Immunotherapy for early-stage, resectable NSCLC: From clinical trial data to guidelines

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Pivotal and recent data on neoadjuvant immunotherapy for patients with NSCLC: How data are changing the approach to surgery

Dr Heather Wakelee
Professor of Medicine,
Stanford University School of Medicine,
Stanford, CA, USA

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What is the rationale for neoadjuvant immunotherapy in patients with resectable, early-stage NSCLC?

Immunotherapy in the neoadjuvant setting

Mode of action

Induction of extensive and strong T cell response

- Re-expansion of reinvigorated cytotoxic CD8+ T cells that can kill the existing tumour, recirculate into the blood and re-expand
- Release of new tumour antigens, which are presented by APCs to prime new T cell responses
- Following resection of the primary tumour, tumour-specific CD8+ T cells have an increased T cell:tumour ratio, which could result in the destruction of the remaining tumour tissue
- After tumour clearance, a stable pool of tumour-specific CD8+ T cells may remain, potentially for the rest of life (as shown in murine models)

APC, antigen-presenting cell.

Shao L, Lou G. *J Thorac Dis.* 2022;14:3565–74.

What pivotal data support the use of neoadjuvant immunotherapy in patients with resectable, early-stage NSCLC?

Neoadjuvant immunotherapy: Phase III data

CheckMate 816 (NCT02998528)

Neoadjuvant nivolumab plus chemotherapy had a significant benefit over chemotherapy alone with respect to EFS and PCR and had no adverse effect on surgical feasibility or surgical outcomes

Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer

- Stage IB-IIIA resectable NSCLC
- 1:1 randomization
- Nivolumab (360 mg) + Pt-ChT vs Pt-ChT alone
- Q3W for 3 weeks before surgery
- Adjuvant Pt-ChT

	Nivolumab + Pt-ChT n=179	Pt-ChT alone n=179
mEFS (months)	31.6	20.8
PCR (%)	24.0	2.2

Magnitude of benefit:

- Greater in patients with stage IIIA disease than in those with stage IB or II disease
- Greater in patients with tumour PD-L1 expression ≥1% than <1%

The addition of nivolumab to neoadjuvant chemotherapy did not increase the incidence of adverse events

Grade 3 or 4 TRAEs:

- **33.5%** of patients in the **Nivo + Pt-ChT** group
- **36.9%** of patients in the **Pt-ChT alone** group

ChT, chemotherapy; EFS, event-free survival; mEFS, median EFS; NSCLC, non-small cell lung cancer; PCR, pathological complete response; PD-L1, programmed death-ligand 1; Pt, platinum; Q3W, every three weeks; TRAE, treatment-related adverse event.

Forde PM, et al. *N Engl J Med.* 2022;386:1973–85.

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Neoadjuvant immunotherapy: Phase III data

CheckMate 816 (NCT02998528): 4-year update

- **Neoadjuvant nivolumab plus chemotherapy sustained EFS and OS separation vs chemotherapy over time and demonstrated the long-term survival benefit of having PCR in patients with resectable NSCLC**
- **An OS benefit was seen with nivolumab plus chemotherapy regardless of Pt backbone or extent of surgical resection**
- **Pre-surgical ctDNA clearance was prognostic for OS**

Neoadjuvant nivolumab plus chemotherapy in resectable NSCLC

	Nivolumab + Pt-ChT n=179	Pt-ChT alone n=179
mEFS (months)	43.8	18.4
4-year EFS rate	49%	38%
mOS (months)	Not reached	Not reached
4-year OS rate	71%	58%

No new safety signals were observed at this update

Grade 3–4 TRAEs:

- **36%** of patients in the **Nivolumab + Pt-ChT** group
- **38%** of patients in the **Pt-ChT alone** group

ChT, chemotherapy; ctDNA, circulating tumour DNA; EFS, event-free survival; mEFS, median EFS; mOS, median OS; OS, overall survival; NSCLC, non-small cell lung cancer; PCR, pathological complete response; Pt, platinum; TRAE, treatment-related adverse event.

Spicer JD, et al. Presented at: ASCO Annual Meeting, Chicago, Il, USA. 31 May–4 June 2024. Abstr. LBA8010.

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How have these data been translated into treatment recommendations and guidelines?

NCCN and ESMO recommendations and guidelines for neoadjuvant immunotherapy

NCCN guidelines (2024)[1]

- All patients should be evaluated for preoperative therapy, with strong consideration for nivolumab or pembrolizumab + chemotherapy for those patients with tumours ≥4 cm or node positive and no contraindications to ICIs
- Neoadjuvant therapy should NOT be used to attempt to induce resectability in patients who do not already meet criteria for resectability on initial evaluation
- Test for PD-L1 status, EGFR mutations, and ALK rearrangements (stages IB–IIIA, IIIB [T3, N2]). PD-L1 status can be incorporated with other clinical factors to determine patients who may benefit from induction ChT and IO

ESMO guidelines (2021)[2]

- In stage IB-IIIA NSCLC, the immune strategy in the (neo)adjuvant setting using ICIs ± ChT is not yet standard

ChT, chemotherapy; ESMO, European Society for Medical Oncology; ICI, immune checkpoint inhibitor; IO, immunotherapy; NCCN, National Comprehensive Cancer Network; NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1.

1. NCCN. Clinical Practice Guidelines in Oncology 2024. Non-small cell lung cancer. Version 6.2024. Available at: www.nccn.org/professionals/physician_gls/pdf/nscl.pdf (accessed 20 June 2024); 2. Remon J, et al. *Ann Oncol.* 2021;32:1637–42.

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What does the real-world evidence tell us about neoadjuvant immunotherapy in patients with resectable, early-stage NSCLC?

Real-world evidence of neoadjuvant immunotherapy

Agent(s)	**PD-1 inhibitor* ± chemotherapy[1]**	**Pembrolizumab or nivolumab + chemotherapy[2]**	**Nivolumab + chemotherapy[3]**	**PD-1 inhibitor† + chemotherapy[4]**
Comparator(s)	**Chemotherapy alone**	**None**	**None**	**Chemotherapy alone**
Study	**Open-label observational two-arm clinical study**	**Real-world observational study**	**Real-world retrospective study**	**Real-world cohort study**
Population	Resectable stage I–III NSCLC (N=51)	Locally advanced NSCLC, including T3–4 + N2 diseases of stage IIIB (N=76)	Locally advanced stage IIIA–IIIB NSCLC (N=46)	Resectable stage III NSCLC (N=59)
Efficacy	Immunotherapy: **41.9% MPR** Chemotherapy alone: **15.0% MPR**	**64% MPR** PEM: 71% MPR (30/42) NIVO: 56% MPR (19/34)	**17.4 % MPR** (8/46) **52.2% PCR** (24/46)	Immunotherapy: **65.3% MPR** (17/26) Chemotherapy alone: **15.1% MPR** (5/33)

Direct comparisons between studies should not be made due to differences in design.

*PD-1 inhibitors included pembrolizumab, nivolumab, sintilimab, and tislelizumab. †PD-1 inhibitors included pembrolizumab, tislelizumab, sintilimab, camrelizumab, and nivolumab.

NIVO, nivolumab; MPR, major pathological response; NSCLC, non-small cell lung cancer; PCR, pathological complete response; PD-1, programmed cell death protein 1; PEM, pembrolizumab.

1. Shen J, et al. *Front Immunol.* 2023;14:1268251; 2. Wu J, et al. *Lung Cancer.* 2022;165:115–23; 3. Zhai H, et al. *Cancer Manag Res.* 2022;14:515–24; 4. Zhou S, et al. *Front Immunol.* 2023;14:1343504.

What's on the horizon for neoadjuvant immunotherapy use in patients with resectable, early-stage NSCLC?

Adjuvant immunotherapy for patients with NSCLC: Key clinical trial data and insights into post-surgical management

Dr Heather Wakelee
Professor of Medicine,
Stanford University School of Medicine,
Stanford, CA, USA

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What are the key data for adjuvant immunotherapy in patients with resected, early-stage NSCLC?

Adjuvant immunotherapy after adjuvant chemotherapy: Phase III data

	Pembrolizumab[1]	Atezolizumab[2]	IMpower010 ≥5-year follow-up data[3]
Agent			
Comparator(s)	**Placebo**	**Best supportive care***	
Study	**PEARLS/KEYNOTE-091** NCT02504372	**IMpower010** NCT02486718	**IMpower010** **≥5-year follow-up data[3]**
Population	Resected stage IB (T ≥4 cm) to IIIA NSCLC (N=1,010)	Resected stage IB (T ≥4 cm) to IIIA NSCLC (N=1,005)	
Efficacy	Median FU: 37.4 months Pembrolizumab (n=506) **mDFS: 58.7 months** Placebo (n=504) **mDFS: 34.9 months**	Median FU: 32.8 months Atezolizumab (n=507) **mDFS: NE** BSC (n=498) **mDFS: 35.3 months** (stage II–IIIA NSCLC and PD-L1 ≥1%)	Median FU: 65.0 months Atezolizumab (n=248) **mDFS: 68.5 months** BSC (n=228) **mDFS: 37.3 months** (stage II–IIIA NSCLC and PD-L1 ≥1%)

Direct comparisons between trials should not be made due to differences in trial design.

*Included observation and regular scans for disease recurrence.

BSC, best supportive care; DFS, disease-free survival; mDFS, median DFS; NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1.

1. Oselin K, et al. *J Clin Oncol.* 2023;41;8520; 2. Felip E, et al. *Lancet.* 2021;398:1344–57; 3. Wakelee HA, et al. Presented at: ASCO Annual Meeting, Chicago, Il, USA. 31 May–4 June 2024. Abstr. LBA8035.

How have these data impacted the current guidelines for post-surgery treatment of patients with early-stage NSCLC?

NCCN and ESMO recommendations and guidelines for adjuvant immunotherapy (1/2)

NCCN guidelines (2024)

- Atezolizumab as an adjuvant therapy option for eligible patients with completely resected (R0) stage IIB–IIIA, stage IIIB (only T3, N2), or high-risk stage IIA NSCLC and PD-L1 ≥1%, negative for EGFR aberrations, or ALK rearrangements, who have previously received adjuvant ChT
- Pembrolizumab as an adjuvant therapy option following adjuvant ChT for eligible patients with completely resected early-stage NSCLC
- Adjuvant ChT (category 1) followed by atezolizumab, pembrolizumab, or osimertinib for eligible patients with the appropriate biomarkers, negative surgical margins, and stage IIB disease, including 1) T1abc–T2a, N1; 2) T2b, N1; or 3) T3, N0 disease

ChT, chemotherapy; ESMO, European Society for Medical Oncology; NCCN, National Comprehensive Cancer Network; NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1.

NCCN. Clinical Practice Guidelines in Oncology 2024. Non-small cell lung cancer. Version 6.2024. Available at: www.nccn.org/professionals/physician_gls/pdf/nscl.pdf (accessed 20 June 2024).

NCCN and ESMO recommendations and guidelines for adjuvant immunotherapy (2/2)

NCCN guidelines (2024)[1]

- For stage IIIA superior sulcus tumours (T4 extension, N0–1) that become resectable after preoperative concurrent chemoradiation, resection followed by ChT is recommended and then atezolizumab, pembrolizumab, or osimertinib, depending on biomarker status

ESMO guidelines (2021)[2]

- In stage IB–IIIA NSCLC, the immune strategy in the (neo)adjuvant setting using ICIs ± ChT is not yet standard

ChT, chemotherapy; ESMO, European Society for Medical Oncology; ICI, immune checkpoint inhibitor; NCCN, National Comprehensive Cancer Network; NSCLC, non-small cell lung cancer.

1. NCCN. Clinical Practice Guidelines in Oncology 2024. Non-small cell lung cancer. Version 6.2024. Available at: www.nccn.org/professionals/physician_gls/pdf/nscl.pdf (accessed 20 June 2024); 2. Remon J, et al. *Ann Oncol.* 2021;32:1637–42.

What criteria can help guide the use of adjuvant immunotherapy following resection to optimize outcomes?

Are there any novel adjuvant immunotherapy regimens under investigation that we should be aware of?

Combining pre- and postoperative immunotherapy for patients with NSCLC: Rationale, clinical data and practical applications

Dr Heather Wakelee
Professor of Medicine,
Stanford University School of Medicine,
Stanford, CA, USA

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What is the rationale behind using immunotherapy both before and after surgery in patients with resectable, early-stage NSCLC, and what is the supporting evidence?

Neoadjuvant + adjuvant immunotherapy: Phase III data

	Pembrolizumab + chemotherapy[1]	Nivolumab + chemotherapy[2]	Durvalumab + chemotherapy[3]
Agent(s)			
Comparator(s)	**Placebo + chemotherapy**	**Placebo + chemotherapy**	**Placebo + chemotherapy**
Study	**KEYNOTE-671** NCT03425643	**CheckMate 77T** NCT04025879	**AEGEAN** NCT03800134
Population	Resectable stage II–IIIB NSCLC (N=797)	Resectable stage IIA–IIIB NSCLC (N=461)	Resectable stage II–IIIB NSCLC (N=802)
Efficacy	Pembrolizumab (n=397) **24-month EFS: 62.4%** **24-month OS: 80.9%** **PCR: 18.1%** Placebo (n=400) **24-month EFS: 40.6%** **24-month OS: 77.6%** **PCR: 4.0%** **EFS HR: 0.58 (95% CI, 0.46–0.72; p<0.001)**	Nivolumab (n=229) **18-month EFS: 70.2%** **PCR: 25.3%** Placebo (n=232) **18-month EFS: 50.0%** **PCR: 4.7%** **EFS HR: 0.58 (97.36% CI, 0.42–0.81; p<0.001)**	Durvalumab (n=400) **24-month EFS: 63.3%** **PCR: 17.2%*** Placebo (n=402) **24-month EFS: 52.4%** **PCR: 4.3%*** **EFS HR: 0.68 (95% CI, 0.53–0.88; p<0.004)**

Direct comparisons between trials should not be made due to differences in trial design.

*Interim analysis of data from 402 patients.

EFS, event-free survival; NSCLC, non-small cell lung cancer; OS, overall survival; PCR, pathological complete response.

1. Wakelee H, et al. *N Engl J Med.* 2023;389:491–503; 2. Cascone T, et al. *N Engl J Med.* 2024;390:1756–69; 3. Heymach JV, et al. *N Engl J Med.* 2023;389:1672–84.

What practical guidance can you give us in terms of using perioperative immunotherapy in clinical practice?

What ongoing clinical trials of perioperative immunotherapy regimens might impact future clinical practice for our patients with resectable, early-stage NSCLC?

Neoadjuvant + adjuvant immunotherapy: Phase III data

Agent(s)	**Tislelizumab + chemotherapy[1]**	**Toripalimab + chemotherapy[2]**
Comparator(s)	**Placebo + chemotherapy**	**Placebo + chemotherapy**
Study	**RATIONALE-315** NCT04379635	**Neotorch** NCT04158440
Population	Stage II–IIIA resectable NSCLC (N=453)	Stage II–III resectable NSCLC (N=501)
Efficacy	**mEFS: Not reached for either arm** **mOS: Not reached for either arm** **A statistically significant difference in EFS** (HR [95% CI], 0.56 [0.40–0.79]; p=0.0003) **favouring tislelizumab** **OS benefit trend** (HR [95% CI], 0.62 [0.39–0.98]; p=0.0193) **favouring tislelizumab**	Toripalimab group (n=202) **mPFS: Not estimable** **MPR: 48.5%** Placebo group (n=202) **mPFS: 15.1 months** **MPR: 8.4%**

Direct comparisons between trials should not be made due to differences in trial design.

CI, confidence interval; EFS, event-free survival; HR, hazard ration; mEFS, median EFS; mOS, median OS; mPFS, median progression-free survival; MPR, major pathological response; NSCLC, non-small cell lung cancer;
OS, overall survival.

1. Yue D, et al. *Ann Oncol.* 2024;35:332–3; 2. Lu S, et al. *JAMA*. 2024;331:201–11.

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