# A key to more possibilities for treating your appropriate patients with resectable NSCLC

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MSD Oncology

# KEYNOTE-671:

## KEYTRUDA® (pembrolizumab) in combination with platinum-containing chemotherapy as neoadjuvant therapy and then continued as adjuvant monotherapy for patients with resectable Stage II, IIIA or IIIB (N2) non-small cell lung carcinoma (NSCLC) (KEYTRUDA perioperative treatment)

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.[1]

These slides are provided to UK healthcare professionals as a resource for data for your personal education. To ensure compliance with all relevant codes and regulations these slides must not be amended.

**1.** KEYTRUDA Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/2498 Accessed: January 2025.

KEYTRUDA® (pembrolizumab)

MSD

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# KEYTRUDA early-stage and advanced NSCLC indications[1]

- **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 NSCLC 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 NSCLC 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 NSCLC 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 NSCLC in adults

- KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic NSCLC 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

- The recommended dose of KEYTRUDA in adults is either 200 mg Q3W or 400 mg Q6W administered intravenously over 30 minutes. For the use of KEYTRUDA as part of combination therapy, see the Summary of Product Characteristics (SmPC) for the concomitant therapies

**Please refer to the Summary of Product Characteristics and Risk Minimisation Materials available on the EMC website before prescribing.**

*ALK*, anaplastic lymphoma kinase; *EGFR*, epidermal growth factor receptor; EMC, Electronic Medicines Compendium; 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: January 2025.

# KEYNOTE-671 indication:

**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[1]

**1.** KEYTRUDA Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/2498 Accessed: January 2025.

# KEYNOTE-671 study design: randomised, double-blind, Phase III[1]

**Resectable Stage II, IIIA or IIIB (N2) NSCLC (AJCC 8th edition)**

- ECOG PS 0–1
- Tumour tissue for PD-L1 evaluation at central lab
- Biopsy of suspicious hilar or mediastinal lymph node(s)
- Untreated, pathologically confirmed (PET scan may be used as surrogate for N1 lymph nodes)*
- No ILD or pneumonitis requiring steroids
- *EGFR/ALKm* permitted

**Stratification factors:**

- Stage (II vs III)
- PD-L1 by 22C3 (TPS <50% vs ≥50%)
- Histology (SQ vs NSQ)
- Region (East Asia vs other)

**R** 1:1 (N=797)

Neoadjuvant phase

**KEYTRUDA** 200 mg Q3W **+ cisplatin** 75 mg/m$^2$ *combined with either* **pemetrexed**† 500 mg/m$^2$ OR **gemcitabine**‡ 1000 mg/m$^2$ for up to 4 cycles

Surgery

4–12w

Adjuvant phase

**KEYTRUDA**§ 200 mg Q3W ≤13 cycles

**Placebo** Q3W **+ cisplatin** 75 mg/m$^2$ *combined with either* **pemetrexed**† 500 mg/m$^2$ OR **gemcitabine**‡ 1000 mg/m$^2$ for up to 4 cycles

Surgery

4–12w

**Placebo**§ Q3W ≤13 cycles

**Dual primary endpoints:**

- EFS per investigator review¶ and OS

**Key secondary endpoints:**

- mPR and pCR per blinded, independent pathology review, and safety

Adapted from Wakelee H, *et al. N Engl J Med* 2023.[1]

*For participants with T2b and T4 tumours.[1] †Permitted for non-squamous disease only.[1] ‡Administered on Days 1 and 8 of cycle; squamous histology only.[1] §Postoperative radiation therapy could be administered for patients with R1-2 resection, extracapsular nodal disease after surgery, and those who do not undergo surgery (followed by adjuvant KEYTRUDA/placebo).[1] ¶EFS defined as time from randomisation to first occurrence of: (i) local PD precluding surgery, (ii) unresectable tumour, (iii) progression or recurrence per RECIST v1.1 by investigator, (iv) death from any cause.[1] AJCC, American Joint Committee on Cancer; *ALKm*, anaplastic lymphoma kinase mutation; DFS, disease-free survival; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EFS, event-free survival; *EGFR*, epidermal growth factor receptor; ILD, interstitial lung disease; mPR, major pathological response; N1, involvement of ipsilateral peribronchial and/or ipsilateral hilar lymph nodes (includes direct extension to intrapulmonary nodes);[1] N2, involvement of the ipsilateral mediastinal and/or subcarinal lymph nodes;[1] NSCLC, non-small cell lung carcinoma; NSQ, non-squamous cell carcinoma; OS, overall survival; pCR, pathological complete response; PET, positron emission tomography; PD, progressive disease; PD-L1, programmed death ligand 1; Q3W, every 3 weeks; R, randomised; RECIST, Response Evaluation Criteria in Solid Tumours; SQ, squamous cell carcinoma; TPS, tumour proportion score; w, weeks.

**1.** Wakelee H, *et al. N Engl J Med* 2023;389:491–503 (including protocol).

# KEYNOTE-671: patient disposition

- Most patients underwent in-study surgery (82.1% in the KEYTRUDA arm vs 79.4% in the placebo arm), **similar to other perioperative IO trials**[1–3]
  - Of those receiving surgery, 92.0% in the KEYTRUDA arm vs 84.2% in the placebo arm had complete (R0) resection[3]
  - Lobectomy was used in 78.8% of patients in the KEYTRUDA arm vs 75.1% in the placebo arm, and pneumonectomy in 11.4% vs 12.3%, respectively[3]
  - **87.4%** of patients in the KEYTRUDA arm completed ≥3 cycles of neoadjuvant KEYTRUDA or placebo vs 87.2% in the placebo arm[2]
  - **73.2%** of patients in the KEYTRUDA arm completed ≥1 cycles of adjuvant KEYTRUDA or placebo vs 66.9% in the placebo arm[2]

**IA1 data**

| Patient disposition, n (%) | | KEYTRUDA | Placebo |
|---|---|---|---|
| **Screening** | Patients screened | 1364 | |
| | Randomised (ITT population) | 397 | 400 |
| **Neoadjuvant treatment** | Received ≥1 dose of neoadjuvant treatment (as-treated population) | 396 | 399 |
| | Completed 4 cycles of KEYTRUDA or placebo | 295 (74.5) | 297 (74.4) |
| | Completed ≥3 cycles of KEYTRUDA or placebo | 346 (87.4) | 348 (87.2) |
| | Continued to surgery and/or radiotherapy | 342 (86.4) | 335 (84.0) |
| | Discontinued all study therapy permanently | 54 (13.6) | 64 (16.0) |
| **In-study surgery underwent in-study radiotherapy*** | Underwent in-study surgery | 325 (82.1) | 317 (79.4) |
| | Underwent in-study radiotherapy | 35 (8.8) | 53 (13.3) |
| | Discontinued all study therapy permanently following surgery | 45 (11.4) | 60 (15.0) |
| | Discontinued all study therapy permanently following radiotherapy | 7 (1.8) | 8 (2.0) |
| **Adjuvant treatment** | Received ≥1 dose of adjuvant treatment | 290 (73.2) | 267 (66.9) |
| | Completed adjuvant treatment | 160 (40.4) | 141 (35.3) |
| | Discontinued adjuvant treatment | 88 (22.2) | 81 (20.3) |
| | Adjuvant treatment ongoing | 42 (10.6) | 45 (11.3) |

Adapted from Wakelee H, *et al. N Engl J Med* 2023. Supplementary appendix.[2]

**Data cut-off date for IA1: 29 July 2022. Median follow-up: 25.2 months.**[1]
*In the KEYTRUDA arm, 307 participants underwent surgery alone, 18 underwent in-study surgery and radiotherapy, and 17 underwent in-study radiotherapy alone. In the placebo arm, 282 participants underwent in-study surgery alone, 35 underwent in-study surgery and radiotherapy, and 18 underwent in-study radiotherapy alone. All percentages are based on the number who received ≥1 dose of neoadjuvant treatment.[1]
IA, interim analysis; IO, immunotherapy; ITT, intention-to-treat; R0, complete resection defined as no invasive cancer at bronchial margin or soft tissue surrounding bronchus, no invasive cancer at pulmonary artery or pulmonary vein margins or surrounding soft tissue, no invasive cancer at medial, lateral, superior and inferior margins of chest wall resection, no minimal margin distance, bronchial dysplasia is considered a negative margin.[1]
**1.** Wakelee H, *et al. N Engl J Med* 2023;389:491–503. **2.** Wakelee H, *et al. N Engl J Med* 2023;389:491–503. Supplementary appendix. **3.** Wakelee H, *et al.* KEYNOTE-671: Randomised, double-blind, Phase 3 study of pembrolizumab or placebo plus platinum-based chemotherapy followed by resection and pembrolizumab or placebo for early-stage NSCLC. ASCO. 2–6 June 2023. Chicago, IL, USA. Abstract: LBA100.

# KEYNOTE-671: patient characteristics

**IA2 data**

| Characteristic, n (%) | | KEYTRUDA | Placebo |
|---|---|---|---|
| **Median age, years (range)** | | 63 (26–83) | 64 (35–81) |
| **Sex** | Male | 279 (70.3) | 284 (71.0) |
| **Race** | American Indian or Alaska Native | 1 (0.3) | 0 |
| | Asian | 124 (31.2) | 125 (31.3) |
| | Black or African American | 6 (1.5) | 10 (2.5) |
| | Multiple | 3 (0.8) | 10 (2.5) |
| | White | 250 (63.0) | 239 (59.8) |
| | Missing data | 13 (3.3) | 16 (4.0) |
| **Geographic region** | East Asia | 123 (31.0) | 121 (30.3) |
| | Not East Asia | 274 (69.0) | 279 (69.8) |
| **ECOG PS** | 0 | 253 (63.7) | 246 (61.5) |
| | 1 | 144 (36.3) | 154 (38.5) |
| **Histology** | Non-squamous | 226 (59.6) | 227 (56.8) |
| | Squamous | 171 (43.1) | 173 (43.3) |

| Characteristic, n (%) | | KEYTRUDA | Placebo |
|---|---|---|---|
| **Smoking status** | Current | 96 (24.2) | 103 (25.8) |
| | Former | 247 (62.2) | 250 (62.5) |
| | Never | 54 (13.6) | 47 (11.8) |
| **Clinical stage** | II | 118 (29.7) | 121 (30.3) |
| | IIIA | 217 (54.7) | 225 (56.3) |
| | IIIB | 62 (15.6) | 54 (13.5) |
| **N status*** | N0 | 148 (37.3) | 142 (35.5) |
| | N1 | 81 (20.4) | 71 (17.8) |
| | N2 | 168 (42.3) | 187 (46.8) |
| **PD-L1 TPS** | ≥50% | 132 (33.2) | 134 (33.5) |
| | 1–49% | 127 (32.0) | 115 (28.8) |
| | <1% | 138 (34.8) | 151 (37.8) |
| **Known *EGFR* mutation†** | | 14 (3.5) | 19 (4.8) |
| **Known *ALK* translocation†** | | 12 (3.0) | 9 (2.3) |

Adapted from Wakelee H, *et al.* ASCO 2023.[1]

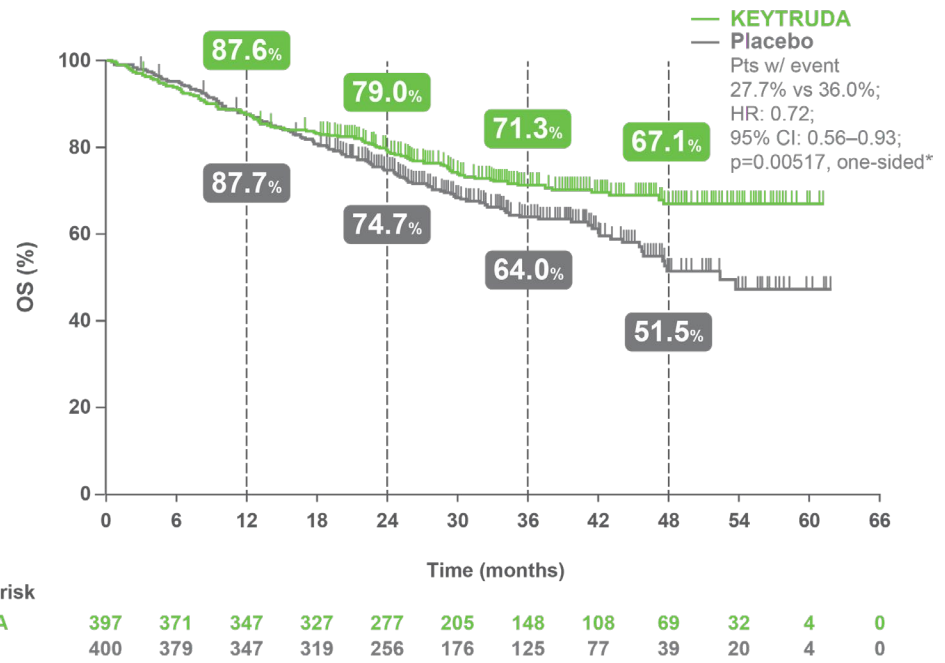
**Data cut-off date for IA1: 29 July 2022. Median follow-up: 25.2 months.**[1]
*As determined by imaging and biopsy.[1] †*EGFR* and *ALK* status were tested locally per investigator discretion. *EGFR* status was unknown in 68.5% in the KEYTRUDA arm and 63.5% in the placebo arm; *ALK* status was unknown in 70.8% and 64.5%, respectively.[1]
*ALK*, anaplastic lymphoma kinase; ECOG PS, Eastern Cooperative Oncology Group Performance Status; *EGFR*, epidermal growth factor receptor; IA, interim analysis; PD-L1, programmed death ligand 1; N, nodal involvement; TPS, tumour proportion score.
**1.** Wakelee H, *et al.* KEYNOTE-671: Randomised, double-blind, Phase 3 study of pembrolizumab or placebo plus platinum-based chemotherapy followed by resection and pembrolizumab or placebo for early-stage NSCLC. ASCO. 2–6 June 2023. Chicago, IL, USA. Abstract: LBA100.

# Dual primary endpoint: OS in ITT population[1–3]

- At IA1, OS was not mature but showed a favourable trend (HR 0.73; 95% CI: 0.54–0.99)[1]
- At IA2, the prespecified interim analysis for OS, **a statistically significant and clinically meaningful OS benefit was shown** with perioperative KEYTRUDA[3]
  - OS HR was 0.72, representing a 28% reduction in risk of death, with the upper confidence interval clearly below unity (95% CI: 0.56–0.93; p=0.00517)[3]
- In the placebo arm, 76.9% of those with recurrence or progressive disease received subsequent therapy, and 50.0% were treated with a PD-1 or PD-L1 inhibitor-based regimen[3]
- The IA2 OS data should be considered mature as the protocol-specified number of OS events was met

**IA2 data**

**OS in the ITT population**




Adapted from Spicer J, *et al.* ESMO 2023.[3]

**Data cut-off date for IA1: 29 July 2022. Median follow-up: 25.2 months.[1] Data cut-off date for IA2: 10 July 2023. Median follow-up: 36.6 months.[3]**
*Crossed significance boundary of 0.00543 (one-sided p-value).[3]
CI, confidence interval; HR, hazard ratio; IA, interim analysis; ITT, intention-to-treat; NR, not reached; mOS, median overall survival; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1.
**1.** Wakelee H, *et al.* KEYNOTE-671: Randomised, double-blind, Phase 3 study of pembrolizumab or placebo plus platinum-based chemotherapy followed by resection and pembrolizumab or placebo for early-stage NSCLC. ASCO. 2–6 June 2023. Chicago, IL, USA. Abstract: LBA100.
**2.** Wakelee H, *et al. N Engl J Med* 2023;389:491–503. **3.** Spicer JB, *et al.* Overall survival in the KEYNOTE-671 study of perioperative pembrolizumab for early-stage NSCLC. ESMO. 20–24 October 2023. Madrid, Spain. Abstract: LBA56.

# Dual primary endpoint: OS in key ITT subgroups[1]

- OS benefit with perioperative KEYTRUDA was **broadly consistent across subgroups**[1]
  - The benefit appeared to be similar regardless of histology, stage and N status*[1]

OS benefit was observed regardless of PD-L1 level, but increased with increasing PD-L1 expression[1]

**IA2 data**

## OS within the ITT population

No. of events/No. of patients

| Subgroup, n (%) | KEYTRUDA | Placebo | HR (95% CI) |
|---|---|---|---|
| **Overall** | 110/397 | 144/400 | 0.72 (0.56–0.93) |
| **Age** | | | |
| <65 y | 54/221 | 82/214 | 0.57 (0.40–0.80) |
| ≥65 y | 56/176 | 62/186 | 0.96 (0.67–1.38) |
| **Sex** | | | |
| Female | 21/118 | 30/116 | 0.69 (0.39–1.20) |
| Male | 89/279 | 114/284 | 0.73 (0.55–0.96) |
| **Race** | | | |
| White | 73/250 | 97/239 | 0.66 (0.49–0.90) |
| All others | 34/134 | 39/145 | 0.93 (0.59–1.48) |
| **Geographic region** | | | |
| East Asia | 32/123 | 30/121 | 1.05 (0.64–1.73) |
| Not East Asia | 78/274 | 114/279 | 0.63 (0.48–0.85) |
| **Smoking status** | | | |
| Current | 31/96 | 48/103 | 0.59 (0.38–0.93) |
| Former | 69/247 | 87/250 | 0.76 (0.56–1.05) |
| Never | 10/54 | 9/47 | 1.00 (0.41–2.46) |
| **Histology** | | | |
| Non-squamous | 49/226 | 64/227 | 0.73 (0.50–1.06) |
| Squamous | 61/171 | 80/173 | 0.71 (0.51–0.99) |

No. of events/No. of patients

| Subgroup, n (%) | KEYTRUDA | Placebo | HR (95% CI) |
|---|---|---|---|
| **Overall** | 110/397 | 144/400 | 0.72 (0.56–0.93) |
| **Clinical stage** | | | |
| II | 26/118 | 39/121 | 0.67 (0.41–1.10) |
| IIIA | 62/217 | 79/224 | 0.74 (0.53–1.03) |
| IIIB | 22/62 | 26/55 | 0.69 (0.39–1.22) |
| **N status** | | | |
| cNO | 40/148 | 52/142 | 0.70 (0.46–1.06) |
| cN1 | 21/81 | 24/71 | 0.74 (0.41–1.33) |
| cN2 | 49/168 | 68/187 | 0.74 (0.52–1.07) |
| **PD-L1 TPS** | | | |
| ≥50% | 23/132 | 39/134 | 0.55 (0.33–0.92) |
| 1–49% | 35/127 | 44/115 | 0.69 (0.44–1.07) |
| <1% | 52/138 | 61/151 | 0.91 (0.63–1.32) |
| ***EGFR* mutation** | | | |
| No | 20/111 | 33/124 | 0.64 (0.37–1.11) |
| Yes | 1/14 | 5/19 | 0.24 (0.03–2.03) |
| Unknown | 89/272 | 106/257 | 0.75 (0.56–0.99) |
| ***ALK* translocation** | | | |
| No | 22/104 | 38/132 | 0.70 (0.41–1.18) |
| Unknown | 87/281 | 105/259 | 0.72 (0.54–0.96) |


Adapted from Spicer J, *et al.* ESMO 2023.[1]

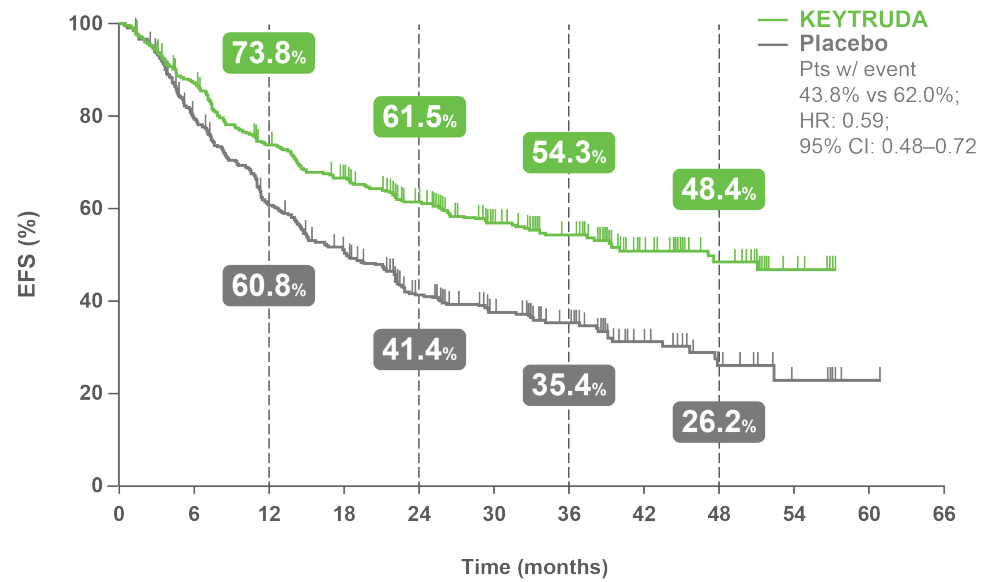
**Data cut-off date for IA2: 10 July 2023. Median follow-up: 36.6 months.**[1]
*Subgroups for Stage IIIA and IIIB and by N status were post hoc, while others were prespecified.[1]
*ALK*, anaplastic lymphoma kinase; CI, confidence interval; *EGFR*, epidermal growth factor receptor; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival; N, nodal involvement; N0, no regional lymph involvement;[2] N1, involvement of ipsilateral peribronchial and/or ipsilateral hilar lymph nodes (includes direct extension to intrapulmonary nodes);[2] N2, involvement of the ipsilateral mediastinal and/or subcarinal lymph nodes;[2] PD-L1, programmed death ligand 1; TPS, tumour proportion score.
**1.** Spicer JB, *et al.* Overall survival in the KEYNOTE-671 study of perioperative pembrolizumab for early-stage NSCLC. ESMO. 20–24 October 2023. Madrid, Spain. Abstract: LBA56.

# Dual primary endpoint: EFS in the ITT population[1–3]

- At IA1, EFS benefit in the overall population was **statistically significant and clinically meaningful**[1,2]
  - EFS HR was 0.58 (95% CI: 0.46–0.72); p<0.00001[2]
  - Median EFS was not reached in the KEYTRUDA arm (95% CI: 34.1–NR) and was 17 months in the placebo arm (95% CI: 14.3–22.0)[2]
- At IA2, with an additional 11 months of follow-up, **the benefit was sustained** with HR: 0.593
  - 3-year EFS was 54.3% with KEYTRUDA vs 35.4% with placebo (~20% absolute increase)[3]
  - Promising 4-year EFS rates of 48.4% with KEYTRUDA vs 26.2% with placebo, indicating a continued gain of ~20% in landmark EFS (although these data are still immature)[3]

**IA2 data**

## EFS in the ITT population




Number at risk

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| KEYTRUDA | 397 | 339 | 282 | 250 | 196 | 142 | 102 | 62 | 37 | 10 | 0 | 0 |
| Placebo | 400 | 308 | 232 | 189 | 128 | 87 | 66 | 34 | 18 | 6 | 1 | 0 |

Adapted from Spicer J, *et al.* ESMO 2023.[3]

**Data cut-off date for IA1: 29 July 2022. Median follow-up: 25.2 months.[2] Data cut-off date for IA2: 10 July 2023. Median follow-up: 36.6 months.[3]**
CI, confidence interval; EFS, event-free survival; HR, hazard ratio; IA, interim analysis; ITT, intention-to-treat; mOS, median overall survival; NR, not reached.

**1.** Wakelee H, *et al.* KEYNOTE-671: Randomised, double-blind, Phase 3 study of pembrolizumab or placebo plus platinum-based chemotherapy followed by resection and pembrolizumab or placebo for early-stage NSCLC. ASCO. 2–6 June 2023. Chicago, Illinois, USA. Abstract: LBA100. **2.** Wakelee H, *et al. N Engl J Med* 2023;389:491–503. **3.** Spicer JB, *et al.* Overall survival in the KEYNOTE-671 study of perioperative pembrolizumab for early-stage NSCLC. ESMO. 20–24 October 2023. Madrid, Spain. Abstract: LBA56.

# Dual primary endpoint: EFS in key ITT subgroups[1,2]

- EFS benefit with perioperative KEYTRUDA was **broadly consistent across subgroups[1,2]**
  - EFS benefit appeared to be similar regardless of age, histology, stage and N status*[1,2]

EFS benefit was observed regardless of PD-L1 level, but increased with increasing PD-L1 expression[1]

**IA2 data**

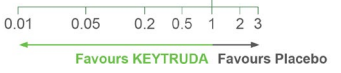
## EFS in the ITT population

No. of events/No. of patients

| Subgroup, n (%) | KEYTRUDA | Placebo | HR (95% CI) |
|---|---|---|---|
| **Overall** | 174/397 | 248/400 | 0.59 (0.48–0.72) |
| **Age** | | | |
| <65 y | 88/221 | 136/214 | 0.51 (0.39–0.67) |
| ≥65 y | 86/176 | 112/186 | 0.70 (0.52–0.92) |
| **Sex** | | | |
| Female | 47/118 | 70/116 | 0.52 (0.36–0.75) |
| Male | 127/279 | 178/284 | 0.62 (0.49–0.78) |
| **Race** | | | |
| White | 109/250 | 151/239 | 0.56 (0.44–0.72) |
| All others | 57/134 | 85/145 | 0.63 (0.45–0.88) |
| **Geographic region** | | | |
| East Asia | 51/123 | 70/121 | 0.63 (0.44–0.91) |
| Not East Asia | 123/274 | 178/279 | 0.57 (0.45–0.72) |
| **Smoking status** | | | |
| Current | 44/96 | 68/103 | 0.53 (0.36–0.77) |
| Former | 105/247 | 155/250 | 0.59 (0.46–0.75) |
| Never | 25/54 | 25/47 | 0.77 (0.44–1.35) |
| **Histology** | | | |
| Non-squamous | 102/226 | 131/227 | 0.66 (0.51–0.86) |
| Squamous | 72/171 | 117/173 | 0.51 (0.38–0.69) |


No. of events/No. of patients

| Subgroup, n (%) | KEYTRUDA | Placebo | HR (95% CI) |
|---|---|---|---|
| **Overall** | 174/397 | 248/400 | 0.59 (0.48–0.72) |
| **Clinical stage** | | | |
| II | 40/118 | 62/121 | 0.59 (0.40–0.88) |
| IIIA | 100/217 | 145/224 | 0.57 (0.44–0.74) |
| IIIB | 34/62 | 41/55 | 0.57 (0.36–0.90) |
| **N status** | | | |
| cNO | 59/148 | 83/142 | 0.58 (0.41–0.81) |
| cN1 | 29/81 | 39/71 | 0.56 (0.35–0.91) |
| cN2 | 86/168 | 126/187 | 0.63 (0.48–0.82) |
| **PD-L1 TPS** | | | |
| ≥50% | 41/132 | 70/134 | 0.48 (0.33–0.71) |
| 1–49% | 55/127 | 76/115 | 0.52 (0.36–0.73) |
| <1% | 78/138 | 102/151 | 0.75 (0.56–1.01) |
| ***EGFR* mutation** | | | |
| No | 42/111 | 72/124 | 0.55 (0.38–0.81) |
| Yes | 5/14 | 13/19 | 0.32 (0.11–0.91) |
| Unknown | 127/272 | 163/257 | 0.62 (0.49–0.79) |
| ***ALK* translocation** | | | |
| No | 42/104 | 85/132 | 0.50 (0.35–0.73) |
| Unknown | 126/281 | 160/259 | 0.62 (0.49–0.78) |



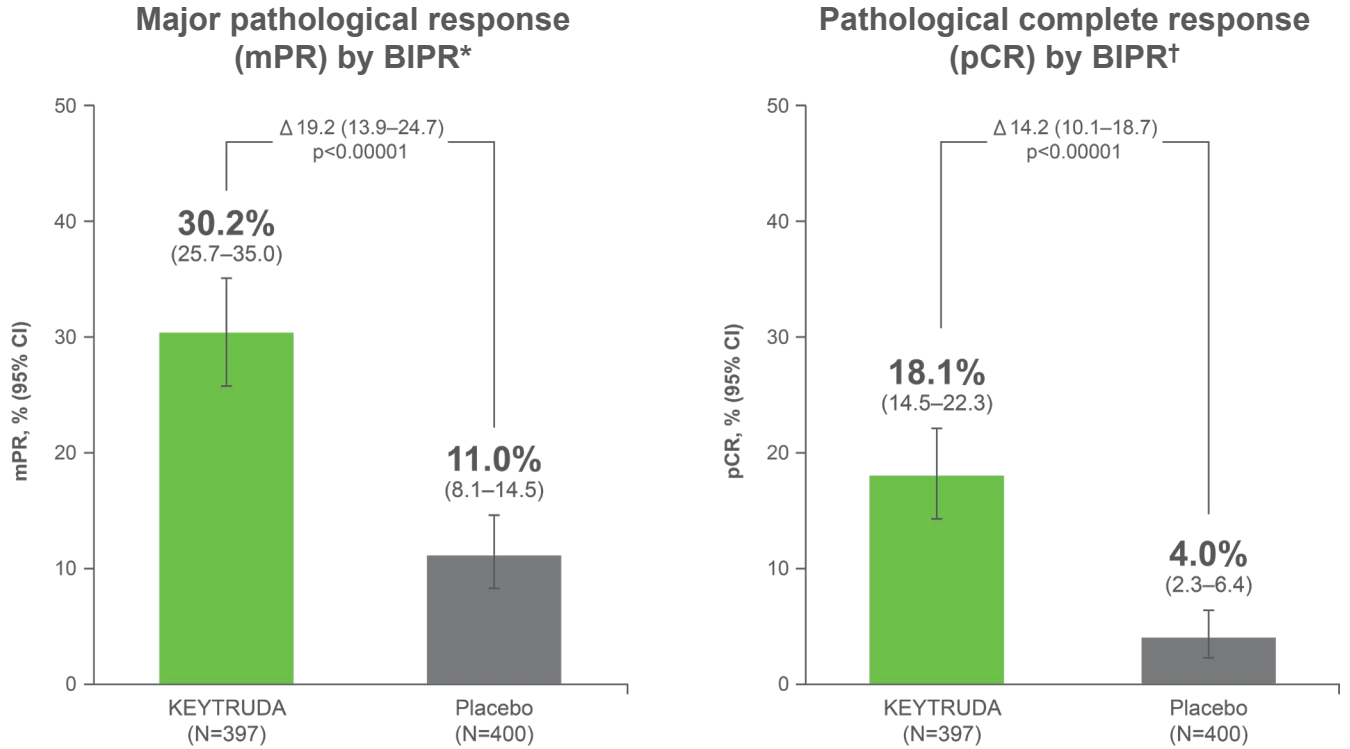

Adapted from Spicer J, *et al*. ESMO 2023.[2]

**Data cut-off date for IA2: 10 July 2023. Median follow-up: 36.6 months.[2]**
*Subgroups for Stage IIIA and IIIB and by N status were post hoc; all other subgroups were prespecified.[1]
*ALK*, anaplastic lymphoma kinase; CI, confidence interval; EFS, event-free survival; *EGFR*, epidermal growth factor receptor; HR, hazard ratio; IA, interim analysis; ITT, intention-to-treat; PD-L1, programmed death ligand 1; N, nodal involvement; N0, no regional lymph involvement;[1] N1, involvement of ipsilateral peribronchial and/or ipsilateral hilar lymph nodes (includes direct extension to intrapulmonary nodes);[1] N2, involvement of the ipsilateral mediastinal and/or subcarinal lymph nodes;[1] TPS, tumour proportion score; y, year.
**1.** Wakelee H, *et al*. *N Engl J Med* 2023;389:491–503. **2.** Spicer JB, *et al*. Overall survival in the KEYNOTE-671 study of perioperative pembrolizumab for early-stage NSCLC. ESMO. 20–24 October 2023. Madrid, Spain. Abstract: LBA56.

# Secondary endpoint: pCR and mPR[1,2]

- **Significantly higher rates of pathologic response** were seen in the KEYTRUDA arm[1,2]
  - Note that the majority of patients did not achieve a pCR (~82%) or an mPR (~70%)[1,2]
  - pCR and mPR were assessed by blinded review and defined by IASLC criteria*†[2]

**IA1 data**




Adapted from Wakelee H, *et al.* ASCO 2023.[1]

**Data cut-off date for IA1: 29 July 2022. Median follow-up: 25.2 months.[2]**
*Per IASLC criteria, mPR was defined as ≤10% viable tumour cells in resected primary tumour and lymph nodes.[1] †Per IASLC criteria, pCR was defined as 0% viable tumour cells in resected primary tumour and lymph nodes.[1]
BIPR, blinded independent pathological review; CI, confidence interval; IASLC, International Association for the Study of Lung Cancer; IA, interim analysis; irPRC, immune-related pathologic response criteria; mPR, major pathologic response; pCR, pathological complete response.
**1.** Wakelee H, *et al.* KEYNOTE-671: Randomised, double-blind, Phase 3 study of pembrolizumab or placebo plus platinum-based chemotherapy followed by resection and pembrolizumab or placebo for early-stage NSCLC. ASCO. 2–6 June 2023. Chicago, IL, USA. Abstract: LBA100.
**2.** Wakelee H, *et al. N Engl J Med* 2023;389:491–503.

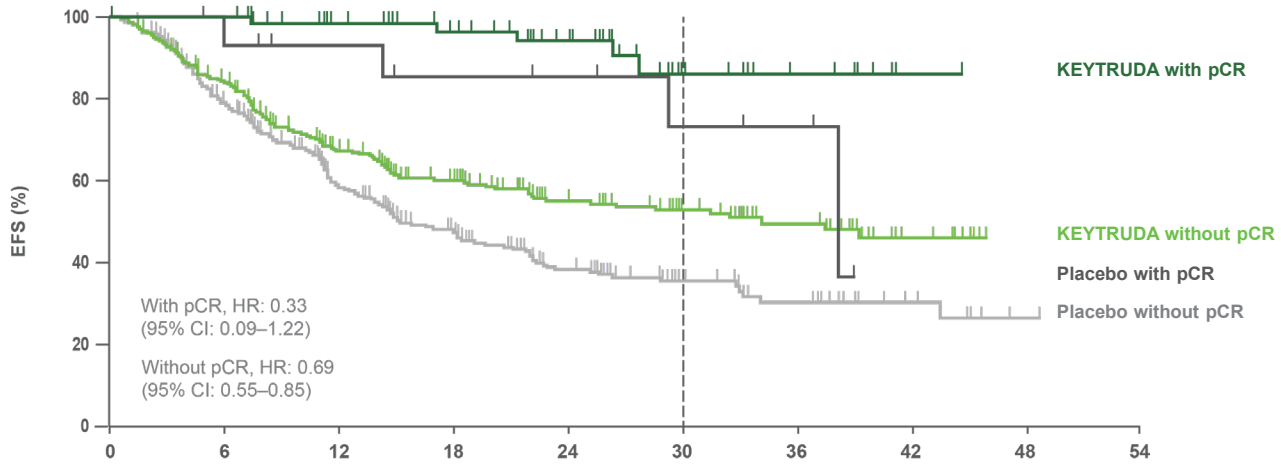
# Exploratory endpoint: EFS by pCR[1,2]

- Exploratory data from IA1* showed EFS benefit in the perioperative KEYTRUDA group **regardless of whether participants had a complete pathologic response or not**[1,2]
  - With pCR, HR: 0.33; without pCR, HR: 0.69[1]
- The EFS benefit in those without pCR is particularly important as it suggests a specific benefit from adjuvant KEYTRUDA

As seen in other trials there is evidence to support pCR as a surrogate endpoint for survival[3]

- However, the majority of patients do not achieve a pCR or mPR and a high unmet medical need exists for this group[1,2]

**IA1 data**




Number at risk

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| KEYTRUDA with pCR | 72 | 72 | 59 | 46 | 33 | 15 | 8 | 1 | 0 | 0 |
| Placebo with pCR | 16 | 14 | 12 | 10 | 9 | 5 | 4 | 0 | 0 | 0 |
| KEYTRUDA without pCR | 325 | 258 | 177 | 126 | 84 | 57 | 34 | 10 | 0 | 0 |
| Placebo without pCR | 384 | 280 | 171 | 114 | 65 | 33 | 20 | 9 | 1 | 0 |

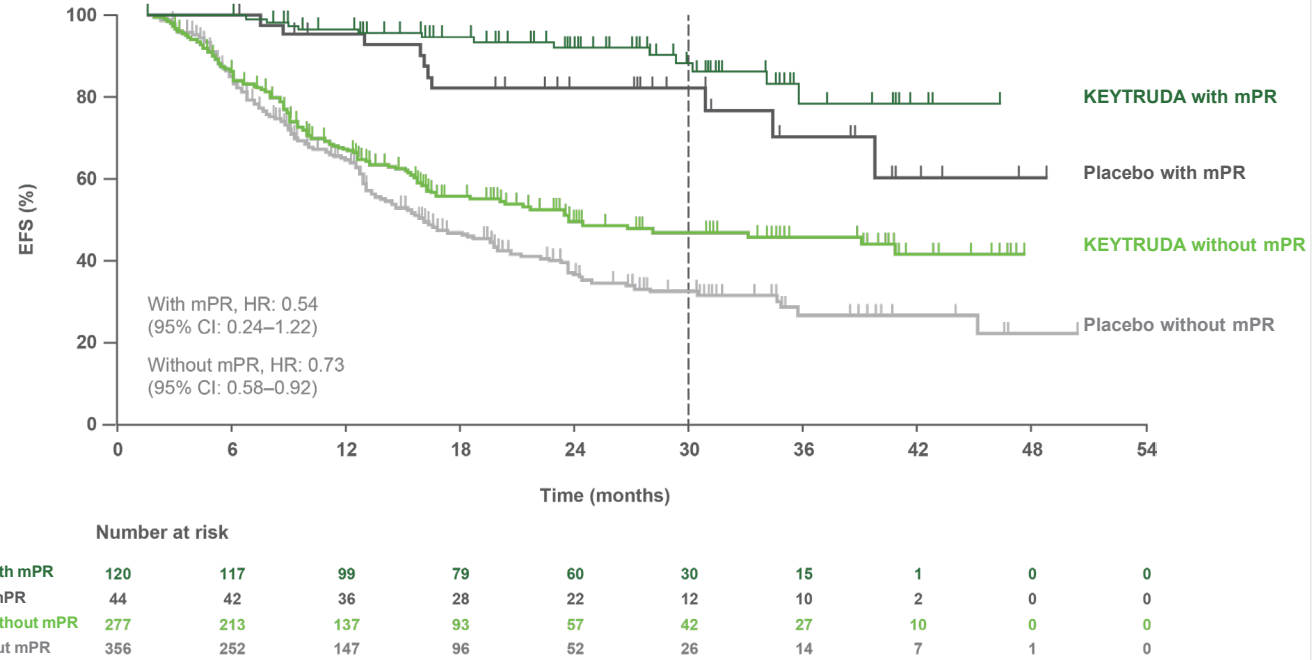
Adapted from Wakelee H, *et al. N Engl J Med* 2023.[2]

**Data cut-off date for IA1: 29 July 2022. Median follow-up: 25.2 months.**[2]
*Exploratory analysis from IA1 was not updated at IA2 as the updated EFS in the ITT was consistent with IA1.[1,2]
CI, confidence interval; EFS, event-free survival; HR, hazard ratio; IA, interim analysis; ITT, intention-to-treat; pCR, pathological complete response.
**1.** Wakelee H, *et al.* KEYNOTE-671: Randomised, double-blind, Phase 3 study of pembrolizumab or placebo plus platinum-based chemotherapy followed by resection and pembrolizumab or placebo for early-stage NSCLC. ASCO. 2–6 June 2023. Chicago, IL, USA. Abstract: LBA100.
**2.** Wakelee H, *et al. N Engl J Med* 2023;389:491–503. **3.** Deutsch JS, *et al. Nat Med* 2024;30:218–228.

# Exploratory endpoint: EFS by mPR[1,2]

- Exploratory data from IA1* showed EFS benefit in the perioperative KEYTRUDA group **regardless of whether participants had a major pathological response or not**[1,2]
  - With mPR, HR: 0.54; without mPR, HR: 0.73[1]

**IA1 data**




Number at risk

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| KEYTRUDA with mPR | 120 | 117 | 99 | 79 | 60 | 30 | 15 | 1 | 0 | 0 |
| Placebo with mPR | 44 | 42 | 36 | 28 | 22 | 12 | 10 | 2 | 0 | 0 |
| KEYTRUDA without mPR | 277 | 213 | 137 | 93 | 57 | 42 | 27 | 10 | 0 | 0 |
| Placebo without mPR | 356 | 252 | 147 | 96 | 52 | 26 | 14 | 7 | 1 | 0 |

Adapted from Wakelee H, *et al. N Engl J Med* 2023.[2]

**Data cut-off date for IA1: 29 July 2022. Median follow-up: 25.2 months.**[2]
*Exploratory analysis from IA1 was not updated at IA2 as the updated EFS in the ITT was consistent with IA1.[1,2]
CI, confidence interval; EFS, event-free survival; HR, hazard ratio; IA, interim analysis; ITT, intention-to-treat; mPR, major pathologic response.
**1.** Wakelee H, *et al.* KEYNOTE-671: Randomised, double-blind, Phase 3 study of pembrolizumab or placebo plus platinum-based chemotherapy followed by resection and pembrolizumab or placebo for early-stage NSCLC. ASCO. 2–6 June 2023. Chicago, IL, USA. Abstract: LBA100.
**2.** Wakelee H, *et al. N Engl J Med* 2023;389:491–503. **3.** Deutsch JS, *et al. Nat Med* 2024;30:218–228.

# KEYNOTE-671: surgical outcomes[1,2]

- Most patients who received at least one dose of neoadjuvant therapy underwent in-trial surgery (82.1% in the KEYTRUDA group vs 79.4% in the placebo group)[1,2]
- Among those who underwent surgery, the most common surgical procedure was lobectomy (78.8% vs 75.1%), and the **majority of patients had complete (R0) resection (92.0% vs 84.2%)[1,2]**

**IA1 data**

| Summary of surgical outcomes, n (%) | | KEYTRUDA (N=325) | Placebo (N=317) |
|---|---|---|---|
| **In-study surgery*** | Resected | 320 (98.5) | 302 (95.3) |
| | *Complete – R0* | 299 (92.0) | 267 (84.2) |
| | *Incomplete – R1* | 17 (5.2) | 31 (9.8) |
| | *Incomplete – R2* | 4 (1.2) | 4 (1.3) |
| | Unresected | 5 (1.5) | 15 (4.7) |
| **Surgical procedure** | Lobectomy | 256 (78.8) | 238 (75.1) |
| | Pneumonectomy | 37 (11.4) | 39 (12.3) |
| | Bilobectomy | 26 (8.0) | 26 (8.2) |
| | Exploratory thoracotomy | 4 (1.2) | 13 (4.1) |
| | Other | 2 (0.6)† | 1 (0.3)‡ |
| **30-day mortality** | | 6 (1.8)§ | 2 (0.6)¶ |

Adapted from Wakelee H, *et al.* ASCO 2023.[2]

**Data cut-off date for IA1: 29 July 2022. Median follow-up: 25.2 months.**[1]
*An additional 8 participants in the KEYTRUDA arm and 7 participants in the placebo arm underwent off-study surgery.[1,2] †Lung segmentectomy (n=1), lung wedge resection (n=1).[1,2] ‡Lymph node dissection only (planned surgery was lung lobectomy; need for more extensive surgery discovered during surgery, but consent was not granted).[1,2] §Pulmonary embolism (n=2), pulmonary haemorrhage due to arterial injury during surgery (n=1), pulmonary sepsis (n=1), respiratory failure (n=1) and septic shock (n=1).[1,2] ¶Respiratory failure (n=1) and pneumonia (n=1).[1,2]
AE, adverse event; IA, interim analysis; R0, complete resection defined as no invasive cancer at bronchial margin or soft tissue surrounding bronchus, no invasive cancer at pulmonary artery or pulmonary vein margins or surrounding soft tissue, no invasive cancer at medial, lateral, superior and inferior margins of chest wall resection, no minimal margin distance, bronchial dysplasia is considered a negative margin.[1] R1, microscopic invasive cancer at bronchial, pulmonary vein or pulmonary arterial margins or surrounding soft tissue, carcinoma *in situ* at bronchial margin; R2, gross residual disease.
**1.** Wakelee H, *et al. N Engl J Med* 2023;389:491–503. **2.** Wakelee H, *et al.* KEYNOTE-671: Randomised, double-blind, Phase 3 study of pembrolizumab or placebo plus platinum-based chemotherapy followed by resection and pembrolizumab or placebo for early-stage NSCLC. ASCO. 2–6 June 2023. Chicago, IL, USA. Abstract: LBA100.

# KEYNOTE-671: safety[1]

- The safety profile of perioperative KEYTRUDA (plus chemotherapy) was **consistent with the safety profiles of the individual components**, and no new safety signals were seen[1]
- Grade 3–5 TRAEs were seen in 45.2% (KEYTRUDA) vs 37.8% (placebo) of patients[1]
  - The most common were nausea, decreased neutrophil count, anaemia, decreased white blood cell count and platelet count[1,2]
  - TRAEs led to discontinuation of all treatment in 13.6% (KEYTRUDA) vs 5.3% (placebo) of patients[2]
- There were 5 TRAE- or IMAE-related deaths in the KEYTRUDA arm vs 3 in the placebo arm[1]
  - There were no new fatal treatment-related adverse events between IA1 and IA2[1]

**IA2 data**

| AE summary across treatment phases | | KEYTRUDA (N=396) | Placebo (N=399) |
|---|---|---|---|
| Study days on KEYTRUDA or placebo, median (range) | | 375.5 days (1–728) | 337.0 days (1–644) |
| Number of KEYTRUDA or placebo administrations, median (range) | | 15 (1–17) | 12 (1–17) |
| **TRAEs, n (%)*** | Any grade | 383 (96.7) | 381 (95.5) |
| | Grade 3–5 | 179 (45.2) | 151 (37.8) |
| | Serious | 73 (18.4) | 58 (14.5) |
| | Led to death | 4 (1.0)† | 3 (0.8)‡ |
| | Led to discontinuation of all study treatment | 54 (13.6) | 21 (5.3) |
| **IMAEs and infusion reactions, n (%)** | Any grade | 103 (26.0) | 36 (9.0) |
| | Grade 3–5 | 26 (6.6) | 6 (1.5) |
| | Serious | 24 (6.1) | 6 (1.5) |
| | Led to death | 1 (0.3)§ | 0 |
| | Led to discontinuation of all study treatment | 23 (5.8) | 3 (0.8) |

Adapted from Spicer J, *et al.* ESMO 2023.[1]

**Data cut-off date for IA2: 10 July 2023. Median follow-up: 36.6 months.[1]**
*Considered by the investigator to be related to chemotherapy, KEYTRUDA and placebo.[1] †AEs leading to death (n=1 each): atrial fibrillation, immune-mediated lung disease, pneumonia and sudden cardiac death.[1] ‡AEs leading to death (n=1 each): acute coronary syndrome, pneumonia and pulmonary haemorrhage.[1] §AE leading to death: pneumonitis (recorded in the database as immune-mediated lung disease).[1]
AE, adverse event; IA, interim analysis; IMAE, immune-mediated adverse event; TRAE, treatment-related adverse event.
**1.** Spicer JB, *et al.* Overall survival in the KEYNOTE-671 study of perioperative pembrolizumab for early-stage NSCLC. ESMO. 20–24 October 2023. Madrid, Spain. Abstract: LBA56. **2.** Wakelee H, *et al. N Engl J Med* 2023;389:491–503.

# KEYNOTE-671: safety[1]

- **Most TRAEs occurred in the neoadjuvant phase,** consistent with neoadjuvant chemotherapy being the main contributor
  - Addition of KEYTRUDA did not substantially increase the rate of any-grade TRAEs (Δ+2.0%), high-grade TRAEs (Δ+4.1%), or discontinuation due to AEs (Δ+1.7%)
- The rate of TRAEs in the adjuvant phase was lower than in the neoadjuvant phase, indicating that **adjuvant KEYTRUDA is generally well-tolerated**
  - Adjuvant KEYTRUDA was associated with an increase in any TRAEs (Δ+22.7%) and high-grade TRAEs (Δ+4.4%)
  - At IA1, more patients received and completed adjuvant therapy with KEYTRUDA than placebo (Δ+5.1%)
  - Only a small proportion discontinued adjuvant therapy due to AEs (9.3% vs 3.3%)

**IA1 data**

| AE summary by treatment phases[1] | | KEYTRUDA (N=396) | Placebo (N=399) |
|---|---|---|---|
| **Neoadjuvant/surgery phase, n (%)** | Any grade TRAE | 379 (95.7) | 374 (93.7) |
| | Grade 3–5 TRAE | 161 (40.7) | 146 (36.6) |
| | TRAE leading to death | 3 (0.8)* | 3 (0.8)† |

| AE summary by treatment phases[1] | | KEYTRUDA (N=396) | Placebo (N=399) |
|---|---|---|---|
| **Adjuvant phase, n (%)** | Any grade TRAE | 158 (54.5) | 85 (31.8) |
| | Grade 3–5 TRAE | 29 (10.0) | 15 (5.6) |
| | TRAE leading to death | 1 (0.3)‡ | 0 |

| Completion/discontinuation by treatment phase[1] | | KEYTRUDA (N=396) | Placebo (N=399) |
|---|---|---|---|
| **Neoadjuvant phase, n (%)** | Completed 4 cycles | 295 (74.5) | 297 (74.4) |
| | Discontinued due to AEs | 8 (2.0) | 1 (0.3) |
| **Surgery phase, n (%)** | Underwent surgery | 325 (82.1) | 317 (79.4) |
| | Did not proceed to adjuvant due to AEs | 19 (4.8) | 10 (2.5) |
| **Adjuvant phase, n (%)** | Received adjuvant | 290 (73.2) | 267 (66.9) |
| | Completed adjuvant | 160 (40.4) | 141 (35.3) |
| | Discontinued due to AEs | 37 (9.3) | 13 (3.3) |

Adapted from Wakelee H, *et al. N Engl J Med* 2023. Supplementary appendix.[1]

**Data cut-off date for IA1: 29 July 2022. Median follow-up: 25.2 months.[1]**

*One patient each due to immune-mediated lung disease, pneumonia, and sudden cardiac death. †One participant each due to acute coronary syndrome, pneumonia, and pulmonary hemorrhage. ‡Due to atrial fibrillation.

AE, adverse event; IA, interim analysis; TRAE, treatment-related adverse event.

**1.** Wakelee H, *et al. N Engl J Med* 2023;389:491–503. Supplementary appendix.

# KEYNOTE-671: summary

## Efficacy

- At IA2, in patients with NSCLC who are at high risk of recurrence following use in combination with platinum-based chemotherapy and continued as adjuvant monotherapy, KEYTRUDA demonstrated a statistically significant and clinically meaningful OS benefit as shown with perioperative KEYTRUDA vs placebo (p=0.00517)[1]
  - **There was a 28% reduction in risk of disease recurrence or death with KEYTRUDA vs placebo (HR: 0.72; 95% CI: 0.56–0.93)[1]**
- At IA1, in patients with NSCLC who are at high risk of recurrence following use in combination with platinum-based chemotherapy and continued as adjuvant monotherapy, KEYTRUDA demonstrated a statistically significant and clinically meaningful EFS benefit as shown vs placebo (HR: 0.58; 95% CI: 0.46–0.72, p<0.00001)[2,3]
  - This benefit was sustained in IA2 (HR: 0.59; 95% CI: 0.48–0.72)[3]
- At IA1, exploratory data showed EFS benefit in the perioperative KEYTRUDA group **regardless of whether participants had a major or complete pathologic response or not:***[2,3]
  - With pCR HR: 0.33; without pCR HR: 0.69
  - With mPR HR: 0.54; without mPR HR: 0.73

## Safety

- In KEYNOTE-671, **no new immune-mediated adverse reactions** were identified with KEYTRUDA[1–3]
- Grade 3–5 treatment-related adverse events were seen in 45.2% of those treated with KEYTRUDA vs 37.8% who received placebo. The most common were: decreased neutrophil count, anaemia, decreased white-cell count and platelet count[1–3]
- The safety of KEYTRUDA as monotherapy has been evaluated in 7631 patients across tumour types in clinical studies. The most frequent adverse reactions with KEYTRUDA were fatigue (31%), diarrhoea (22%) and nausea (20%)[4]

*Exploratory analysis from IA1 was not updated at IA2, as the updated EFS in the ITT was consistent with IA1.[2,3]
CI, confidence interval; EFS, event-free survival; HR, hazard ratio; IA, interim analysis; ITT, intention-to-treat; NSCLC, non–small cell lung carcinoma; OS, overall survival; mPR, major pathologic response; pCR, pathological complete response.
**1.** Spicer JB, *et al.* Overall survival in the KEYNOTE-671 study of perioperative pembrolizumab for early-stage NSCLC. ESMO. 20–24 October 2023. Madrid, Spain. Abstract: LBA56. **2.** Wakelee H, *et al.* KEYNOTE-671: Randomised, double-blind, Phase 3 study of pembrolizumab or placebo plus platinum-based chemotherapy followed by resection and pembrolizumab or placebo for early-stage NSCLC. ASCO. 2–6 June 2023. Chicago, IL, USA. Abstract: LBA100. **3.** Wakelee H, *et al. N Engl J Med* 2023;389:491–503. **4.** KEYTRUDA Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/2498 Accessed: January 2025.

# KEYTRUDA offers flexibility of dosing[1]

**Administered as an IV infusion**

**Over 30 minutes**

**200 mg Q3W or 400 mg Q6W**

### After preparation of infusion

Chemical and physical in-use stability has been demonstrated for up to 42 days at 2°C to 8°C or at 23°C to 27°C. Protect from light.[1] From a microbiological point of view, the product, once diluted, should be used immediately. The diluted solution must not be frozen. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 7 days at 2°C to 8°C, or 12 hours at room temperature, unless dilution has taken place in controlled and validated aseptic conditions. If refrigerated, the vials and/or intravenous bags must be allowed to come to room temperature prior to use.[1]

### Assessment of regimens

The 200 mg Q3W regimen has been assessed in Phase I and II registration studies across a multitude of indications of KEYTRUDA.[1] An exposure-response evaluation, using modelling and simulation, led to the approval of the 400 mg Q6W dosing for monotherapy and combination therapy.[1]

IV, intravenous; Q3W, every 3 weeks; Q6W, every 6 weeks.

**1.** KEYTRUDA Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/2498 Accessed: January 2025.