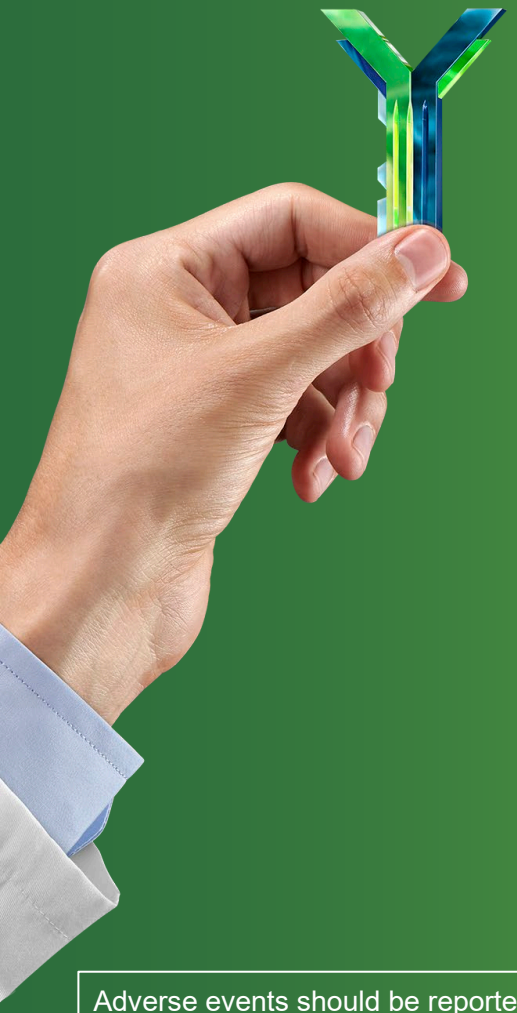


A key to more possibilities

for treating your appropriate patients

with resectable NSCLC

MSD Oncology

KEYNOTE-091: KEYTRUDA (pembrolizumab) versus placebo as adjuvant therapy for completely resected Stage IB–IIIA non-small cell lung cancer (NSCLC) (PEARLS/KEYNOTE-091)

KEYTRUDA as monotherapy is indicated for the adjuvant treatment of adults with non-small cell lung carcinoma who are at high risk of recurrence following complete resection and platinum-based chemotherapy.[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: April 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: April 2024.

KEYTRUDA® (pembrolizumab)

MSD

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: 020 8154 8000). **By clicking the above link you will leave the MSD website and be taken to the MHRA website.**

GB prescribing information can be found here.
NI prescribing information can be found here.
If using a downloaded version of this material, please ensure that you are accessing the most recent version of the prescribing information.

Job code: GB-PDO-03052 | Date of preparation: April 2024

Links to external sites

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

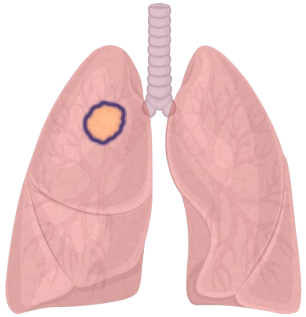
- MSD do not review or control the content of any third-party website
- MSD neither endorse nor are responsible for the accuracy, content, practices or standards of any third-party sources

Understanding the staging of NSCLC

The AJCC TNM classification system (8th edition)[1]

A tumour is described using three components: T for extent of the primary tumour, N for involvement of lymph nodes and M for distant metastases.[1] On slide 12 you can find a table highlighting the differences in staging between the 7th and 8th edition.

Tumour | Node | Metastases



Category	Subcategory	Tumour size	Invasiveness
T1	T1mi	≤3 cm	Surrounded by lung or visceral pleura; no invasion in main bronchus; T1mi is minimally invasive adenocarcinoma with mainly lepidic pattern and ≤5 mm invasion; superficial spreading tumour of any size limited to the bronchial wall and may extend proximal to the main bronchus, also classified as T1a
	T1a	≤1 cm (or superficial spreading tumour of any size; see invasiveness column)	
	T1b	>1 and ≤2 cm	
	T1c	>2 and ≤3 cm	
T2	T2a	>3 and ≤4 cm (or if size cannot be determined)	Tumour >3 cm but ≤5 cm or any of the following: • Involves main bronchus without carina • Invades visceral pleura (PL1 or PL2) • Associated with atelectasis or obstructive pneumonitis extending to the hilar region, in part or all of the lung
	T2b	>4 and ≤5 cm	
T3	-	>5 and ≤7 cm (or see invasiveness column)	Tumour is T3 if directly invades parietal pleura (PL3), chest wall, phrenic nerve, or parietal pericardium; or with separate tumour nodules in the same lobe
T4	-	>7 cm (or see invasiveness column)	Tumour of any size is T4 if invades diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, or carina; or with tumour nodules in a different lobe of the same lung lobe

Adapted from Amin MB, *et al*, 2017.[1]

The combined T, N and M values determine cancer stage.[1]

AJCC, American Joint Committee on Cancer; M, metastases; N, nodes; NSCLC, non-small cell lung carcinoma; T, tumour.

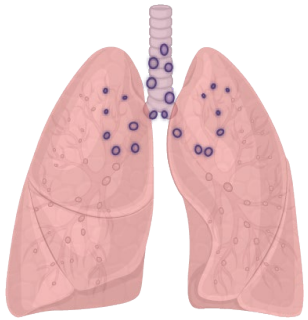
1. Amin MB, Edge S, Greene F, *et al*. eds. AJCC Cancer Staging Manual. 8th ed. Springer International Publishing. 2017.

Understanding the staging of NSCLC

The AJCC TNM classification system (8th edition)[1]

A tumour is described using three components: T for extent of the primary tumour, N for involvement of lymph nodes and M for distant metastases.[1]

Tumour | **Node** | Metastases



Category	Invasiveness
N0	No regional lymph node metastasis
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary lymph nodes
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph nodes
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene or supraclavicular lymph nodes

Adapted from Amin MB, *et al*, 2017.[1]

The combined T, N and M values determine cancer stage.[1]

AJCC, American Joint Committee on Cancer; M, metastases; N, nodes; NSCLC, non-small cell lung carcinoma; T, tumour.

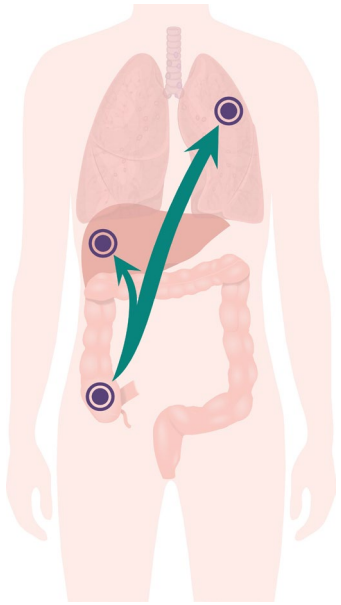
1. Amin MB, Edge S, Greene F, *et al*. eds. AJCC Cancer Staging Manual. 8th ed. Springer International Publishing. 2017.

Understanding the staging of NSCLC

The AJCC TNM classification system (8th edition)[1]

A tumour is described using three components: T for extent of the primary tumour, N for involvement of lymph nodes and M for distant metastases.[1]

Tumour | Node | **Metastases**



Category	Subcategory	Invasiveness
M0	-	No distant metastasis
M1	M1a	Separate nodules in contralateral lung lobe; malignant pleural or pericardial effusion; pleural or pericardial nodules; most pleural (pericardial) effusions result from tumour; in some cases, multiple microscopic examinations of pleural fluid are negative, fluid is non bloody and not an exudate. If effusion is not tumour-related, effusion should be excluded as staging descriptor
	M1b	Single extrathoracic metastasis in one organ
	M1c	Multiple extrathoracic metastases in one or more organs

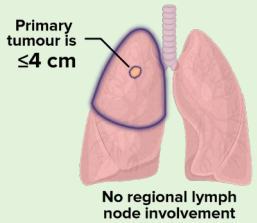
Adapted from Amin MB, *et al*, 2017.[1]

The combined T, N and M values determine cancer stage.[1]

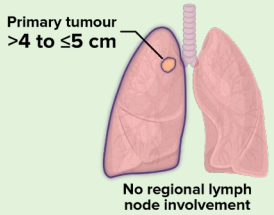
AJCC, American Joint Committee on Cancer; M, metastases; N, nodes; NSCLC, non-small cell lung carcinoma; T, tumour.

1. Amin MB, Edge S, Greene F, *et al*. eds. AJCC Cancer Staging Manual. 8th ed. Springer International Publishing. 2017.

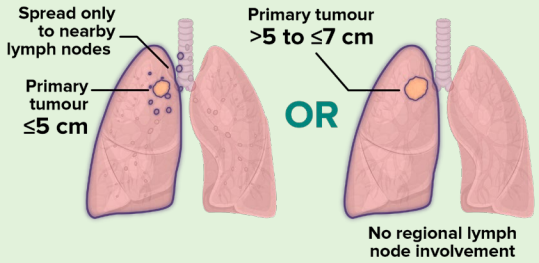
The AJCC TNM system (8th edition) can be used to stage NSCLC[1]



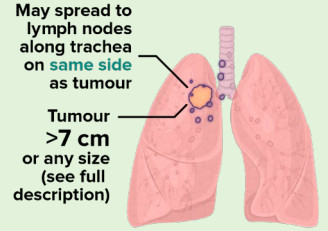
Stage I



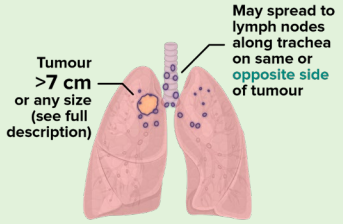
Stage IIA



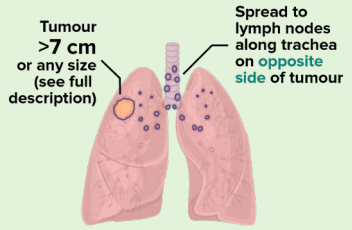
Stage IIB



Stage IIIA



Stage IIIB



Stage IIIC

Resection may be considered as an option for patients with operable/resectable Stage I–IIIB NSCLC.

Stage I

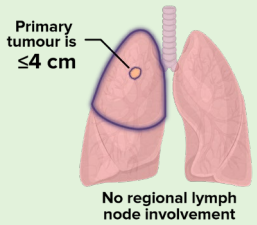
Stage	T	N	M
IA1	T1mi,a	N0	M0
IA2	T1b	N0	M0
IA3	T1c	N0	M0
IB	T2a	N0	M0

Adapted from Amin MB, *et al*, 2017.[1]

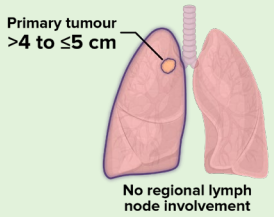
AJCC, American Joint Committee on Cancer; M, metastases; N, nodes; NSCLC, non-small cell lung carcinoma; T, tumour.

1. Amin MB, Edge S, Greene F, *et al*. eds. AJCC Cancer Staging Manual. 8th ed. Springer International Publishing. 2017.

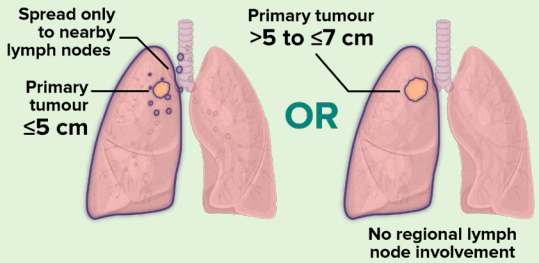
The AJCC TNM system (8th edition) can be used to stage NSCLC[1]



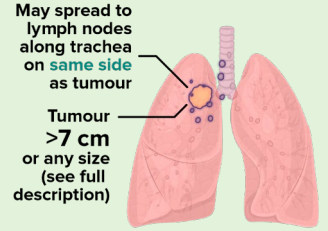
Stage I



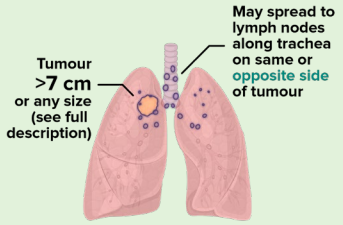
Stage IIA



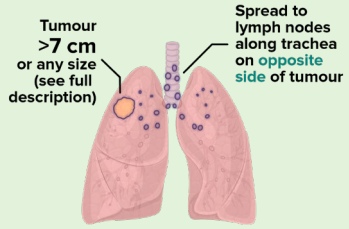
Stage IIB



Stage IIIA



Stage IIIB



Stage IIIC

Resection may be considered as an option for patients with operable/resectable Stage I–IIIB NSCLC.

Stage IIA

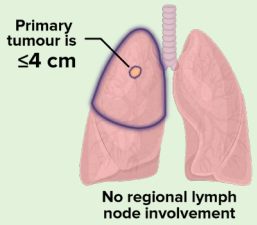
Stage	T	N	M
IIA	T2b	N0	M0

Adapted from Amin MB, *et al*, 2017.[1]

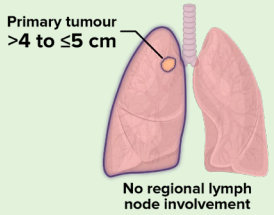
AJCC, American Joint Committee on Cancer; M, metastases; N, nodes; NSCLC, non-small cell lung carcinoma; T, tumour.

1. Amin MB, Edge S, Greene F, *et al*. eds. AJCC Cancer Staging Manual. 8th ed. Springer International Publishing. 2017.

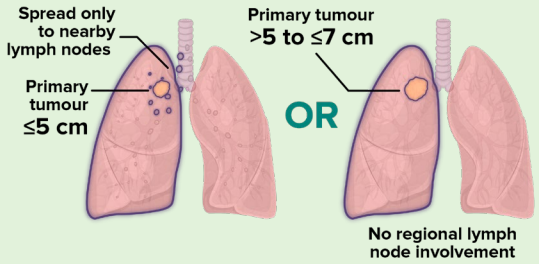
The AJCC TNM system (8th edition) can be used to stage NSCLC[1]



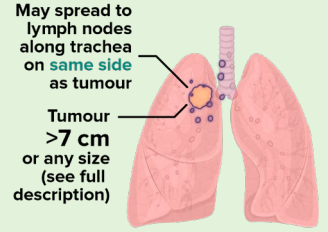
Stage I



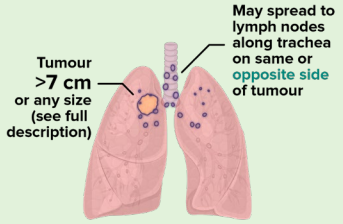
Stage IIA



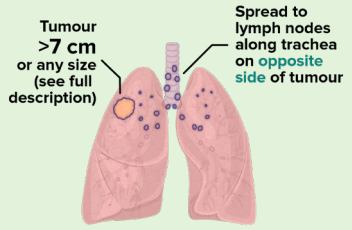
Stage IIB



Stage IIIA



Stage IIIB



Stage IIIC

Resection may be considered as an option for patients with operable/resectable Stage I–IIIB NSCLC.

Stage IIB

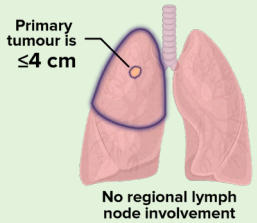
Stage	T	N	M
IIB	T1a,b,c	N1	M0
	T2a,b	N1	M0
	T3	N0	M0

Adapted from Amin MB, *et al*, 2017.[1]

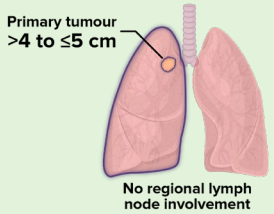
AJCC, American Joint Committee on Cancer; M, metastases; N, nodes; NSCLC, non-small cell lung carcinoma; T, tumour.

1. Amin MB, Edge S, Greene F, *et al*. eds. AJCC Cancer Staging Manual. 8th ed. Springer International Publishing. 2017.

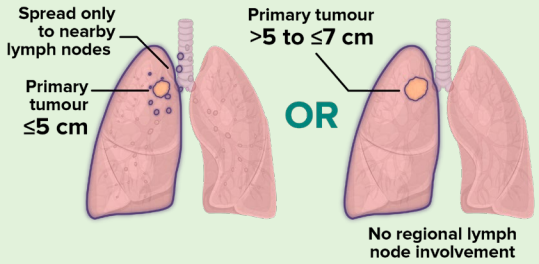
The AJCC TNM system (8th edition) can be used to stage NSCLC[1]



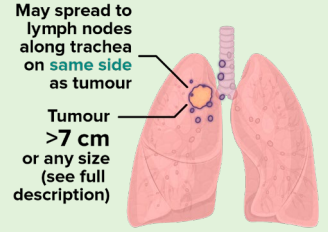
Stage I



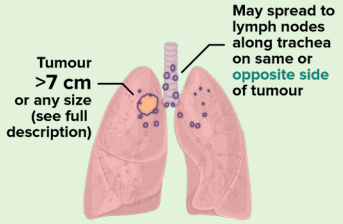
Stage IIA



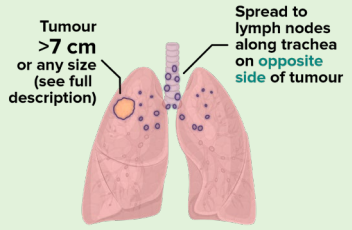
Stage IIB



Stage IIIA



Stage IIIB



Stage IIIC

Resection may be considered as an option for patients with operable/resectable Stage I–IIIB NSCLC.

Stage IIIA

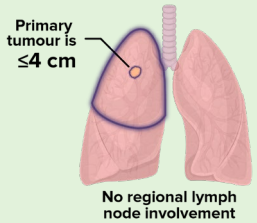
Stage	T	N	M
IIIA	T1a,b,c	N2	M0
	T2a,b	N2	M0
	T3	N1	M0
	T4	N0	M0
	T4	N1	M0

Adapted from Amin MB, *et al*, 2017.[1]

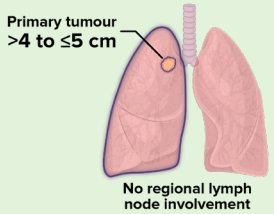
AJCC, American Joint Committee on Cancer; M, metastases; N, nodes; NSCLC, non-small cell lung carcinoma; T, tumour.

1. Amin MB, Edge S, Greene F, *et al*. eds. AJCC Cancer Staging Manual. 8th ed. Springer International Publishing. 2017.

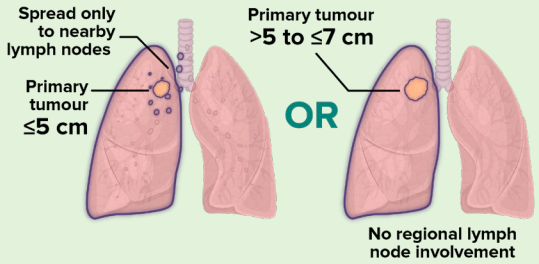
The AJCC TNM system (8th edition) can be used to stage NSCLC[1]



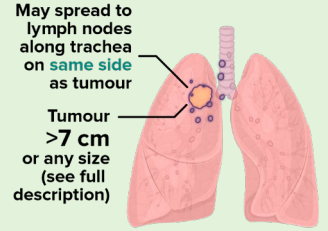
Stage I



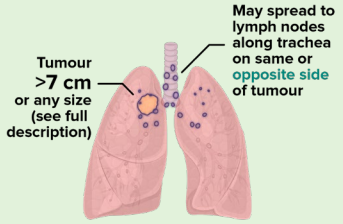
Stage IIA



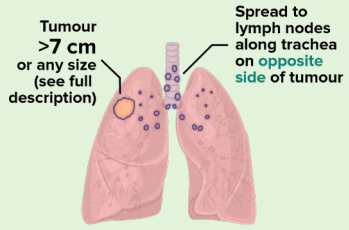
Stage IIB



Stage IIIA



Stage IIIB



Stage IIIC

Resection may be considered as an option for patients with operable/resectable Stage I–IIIB NSCLC.

Stage IIIB

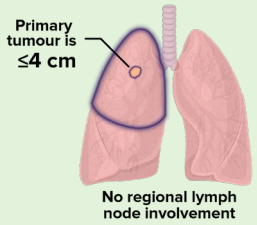
Stage	T	N	M
IIIB	T1a,b,c	N3	M0
	T2a,b	N3	M0
	T3	N2	M0
	T4	N2	M0

Adapted from Amin MB, *et al*, 2017.[1]

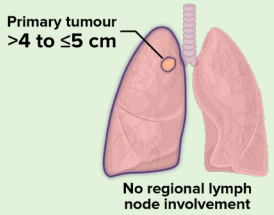
AJCC, American Joint Committee on Cancer; M, metastases; N, nodes; NSCLC, non-small cell lung carcinoma; T, tumour.

1. Amin MB, Edge S, Greene F, *et al*. eds. AJCC Cancer Staging Manual. 8th ed. Springer International Publishing. 2017.

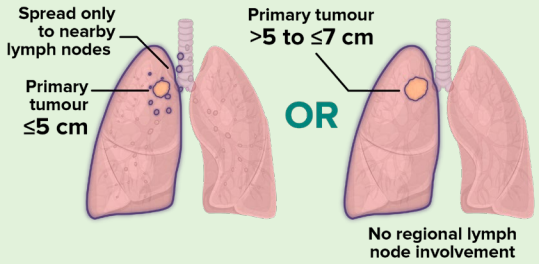
The AJCC TNM system (8th edition) can be used to stage NSCLC[1]



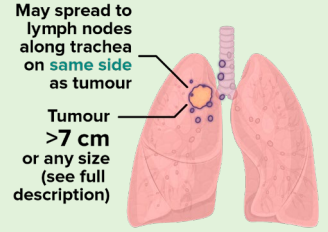
Stage I



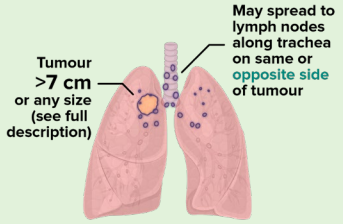
Stage IIA



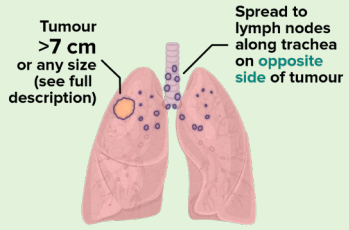
Stage IIB



Stage IIIA



Stage IIIB



Stage IIIC

Resection may be considered as an option for patients with operable/resectable Stage I–IIIB NSCLC.

Stage IIIC

Stage	T	N	M
IIIC	T3	N3	M0
	T4	N3	M0

Adapted from Amin MB, *et al*, 2017.[1]

AJCC, American Joint Committee on Cancer; M, metastases; N, nodes; NSCLC, non-small cell lung carcinoma; T, tumour.

1. Amin MB, Edge S, Greene F, *et al*. eds. AJCC Cancer Staging Manual. 8th ed. Springer International Publishing. 2017.

Staging reclassification between TNM editions

TNM 7th edition[1]

			N0	N1	N2	N3
T1	T1a		IA	IIA	IIIA	IIIB
	T1b		IA	IIA	IIIA	IIIB
T2	T2a	>3cm ≤ 5cm	IB	IIA	IIIA	IIIB
	T2b		IIA	IIB	IIIA	IIIB
T3			IIIB	IIIA	IIIA	IIIB
T4			IIIA	IIIA	IIIB	IIIB
M1	M1a		IV	IV	IV	IV
	M1b		IV	IV	IV	IV

TNM 8th edition[2]

			N0	N1	N2	N3
T1	T1a		IA1	IIB	IIIA	IIIB
	T1b		IA2	IIB	IIIA	IIIB
	T1c		IA3	IIB	IIIA	IIIB
T2	T2a	>3cm ≤ 4cm	IB	IIB	IIIA	IIIB
	T2b	>4cm ≤ 5cm	IIA	IIB	IIIA	IIIB
T3			IIIB	IIIA	IIIB	IIIC
T4			IIIA	IIIA	IIIB	IIIC
M1	M1a		IVA	IVA	IVA	IVA
	M1b		IVA	IVA	IVA	IVA
	M1c		IVB	IVB	IVB	IVB

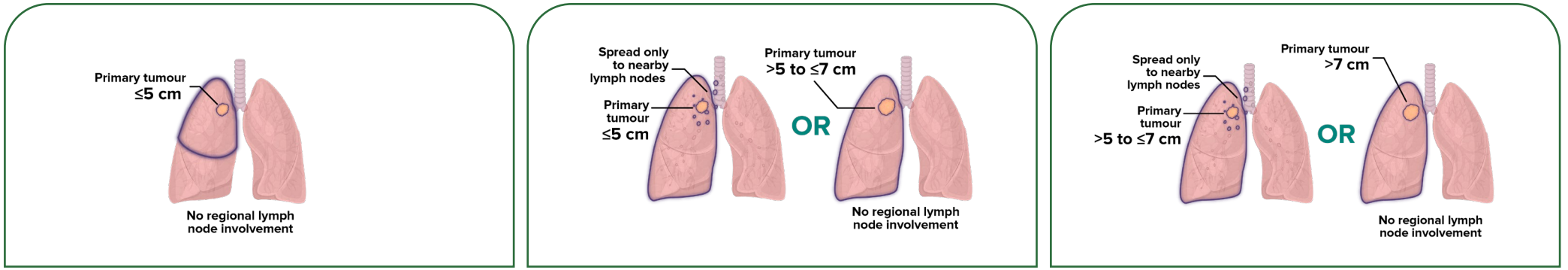
Red line indicates stages in relation to KEYNOTE-091

M, metastases; N, nodes; T, tumour.

1. Mirsadraee S, *et al*. *World J Radiol*. 2012;4(4):128-134. **2.** Detterbeck, FC. *J Thorac Cardio Surg*. 2018;155(1):356-359.

Updated AJCC TNM staging system: 7th edition vs 8th edition[1,2]

7th Edition | 8th Edition



Stage	IA	IB	IIA	IIB
TNM	T1a, b, N0, M0	T2a, N0, M0	T1a, b, N1, M0 T2a, N1, M0 T2b, N0, M0	T1b, N1, M0 T3, N0, M0

Adapted from Amin MB, *et al.* 2017[1] and Edge SB, *et al.* 2010.[2]

According to the 8th edition, tumours previously categorised Stage IB may now be considered IIA.[1,3]

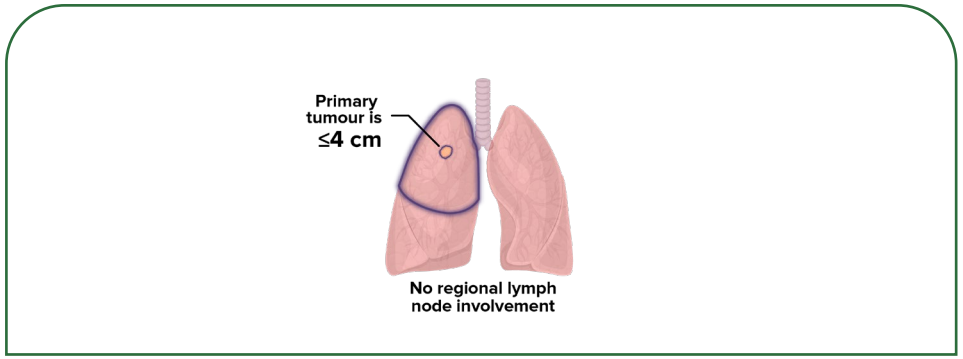
Refinement of NSCLC staging is a constant process and incorporates new understanding of cancer biology and other prognostic factors.[1]

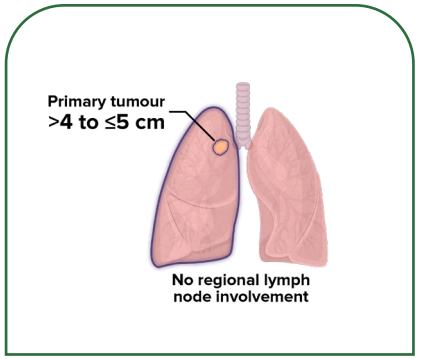
AJCC, American Joint Committee on Cancer; M, metastases; N, nodes; NSCLC, non-small cell lung carcinoma; T, tumour.

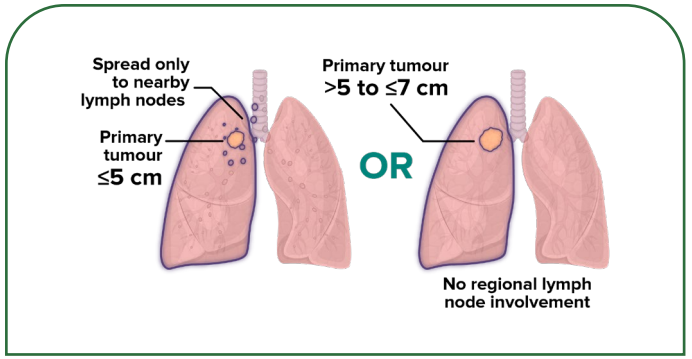
1. Amin MB, Edge S, Greene F, *et al.* eds. AJCC Cancer Staging Manual. 8th ed. Springer International Publishing. 2017. **2.** Edge SB, Byrd DR, Compton CC, *et al.* eds. AJCC Cancer Staging Manual. 7th ed. Springer International Publishing. 2010. **3.** Rami-Porta R, *et al. CA Cancer J Clin* 2017;67:138–155.

Updated AJCC TNM staging system: 7th edition vs 8th edition[1,3]

7th Edition | 8th Edition







Stage	IA1	IA2	IA3	IB	IIA	IIB
TNM	T1mi, a, N0, M0	T1b, N0, M0	T1c, N0, M0	T2a, N0, M0	T2b, N0, M0	T1a, b, c, N1, M0 T2a, b, N1, M0 T3, N0, M0

Adapted from Amin MB, *et al.* 2017[1] and Rami-Porta R, *et al.* 2017.[3]

According to the 8th edition, tumours previously categorised Stage IB may now be considered IIA.[1,3]

Refinement of NSCLC staging is a constant process and incorporates new understanding of cancer biology and other prognostic factors.[1]

AJCC, American Joint Committee on Cancer; M, metastases; N, nodes; NSCLC, non-small cell lung carcinoma; T, tumour.

1. Amin MB, Edge S, Greene F, *et al.* eds. AJCC Cancer Staging Manual. 8th ed. Springer International Publishing. 2017. **2.** Edge SB, Byrd DR, Compton CC, *et al.* eds. AJCC Cancer Staging Manual. 7th ed. Springer International Publishing. 2010. **3.** Rami-Porta R, et al. CA Cancer J Clin 2017;67:138-155.

NSCLC survival rates by stage[1]

In a study of patients with early-stage NSCLC (Stage IB-IIIA), two-thirds experienced disease recurrence during 4.5 years of follow-up, even after curative resection.*[1]

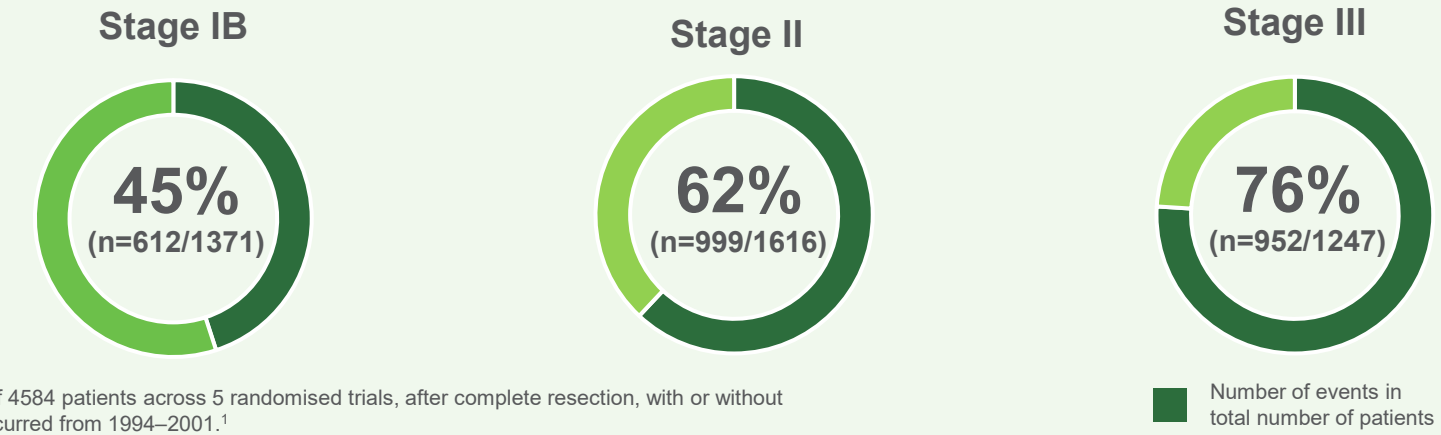
Real-world disease-free survival (rwDFS) by stage:[1]

Stage	Median rwDFS	5-year rwDFS
IB	40.9 months	38.9%
II	24.4 months	29.1%
IIIA	13.8 months	21.5%

*Based on 1761 patients from the SEER-Medicare database (2007–2019) with early-stage resected NSCLC.
NSCLC, non-small cell lung carcinoma; rwDFS, real-world disease-free survival; SEER, Surveillance, Epidemiology, and End Results.
1. West H, *et al*. *Clin Lung Cancer* 2023;24:260-268.

Disease recurrence can occur, even after resection, with or without chemotherapy[1]

Rate of recurrence or death within 5 years by stage[1]



The rate of recurrence or death is based on a 2008 pooled analysis of 4584 patients across 5 randomised trials, after complete resection, with or without adjuvant chemotherapy. The trials included in this pooled analysis occurred from 1994–2001.[1]

Lung Adjuvant Cisplatin Evaluation: a pooled analysis by the LACE collaborative group[1]

- The Lung Adjuvant Cisplatin Evaluation (LACE) study was a pooled analysis of 5 randomised trials conducted by the LACE Collaborative Group. The study evaluated the use of cisplatin-based chemotherapy as an adjuvant treatment for patients with NSCLC. The primary endpoint was overall survival (OS) and a secondary endpoint was disease-free survival (DFS)

Study population[1]

- Individual patient data were collected and pooled from 5 trials, including 4584 patients who underwent complete resection. Of these patients, 2281 received adjuvant chemotherapy. The interactions between patient subgroups or treatment types, and chemotherapy effect on OS were analysed using hazard ratios and log-rank tests stratified by trial

Inclusion and exclusion criteria[1]

- Trials eligible for inclusion were those that either randomly assigned more than 300 patients with completely resected NSCLC to receive postoperative cisplatin-based chemotherapy versus no chemotherapy, or cisplatin-based chemotherapy plus postoperative radiotherapy (administered sequentially) versus postoperative radiotherapy alone

NSCLC, non–small cell lung cancer.

1. Pignon JP, *et al. J Clin Oncol* 2008;26:3552–3559.

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

- **KEYTRUDA as monotherapy is indicated for the adjuvant treatment of adults with NSCLC who are at high risk of recurrence follo wing 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
- Refer to the Summary of Product Characteristics and Risk Minimisation Materials available on the EMC website before prescribing, in order to help reduce the risks associated with KEYTRUDA

ALK, anaplastic lymphoma kinase; *EGFR*, epidermal growth factor receptor; EMC, Electronic Medicines Compendium; NSCLC, non-small cell lung cancer; 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: April 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: April 2024.

KEYNOTE-091 Indication: 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[1,2]

NSCLC, non-small cell lung cancer.

1. KEYTRUDA Summary of Product Characteristics. Great Britain. Available at: https://www.medicines.org.uk/emc/product/2498 Accessed: April 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: April 2024.

KEYNOTE-091 study design:[1–4] randomised, triple-blind, Phase III trial across 29 countries

Patients:
- High risk of recurrence,* completely resected Stage IB (T2a ≥4 cm), II or IIIA NSCLC, regardless of PD-L1 expression
- No prior neoadjuvant radiotherapy and/or neoadjuvant chemotherapy
- No prior or planned adjuvant radiotherapy for current malignancy
- May or may not have received adjuvant chemotherapy (up to 4 cycles)
- No active autoimmune disease requiring systemic therapy
- No medical condition requiring immunosuppression
- Not received >4 cycles of adjuvant chemotherapy

1–4 cycles of adjuvant chemo
Considered for Stage IB (T≥4cm)
Strongly recommended for Stage II and IIIA*†
N=1177

R 1:1

Pembrolizumab
200 mg IV Q3W
≤18 cycles

Placebo
IV Q3W ≤18 cycles

Survival follow-up

Stratification factors:
- Stage (IB vs II vs IIIA)
- Use of adjuvant chemotherapy (No vs Yes)
- PD-L1 status: TPS <1% vs 1 to 49% vs > 50%
- Regions (Western vs Eastern Europe vs Asia vs RoW)

Dual primary endpoints:
- DFS (all patients)
- DFS (PD-L1 TPS ≥50%)

Secondary endpoints:
- DFS (PD-L1 TPS ≥1%)
- OS (all patients, PD-L1 TPS ≥50%, PD-L1 TPS ≥1%)
- Lung cancer-specific survival (LCSS; all patients)
- Safety

*The following selection criteria define patients with high risk of recurrence who are included in the therapeutic indication and are reflective of the patient population with Stage IB (T2a ≥4 cm), II or IIIA according to the 7th edition staging system: Tumour size ≥4 cm; or tumours of any size that are either accompanied by N1 or N2 status; or tumours that are invasive of thoracic structures (directly invade the parietal pleura, chest wall, diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina); or tumours that involve the main bronchus <2 cm distal to the carina but without involvement of the carina; or tumours that are associated with atelectasis or obstructive pneumonitis of the entire lung; or tumours with separate nodule(s) in the same lobe or different ipsilateral lobe as the primary. The study did not include patients who had N2 status with tumours also invading the mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina, or with separate tumour nodule(s) in a different ipsilateral lobe.
†Adjuvant chemotherapy was considered for Stage IB (T ≥4 cm 0 disease and strongly recommended for Stage II and IIA disease, limited to ≥4 cycles.
DFS, disease-free survival; IV, intravenous; NSCLC, non-small cell lung cancer; OS, overall survival; PD-L1, programmed death ligand-1; Q3W, once every 3 weeks; R, randomisation; RoW, rest of world; TPS, tumour proportion score.
1. O'Brien M, *et al. Lancet Oncol* 2022;2023:1274–1286. **2.** Paz-Ares L, *et al.* Pembrolizumab (pembro) versus placebo for early-stage non-small cell lung cancer (NSCLC) following complete resection and adjuvant chemotherapy (chemo) when indicated: Randomized, triple-blind, phase III EORTC-1416-LCG/ETOP 8-15 – PEARLS/KEYNOTE-091 study. ESMO Virtual Plenary. 17 March 2022. **3.** O'Brien M, *et al.* EORTC-1416-LCG/ETOP 8-15 – PEARLS/KEYNOTE-091 study of pembrolizumab versus placebo for completely resected early-stage non-small cell lung cancer (NSCLC): Outcomes in subgroups related to surgery, disease burden, and adjuvant chemotherapy use. ASCO. 3–7 June 2022. Chicago, IL, USA. Abstract: 8512. **4.** KEYTRUDA Summary of Product Characteristics. Great Britain. Available at: https://www.medicines.org.uk/emc/product/2498 Accessed: April 2024.

KEYNOTE-091: patient baseline characteristics[1,2]

Of 1177 patients randomised, 1010 (86%) received adjuvant platinum-based chemotherapy following complete resection

Characteristic, n (%)	Patients who received adjuvant platinum-based chemotherapy (N=1010)
Age, median (range), years	64 (35–84)
Age, ≥65 years	49
Male	687 (68)
White	778 (77)
Asian	182 (18)
Western Europe	525 (52)
Eastern Europe	202 (20)
Asia	172 (17)
Rest of world	111 (11)

Characteristic, n (%) *(continued)*	Patients who received adjuvant platinum-based chemotherapy (N=1010)
Current or former smoker	867 (86)
ECOG PS 1	394 (39)
Stage of disease at diagnosis*	
IB (T2a ≥4 cm)	121 (12)
II	576 (57)
IIIA	313 (31)
PD-L1 expression	
TPS <1%	394 (39)
TPS 1%–49%	333 (33)
TPS ≥50%	283 (28)

Characteristic, n (%) *(continued)*	Patients who received adjuvant platinum-based chemotherapy (N=1010)
EGFR mutations	
Known	71 (7)
Without	384 (38)
Unknown	566 (56)

*As defined per AJCC 7th edition.

AJCC, American Joint Committee on Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; PD-L1, programmed death ligand-1; TPS, tumour proportion score.

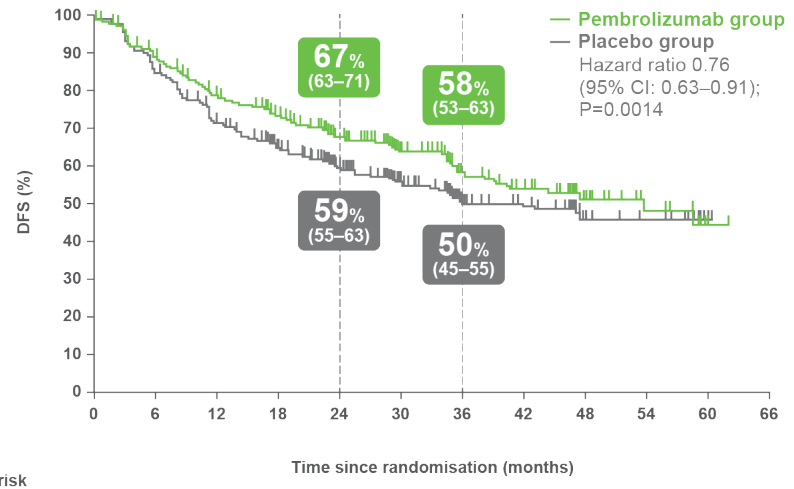
1. KEYTRUDA Summary of Product Characteristics. Great Britain. Available at: https://www.medicines.org.uk/emc/product/2498 Accessed: April 2024. **2.** KEYTRUDA Summary of Product Characteristics. Northern Ireland. Available at: https://www.emcmedicines.com/en-gb/northernireland/medicine?id=ce680467-8438-4e60-ab4f-dfab6767ccbe&type=smpc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

Primary endpoint: DFS in ITT populations[1–3]

IA3 (final DFS analysis) top-line summary of results for primary endpoints

Endpoints (pembrolizumab vs placebo)		No. events (IF)	HR (95% CI)	Median (months)	p-value boundary	Observed p-value	Outcome
Primary	DFS in the overall population	561 (102%)	0.81 (0.68–0.96)	53.8 vs 43.0	–	0.00812	Not tested (success criterion met at IA2)
	DFS in TPS ≥50%	140 (99%)	0.83 (0.59–1.16)	67.0 vs 47.6	0.01038	0.13499	Not positive

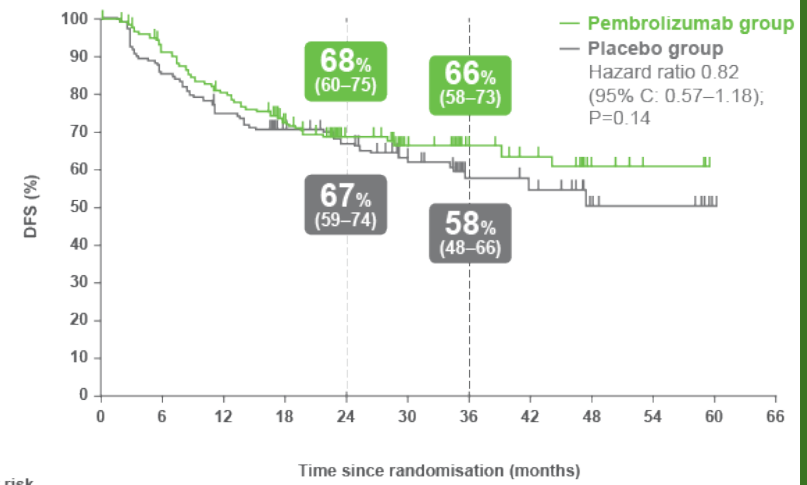
Kaplan-Meier estimates of DFS in KEYNOTE-091 for overall population



Number at risk (number censored)												
Pembrolizumab	590	493	434	358	264	185	82	70	28	16	1	0
	(0)	(30)	(36)	(84)	(150)	(216)	(306)	(313)	(352)	(363)	(377)	(378)
Placebo	587	493	409	326	241	160	72	57	22	18	1	0
	(0)	(5)	(13)	(56)	(118)	(183)	(259)	(273)	(305)	(309)	(326)	(327)

Adapted from O'Brien M, *et al*, 2022[3]

Kaplan-Meier estimates of DFS in KEYNOTE-091 for PD-L1 TPS ≥50%



Number at risk (number censored)												
Pembrolizumab	168	145	126	99	69	50	26	22	7	4	0	0
	(0)	(8)	(9)	(24)	(49)	(66)	(90)	(93)	(107)	(110)	(114)	(114)
Placebo	165	140	121	100	75	54	28	22	8	6	1	0
	(0)	(0)	(2)	(16)	(37)	(53)	(76)	(81)	(94)	(96)	(101)	(102)

Adapted from O'Brien M, *et al*, 2022[3]

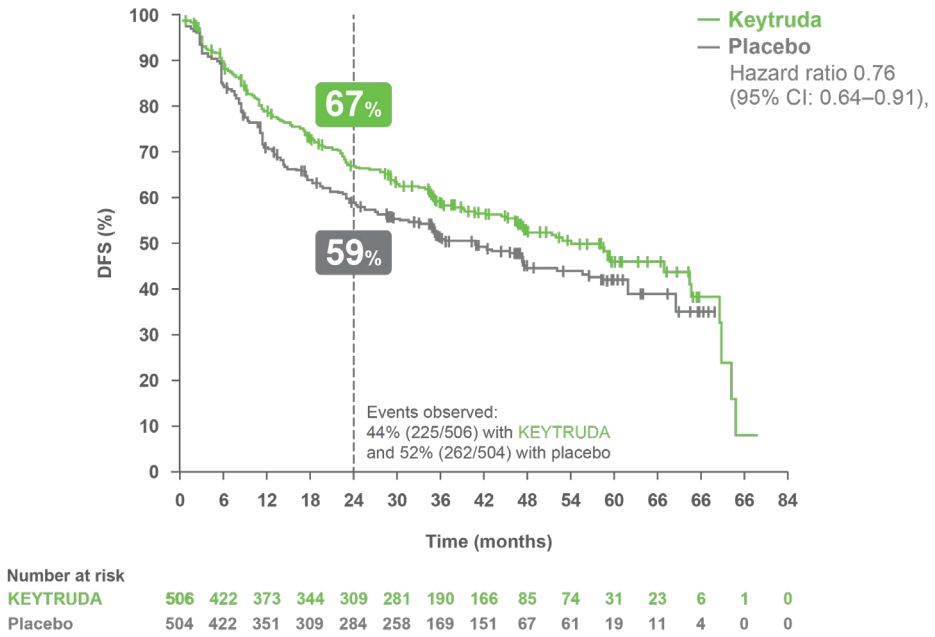
KEYTRUDA is licensed for use as a monotherapy for the adjuvant treatment of adults with NSCLC who are at high risk of recurrence following complete resection and platinum-based chemotherapy. The results of the ITT population are presented as this is the primary endpoint of the study. It allows the results in the licensed population (a subgroup of the ITT population) to be viewed in context of the primary endpoint.[1–3]

CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; IA, interim analysis; IF, information fraction; ITT, intention-to-treat; NSCLC, non–small cell lung cancer; 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: April 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: April 2024. **3.** O'Brien M, *et al. Lancet Oncol* 2022;23:1274–1286.

KEYNOTE-091 exploratory analysis: DFS (patients who received adjuvant chemotherapy)

Kaplan-Meier estimates of DFS in KEYNOTE-091 for patients who received adjuvant chemotherapy



Adapted from KEYTRUDA SmPC[1,2]

IA3 analysis of DFS (primary censoring rule) – multivariate analysis – ITT population – with adjuvant chemotherapy

Treatment	N	Number of events (%)	Person-months	Event rate/100 person-months	Median DFS* (months) (95% CI)	DFS rate at Month 12 in % (95% CI)	vs placebo	
							Hazard ratio (95% CI)	P-value
Pembrolizumab	506	225 (44.5)	15754.5	1.4	53.8 (46.2, 70.4)	78.7 (74.8, 82.1)	0.76 (0.64, 0.91)	0.00150
Placebo	504	262 (52.0)	14614.8	1.8	40.5 (32.9, 47.4)	71.0 (66.8, 74.7)	–	–

Adapted from KN-091 EPAR report, 2023[3]

Median DFS for patients who received adjuvant chemotherapy

~4.5 years*
KEYTRUDA: median 53.8 months
(95% CI: 46.2–70.4 months)

vs

~3.4 years†
Placebo: median 40.5 months
(95% CI: 32.9–47.4 months)

KEYTRUDA is licensed for use as a monotherapy for the adjuvant treatment of adults with NSCLC who are at high risk of recurrence following complete resection and platinum-based chemotherapy. The results of the ITT population are presented as this is the primary endpoint of the study. It allows the results in the licensed population (a subgroup of the ITT population) to be viewed in context of the primary endpoint.[1,2,4]

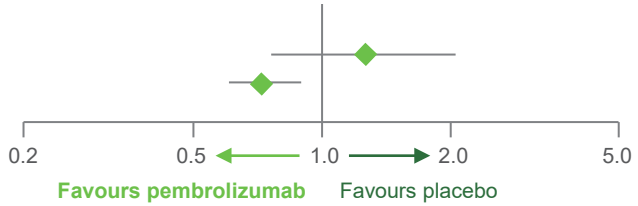
*4.483 years (53.8 months).
†3.375 (40.5 months).
CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; IA, interim analysis; ITT, intention-to-treat; NSCLC, non-small cell lung cancer; OS, overall survival.

1. KEYTRUDA Summary of Product Characteristics. Great Britain. Available at: https://www.medicines.org.uk/emc/product/2498 Accessed: April 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: April 2024. **3.** European Medicines Agency. European public assessment report: Keytruda. Available at: https://www.ema.europa.eu/en/documents/overview/keytruda-epar-medicine-overview_en.pdf Accessed April 2024. **4.** O'Brien M, *et al. Lancet Oncol* 2022;23:1274–1286

KEYNOTE-091 exploratory analysis: DFS (patients who received adjuvant chemotherapy) continued[1,2]

- The licensed indication is limited to those that received adjuvant chemotherapy due to results from O'Brien *et al.* 2022
- The hazard ratio (HR) of those that received adjuvant chemotherapy favoured KEYTRUDA (HR: 0.73 (0.60–0.89)) vs those who did not receive adjuvant chemotherapy (HR: 1.25 (0.76–2.05))

Received adjuvant chemotherapy		
No	35/84	29/83
Yes	177/506	231/504



Adapted from O'Brien, *et al*. 2022.

KEYTRUDA is licensed for use as a monotherapy for the adjuvant treatment of adults with NSCLC who are at high risk of recurrence following complete resection and platinum-based chemotherapy. The results of the ITT population are presented as this is the primary endpoint of the study. It allows the results in the licensed population (a subgroup of the ITT population) to be viewed in context of the primary endpoint.[1–3]

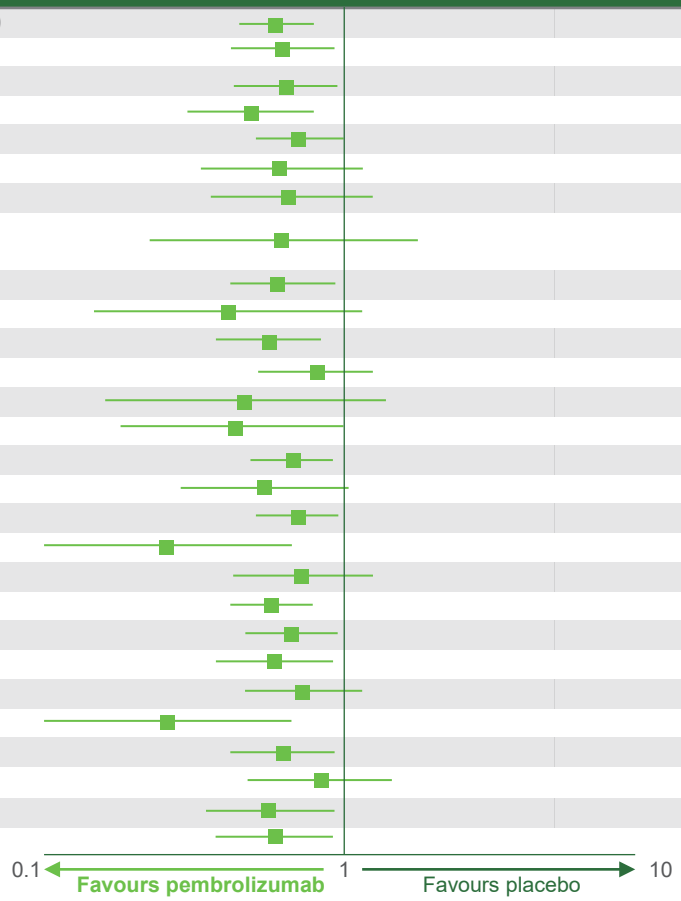
DFS, disease-free survival; HR, hazard ratio; ITT, intention-to-treat; NSCLC, non-small cell lung cancer.

1. KEYTRUDA Summary of Product Characteristics. Great Britain. Available at: https://www.medicines.org.uk/emc/product/2498 Accessed: April 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: April 2024. **3.** O'Brien M, *et al. Lancet Oncol* 2022;23:1274–1286

KEYNOTE-091 exploratory analysis: DFS by key subgroups in patients who received adjuvant chemotherapy[1]

Median follow up: 37.4 months

		No. of Events/No. of Patients	HR (95% CI)
Overall		408/1010	0.73 (0.60–0.89)
Age	<65y	203/516	0.72 (0.55–0.96)
	≥65y	205/494	0.74 (0.56–0.98)
Sex	Female	138/324	0.61 (0.44–0.86)
	Male	270/686	0.79 (0.62–1.00)
Geographic region	Asia	79/174	0.71 (0.46–1.11)
	Eastern Europe	83/201	0.75 (0.49–1.16)
	Rest of the World	30/108	0.72 (0.35–1.49)
	Western Europe	216/527	0.71 (0.54–0.93)
Stage at baseline	IB	32/115	0.54 (0.26–1.10)
	II	210/576	0.67 (0.51–0.89)
	IIIA	164/317	0.87 (0.64–1.18)
Adjuvant chemo cycles	1 or 2	28/67	0.59 (0.28–1.26)
	3	47/112	0.56 (0.30–1.02)
	4	333/830	0.77 (0.62–0.95)
Smoking status	Never smoker	73/137	0.65 (0.41–1.02)
	Former smoker	291/737	0.78 (0.62–0.98)
	Current smoker	44/136	0.39 (0.20–0.76)
Histology	Squamous	110/341	0.80 (0.55–1.17)
	Nonsquamous	298/669	0.68 (0.54–0.85)
ECOG PS	0	245/618	0.76 (0.59–0.98)
	1	163/392	0.69 (0.50–0.95)
EGFR mutation status	No	165/382	0.80 (0.59–1.08)
	Yes	37/66	0.39 (0.20–0.76)
	Unknown	206/562	0.72 (0.55–0.95)
PD-L1 status	TPS ≥50%	100/284	0.89 (0.60–1.32)*
	TPS 1%–49%	140/330	0.67 (0.48–0.94)
	TPS <1%	168/396	0.69 (0.51–0.94)



Adapted from Oselin K. Presented at ASCO 2023. Abstract 8520.

Data cut-off date: September 20, 2021. *For the PD-L1 TPS ≥50% subgroup, HR for DFS by multivariate Cox regression model with treatment adjusted by stratification factors, histology (squamous vs nonsquamous), and smoking status (never vs former/current) was 0.80 (95% CI: 0.54–1.20).
DFS: disease-free survival; ECOG PS: ECOG PS: Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; PD-L1, programmed death ligand-1.
1. Oselin K *et al*. Presented at ASCO 2023; Abstract 8520.

Interim DFS and OS analysis in ITT population[1]

IA3 (final DFS analysis) top-line summary of results for primary and key secondary endpoints

Endpoints (pembrolizumab vs placebo)		No events (IFe)	HR (95% CI)	Median (months)	p-value boundary	Observed p-value	Outcome
Primary	DFS in the overall population	561 (102%)	0.81 (0.68–0.96)	53.8 vs 43.0	–	0.00812	Not tested (success criterion met at IA2)
	DFS in TPS ≥50%	140 (99%)	0.83 (0.59–1.16)	67.0 vs 47.6	0.01038	0.13499	Not positive
Key secondary	DFS in TPS ≥1%	331 (102%)	0.78 (0.62–0.97)	58.7 vs 42.8	–	0.01327	Not tested
	OS in the overall population	290	0.87 (0.69–1.10)	NR vs NR	–	0.11792	Not positive; to be tested again at next IA
	OS in TPS ≥50%	67	0.93 (0.57–1.50)	NR vs NR	–	0.37780	Not positive; to be tested again at next IA
	OS in TPS ≥1%	165	0.83 (0.61–1.13)	NR vs NR	–	0.12390	Not tested; to be tested once positive in TPS ≥50%

Adapted from KN-091 EPAR report, 2023[1]

KEYTRUDA is licensed for use as a monotherapy for the adjuvant treatment of adults with NSCLC who are at high risk of recurrence following complete resection and platinum-based chemotherapy. The results of the ITT population are presented as this is the primary endpoint of the study. It allows the results in the licensed population (a subgroup of the ITT population) to be viewed in context of the primary endpoint.[1–3]

CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; IA, interim analysis; ITT, intention-to-treat; NR, not reached; NSCLC, non–small cell lung cancer; OS, overall survival; TPS, tumour proportion score.

1. European Medicines Agency. European public assessment report: Keytruda. Available at: https://www.ema.europa.eu/en/documents/overview/keytruda-epar-medicine-overview_en.pdf Accessed April 2024. **2.** KEYTRUDA Summary of Product Characteristics. Great Britain. Available at: https://www.medicines.org.uk/emc/product/2498 Accessed: April 2024. **3.** 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: April 2024.

KEYNOTE-091 safety profile (as-treated population)[1,2]

The adverse event profile observed with KEYTRUDA was similar to that in previous studies of KEYTRUDA monotherapy, including of locally advanced or metastatic NSCLC and of adjuvant therapy for melanoma and renal-cell carcinoma.[1]

The most common adverse events (occurring in ≥15% of patients) of any grade in both KEYTRUDA and placebo group*[2]

	KEYTRUDA group (n=580)	Placebo group (n=581)
Any event n (%)	556 (95.9%)	529 (91.0%)
Increased bodyweight	132 (22.8%)	168 (28.9%)
Pruritis	125 (21.6%)	74 (12.7%)
Hypothyroidism	120 (20.7%)	27 (4.6%)
Arthralgia	107 (18.4%)	72 (12.4%)
Diarrhoea	106 (18.3%)	83 (14.3%)
Fatigue	96 (16.6%)	89 (15.3%)
Cough	87 (15.0%)	98 (16.9%)

Adapted from Besse B, *et al.* 2023[2]

Adverse events of any grade and cause:[2]
95.9% of KEYTRUDA patients (556/580)
91.0% of placebo patients (529/581)

Adverse events of ≥Grade 3:[2]
34.1% of KEYTRUDA patients (198/580)
25.8% of placebo patients (150/581)

The 4 doses were 2 mg/kg bodyweight every 3 weeks, 200 mg every 3 weeks, or 10 mg/kg bodyweight every 2 or 3 weeks.
*IA3 data set. At time of final DFS analysis. Data cut-off date: 24 January 2023.
DFS, disease-free survival; IA, interim analysis; NSCLC, non–small cell lung cancer.
1. O'Brien M, *et al. Lancet Oncol* 2022;23:1274–1286. **2.** Besse B. Adjuvant pembrolizumab versus placebo for early-stage NSCLC after resection and optional chemotherapy: updated results from PEARLS/KEYNOTE-091. ESMO Immuno-oncology. 6–8 December 2023. Geneva, Switzerland.

KEYNOTE-091: safety profile (as-treated population)[1,2]

Median follow-up: 37.4 months.
Data cut-off date: 20 September 2021.

	Pembrolizumab group (n=580)				Placebo group (n=581)			
	Grade 1-2	Grade 3	Grade 4	Grade 5	Grade 1-2	Grade 3	Grade 4	Grade 5
Any event	358 (62%)	166 (29%)	21 (4%)	11 (2%)	379 (65%)	130 (22%)	14 (2%)	6 (1%)
Increased bodyweight	127 (22%)	6 (1%)	0	0	159 (27%)	9 (2%)	0	0
Pruritus	124 (21%)	1 (<1%)	0	0	72 (12%)	2 (<1%)	0	0
Hypothyroidism	119 (21%)	1 (<1%)	0	0	27 (5%)	0	0	0
Arthralgia	104 (18%)	4 (1%)	0	0	74 (13%)	1 (<1%)	0	0
Diarrhoea	99 (17%)	7 (1%)	0	0	81(14%)	2 (<1%)	0	0
Fatigue	95 (16%)	1 (<1%)	0	0	86(15%)	3 (<1%)	0	0
Cough	86 (15%)	1 (<1%)	0	0	98(17%)	0	0	0
Hypertension	32 (6%)	35 (6%)	0	0	42(7%)	32 (6%)	0	0
Dyspnoea	58 (10%)	8 (1%)	0	0	65(11%)	7 (1%)	0	0
Hyperthyroidism	61 (11%)	1 (<1%)	0	0	17(3%)	0	0	0
Upper respiratory tract infection	53 (9%)	0	0	0	55(9%)	0	0	0
Nausea	51(9%)	1 (<1%)	0	0	37(6%)	0	0	0
Nasopharyngitis	50 (9%)	0	0	0	32 (6%)	0	0	0
Rash	47 (8%)	2 (<1%)	0	0	29(5%)	0	0	0
Increased alanine aminotransferase	42 (7%)	4 (1%)	0	0	31 (5%)	3 (1%)	0	0
Back pain	44 (8%)	1 (<1%)	0	0	46 (8%)	0	0	0
Headache	43 (7%)	2 (<1%)	0	0	45 (8%)	1 (<1%)	0	0

Data are n (%).
Adapted from O'Brien M, *et al.* 2022.[1]

Adverse events of any grade and cause:[2]
95.9% of KEYTRUDA patients (556/580)
91.0% of placebo patients (529/581)

Adverse events of ≥Grade 3:[2]
34.1% of KEYTRUDA patients (198/580)
25.8% of placebo patients (150/581)

The 4 doses were 2 mg/kg bodyweight every 3 weeks, 200 mg every 3 weeks, or 10 mg/kg bodyweight every 2 or 3 weeks.
DFS, disease-free survival; IA, interim analysis; NSCLC, non–small cell lung cancer.
1. O'Brien M, *et al. Lancet Oncol* 2022;23:1274–1286. **2.** Besse B. Adjuvant pembrolizumab versus placebo for early-stage NSCLC after resection and optional chemotherapy: updated results from PEARLS/KEYNOTE-091. ESMO Immuno-oncology. 6–8 December 2023. Geneva, Switzerland.

KEYNOTE-091 safety profile (as-treated population)[1,2]

The adverse event profile observed with KEYTRUDA was similar to that in previous studies of KEYTRUDA monotherapy, including of locally advanced or metastatic NSCLC and of adjuvant therapy for melanoma and renal-cell carcinoma.[1]

The most common adverse events (occurring in ≥15% of patients) of any grade in both KEYTRUDA and placebo group*[2]

	Pembrolizumab group (n=580)				Placebo group (n=581)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1-2	Grade 3	Grade 4	Grade 5
Asthenia	41 (7%)	3 (1%)	0	0	29 (5%)	3 (1%)	0	0
Maculopapular rash	40 (7%)	3 (1%)	0	0	20 (3%)	0	0	0
Increased aspartate aminotransferase	39 (7%)	2 (<1%)	0	0	28 (5%)	4 (1%)	0	0
Decreased appetite	40 (7%)	1 (<1%)	0	0	26 (4%)	1 (<1%)	0	0
Decreased bodyweight	39 (7%)	0	0	0	25 (4%)	0	0	0
Increased blood creatinine	38 (7%)	0	0	0	32 (6%)	0	0	0
Myalgia	35 (6%)	2 (<1%)	0	0	15 (3%)	0	0	0
Productive cough	37 (6%)	0	0	0	15 (3%)	0	0	0
Constipation	35 (6%)	0	0	0	41 (7%)	0	0	0
Influenza-like illness	34 (6%)	0	0	0	32 (6%)	0	0	0
Pneumonitis	27 (5%)	5 (1%)	2 (<1%)	0	12 (2%)	4 (1%)	0	0
Pyrexia	31 (5%)	1 (<1%)	0	0	33 (6%)	1 (<1%)	0	0
Dry skin	31 (5%)	0	0	0	21 (4%)	0	0	0
Pain in extremity	18 (3%)	0	0	0	30 (5%)	1 (<1%)	0	0
Paraesthesia	18 (3%)	0	0	0	32 (6%)	0	0	0

Data are n (%).
Adapted from O'Brien M, *et al.* 2022.[1]

The 4 doses were 2 mg/kg bodyweight every 3 weeks, 200 mg every 3 weeks, or 10 mg/kg bodyweight every 2 or 3 weeks.
*IA3 data set. At time of final DFS analysis. Data cut-off date: 24 January 2023.
NSCLC, non–small cell lung cancer.

1. O'Brien M, *et al. Lancet Oncol* 2022;23:1274–1286.

KEYNOTE-091: summary adverse events in ITT

Median follow-up: 37.4 months
Data cut-off date: 20 September 2021

	Pembrolizumab group (n=580)				Placebo group (n=581)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1-2	Grade 3	Grade 4	Grade 5
Any event	180 (31%)	38 (7%)	6 (1%)	2 (<1%)	64 (11%)	11 (2%)	0	0
Hypothyroidism	119 (21%)	1 (<1%)	0	0	27 (5%)	0	0	0
Hyperthyroidism	61 (11%)	1 (<1%)	0	0	17 (3%)	0	0	0
Pneumonitis	32 (6%)	6 (1%)	2 (<1%)	0	13 (2%)	4 (1%)	0	0
Severe skin reactions	5 (1%)	11 (2%)	0	0	2 (<1%)	2 (<1%)	0	0
Colitis	10 (2%)	4 (1%)	0	0	4 (1%)	1(<1%)	0	0
Adrenal insufficiency	6 (1%)	4 (1%)	0	0	0	0	0	0
Hepatitis	1 (<1%)	5 (1%)	4 (<1%)	0	2 (<1%)	2 (<1%)	0	0
Hypophysitis	4 (1%)	3 (1%)	0	0	0	0	0	0
Thyroiditis	6 (1%)	0	0	0	1(<1%)	0	0	0
Infusion reactions	5 (1%)	0	0	0	4 (<1%)	0	0	0
Myocarditis	1 (<1%)	2 (<1%)	0	2 (<1%)	0	1(<1%)	0	0
Nephritis	4 (<1%)	0	0	0	0	0	0	0
Pancreatitis	2 (<1%)	0	0	0	1(<1%)	1(<1%)	0	0
Myositis	1 (<1%)	0	0	0	0	0	0	0
Sarcoidosis	0	1 (<1%)	0	0	0	0	0	0
Type 1 diabetes	0	1 (<1%)	0	0	0	0	0	0
Vasculitis	0	1 (<1%)	0	0	0	0	0	0

Data are n (%). Potentially immune-mediated adverse events and infusion reactions were based on a list of terms prepared by the sponsor and were considered regardless of attribution to trial treatment by the investigator. In addition to the specific preferred terms listed, related terms were included.
Adapted from O'Brien M, *et al.* 2022.[1]

The 4 doses were 2 mg/kg bodyweight every 3 weeks, 200 mg every 3 weeks, or 10 mg/kg bodyweight every 2 or 3 weeks.

1. O'Brien M, *et al. Lancet Oncol* 2022;23:1274–1286.

KEYNOTE-091 safety profile: treatment-related adverse events[1]

Treatment-related adverse events in both KEYTRUDA and placebo group (as-treated population)*[1]

	KEYTRUDA group (n=580)	Placebo group (n=581)
Any event n (%)	436 (75.2%)	305 (52.5%)
Grade ≥3	89 (15.3%)	25 (4.3%)

Adapted from Besse B, *et al.* 2022.[1]

The 4 doses were 2 mg/kg bodyweight every 3 weeks, 200 mg every 3 weeks, or 10 mg/kg bodyweight every 2 or 3 weeks.
*IA3 data set. At time of final DFS analysis. Data cut-off date: 24 January 2023.

1. Besse B. Adjuvant pembrolizumab versus placebo for early-stage NSCLC after resection and optional chemotherapy: updated results from PEARLS/KEYNOTE-091. ESMO Immuno-oncology. 6–8 December 2023. Geneva, Switzerland.

Safety profile: immune-mediated adverse events and infusion reactions*[1]

The most common immune-mediated adverse events and infusion reactions (occurring in ≥1% of patients) of any grade in both KEYTRUDA and placebo group (as-treated population)†[1]

	KEYTRUDA group (n=580)	Placebo group (n=581)
Any event n (%)	227 (39.1%)	76 (13.1%)
Hypothyroidism	120 (20.7%)	27 (4.6%)
Hyperthyroidism	62 (10.7%)	17 (2.9%)
Pneumonitis	40 (6.9%)	17 (2.9%)
Severe skin reactions	16 (2.8%)	4 (0.7%)
Colitis	14 (2.4%)	5 (0.9%)
Adrenal insufficiency	10 (1.7%)	0 (0.0%)
Hepatitis	9 (1.6%)	4 (0.7%)
Hypophysitis	7 (1.2%)	0 (0.0%)
Thyroiditis	6 (1.0%)	1 (0.2%)

Adapted from Besse B, *et al.* 2022.[1]

Immune-mediated adverse events and infusion reactions of any grade and cause:[1]

39.1% of KEYTRUDA patients (227/580)
13.1% of placebo patients (76/581)

Immune-mediated adverse events and infusion reactions of ≥Grade 3:[1]

7.9% of KEYTRUDA patients (46/580)
1.9% of placebo patients (11/581)

The 4 doses were 2 mg/kg bodyweight every 3 weeks, 200 mg every 3 weeks, or 10 mg/kg bodyweight every 2 or 3 weeks.
*Immune-mediated adverse events and infusion reactions were based on a list of preferred terms intended to capture known risks of KEYTRUDA and were considered regardless of attribution to study treatment by the investigator.
†IA3 data set. At time of final DFS analysis. Data cut-off date: 24 January 2023.
1. Besse B. Adjuvant pembrolizumab versus placebo for early-stage NSCLC after resection and optional chemotherapy: updated results from PEARLS/KEYNOTE-091. ESMO Immuno-oncology. 6–8 December 2023. Geneva, Switzerland.

KEYTRUDA as monotherapy safety profile[1,2]

- The safety of KEYTRUDA as a monotherapy has been evaluated in 7631 patients across tumour types and across 4 doses* (median observation time: 8.5 months; range: 1 day to 39 months)
- The most frequent ARs with KEYTRUDA were:
  - Fatigue (31%)
  - Diarrhoea (22%)
  - Nausea (20%)
- The majority of ARs with KEYTRUDA monotherapy were of Grade 1 or 2 severity
  - The most serious of these were immune-mediated ARs and severe infusion-related reactions
- The incidences of immune-mediated ARs with KEYTRUDA were:
  - 37% for all grades; 9% for Grade 3–5 for monotherapy in the adjuvant setting
  - 25% for all grades; 6% for Grade 3–5 in the metastatic setting
- No new immune-mediated ARs were identified in the adjuvant setting

In patients with NSCLC and other tumour types receiving KEYTRUDA as monotherapy in the adjuvant setting (n=2060), the incidence of hypothyroidism was 18.5%; the incidence of hyperthyroidism was 11%.

*The 4 doses were 2 mg/kg bodyweight every 3 weeks, 200 mg every 3 weeks, or 10 mg/kg bodyweight every 2 or 3 weeks.
AR, adverse reaction; NSCLC, non–small cell lung cancer.
1. KEYTRUDA Summary of Product Characteristics. Great Britain. Available at: https://www.medicines.org.uk/emc/product/2498 Accessed: April 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: April 2024.

KEYNOTE-091: summary

Efficacy

- At the final analysis for DFS (median follow-up time of 46.7 months), in patients with NSCLC who are at high risk of recurrence following complete resection and platinum-based chemotherapy, regardless of PD-L1 expression, KEYTRUDA demonstrated a clinically meaningful improvement in DFS* vs placebo[1,2]
  - **In the group of patients that received adjuvant chemotherapy there was a 24% reduction in risk of disease recurrence or death with KEYTRUDA vs placebo** (HR: 0.76; 95% CI: 0.64–0.91)†
- In the group of patients that received adjuvant chemotherapy a median DFS of nearly 4.5 years (53.8 months; 95% CI: 46.2–70.4) was seen with KEYTRUDA vs nearly 3.4 years with placebo (40.5 months; 95% CI: 32.9–47.4)
- OS results were not yet mature, with 58% of prespecified events in the overall population
  - An exploratory analysis of OS suggested a trend in favour of pembrolizumab compared to placebo with a HR of 0.79 (95% CI: 0.62–1.01) in patients who received adjuvant chemotherapy

Safety[1,2]

- In KEYNOTE-091, no new immune-related adverse reactions were identified with KEYTRUDA in the adjuvant setting
- As monotherapy for NSCLC, pneumonitis occurred in 206 (6.1%), including Grade 2, 3, 4, or 5 cases in 92 (2.7%), 56 (1.7%), 16 (0.5%) and 9 (0.3%), respectively
- The safety of KEYTRUDA as monotherapy has been evaluated in 7,631 patients across tumour types in clinical studies. The most frequent adverse reactions with KEYTRUDA were fatigue (31%), diarrhoea (22%), and nausea (20%)

KEYTRUDA is licensed for use as a monotherapy for the adjuvant treatment of adults with NSCLC who are at high risk of recurrence following complete resection and platinum-based chemotherapy. The results of the ITT population are presented as this is the primary endpoint of the study. It allows the results in the licensed population (a subgroup of the ITT population) to be viewed in context of the primary endpoint.[1–3]

*Investigator-assessed DFS was defined as the time between the date of randomisation and the date of first recurrence (local/regional recurrence, distant metastasis), a second malignancy, or death, whichever occurred first.
†HR based on the multivariate Cox regression model.
CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; NSCLC, non–small cell lung cancer; OS, overall survival; PD-L1, programmed death-ligand 1.
1. KEYTRUDA Summary of Product Characteristics. Great Britain. Available at: https://www.medicines.org.uk/emc/product/2498 Accessed: April 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: April 2024. **3.** Besse B. Adjuvant pembrolizumab versus placebo for early-stage NSCLC after resection and optional chemotherapy: updated results from PEARLS/KEYNOTE-091. ESMO Immuno-oncology. 6–8 December 2023. Geneva, Switzerland.

KEYTRUDA offers flexibility of dosing[1,2]

Administered as an IV infusion

Over 30 minutes

200 mg Q3W or 400 mg Q6W

The 200 mg Q3W regimen has been assessed in Phase I and II registration studies across a multitude of indications of KEYTRUDA. 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, once every 3 weeks; Q6W, once every 6 weeks.

1. KEYTRUDA Summary of Product Characteristics. Great Britain. Available at: https://www.medicines.org.uk/emc/product/2498 Accessed: April 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: April 2024.