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.[1,2]

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. Great Britain. Available at: https://www.medicines.org.uk/emc/product/2498 Accessed: October 2024.
2. KEYTRUDA Summary of Product Characteristics. Northern Ireland. Available at: https://www.emcmedicines.com/en-gb/northernireland/medicine?id=ce680467-8438-4e60-ab4f-dfab6767ccbe&type=smpc Accessed: October 2024.

KEYTRUDA® (pembrolizumab)

MSD

Links to external sites

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KEYTRUDA early-stage and advanced NSCLC indications[1,2]

- **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 as monotherapy is either 200 mg every 3 weeks or 400 mg every 6 weeks administered as an intravenous infusion over 30 minutes. The recommended dose of KEYTRUDA as part of combination therapy is 200 mg every 3 weeks administered as an intravenous infusion over 30 minutes

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. Great Britain. Available at: https://www.medicines.org.uk/emc/product/2498 Accessed: October 2024. **2.** KEYTRUDA Summary of Product Characteristics. Northern Ireland. Available at: https://www.emcmedicines.com/en-gb/northernireland/medicine?id=ce680467-8438-4e60-ab4f-dfab6767ccbe&type=smpc Accessed: October 2024.

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[1,2]

1. KEYTRUDA Summary of Product Characteristics. Great Britain. Available at: https://www.medicines.org.uk/emc/product/2498 Accessed: October 2024.
2. KEYTRUDA Summary of Product Characteristics. Northern Ireland. Available at: https://www.emcmedicines.com/en-gb/northernireland/medicine?id=ce680467-8438-4e60-ab4f-dfab6767ccbe&type=smpc Accessed: October 2024.

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

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

Adjuvant phase

KEYTRUDA§ 200 mg Q3W ≤13 cycles

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]

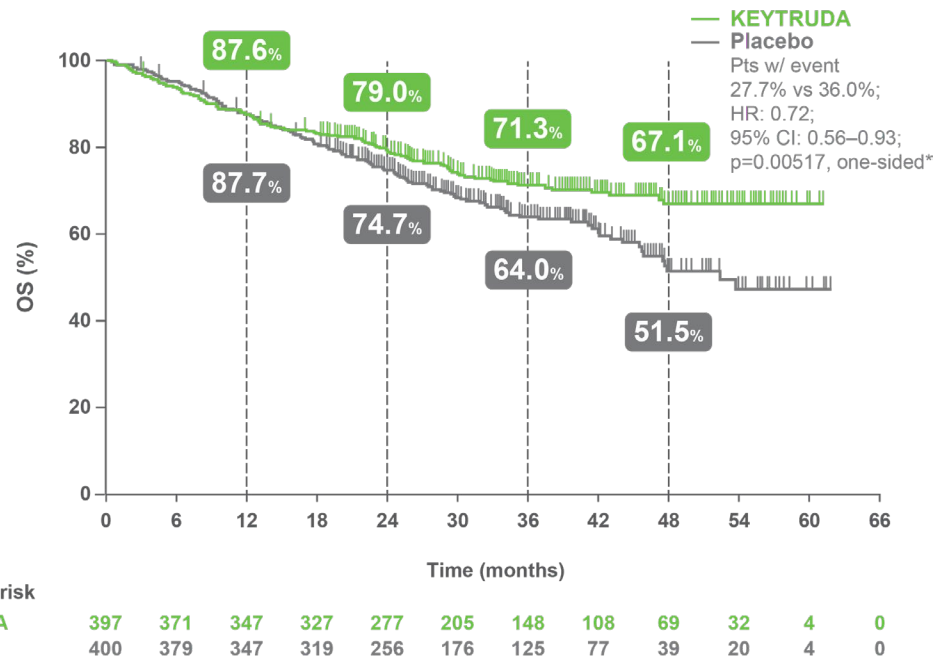
Data cut-off date for IA1: 29 July 2022. Median follow-up: 25.2 months.[1]
*As determined by imaging and biopsy.[1] †*EGFR* and *ALK* status were tested locally per investigator discretion. *EGFR* status was unknown in 68.5% in the KEYTRUDA arm and 63.5% in the placebo arm; *ALK* status was unknown in 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]

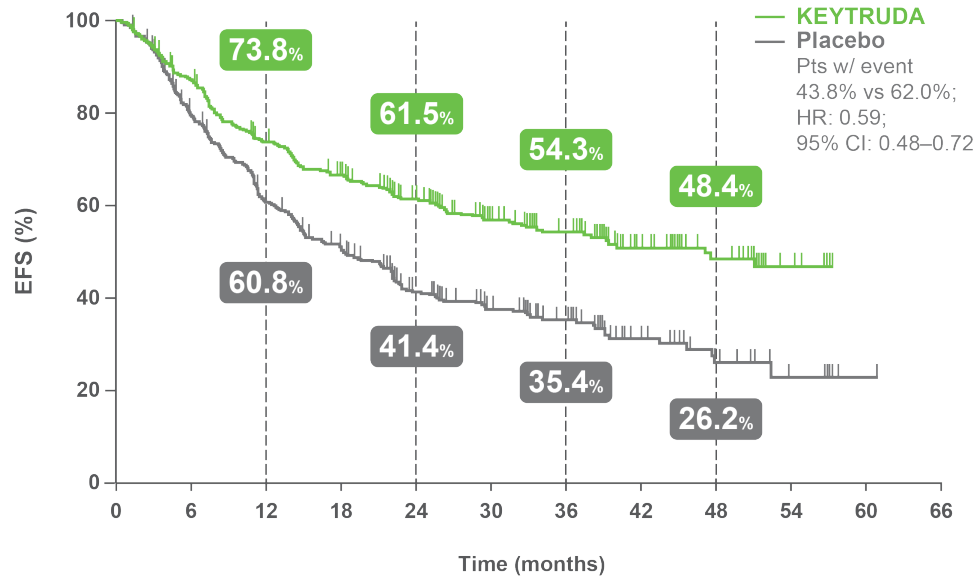
Data cut-off date for IA2: 10 July 2023. Median follow-up: 36.6 months.[1]
*Subgroups for Stage IIIA and IIIB and by N status were post hoc, while others were prespecified.[1]
ALK, anaplastic lymphoma kinase; CI, confidence interval; *EGFR*, epidermal growth factor receptor; HR, hazard ratio; ITT, intention-to-treat; 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

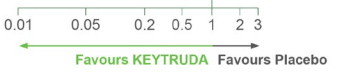
EFS in the ITT population

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)



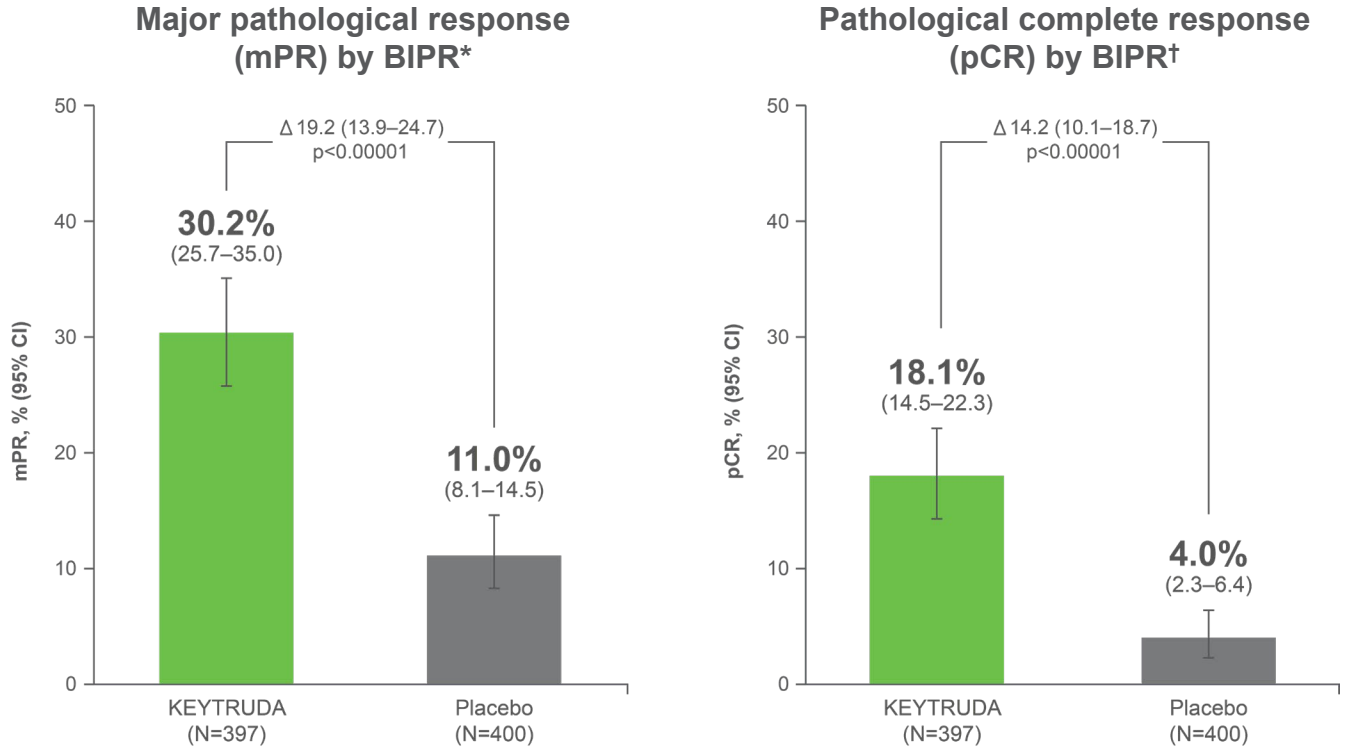
Adapted from Spicer J, *et al*. ESMO 2023.[2]

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.

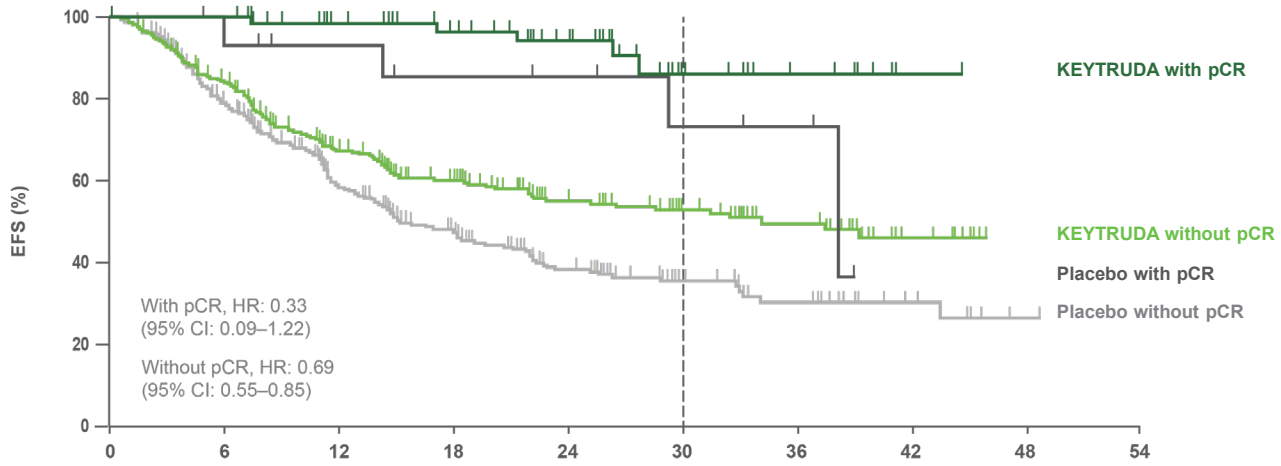
Exploratory endpoint: EFS by pCR[1,2]

- 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

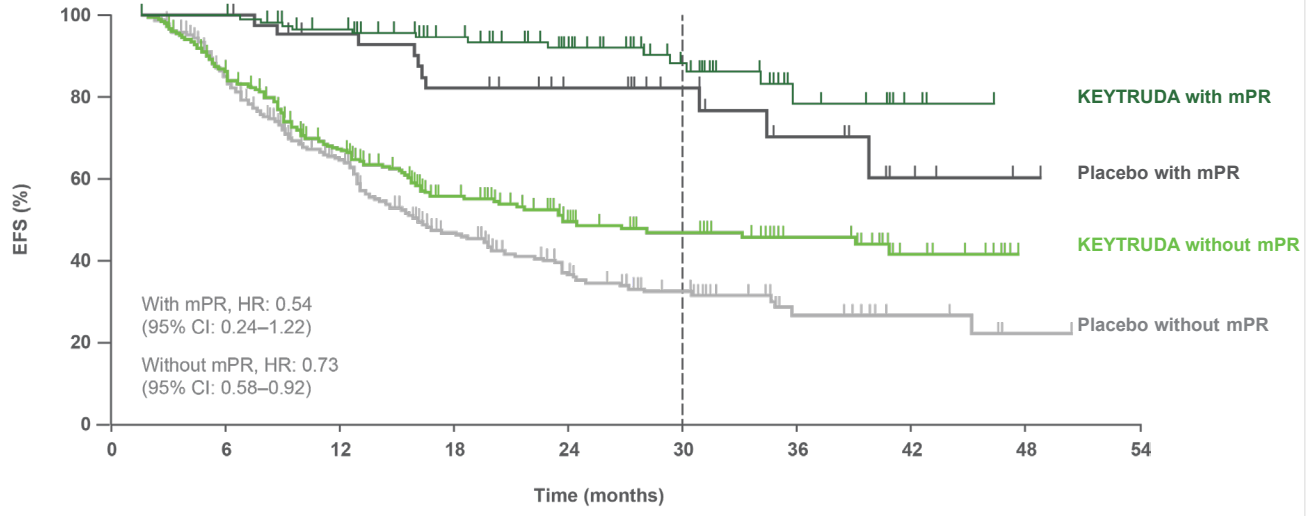
Adapted from Wakelee H, *et al. N Engl J Med* 2023.[2]

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%)[4,5]

*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. Great Britain. Available at: https://www.medicines.org.uk/emc/product/2498 Accessed: October 2024. **5.** KEYTRUDA Summary of Product Characteristics. Northern Ireland. Available at: https://www.emcmedicines.com/en-gb/northernireland/medicine?id=ce680467-8438-4e60-ab4f-dfab6767ccbe&type=smpc Accessed: October 2024.

KEYTRUDA offers flexibility of dosing[1,2]

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.[1,2] 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.[1,2]

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.[1,2] An exposure-response evaluation, using modelling and simulation, led to the approval of the 400 mg Q6W dosing for monotherapy and combination therapy.[1,2]

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

1. KEYTRUDA Summary of Product Characteristics. Great Britain. Available at: https://www.medicines.org.uk/emc/product/2498 Accessed: October 2024.
2. KEYTRUDA Summary of Product Characteristics. Northern Ireland. Available at: https://www.emcmedicines.com/en-gb/northernireland/medicine?id=ce680467-8438-4e60-ab4f-dfab6767ccbe&type=smpc Accessed: October 2024.