

# **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

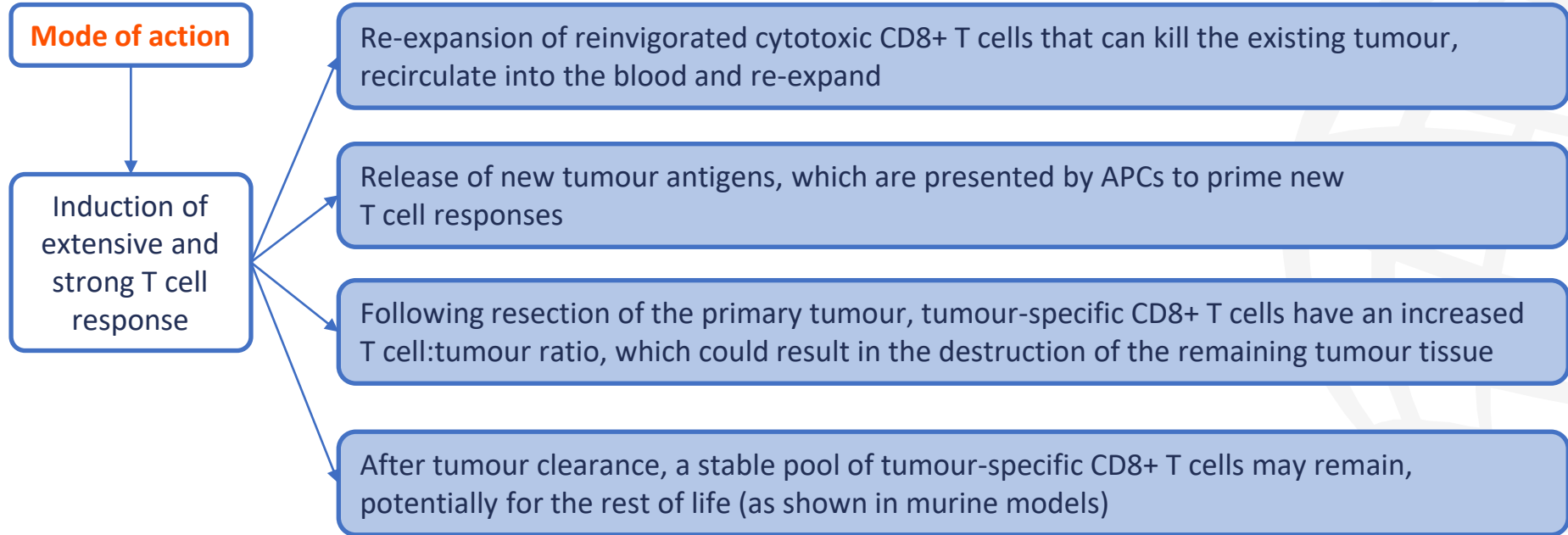
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**What is the rationale for  
neoadjuvant immunotherapy  
in patients with resectable,  
early-stage NSCLC?**

# Immunotherapy in the neoadjuvant setting



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**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  $\geq 1\%$  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.

# 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.





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

# NCCN and ESMO recommendations and guidelines for neoadjuvant immunotherapy



## NCCN guidelines (2024)<sup>1</sup>

- All patients should be evaluated for preoperative therapy, with strong consideration for nivolumab or pembrolizumab + chemotherapy for those patients with tumours  $\geq 4$  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

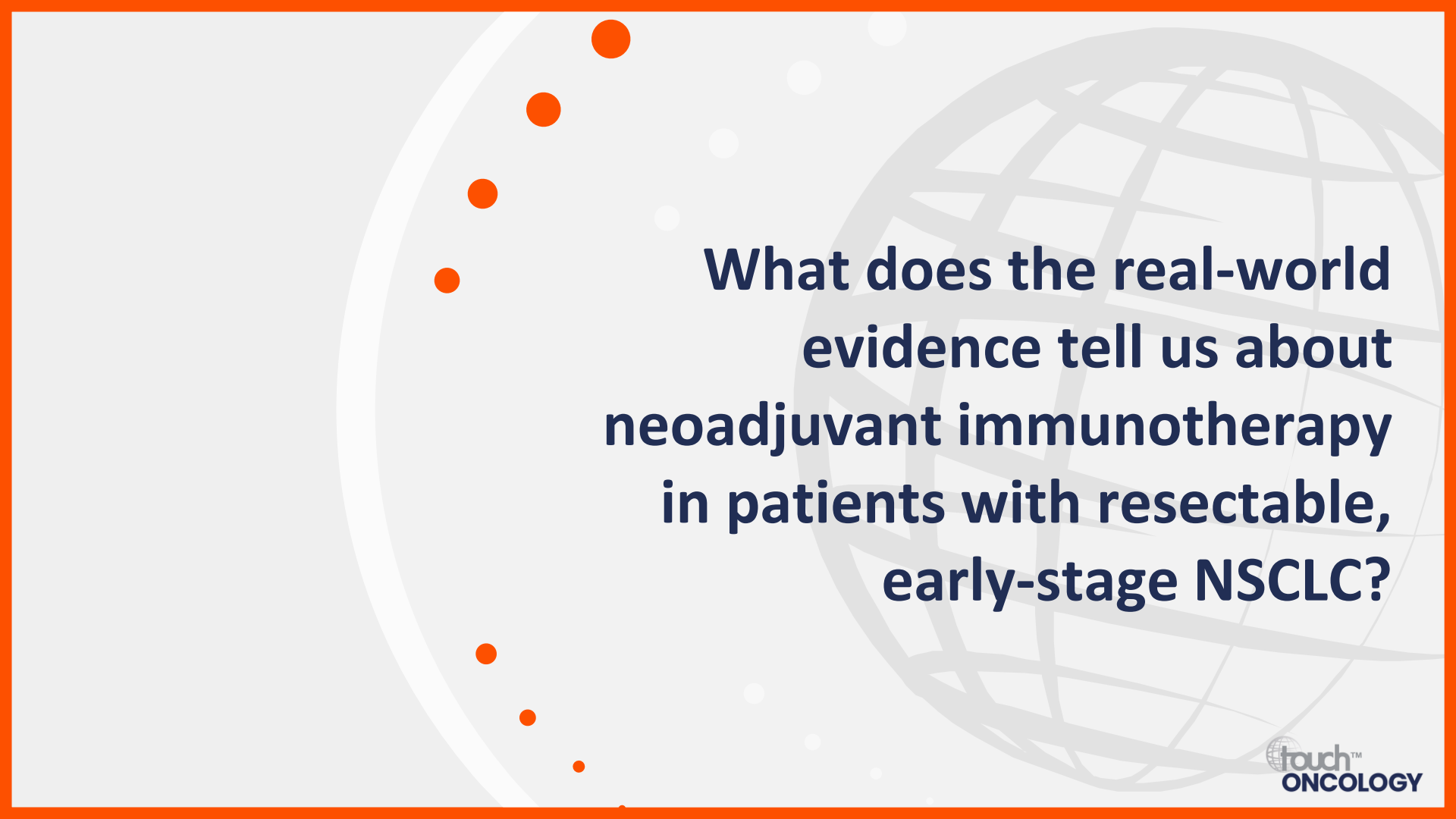


## ESMO guidelines (2021)<sup>2</sup>

- In stage IB–IIIA NSCLC, the immune strategy in the (neo)adjuvant setting using ICIs  $\pm$  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](http://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 does the real-world  
evidence tell us about  
neoadjuvant immunotherapy  
in patients with resectable,  
early-stage NSCLC?**

# Real-world evidence of neoadjuvant immunotherapy

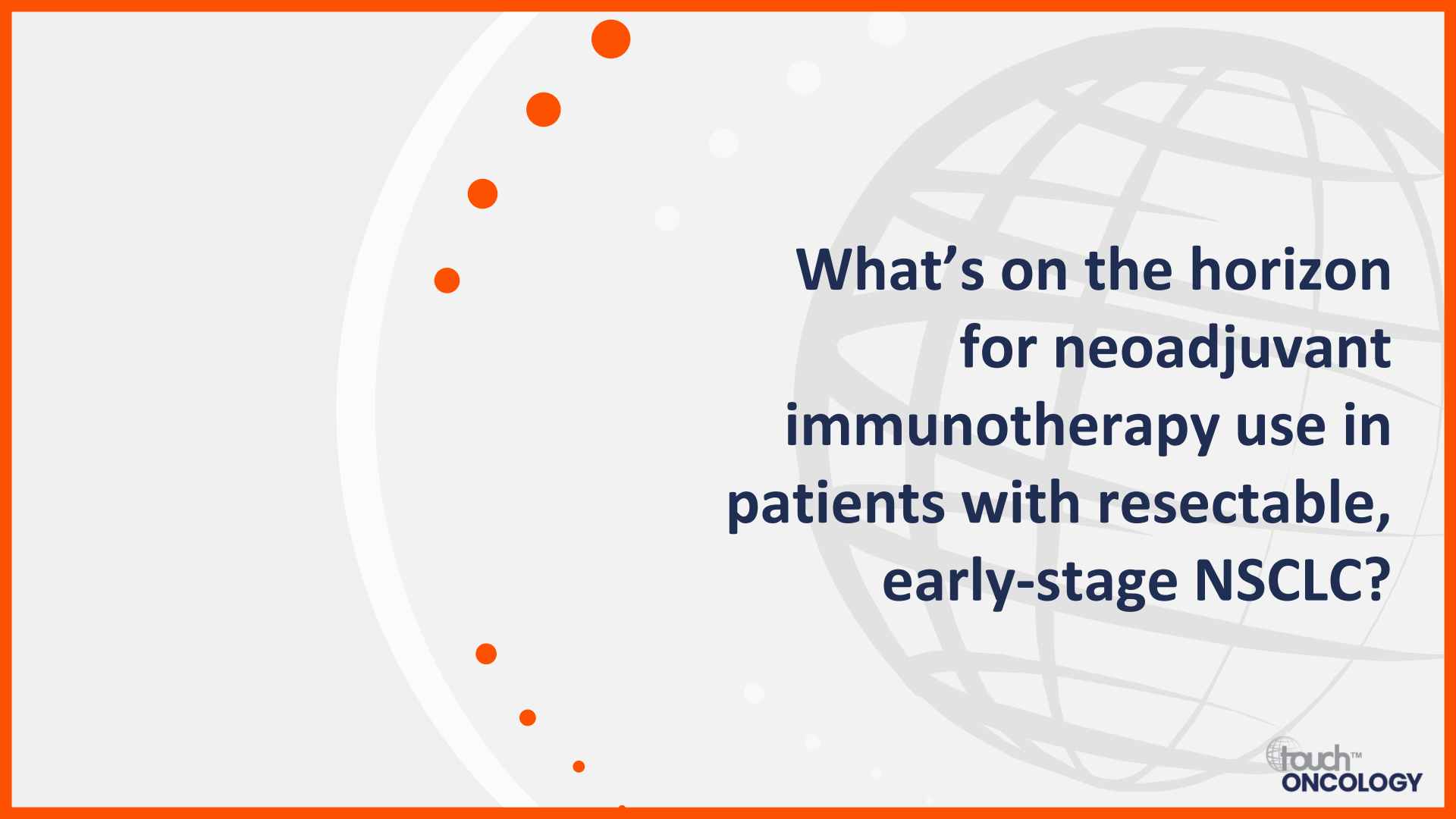
Agent(s)	PD-1 inhibitor* ± chemotherapy <sup>1</sup>	Pembrolizumab or nivolumab + chemotherapy <sup>2</sup>	Nivolumab + chemotherapy <sup>3</sup>	PD-1 inhibitor <sup>†</sup> + chemotherapy <sup>4</sup>
Comparator(s)	Chemotherapy alone	None	None	Chemotherapy alone
Study	Open-label observational two-arm 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: <b>41.9% MPR</b> Chemotherapy alone: <b>15.0% MPR</b>	<b>64% MPR</b> PEM: 71% MPR (30/42) NIVO: 56% MPR (19/34)	<b>17.4 % MPR (8/46)</b> <b>52.2% PCR (24/46)</b>	Immunotherapy: <b>65.3% MPR (17/26)</b> Chemotherapy alone: <b>15.1% MPR (5/33)</b>

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.



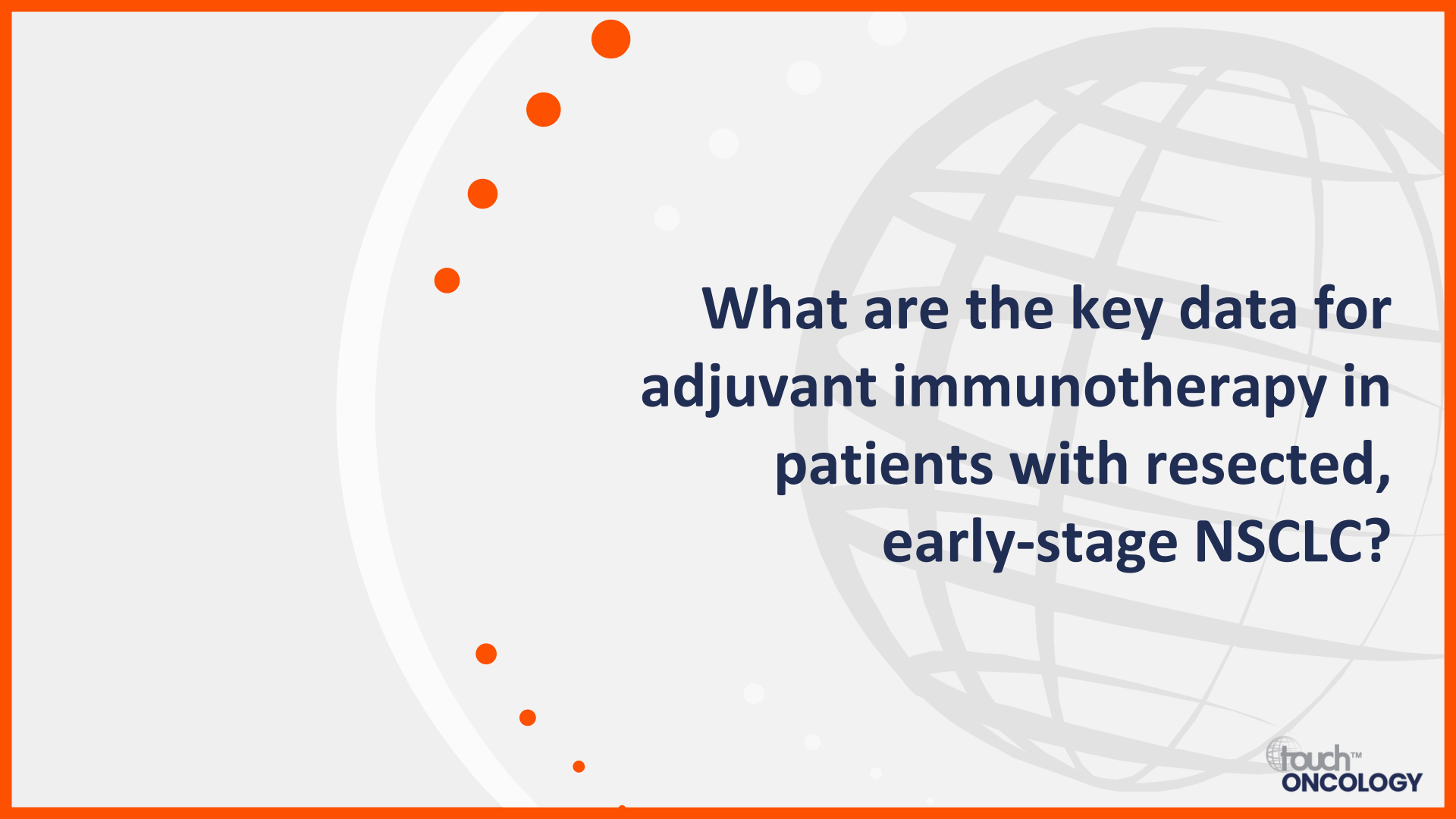
**What's on the horizon  
for neoadjuvant  
immunotherapy use in  
patients with resectable,  
early-stage NSCLC?**

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

## Dr Heather Wakelee






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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

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

- 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)<sup>2</sup>

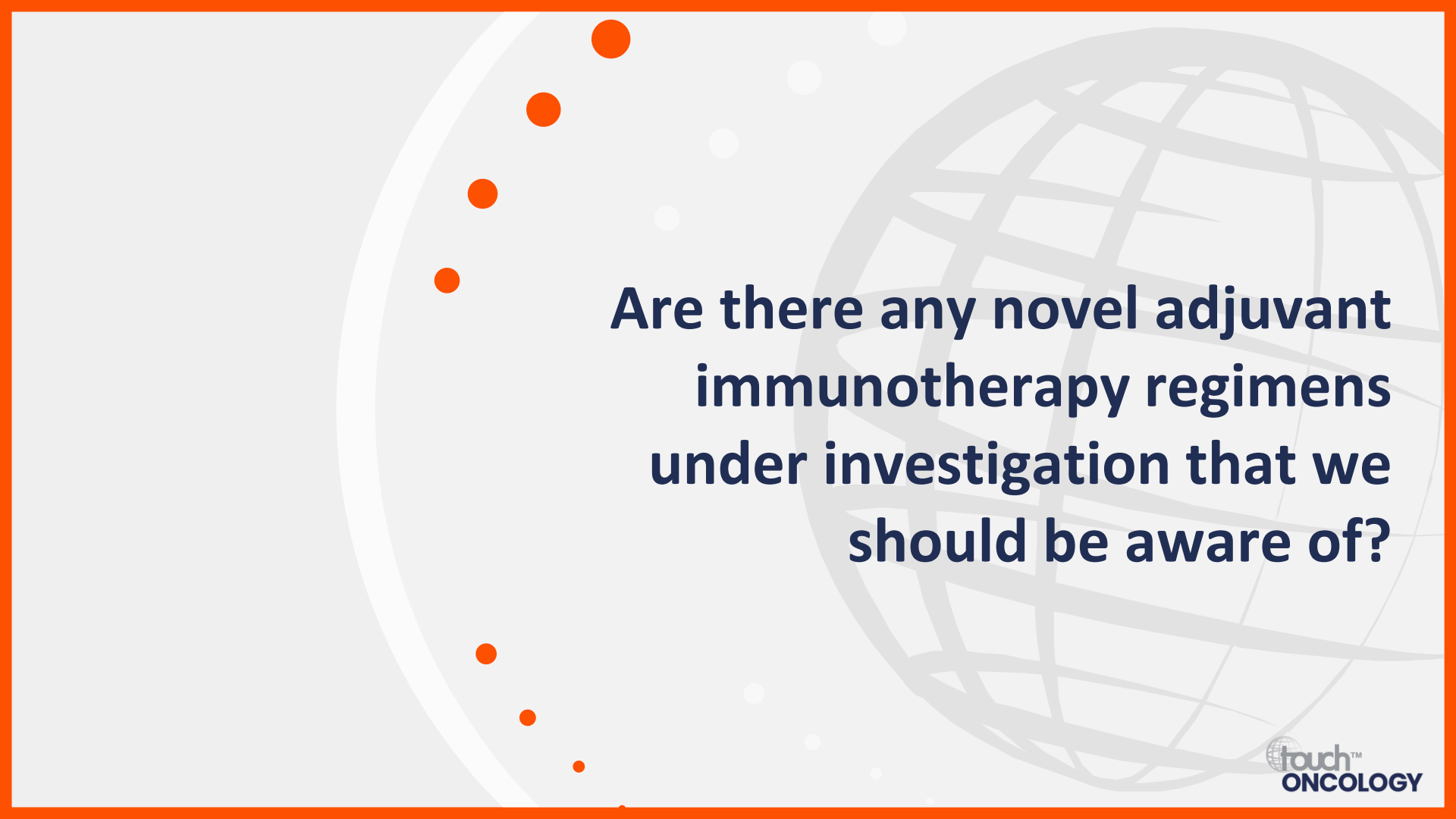
- In stage IB–IIIA NSCLC, the immune strategy in the (neo)adjuvant setting using ICIs ± ChT is not yet standard

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](http://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

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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

Agent(s)	Pembrolizumab + chemotherapy <sup>1</sup>	Nivolumab + chemotherapy <sup>2</sup>	Durvalumab + chemotherapy <sup>3</sup>
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?**

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**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

<b>Agent(s)</b> 	Tislelizumab + chemotherapy <sup>1</sup>	Toripalimab + chemotherapy <sup>2</sup>
<b>Comparator(s)</b> 	Placebo + chemotherapy	Placebo + chemotherapy
<b>Study</b> 	RATIONALE-315 NCT04379635	Neotorch NCT04158440
<b>Population</b> 	Stage II–IIIA resectable NSCLC (N=453)	Stage II–III resectable NSCLC (N=501)
<b>Efficacy</b> 	<p>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</p>	<p>Toripalimab group (n=202)                      mPFS: Not estimable                      MPR: 48.5%                      Placebo group (n=202)                      mPFS: 15.1 months                      MPR: 8.4%</p>

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

CI, confidence interval; EFS, event-free survival; HR, hazard ratio; 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.