vedotin when given on the same day.

Appendix 3: MK-3475A-D77 study[14]

Study design

MK-3475A-D77 was a randomised, multicentre, open-label, active-controlled, Phase III, non-inferiority study comparing KEYTRUDA SC and KEYTRUDA IV, each in combination with chemotherapy for first-line mNSCLC patients across histologies and PD-L1 TPS expression status. 377 patients were randomised 2:1 between KEYTRUDA SC 790 mg Q6W and KEYTRUDA IV 400 mg Q6W. The data cut-off date was 12 July 2024, and the median duration of follow-up was 9.6 months [range 6.2-16.4 months].

Pembrolizumab overall drug exposure for KEYTRUDA SC was non-inferior to that of KEYTRUDA IV

Non-inferiority margin was prespecified as 0.8.

Co-primary endpoints (non-inferiority of KEYTRUDA SC vs KEYTRUDA IV) based on:

	KEYTRUDA SC + chemotherapy (n=245)[a]	**KEYTRUDA IV + chemotherapy** (n=126)
Cycle 1 $AUC_{0\text{-}6wks}$,[b] µg·day/mL		
Geometric mean (95% CI)	**1633.24** (1555.23–1715.15)	**1437.58** (1373.68–1504.46)
Geometric %CV	**40.4**	**26.2**
Geometric mean ratio[c] (96% CI)	**1.14** (1.06–1.22); p<0.0001[d]	
	KEYTRUDA SC + chemotherapy (n=202)	**KEYTRUDA IV + chemotherapy** (n=101)
Steady state (Cycle 3) C_{trough},[e] (µg/mL)		
Geometric mean (95% CI)	**39.23** (37.04–41.55)	**23.49** (21.61–25.54)
Geometric%CV	43.3	44.2
Geometric mean ratio[c] (94% CI)	**1.67** (1.52–1.84)[f]; p<0.0001	

[a]Six participants in the KEYTRUDA SC arm were excluded from the pharmacokinetics modelling analysis due to clinically meaningful protocol deviation (n=4) and to absence of Cycle 1 samples for pharmacokinetics analysis (n=2); [b]AUC (area under the curve) = the total amount of the drug reaching the systemic circulation; [c]KEYTRUDA SC + chemotherapy vs KEYTRUDA IV + chemotherapy; [d]The one-sided *P* value non-inferiority boundary is 0.02 for the analysis of cycle 1 $AUC_{0\text{-}6wks}$; [e]C_{trough} (trough concentration) = lowest concentration of drug in the blood; [f]The one-sided *P* value noninferiority boundary is 0.03 for the analysis of Cycle 3 (steady state) C_{trough}.

Efficacy endpoints were comparable between KEYTRUDA SC and KEYTRUDA IV

Secondary efficacy endpoints were based on a descriptive analysis and not powered to demonstrate statistical significance.

	KEYTRUDA SC + chemotherapy (n=251)	**KEYTRUDA IV + chemotherapy** (n=126)
ORR,[a,b] % (95% CI)	45.4 (39.1–51.8)	42.1 (33.3–51.2)
Complete response, %	3.2	1.6
Partial response, %	42.2	40.5
Difference in ORR,[c] % (95% CI)	3.5 (-7.0–13.7)	
OS event rate (not yet mature)		
Deaths, n (%)	61 (24.3)	37 (29.4)
Hazard ratio (95% CI)	0.81 (0.53–1.22)	
Median PFS,[a] mo (95% CI)	8.1 (6.3–8.3)	7.8 (6.2–9.7)
Hazard ratio (95% CI)	1.05 (0.78–1.43)	

[a]As assessed by BICR using RECIST v1.1; [b]Based on patients with a best overall response as confirmed complete or partial response; [c]KEYTRUDA SC arm minus KEYTRUDA IV arm; based on stratified Miettinen and Nurminen Method.

The immunogenicity profile of KEYTRUDA SC was consistent with the known immunogenicity profile of KEYTRUDA IV

For participants who were ADA positive, the pembrolizumab exposure was comparable to that for participants who were ADA negative and treated by the same route of administration.

Observed incidence of ADAs, n (%)[a]	**KEYTRUDA SC + chemotherapy** (n=211)	**KEYTRUDA IV + chemotherapy** (n=114)
Developed anti-pembrolizumab antibodies	3 (1.4)	1 (0.9)
Developed neutralising antibodies against pembrolizumab	1 (0.5)	0 (0)

[a]Because of the low occurrence of anti-pembrolizumab or anti-berahylauronidase antibodies, the effect of these antibodies on the pharmacokinetics, safety and effectiveness of KEYTRUDA SC is unknown.

Observed incidence of ADAs, n (%)[a,b]	**KEYTRUDA SC + chemotherapy** (n=194)	**KEYTRUDA IV + chemotherapy**
Developed anti-berahyaluronidase alfa antibodies	3 (1.5)	NA

[a]Because of the low occurrence of anti-pembrolizumab or anti-berahylauronidase antibodies, the effect of these antibodies on the pharmacokinetics, safety and effectiveness of KEYTRUDA SC is unknown; [b]No analysis of neutralising antibodies was performed for berahyaluronidase alfa ADA-positive samples.

The safety profile of KEYTRUDA SC was consistent with the known safety profile of KEYTRUDA IV, with an addition of injection-site reactions

Participants, n (%)[a]	**KEYTRUDA SC + chemotherapy** (n=251)	**KEYTRUDA IV + chemotherapy** (n=126)
First-line treatment: median time on treatment	6.87 months (1 day–13.2 months)	6.21 months (1 day–15.9 months)
AEs, ≥1	249 (99.2)	123 (97.6)
TRAEs[b]	226 (90.0)	121 (96.0)
Grade 3–5	118 (47.0)	60 (47.6)
Serious	53 (21.1)	25 (19.8)
Discontinuation of any treatment due to a TRAE[b]	44 (17.5)	19 (15.1)
Discontinued KEYTRUDA SC vs KEYTRUDA IV	21 (8.4)	11 (8.7)
Discontinued chemotherapy	38 (15.1)	15 (11.9)
Deaths due to TRAEs[b]	9 (3.6)[c]	3 (2.4)[d]

[a]Participants are counted a single time for each applicable row and column. Non-serious AEs up to 30 days after the last dose and serious AEs up to 90 days after the last dose are included; [b]Determined by the investigator to be related to treatment; [c]Includes febrile neutropenia (n=3), neutropenic colitis (n=1), neutropenic sepsis (n=1), parotitis (n=1), pneumonia (n=1), septic shock (n=1) and pneumonitis (n=1); [d] Includes septic shock (n=2) and multiple organ dysfunction syndrome (n=1).

Similar proportions of patients in the two treatment arms experienced one or more serious AEs. The most frequent serious AEs included pneumonia, febrile neutropenia, thrombocytopenia, neutropenia, anaemia, and pulmonary embolism.

In total, 38 patients in the study had an AE that resulted in death, including 26 (10.4%) patients in the KEYTRUDA SC arm and 12 (9.5%) patients in the KEYTRUDA IV arm.

All injection-site reactions were Grade 1:

- For patients receiving KEYTRUDA SC, injection-site reactions occurred in 2.4% (6/251) of patients
- The reported injection-site reactions included terms of injection-site reaction (0.8%), injection-site erythema (0.4%), injection-site haemorrhage (0.4%), injection-site induration (0.4%) and injection-site pain (0.4%)

- The median time to onset of the first injection-site AEs from the most recent dose administration was 2.0 days (range 1–2 days)
- The median duration of the first event of injection-site AE was 5.5 days (range 2–20 days)
- No participant discontinued treatment in the KEYTRUDA SC arm due to injection-site AEs

Appendix 4: Time & Motion study

KEYTRUDA SC is administered over 1 or 2 minutes, and may lead to important time and resource efficiencies[1,13]

A prospective observational Time & Motion study across 17 sites participating in MK-3475A-D77 across eight countries in Europe (n=4), South America (n=3) and Asia (n=1).[13] In total, 212 observations were analysed (KEYTRUDA SC, n=153; KEYTRUDA IV, n=59).[13] Process tasks were selected and observed to quantify and compare active HCP time (associated with preparation and administration processes), patient time (in the chair/bed, treatment room and healthcare facility) and consumables usage.[13]

KEYTRUDA SC offers a 93% reduction in drug administration time compared to KEYTRUDA IV, as KEYTRUDA SC is administered over 1 or 2 minutes and KEYTRUDA IV is administered over 30 minutes.[1,3]

Active HCP time per visit for treatment preparation of KEYTRUDA SC vs IV[13]

In the study, there was a **44.3% reduction in active HCP time** for the preparation process with KEYTRUDA SC vs KEYTRUDA IV (5.1 minutes vs 9.1 minutes, respectively).[a]

Collect KEYTRUDA IV vial(s) and allow to warm up	Calculate volume of KEYTRUDA IV and saline	Collect consumables for IV preparation	Draw KEYTRUDA IV from vial(s)	Add KEYTRUDA IV to saline	Inspect infusion bag for particles or discolouration	Waste disposal	Storage of prepared infusion bag
2.1 mins	0.7 mins	1.1 mins	1.5 mins	0.9 mins	0.9 mins	0.5 mins	1.4 mins

Collect KEYTRUDA SC vial and allow to warm up	Collect consumables for KEYTRUDA SC preparation	Draw KEYTRUDA SC into syringe	Change needle and storage of prepared KEYTRUDA SC syringe
1.6 mins	0.9 mins	1.4 mins	1.2 mins

[a]Numbers have been rounded to nearest decimal place, so totals may not sum exactly to the overall values.

Active HCP time per visit for treatment administration process of KEYTRUDA SC vs IV[13]

In the study, there was a **46.3% reduction in active HCP time** for the administration process with KEYTRUDA SC vs KEYTRUDA IV (8.9 minutes vs 16.7 minutes, respectively).[a]

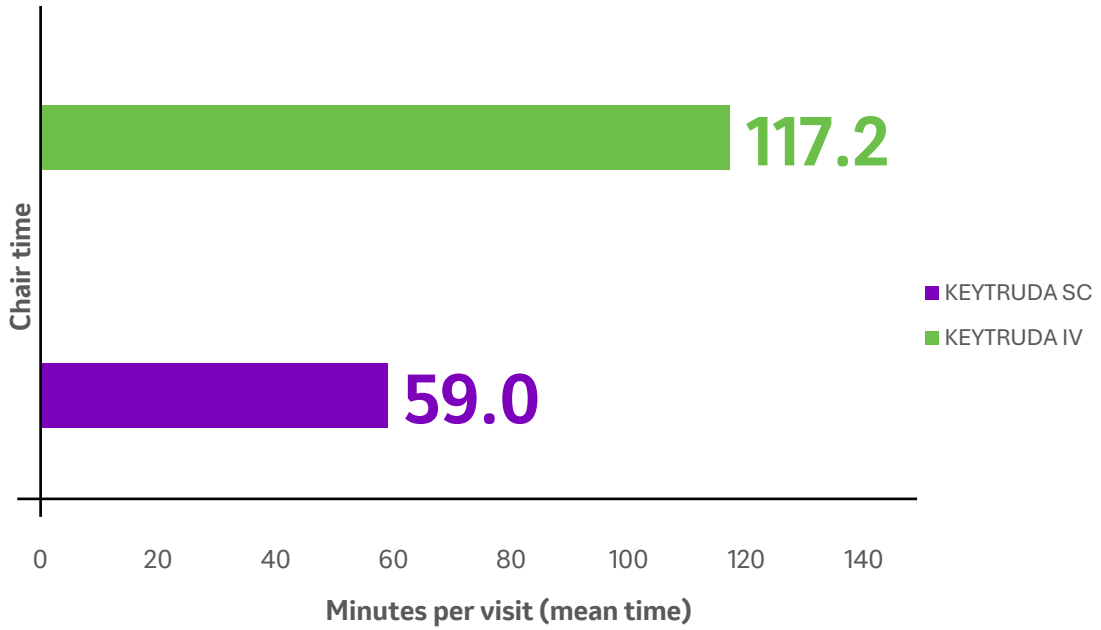
Bring KEYTRUDA IV and consumables to patients	Install peripheral access and line flush or flush central access	Infusion initiation	Patient monitoring during infusion	Infusion completion and waste disposal	Post-infusion record keeping	Post-infusion monitoring
1.2 mins	2.0 mins	1.2 mins	2.9 mins	3.7 mins	3.5 mins	2.1 mins

Bring KEYTRUDA SC and consumables to patient	Administer KEYTRUDA SC injection	Waste disposal	Post-injection record keeping	Post-injection monitoring
1.1 mins	3.4 mins	0.6 mins	2.3 mins	1.6 mins

[a]Numbers have been rounded to nearest decimal place, so totals may not sum exactly to the overall values.

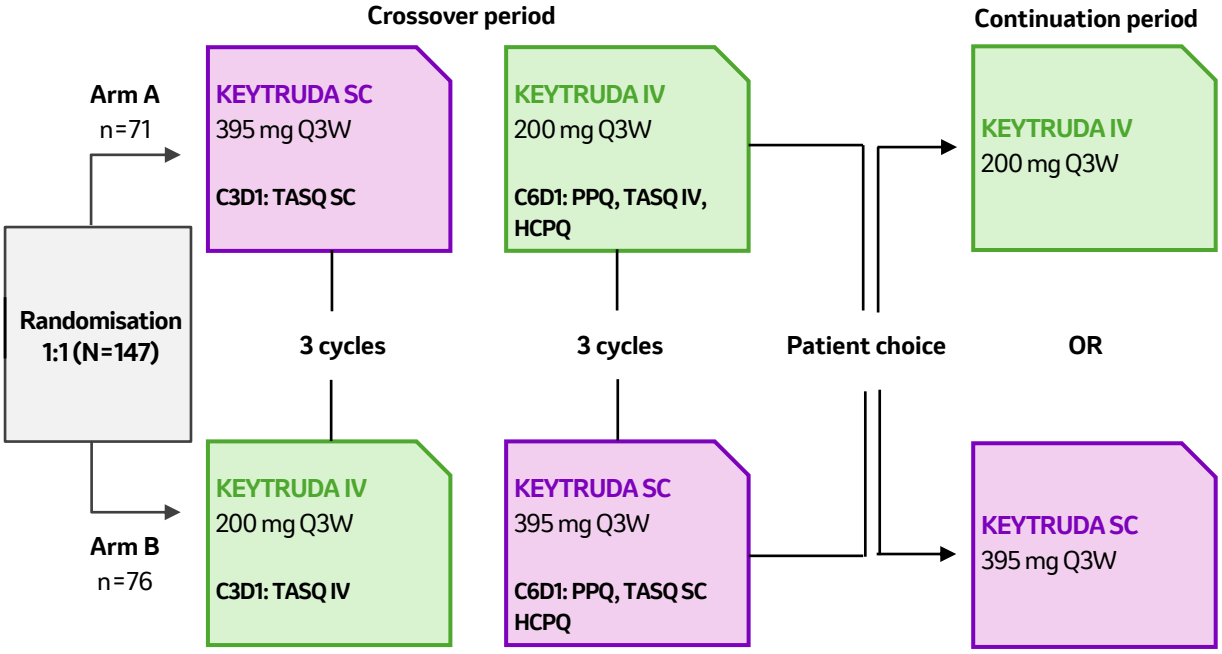
***Patient chair time*[13]**

In the study, there was a **49.6% reduction in patient chair time** with KEYTRUDA SC vs KEYTRUDA IV (59.0 minutes vs 117.2 minutes).



Appendix 5: MK-3475A-F11 study[15]

A Phase II, crossover study of participant-reported preference for KEYTRUDA SC or KEYTRUDA IV[a]



Participants	Primary endpoint	Secondary endpoints
• Age ≥18 years • Resected Stage IIB, IIC, or III melanoma OR • Intermediate-high or high risk resected RCC OR • Newly diagnosed, untreated Stage IV NSCLC with PD-L1 TPS ≥50% • ECOG PS 0 or 1 • No pneumonitis or interstitial lung disease	Participant preference for KEYTRUDA SC or KEYTRUDA IV (PPQ question 1)	• Reasons for preference (PPQ question 3) • Participant satisfaction with route of administration (TASQ-SC/IV) • Participant choice of administration for continuation period • HCP preference for route of administration (HCPQ) • Safety and tolerability

- Participants received up to a total of 17 cycles of treatment for melanoma or RCC, and up to a total of 35 cycles of treatment for NSCLC
- The analysis population for participant preference included all randomised participants who received 3 cycles of KEYTRUDA SC and 3 cycles of KEYTRUDA IV during the crossover period and completed the PPQ after the administration of study treatment on Day 1 of Cycle 6 (N=118)
- The safety analysis population included all randomised participants who received at least 1 dose of study treatment (N=147)
- The median follow-up was 10.8 months (range 4.0–14.8). The data cut-off date was 9 April 2025

[a]Randomisation stratified by ECOG PS and tumour type; KEYTRUDA SC is KEYTRUDA at 165 mg/mL with berahyaluronidase alfa at 2000 U/mL (injection volume ~2.4 mL).

2/3 of patients and HCPs prefer KEYTRUDA SC over KEYTRUDA IV

Top reasons for patient preference for SC administration:	***Top reasons for HCP preference for SC administration:***
• Requires less time in clinic (64%) • Feels more comfortable during administration (62%) 'Lower level of injection-site pain' (38%) and 'Feels less emotionally distressing' (21%) were other reasons for preference	• Ease of administration; more convenient to administer (95%) • Length of administration time; time required to administer (95%) 'Patient's body type' (10%) was another reason for preference

- More patients chose to continue with KEYTRUDA SC than KEYTRUDA IV (68% vs 32%, respectively) after Cycle 6 in the treatment continuation period

Safety findings were comparable within arms, pre- and post-switch

Safety findings were comparable within arms pre-and post-switch, indicating the safety of switching from one route of administration to the other.

	Arm A (SC → IV)		**Arm B (IV→SC)**	
Participants, n (%)	**Cycles 1–3** (n=71)	**Cycles 4–6** (n=65)	**Cycles 1–3** (n=76)	**Cycles 4–6** (n=70)
With one or more TRAEs[a]	**40 (56)**	**21 (32)**	**36 (47)**	**42 (60)**
Grade 3–5	1 (1)	2 (3)	5 (7)	3 (4)
Serious	1 (1)	1 (2)	2 (3)	2 (3)
Died	0	0	0	0
Discontinued treatment	1 (1)	1 (2)	1 (1)	1 (1)
Discontinued treatment due to serious TRAE	1 (1)	1 (2)	0	1 (1)

[a]Determined by the investigator to be related to study treatment.

Injection-site AEs with KEYTRUDA SC administration were similar regardless of the order in which treatment was given. Injection-site AEs during KEYTRUDA SC administration cycles of the crossover period occurred in 9 (13%; Arm A) and 11 (16%; Arm B) participants.

- The most frequent injection-site AE reported overall was injection-site pain (n=10; 7%)
- All injection-site AEs were Grade 1, except for two Grade 2 AEs in Arm B (injection-site pain and injection-site reaction)

Appendix 6: Fertility, pregnancy and lactation[1]

Women of childbearing potential

Women of childbearing potential should use effective contraception during treatment with KEYTRUDA and for at least 4 months after the last dose of KEYTRUDA.

Pregnancy

There are no data on the use of KEYTRUDA in pregnant women. Animal reproduction studies have not been conducted with KEYTRUDA; however, in murine models of pregnancy, blockade of PD-L1 signalling has been shown to disrupt tolerance to the foetus and to result in an increased foetal loss. These results indicate a potential risk, based on its mechanism of action, that administration of KEYTRUDA during pregnancy could cause foetal harm, including increased rates of abortion or stillbirth. Human IgG4 are known to cross the placental barrier; therefore, being an IgG4, KEYTRUDA has the potential to be transmitted from the mother to the developing foetus. KEYTRUDA should not be used during pregnancy unless the clinical condition of the woman requires treatment with KEYTRUDA.

Breast-feeding

It is unknown whether KEYTRUDA is secreted in human milk. Since it is known that antibodies can be secreted in human milk, a risk to the newborns/infants cannot be excluded. A decision should be made whether to discontinue breast-feeding or to discontinue KEYTRUDA, taking into account the benefit of breast-feeding for the child and the benefit of KEYTRUDA therapy for the woman.

Fertility

No clinical data are available on the possible effects of KEYTRUDA on fertility. There were no notable effects in the male and female reproductive organs in monkeys based on 1-month and 6-month repeat-dose toxicity studies.

Appendix 7: Special warnings and precautions for use[1]

Immune-mediated adverse reactions

Immune-mediated adverse reactions, including severe and fatal cases, have occurred in patients receiving KEYTRUDA. Most immune-mediated adverse reactions occurring during treatment with KEYTRUDA were reversible and managed with interruptions of KEYTRUDA, administration of corticosteroids and/or supportive care.

Immune-mediated adverse reactions have also occurred after the last dose of KEYTRUDA. Immune-mediated adverse reactions affecting more than one body system can occur simultaneously.

For suspected immune-mediated adverse reactions, adequate evaluation to confirm aetiology or exclude other causes should be ensured. Based on the severity of the adverse reaction, KEYTRUDA should be withheld and corticosteroids administered. Upon improvement to Grade ≤ 1, corticosteroid taper should be initiated and continued over at least 1 month. Based on limited data from clinical studies in patients whose immune-mediated adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants can be considered.

KEYTRUDA may be restarted within 12 weeks after last dose of KEYTRUDA if the adverse reaction recovers to Grade ≤ 1 and corticosteroid dose has been reduced to ≤ 10 mg prednisone or equivalent per day.

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.

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

Immune-mediated pneumonitis

Pneumonitis has been reported in patients receiving KEYTRUDA. Patients should be monitored for signs and symptoms of pneumonitis. Suspected pneumonitis should be confirmed with radiographic imaging and other causes excluded. Corticosteroids should be administered for Grade ≥ 2 events (initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper); KEYTRUDA should be withheld for Grade 2 pneumonitis, and permanently discontinued for Grade 3, Grade 4 or recurrent Grade 2 pneumonitis.

Immune-mediated colitis

Colitis has been reported in patients receiving KEYTRUDA. Patients should be monitored for signs and symptoms of colitis, and other causes excluded. Corticosteroids should be administered for Grade ≥ 2 events (initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper); KEYTRUDA should be withheld for Grade 2 or Grade 3 colitis, and permanently discontinued for Grade 4 or recurrent Grade 3 colitis. The potential risk of gastrointestinal perforation should be taken into consideration.

Immune-mediated hepatitis

Hepatitis has been reported in patients receiving KEYTRUDA. Patients should be monitored for changes in liver function (at the start of treatment, periodically during treatment and as indicated based on clinical evaluation) and symptoms of hepatitis, and other causes excluded. Corticosteroids should be administered (initial dose of 0.5-1 mg/kg/day (for Grade 2 events) and 1-2 mg/kg/day (for

Grade ≥ 3 events) prednisone or equivalent followed by a taper) and, based on severity of liver enzyme elevations, KEYTRUDA should be withheld or discontinued.

Immune-mediated nephritis

Nephritis has been reported in patients receiving KEYTRUDA. Patients should be monitored for changes in renal function, and other causes of renal dysfunction excluded. Corticosteroids should be administered for Grade ≥ 2 events (initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper) and, based on severity of creatinine elevations, KEYTRUDA should be withheld for Grade 2, and permanently discontinued for Grade 3 or Grade 4 nephritis.

Immune-mediated endocrinopathies

Severe endocrinopathies, including adrenal insufficiency, hypophysitis, type 1 diabetes mellitus, diabetic ketoacidosis, hypothyroidism, and hyperthyroidism have been observed with KEYTRUDA treatment.

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

Adrenal insufficiency (primary and secondary) has been reported in patients receiving KEYTRUDA. Hypophysitis has also been reported in patients receiving KEYTRUDA. Patients should be monitored for signs and symptoms of adrenal insufficiency and hypophysitis (including hypopituitarism) and other causes excluded. Corticosteroids to treat adrenal insufficiency and other hormone replacement should be administered as clinically indicated. KEYTRUDA should be withheld for Grade 2 adrenal insufficiency or hypophysitis until the event is controlled with hormone replacement. KEYTRUDA should be withheld or discontinued for Grades 3 or 4 adrenal insufficiency or symptomatic hypophysitis. Continuation of KEYTRUDA may be considered, after corticosteroid taper, if needed. Pituitary function and hormone levels should be monitored to ensure appropriate hormone replacement.

Type 1 diabetes mellitus, including diabetic ketoacidosis, has been reported in patients receiving KEYTRUDA. Patients should be monitored for hyperglycaemia or other signs and symptoms of diabetes. Insulin should be administered for type 1 diabetes, and KEYTRUDA should be withheld in cases of type 1 diabetes associated with Grade ≥ 3 hyperglycaemia or ketoacidosis until metabolic control is achieved.

Thyroid disorders, including hypothyroidism, hyperthyroidism and thyroiditis, have been reported in patients receiving KEYTRUDA and can occur at any time during treatment. Hypothyroidism is more frequently reported in patients with HNSCC with prior radiation therapy. Patients should be monitored 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. Hypothyroidism may be managed with replacement therapy without treatment interruption and without corticosteroids.

Hyperthyroidism may be managed symptomatically. KEYTRUDA should be withheld for Grade ≥ 3 until recovery to Grade ≤ 1 hyperthyroidism. Thyroid function and hormone levels should be monitored to ensure appropriate hormone 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.

Immune-mediated skin adverse reactions

Immune-mediated severe skin reactions have been reported in patients receiving KEYTRUDA. Patients should be monitored for suspected severe skin reactions and other causes should be excluded. Based on the severity of the adverse reaction, KEYTRUDA should be withheld for Grade 3

skin reactions until recovery to Grade ≤ 1 or permanently discontinued for Grade 4 skin reactions, and corticosteroids should be administered.

Cases of SJS and TEN have been reported in patients receiving KEYTRUDA. For suspected SJS or TEN, KEYTRUDA should be withheld and the patient should be referred to a specialised unit for assessment and treatment. If SJS or TEN is confirmed, KEYTRUDA should be permanently discontinued.

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 anti-cancer agents.

Other immune-mediated adverse reactions

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, hypoparathyroidism and pericarditis.

Based on the severity and type of the adverse reaction, KEYTRUDA should be withheld for Grade 2 or Grade 3 events and corticosteroids administered.

KEYTRUDA may be restarted within 12 weeks after last dose of KEYTRUDA if the adverse reaction recovers to Grade ≤ 1 and corticosteroid dose has been reduced to ≤ 10 mg prednisone or equivalent per day.

KEYTRUDA must be permanently discontinued for any Grade 3 immune-mediated adverse reaction that recurs and for any Grade 4 immune-mediated adverse reaction.

For Grades 3 or 4 myocarditis, encephalitis or Guillain-Barré syndrome, KEYTRUDA should be permanently discontinued.

Transplant-related adverse reactions

Solid organ transplant rejection

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 versus the risk of possible organ rejection should be considered in these patients.

Complications of allogeneic HSCT

Allogeneic HSCT after treatment with KEYTRUDA: Cases of GVHD and hepatic 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 versus the risk of possible GVHD in patients with a history of allogeneic HSCT.

Disease-specific precautions

Use of KEYTRUDA in urothelial carcinoma patients who have received prior platinum-containing chemotherapy

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.

Use of KEYTRUDA in urothelial carcinoma for patients who are considered ineligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with CPS ≥ 10

The baseline and prognostic disease characteristics of the study population of KEYNOTE-052 included a proportion of patients eligible for a carboplatin-based combination, for whom the benefit has been assessed in a comparative study (KEYNOTE-361). In KEYNOTE-361, a higher number of deaths within 6 months of treatment initiation followed by a long-term survival benefit was observed with KEYTRUDA monotherapy compared to chemotherapy. No specific factor(s) associated with early deaths could be identified. Physicians should consider the delayed onset of KEYTRUDA effect before initiating treatment in patients with urothelial carcinoma who are considered eligible for carboplatin-based combination chemotherapy.

KEYNOTE-052 also included patients eligible for mono-chemotherapy, for whom no randomised data are available. In addition, no safety and efficacy data are available in frailer patients (e.g. ECOG performance status 3) considered not eligible for chemotherapy. In the absence of these data, KEYTRUDA should be used with caution in this population after careful consideration of the potential risk-benefit on an individual basis.

Use of KEYTRUDA for first-line treatment of patients with NSCLC

In general, the frequency of adverse reactions for KEYTRUDA combination therapy is observed to be higher than for KEYTRUDA monotherapy or chemotherapy alone, reflecting the contributions of each of these components. A direct comparison of KEYTRUDA when used in combination with chemotherapy to KEYTRUDA monotherapy is not available.

Physicians should consider the benefit/risk balance of the available treatment options (KEYTRUDA monotherapy or KEYTRUDA in combination with chemotherapy) before initiating treatment in previously untreated patients with NSCLC whose tumours express PD-L1.

In KEYNOTE-042, a higher number of deaths within 4 months of treatment initiation followed by a long-term survival benefit was observed with KEYTRUDA monotherapy compared to chemotherapy.

Use of KEYTRUDA for first-line treatment of patients with HNSCC

In general, the frequency of adverse reactions for KEYTRUDA combination therapy is observed to be higher than for KEYTRUDA monotherapy or chemotherapy alone, reflecting the contributions of each of these components.

Physicians should consider the benefit/risk balance of the available treatment options (KEYTRUDA monotherapy or KEYTRUDA in combination with chemotherapy) before initiating treatment in patients with HNSCC whose tumours express PD-L1.

Use of KEYTRUDA for treatment of patients with advanced or recurrent MSI-H or dMMR EC

A direct comparison of KEYTRUDA when used in combination with lenvatinib to KEYTRUDA monotherapy is not available. Physicians should consider the benefit/risk balance of the available treatment options (KEYTRUDA monotherapy or KEYTRUDA in combination with lenvatinib) before initiating treatment in patients with advanced or recurrent MSI-H or dMMR EC.

Use of KEYTRUDA for adjuvant treatment of patients with melanoma

A trend toward increased frequency of severe and serious adverse reactions in patients ≥ 75 years was observed. Safety data of KEYTRUDA in the adjuvant melanoma setting in patients ≥ 75 years are limited.

Use of KEYTRUDA in combination with axitinib for first-line treatment of patients with RCC

When KEYTRUDA is given with axitinib, higher than expected frequencies of Grades 3 and 4 ALT and AST elevations have been reported in patients with advanced RCC. Liver enzymes should be monitored before initiation of and periodically throughout treatment. More frequent monitoring of liver enzymes as compared to when the medicines are used in monotherapy may be considered. Medical management guidelines for both medicines should be followed (refer to the SmPC for axitinib).

Use of KEYTRUDA for first-line treatment of patients with MSI-H/dMMR CRC

In KEYNOTE-177, the hazard rates for overall survival events were greater for KEYTRUDA compared with chemotherapy for the first 4 months of treatment, followed by a long-term survival benefit for KEYTRUDA.

Use of KEYTRUDA for first-line treatment of patients with BTC

Cholangitis and biliary tract infections are not uncommon in patients with BTC. Cholangitis events were reported in KEYNOTE-966 in both treatment groups (11.2% [n=59] of participants in the KEYTRUDA plus chemotherapy arm and 10.3% [n=55] of participants in the placebo plus chemotherapy arm). Patients with biliary stents and drains (n=74) were at increased risk of cholangitis and biliary tract infections in KEYNOTE-966 (39.4% [n=13] of participants in the KEYTRUDA plus chemotherapy arm vs. 29.3% [n=12] of participants in the placebo plus chemotherapy arm). Patients with BTC (especially those with biliary stents) should be closely monitored for development of cholangitis or biliary tract infections before initiation of treatment and, regularly, thereafter.

Appendix 8: Summary of the safety profile[1]

KEYTRUDA in monotherapy

The safety of KEYTRUDA IV as monotherapy has been evaluated in 7 631 patients across tumour types and 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. In this patient population, the median observation time was 8.5 months (range: 1 day to 39 months) and the most frequent adverse reactions with KEYTRUDA were fatigue (31%), diarrhoea (22%), and nausea (20%). The majority of adverse reactions reported for monotherapy were of Grades 1 or 2 severity. The most serious adverse reactions were immune-mediated adverse reactions and severe infusion-related reactions. The incidences of immune-mediated adverse reactions were 37% all Grades and 9% for Grades 3-5 for KEYTRUDA monotherapy in the adjuvant setting and 25% all Grades and 6% for Grades 3-5 in the metastatic setting. No new immune-mediated adverse reactions were identified in the adjuvant setting.

KEYTRUDA in combination with chemotherapy, radiation therapy (RT) or chemoradiotherapy (CRT)

When KEYTRUDA is administered in combination, refer to the SmPC for the respective combination therapy components prior to initiation of treatment.

The safety of KEYTRUDA IV in combination with chemotherapy, RT or CRT has been evaluated in 6695 patients across tumour types receiving 200 mg, 2 mg/kg bw or 10 mg/kg bw KEYTRUDA every 3 weeks, in clinical studies. In this patient population, the most frequent adverse reactions were anaemia (50%), nausea (51%), diarrhoea (35%), fatigue (35%), constipation (32%), vomiting (27%), neutrophil count decreased (26%), and decreased appetite (26%).

Incidences of Grades 3-5 adverse reactions were:

- **NSCLC:** 69% for KEYTRUDA combination therapy and 61% for chemotherapy alone
- **HNSCC:** 80% for KEYTRUDA combination therapy (chemotherapy or RT with or without chemotherapy) and 79% for chemotherapy plus cetuximab or RT with or without chemotherapy
- **Oesophageal carcinoma:** 86% for KEYTRUDA combination therapy and 83% for chemotherapy alone
- **TNBC:** 80% for KEYTRUDA combination therapy and 77% for chemotherapy alone
- **Cervical cancer:** 77% for KEYTRUDA combination therapy (chemotherapy with or without bevacizumab or in combination with CRT) and 71% for chemotherapy with or without bevacizumab or CRT alone
- **Gastric cancer:** 74% for KEYTRUDA combination therapy (chemotherapy with or without trastuzumab) and 68% for chemotherapy with or without trastuzumab
- **BTC:** 85% for KEYTRUDA combination therapy and 84% for chemotherapy alone
- **EC:** 59% for KEYTRUDA combination therapy and 46% for chemotherapy alone

KEYTRUDA in combination with TKI

When KEYTRUDA 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 Lenvatinib Eisai and for advanced EC see the SmPC for Lenvatinib Eisai.

The safety of intravenous 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

5 mg twice daily or lenvatinib 20 mg once daily in clinical studies, as appropriate. In these patient populations, the most frequent adverse reactions were diarrhoea (58%), hypertension (54%), hypothyroidism (46%), fatigue (41%), decreased appetite (40%), nausea (40%), arthralgia (30%), vomiting (28%), weight decreased (28%), dysphonia (28%), abdominal pain (28%), proteinuria (27%), palmar-plantar erythrodysaesthesia syndrome (26%), rash (26%), stomatitis (25%), constipation (25%), musculoskeletal pain (23%), headache (23%) and cough (21%).

Incidences of Grades 3–5 adverse reactions were:

- **RCC:** 80% for KEYTRUDA in combination with either axitinib or lenvatinib and 71% for sunitinib alone
- **EC:** 89% for KEYTRUDA in combination with lenvatinib and 73% for chemotherapy alone

Appendix 9: Management of adverse reactions[1]

Consult the relevant SmPCs for more information on management of adverse reactions.

KEYTRUDA, as monotherapy or as combination therapy, should be permanently discontinued for Grade 4 or recurrent Grade 3 immune-mediated adverse reactions, unless otherwise specified in the SmPC.

KEYTRUDA in combination with axitinib in RCC

For RCC patients treated with KEYTRUDA in combination with axitinib, see the SmPC regarding dosing of axitinib.

For liver enzyme elevations, in patients with RCC being treated with KEYTRUDA in combination with axitinib:

- If ALT or AST ≥ 3 times ULN but < 10 times ULN without concurrent total bilirubin ≥ 2 times ULN, both KEYTRUDA and axitinib should be withheld until these adverse reactions recover to Grades 0–1. Corticosteroid therapy may be considered. Rechallenge with a single medicine or sequential rechallenge with both medicines after recovery may be considered. If rechallenging with axitinib, dose reduction as per the axitinib SmPC may be considered
- If ALT or AST ≥ 10 times ULN or > 3 times ULN with concurrent total bilirubin ≥ 2 times ULN, both KEYTRUDA and axitinib should be permanently discontinued and corticosteroid therapy may be considered

KEYTRUDA in combination with lenvatinib

When used in combination with lenvatinib, one or both medicines should be interrupted as appropriate. Lenvatinib should be withheld, dose reduced, or discontinued in accordance with the instructions in the lenvatinib SmPC for combination with KEYTRUDA. No dose reductions are recommended for KEYTRUDA.

Acronyms:

AE, adverse event; AID, autoimmune disease; ALK, anaplastic lymphoma kinase; ALT, alanine aminotransferase; ASCT, autologous stem cell transplant; AST, aspartate aminotransferase; AUC, area under curve; BICR, blinded independent central review; BTC, biliary tract carcinoma; bw, body weight; C3D1, Cycle 3 day 1; C6D1, Cycle 6 day 1; cHL, Classical Hodgkin lymphoma; CI, confidence intervals; CPS, combined positive score; CR, complete response; CRC, colorectal cancer; CRT, chemoradiotherapy; CV, coefficient of variation; dMMR, mismatch repair deficient; EC, endometrial cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; GEJ, gastro-oesophageal junction; GVHD, graft-versus-host-disease; HCP, healthcare professional; HCPQ, HCP Preference Questionnaire; hepatic VOD, hepatic veno-occlusive disease; HNSCC, head and neck squamous cell carcinoma; HSCT, Heamatopoietic Stem Cell Transplant; IgG4, immunoglobulin G subclass 4; mNSCLC, metastatic non-small cell lung carcinoma; mo, month; MSI-H, microsatellite instability high; n, number; NHS, National Health Service; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; p, probability; PD-L1, programmed death-ligand 1; PD-L2, programmed death-ligand 2; PFS, progression-free survival; PK, pharmacokinetics; PPQ, patient preference questionnaire; PR, partial response; Q3W, every 3 weeks; Q6W, every 6 weeks; RCC, renal cell carcinoma; RECIST v1.1, Response Evaluation Criteria in Solid Tumours v1.1; SJS, Stevens-Johnson syndrome; SmPC, Summary of Product Characteristics; T&M, Time & Motion; TASQ, Therapy Administration Satisfaction Questionnaire; TEN, toxic epidermal necrolysis; TKI, tyrosine kinase inhibitor; TNBC, triple negative breast cancer; TPS, tumour proportion score; TRAE, treatment-related adverse event; ULN, upper limit of normal

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