Prescribing information GB | NI

KEYTRUDA® (pembrolizumab) plus pemetrexed and platinum chemotherapy for the first-line treatment of patients with metastatic non-squamous NSCLC with a PD-L1 TPS <1%: A clinical perspective

KEYTRUDA®, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of metastatic non-squamous non-small cell lung carcinoma (NSCLC) in adults whose tumours have no EGFR or ALK positive mutations[1]

Explore the case study

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

Refer to the Summary of Product Characteristics before prescribing KEYTRUDA® to help minimise the risks associated with treatment. Prescribing information can be found at the top of each page in the document.

MSD

KEYTRUDA® (pembrolizumab)

This case study is for UK healthcare professionals only. The patient provided consent for the case to be shared. Please note that this is one individual patient and cases may vary.
ALK, anaplastic lymphoma kinase receptor; **EGFR**, epidermal growth factor receptor; **IO**, immunotherapy; **NSCLC**, non-small cell lung carcinoma; **PD-L1**, programmed death-ligand 1; **TPS**, tumour proportion score.

1. KEYTRUDA® Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/2498. Accessed April 2023.

GB-PDO-02598 | April 2023

Merck Sharp & Dohme (UK) Limited, 120 Moorgrate, London, EC2M 6UR

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Meet Joe

Age: 65 years
Occupation: Retired taxi driver
Personal life: Married with a close family

Joe presented with:
No signs and symptoms but relapsed after surgery

How could choosing immunotherapy (IO) combination in first-line help patients like Joe with metastatic non-squamous NSCLC and a PD-L1 TPS <1%?

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KEYTRUDA® (pembrolizumab)

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Joe, 65 years old
Occupation: Retired taxi driver
Lifestyle: Married with a close family

Presenting complaint:
None – patient relapsed after surgery

Medical history:
Ex-smoker with mild COPD;
No other significant co-morbidities;
On salbutamol and beclomethasone inhalers;
No known drug allergies

Radical resection

Right upper lobectomy for a pT1 pN0 M0 R0 adenocarcinoma
- EGFRwt
- ALK/ROS1neg
- PD-L1 0%

FEB 2017

Follow-up

Progression with bilateral lung metastases and a liver deposit
- ECOG PS 1 at presentation to oncology
- Metastatic disease detected

SEPT 2019

Joe's family provide excellent emotional support and he had a positive outlook

Explore more

What first-line treatment options are available for patients like Joe?

The links to the prescribing information at the top of each page directs users to an external website.
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ALK, anaplastic lymphoma kinase receptor; **COPD**, chronic obstructive pulmonary disease; **ECOG**, Eastern Cooperative Oncology Group; **EGFRwt**, wild type epidermal growth factor; **M0**, no metastasis; **N0**, not spread to nearby lymph node; **R0**, resection for cure or complete remission; **ROS1**, c-ros oncogene 1; **PD-L1**, programmed death-ligand 1; **PS**, performance status; **T1**, tumour stage 1.

KEYTRUDA® (pembrolizumab)

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Joe, 65 years old

Diagnosis: Metastatic (post resection) non-squamous NSCLC

- EGFRwt
- ALK/ROS1neg
- PD-L1 0%

IO + chemotherapy

OCT 2019

Starts first-line KEYTRUDA®[1]* + pemetrexed[2] + carboplatin[3]

NOV 2019

Neutropenic sepsis during treatment cycle 1

- Dose reduction 25% from treatment cycle 2

JAN 2020

Partial response determined by CT

MAR 2020

Covid infection

- ✕ Stopped maintenance pemetrexed
- ✓ Continued KEYTRUDA®

APR 2020

- **Grade 1 hepatitis during treatment cycle 6**
- **Grade 1 acute kidney injury**
- **Slight volume increase of lung lesions determined by CT**

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Explore more

How would you manage these adverse events?

The links to the prescribing information at the top of each page directs users to an external website.
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*Safety and tolerability of KEYTRUDA® is comparable between Q3W and Q6W regimen. Based on the modelling and simulation of dose/exposure relationships as per Section 5.1 of the SmPC.[1]
ALK, anaplastic lymphoma kinase receptor; **CT**, computerised tomography; **EGFRwt**, wild type epidermal growth factor receptor; **IO**, immunotherapy; **NSCLC**, non-small cell lung carcinoma; **Q3W**, every 3 weeks; **Q6W**, every 6 weeks; **ROS1**, c-ros oncogene 1; **PD-L1**, programmed death-ligand 1.
1. KEYTRUDA® Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/2498. Accessed April 2023; 2. Pemetrexed Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/12684/smpc. Accessed April 2023; 3. Carboplatin Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/3787. Accessed April 2023.

KEYTRUDA® (pembrolizumab)

Prescribing information GB | NI

Joe, 65 years old

Diagnosis: Metastatic (post resection) non-squamous NSCLC

- EGFRwt
- ALK/ROS1neg
- PD-L1 0%

DEC 2020

Disease progression determined by CT following 14 months of immuno-chemotherapy with KEYTRUDA®[1] plus pemetrexed[2] and platinum chemotherapy

JAN 2021

Started second-line treatment with carboplatin[3] + vinorelbine[4]*

*Please refer to the referenced SmPC and view licensed indications before prescribing as the use of this product in this setting is off license and is reflective of the HCPs personal clinical decision making.

MAR 2021

Partial response determined by CT

DEC 2021

Disease progression

Molecular profiling identified *STK11* and *KRASG12C* mutation

MAR 2022

Started third-line treatment with sotorasib[5] after exploring clinical trial entry (MATRIX study)

MAY 2022

Partial response determined by CT

DEC 2022

Disease progression in both lungs

Started fourth-line treatment with carboplatin[3] + gemcitabine[6]*

*Please refer to the referenced SmPC and view licensed indications before prescribing as the use of this product in this setting is off license and is reflective of the HCPs personal clinical decision making.

JAN 2023

Good clinical response

Explore KEYTRUDA® combination therapy outcomes and safety data at Years 1 and 5 in the KEYNOTE-189 study

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The links to the prescribing information at the top of each page directs users to an external website.
The patient provided consent for the case to be shared. Please note that this is one individual patient and cases may vary.
ALK, anaplastic lymphoma kinase receptor; **CT**, computerised tomography; **EGFRwt**, wild type epidermal growth factor receptor; **KRASG12C**, Kirsten rat sarcoma viral oncogene with glycine-to-cysteine substitution in codon 12; **NSCLC**, non-small cell lung carcinoma; **PD-L1**, programmed death-ligand 1; **ROS1**, c-ros oncogene 1; **STK11**, Serine/threonine kinase 11.

1. KEYTRUDA® Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/2498. Accessed April 2023; 2. Pemetrexed Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/12684/smpc. Accessed April 2023; 3. Carboplatin Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/3787. Accessed April 2023; 4. Vinorelbine Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/3912/smpc. Accessed April 2023; 5. Sotorasib Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/12871. Accessed April 2023; 6. Gemcitabine Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/7298/smpc. Accessed April 2023.

KEYTRUDA® (pembrolizumab)

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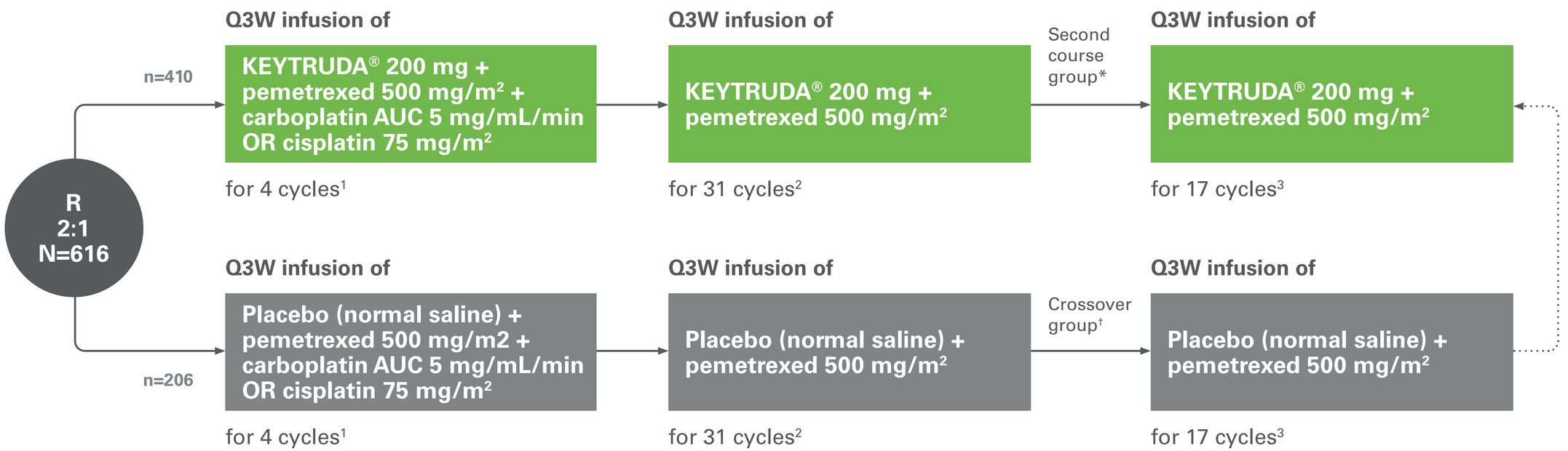
KEYNOTE-189 trial with KEYTRUDA®: Study design[1-3]

KEYNOTE-189 is a **randomised, double-blind, active-controlled, phase 3 trial** in patients with previously untreated metastatic non-squamous NSCLC with no EGFR or ALK positive mutations.

The primary endpoints of this study were **overall survival** and **progression-free survival**.

Inclusion criteria[1]:
- ≥18 years of age
- Untreated metastatic, non-squamous NSCLC
- No sensitizing EGFR or ALK mutations



The links to the prescribing information at the top of each page directs users to an external website.

*Patients who had disease progression or better after completing 35 cycles of KEYTRUDA® or had stopped trial treatment after achieving complete response and received ≥8 cycles of treatment, but then experienced disease progression, could receive second-course KEYTRUDA® monotherapy for 17 cycles if they had no new anticancer treatment since their last dose of KEYTRUDA®.[3]

†To be eligible for crossover to KEYTRUDA® monotherapy, disease progression had to have been verified by blinded, independent, central radiologist review and all safety criteria had to have been met.[1]

ALK, anaplastic lymphoma kinase receptor; **AUC**, area under the curve; **EGFR**, epidermal growth factor receptor; **NSCLC**, non-small cell lung carcinoma; **Q3W**, every 3 week; **R**, randomisation.

1. Gandhi L, et al. *New Eng J Med.* 2018;378:2078–2092; 2. Gandhi L, et al. Presented at the 2018 American Association of Cancer Research (AACR) annual meeting, 14–18 April 2018, Chicago, USA; 3. Gray JE, et al. Presented virtually at the 2020 World Conference on Lung Cancer (WCLC), 28–31 January 2021.

KEYTRUDA® (pembrolizumab)

Prescribing information GB | NI

Patients treated with KEYTRUDA® combination therapy had a greater PFS benefit compared with the placebo group at 10.5 months with the trend towards treatment benefit maintained at 5 years: data from the KEYNOTE-189 trial

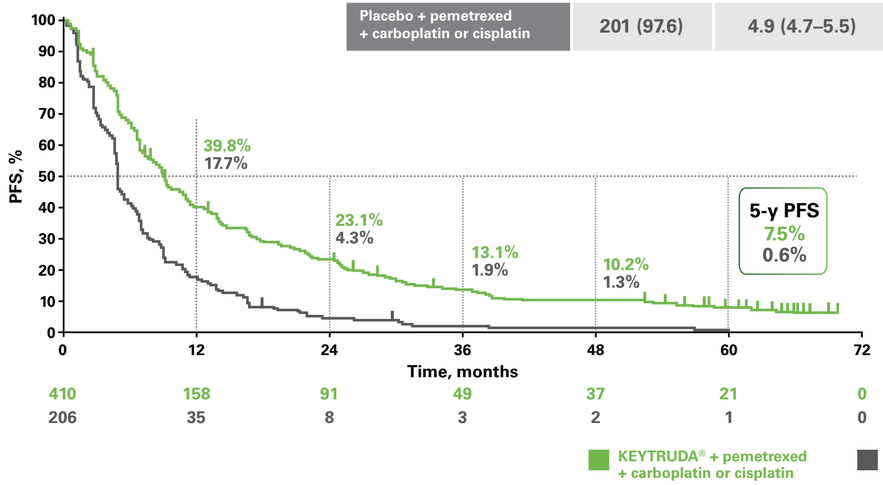
AT 10.5 MONTHS
(median follow-up)

PFS was significantly greater among patients in the **KEYTRUDA®** combination group, with a **48% reduced risk of progression or death** compared with the placebo group **(HR: 0.52; 95% CI: 0.43–0.64; p<0.001).**[1]

Median PFS was **8.8 months (95% CI: 7.6–9.2)** in the **KEYTRUDA®** combination group, compared with **4.9 months (95% CI: 4.7–5.5)** in the placebo group.[1]

At 5 years, KEYTRUDA® combination therapy continued to demonstrate a trend towards treatment benefit[2]*

	Events n (%)	Median (95% CI)	HR (95% CI)
KEYTRUDA® + pemetrexed + carboplatin or cisplatin	369 (90.0)	9.0 (8.1–10.4)	0.50 (0.42–0.60) p = not tested
Placebo + pemetrexed + carboplatin or cisplatin	201 (97.6)	4.9 (4.7–5.5)	



64.6 months
Median follow-up

The links to the prescribing information at the top of each page directs users to an external website.
*Exploratory analysis; significance was not tested and no statistical conclusions can be drawn from this analysis.
CI, confidence interval; **HR**, hazard ratio; **PFS**, progression-free survival.
1. Gandhi L, et al. *New Eng J Med.* 2018;378:2078–2092; 2. Garassino MC, et al. Presented at the ESMO meeting, 9–13 September 2022, Paris, France and Virtual.

KEYTRUDA® (pembrolizumab)

Patients treated with KEYTRUDA® combination therapy had a greater OS benefit compared with the placebo group at 10.5 months with the trend towards treatment benefit maintained at 5 years: data from the KEYNOTE-189 trial

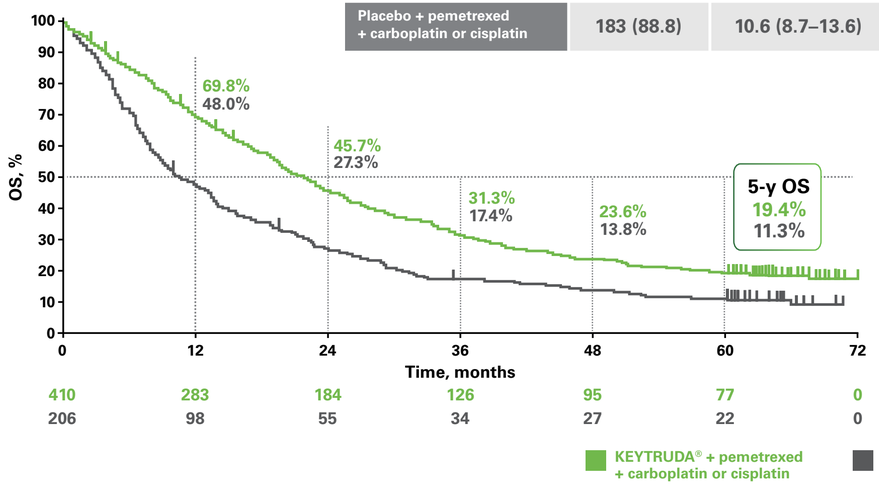
AT 10.5 MONTHS
(median follow-up)

OS was greater among patients in the **KEYTRUDA®** combination group, with a **51% reduced risk of death** compared with the placebo group **(HR: 0.49; 95% CI: 0.38–0.64; p<0.001)**.[1]

Improvement in OS was seen across all PD-L1 categories that were evaluated.[1]

At 5 years, KEYTRUDA® combination therapy continued to demonstrate a trend towards treatment benefit[2]*

	Events n (%)	Median (95% CI)	HR (95% CI)
KEYTRUDA® + pemetrexed + carboplatin or cisplatin	329 (80.2)	22.0 (19.5–24.5)	0.60 (0.50–0.72) p = not tested
Placebo + pemetrexed + carboplatin or cisplatin	183 (88.8)	10.6 (8.7–13.6)	



64.6 months
Median follow-up

The links to the prescribing information at the top of each page directs users to an external website.
*Exploratory analysis; significance was not tested and no statistical conclusions can be drawn from this analysis.
CI, confidence interval; **HR**, hazard ratio; **OS**, overall survival; **PD-L1**, programmed death-ligand 1.
1. Gandhi L, et al. *New Eng J Med.* 2018;378:2078–2092; 2. Garassino MC, et al. Presented at the ESMO meeting, 9–13 September 2022, Paris, France and Virtual.

KEYTRUDA® (pembrolizumab)

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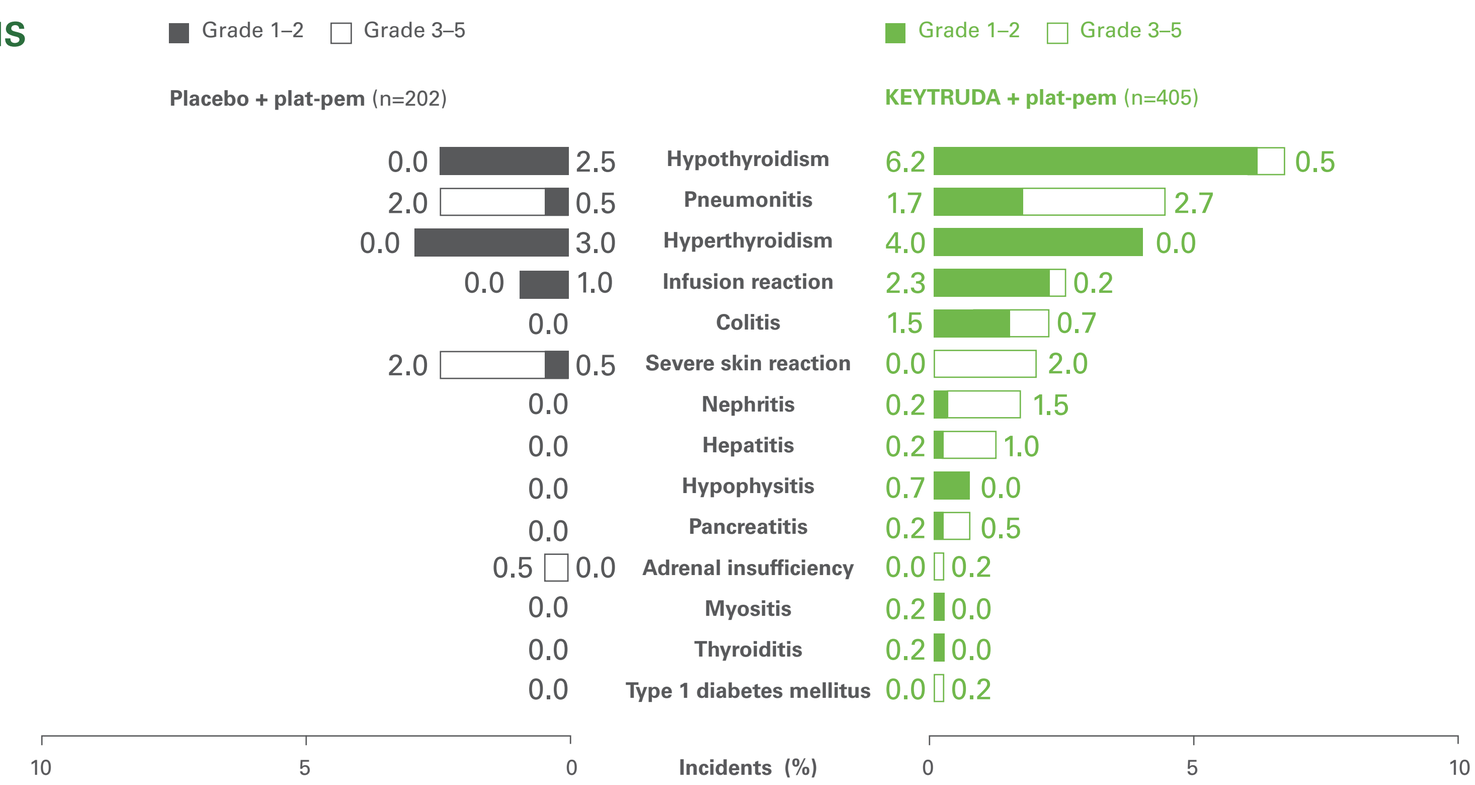
Immune-mediated AEs with KEYTRUDA® combination therapy at 10.5 months: data from the KEYNOTE-189 trial (original analysis)*†

AT 10.5 MONTHS
(median follow-up)



The links to the prescribing information at the top of each page directs users to an external website.
*Regardless of attribution to a trial drug by the investigator.
†AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0.
AE, adverse event.
1. Gandhi L, et al. *New Eng J Med.* 2018;378:2078–2092.

KEYTRUDA® (pembrolizumab)

Prescribing information GB | NI

Patients treated with KEYTRUDA® combination therapy had manageable toxicity at 5 years, consistent with previous reports[1]: data from the KEYNOTE-189 trial (follow-up analysis)

AT 64.6 MONTHS
(median follow-up)

Adverse event, n (%)	All treated patients		35 cycles of KEYTRUDA® n = 57
	KEYTRUDA® + pemetrexed + carboplatin or cisplatin n = 405	Placebo + pemetrexed + carboplatin or cisplatin n = 202	
Any AE	404 (99.8)	200 (99.0)	57 (100)
Grade 3–5	295 (72.8)	136 (67.3)	38 (66.7)
Led to discontinuation of any treatment component	145 (35.8)	35 (17.3)	19 (33.3)
Led to death	29 (7.2)	14 (6.9)	
Treatment related AE	377 (93.1)	183 (90.6)	56 (98.2)
Grade 3–5	212 (52.3)	85 (42.1)	27 (47.4)
Immune-mediated AEs and infusion reactions*	113 (27.9)	27 (13.4)	23 (40.4)
Grade 3–5	52 (12.8)	9 (4.5)	7 (12.3)

The links to the prescribing information at the top of each page directs users to an external website.
*Events considered regardless of attribution to treatment or immune relatedness by the investigator.
AE, adverse event.
1. Garassino MC, et al. Presented at the ESMO meeting, 9–13 September 2022, Paris, France and Virtual.

KEYTRUDA® (pembrolizumab)

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What treatment options are available to patients like Joe?

Patients with metastatic non-squamous NSCLC whose tumours have no EGFR or ALK positive mutations are eligible for the following first-line treatment options[1]*

Combination IO + chemotherapy[1]

For patients like Joe with **no targetable mutations or PD-L1<50%**, this would include:[1]

KEYTRUDA®[2] + pemetrexed[3] + platinum chemotherapy or

Atezolizumab[4] + bevacizumab + carboplatin + paclitaxel

Chemotherapy alone[1]

For patients like Joe with **no targetable mutations or PD-L1<50%**, this would include:[1]

Platinum doublet chemotherapy or pemetrexed[3] + cisplatin

All treatment choices are based on shared decisions between patient and clinician[1]

The links to the prescribing information at the top of each page directs users to an external website.
The patient provided consent for the case to be shared. Please note that this is one individual patient and cases may vary.
*The treatment options stated were specifically available in September 2019. Please refer to the NICE/Blueteq guidelines for the most up to date information.
ALK, anaplastic lymphoma kinase receptor; **EGFR**, epidermal growth factor receptor gene; **IO**, immunotherapy; **NSCLC**, non-small cell lung carcinoma; **PDL1**, programmed death-ligand 1.
1. NICE Guidance NG122. September 2022. Available at: https://www.nice.org.uk/guidance/ng122/resources/interactive-pdf-of-all-treatment-pathways-for-squamous-and-nonsquamous-advanced-nonsmallcell-lung-cancer-pdf-11189888174. Accessed April 2023; 2. KEYTRUDA® Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/2498. Accessed April 2023; 3. Pemetrexed Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/12684/smpc. Accessed April 2023; 4. Atezolizumab Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/8442/smpc#gref. Accessed April 2023.

KEYTRUDA® (pembrolizumab)

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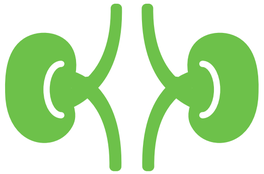
How were these AEs managed?

Grade 1 hepatitis during treatment cycle 6

Resolved without steroids

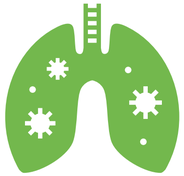
Grade 1 acute kidney injury



Pemetrexed[1] was discontinued due to abnormal kidney function*

In the KEYNOTE-189 trial, acute kidney injury occurred more frequently in the KEYTRUDA® arm than in the placebo arm (5.2% vs 0.5%). 9/19 of grade ≤3 resolved or was resolving at the time of analysis[2,3]

Slight volume increase of lung lesions determined by CT



Decided to use iRECIST to determine radiological progression: there was **no clinical deterioration**

With ongoing **maintenance on KEYTRUDA®**[3] alone (pemetrexed[1] was discontinued due to abnormal kidney function)

3-monthly CT scans and a nurse review at week 6 to check on clinical evolution

The links to the prescribing information at the top of each page directs users to an external website.
*The pemetrexed SmPC states pemetrexed in patients with CrCl <45mL/min is not recommended.[1]
AE, adverse event; **CT**, computerised tomography; **RECIST**, Response Evaluation Criteria in Solid Tumours.
1. Pemetrexed Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/12684/smpc. Accessed April 2023; 2. Gandhi L, et al. *New Eng J Med.* 2018;378:2078–2092;
3. KEYTRUDA® Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/2498. Accessed April 2023.

KEYTRUDA® (pembrolizumab)