Current and future considerations for the use of immune checkpoint inhibitors in non-small cell lung cancer

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Spotlight on immunotherapy for the treatment of early-stage NSCLC

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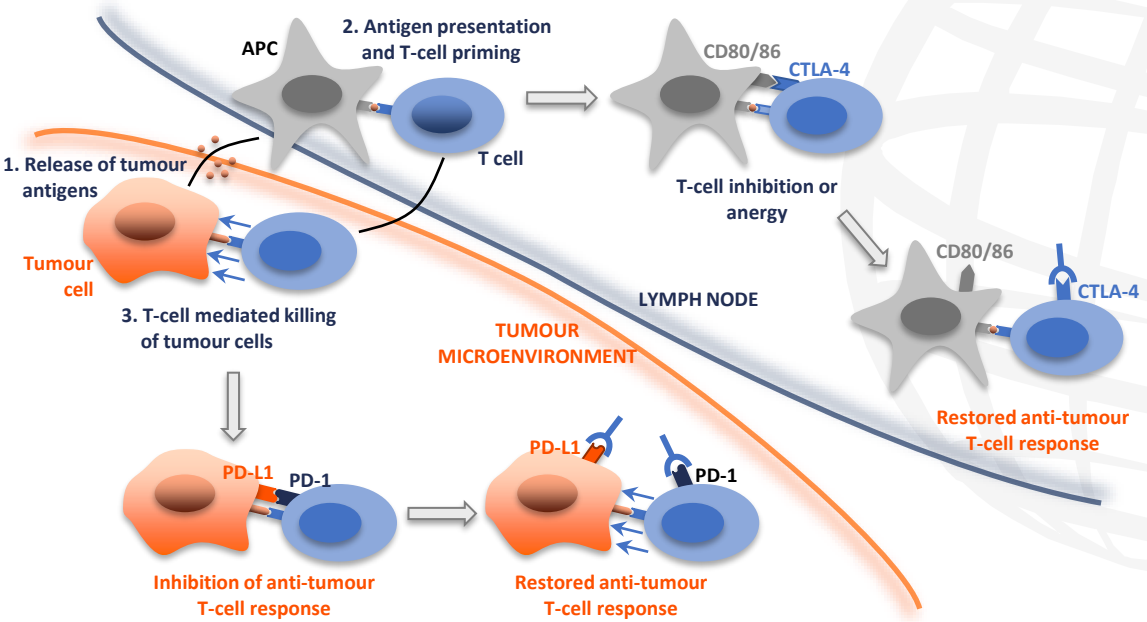
Immune checkpoints and anti-tumour immunity

PD-L1, PD-1 and CTLA-4[1,2]

- **PD-1 and CTLA-4** are immunoregulatory receptors expressed on **T lymphocytes**[2]
- Engagement of **CTLA-4 by CD80/86** and of **PD-1 by PD-L1, suppresses T-cell responses** to prevent immune-mediated tissue damage[2]

! The PD-1/PD-L1 and CTLA-4 pathways contribute to tumour immune escape and can be targeted by immunotherapy[1,2]

Tumour immune escape and checkpoint inhibitors[1,2]



APC, antigen-presenting cell; CD, cluster of differentiation; CTLA-4, cytotoxic T-lymphocyte antigen 4; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

1. Kim HC, et al. *Tuberc Respir Dis (Seoul).* 2020;83:14–9; 2. Seidel JA, et al. *Front Oncol.* 2018;8:1–14.

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Checkpoint inhibitors for early-stage NSCLC

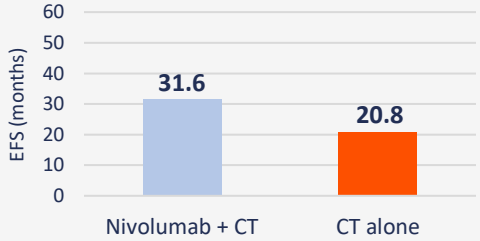
Neoadjuvant treatment

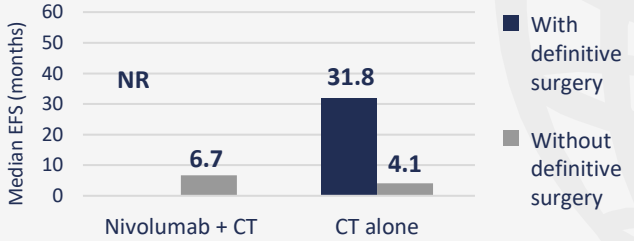
Nivolumab

CheckMate 816[1,2]

Resectable stage IB to IIIA NSCLC (N=358)

Randomized 1:1 to neoadjuvant **nivolumab** + CT or CT alone





Nivolumab + CT demonstrated improved EFS vs CT alone[1]

Nivolumab + CT demonstrated long-term EFS benefit vs CT alone in patients who had definitive surgery[2]

CT, chemotherapy; EFS, event-free survival; NR, not reached; NSCLC, non-small cell lung cancer.

1. Forde PM, et al. *N Engl J Med.* 2022;386:1973–85; 2. Spicer J, et al. Presented at: ASCO 2023, Chicago, IL, USA. 2–6 June 2023. Abstr 8521.

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Checkpoint inhibitors for early-stage NSCLC

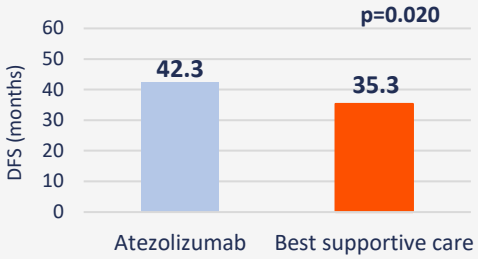
Adjuvant treatment

Atezolizumab

IMpower010[1]

Resected stage IB to IIIA NSCLC (N=1,005)

Randomized 1:1 to **atezolizumab** or best supportive care



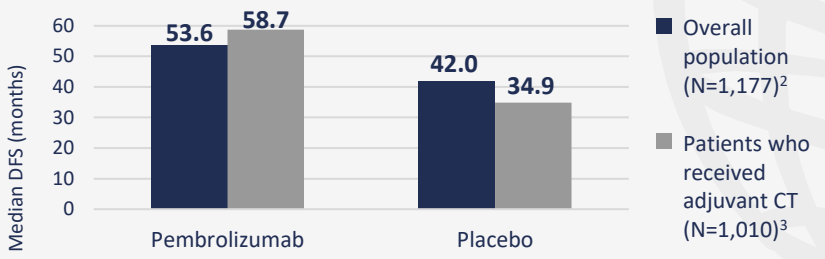
Atezolizumab showed higher efficacy with similar AE rates vs best supportive care

Pembrolizumab

PEARLS/KEYNOTE-091[2,3]

Resected stage IB, II or IIIA NSCLC

Randomized 1:1 to **pembrolizumab** or placebo



Pembrolizumab treatment demonstrated higher DFS vs placebo in all patients[2] and in the subgroup who received prior adjuvant CT[3]

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

AE, adverse event; CT, chemotherapy; DFS, disease-free survival; NSCLC, non-small cell lung cancer.

1. Felip E, et al. *Lancet.* 2021;398:1344–57; 2. O'Brien M, et al. *Lancet Oncol.* 2022;23:1274–86; 3. Oselin K, et al. Presented at: ASCO 2023, Chicago, IL, USA. 2–6 June 2023. Abstr 8520.

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Key ongoing phase III trials in early-stage NSCLC

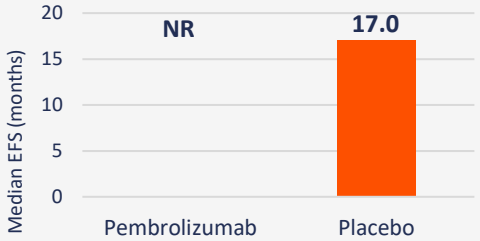
Neoadjuvant and adjuvant treatment

Pembrolizumab

KEYNOTE-671

Resectable, stage II, IIIA and IIIB NSCLC (N=797)

Randomized 1:1 to neoadjuvant CT + **pembrolizumab** followed by resection + **pembrolizumab** or neoadjuvant CT **+ placebo** followed by resection + **placebo**



EFS was significantly improved with neoadjuvant pembrolizumab + CT followed by resection and adjuvant pembrolizumab vs neoadjuvant placebo + CT followed by resection and adjuvant placebo[1]

CT, chemotherapy; EFS, event-free survival; NR, not reached; NSCLC, non-small cell lung cancer.

Wakelee HA, et al. *J Clin Oncol.* 2023;41(Suppl.):Abstr LBA100.

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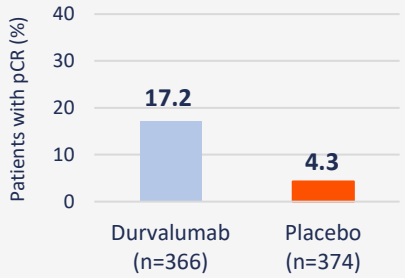
Key ongoing phase III trials in early-stage NSCLC

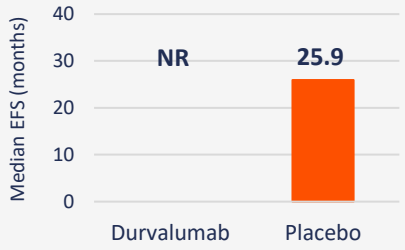
Neoadjuvant and adjuvant treatment

Durvalumab

AEGEAN[1]

- Resectable stage II, IIIA and IIIB NSCLC
- Randomized 1:1 to neoadjuvant CT + **durvalumab** or placebo
- pCR and EFS





Atezolizumab

IMpower030[2]

- Resectable stage II, IIIA and IIIB NSCLC
- Randomized 1:1 to **atezolizumab** + CT vs placebo + CT
- EFS

Nivolumab

CheckMate-77T[3]

- Resectable stage II and III NSCLC
- Randomized 1:1 to neoadjuvant CT + **nivolumab** or placebo
- EFS

CT, chemotherapy; EFS, event-free survival; NR, not reached; NSCLC, non-small cell lung cancer; pCR, pathological complete response.

1. Heymach JV, et al. *Cancer Res.* 2023;83(Suppl.):CT005; 2. ClinicalTrials.gov. NCT03456063. Available at: www.clinicaltrials.gov/ct2/show/NCT03456063 (accessed 7 June 2023);
3. ClinicalTrials.gov. NCT04025879. Available at: www.clinicaltrials.gov/ct2/show/NCT04025879 (accessed 7 June 2023).

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Examining the role of biomarkers in NSCLC

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Current recommendations for biomarker testing

Clinical presentation*	**Establish histological subtype with adequate tissue for molecular testing**	
Histological subtype	**Adenocarcinoma Large cell NSCLC not otherwise specified**	**Squamous cell carcinoma**
Biomarker testing	**Consider broad, panel-based testing of oncogenic drivers and PD-L1**	**Consider broad, panel-based testing of oncogenic drivers and PD-L1†**

*Stage IVA, advanced or metastatic disease; †molecular testing not recommended by ESMO in squamous cell carcinoma except in never, long-time ex- or light smokers.
ESMO, European Society for Medical Oncology; NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1.
NCCN. Non-small cell lung cancer. V2.2023. Available at: www.nccn.org/professionals/physician_gls/pdf/nscl.pdf (accessed 10 March 2023).

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Guidelines for genetic testing in advanced non-squamous NSCLC

Guidelines recommend **broad, panel-based testing prior to initiation of therapy** for advanced or metastatic NSCLC[1,2]

Recommendations also include testing for **PD-L1 expression**[1,2]

The frequency of testing for *EGFR*, *BRAF*, *NTRK*, *MET*, *RET*, *KRAS*, *ROS1*, *ALK* and *HER2* was reported to be **69–80%** among US-based physicians (N=170)[3]

Genetic alteration	ESMO[1]	NCCN[2]
EGFR mutation	✓*	✓
ALK rearrangement	✓†	✓
ROS1 rearrangement	✓	✓
BRAF mutation	✓	✓
NTRK rearrangement	✓	✗
*NTRK*1/2/3 fusions	✗	✓
KRAS mutation	✗	✓
*MET*ex14 skipping	✗	✓
RET rearrangement	✗	✓
ERBB (*HER2*) mutation	✗	✓

*Mandatory for early and locally advanced NSCLC. †*ALK* fusion status optional for early and locally advanced NSCLC.
ALK, anaplastic lymphoma kinase; BRAF, B-Raf proto-oncogene; EGFR, epidermal growth factor receptor; ERBB2, Erb-B2 receptor tyrosine kinase 2; ESMO, European Society for Medical Oncology; HER2, human epidermal growth factor receptor 2; KRAS, Kirsten rat sarcoma virus proto-oncogene; MET, mesenchymal-epithelial transition; METex14, MET exon 14 skipping; NCCN, National Comprehensive Cancer Network; NSCLC, non-small cell lung cancer; NTRK, neurotrophic tyrosine receptor kinase; PD-L1, programmed death-ligand 1; RET, rearranged during transfection; ROS1, c-ros oncogene 1. 1. ESMO Pocket Guideline. 2022. Available at: http://interactiveguidelines.esmo.org/esmo-web-app/toc/index.php?subjectAreaID=1&loadPdf=1 (accessed June 2023); 2. NCCN. Non-small cell lung cancer. V2.2023. Available at: www.nccn.org/professionals/physician_gls/pdf/nscl.pdf (accessed 7 June 2023); 3. Mileham KF, et al. *Cancer Med.* 2022;11:530–8.

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Key phase III trial data supporting PD-L1 testing in late-stage NSCLC

Late-stage NSCLC

Pembrolizumab

KEYNOTE-042[1]

Locally advanced or metastatic NSCLC without sensitizing *EGFR* or *ALK* genetic alterations, PD-L1 TPS ≥1% (N=1,274)

Randomized 1:1 to **pembrolizumab** or CT

OS significantly longer with pembrolizumab vs CT in all TPS groups

PD-L1 ≥50% HR: 0.69
(95% CI 0.56–0.85, p=0.0003)

PD-L1 ≥20% HR: 0.77
(95% CI 0.64–0.92, p=0.0020)

PD-L1 ≥1% HR: 0.81
(95% CI 0.71–0.93, p=0·0018)

Durvalumab

PACIFIC[2]

Unresectable, stage III NSCLC with no disease progression after ≥2 cycles of Pt-based CRT (N=713)

Randomized 2:1 to **durvalumab** or placebo

Post hoc analysis showed **PFS benefit** with durvalumab across all PD-L1 subgroups

OS benefit across all PD-L1 subgroups except PD-L1 <1%

Durvalumab + tremelimumab

MYSTIC[3]

Untreated stage IV NSCLC without sensitizing *EGFR* or *ALK* genetic alterations (N=1,118)

Randomized 1:1:1 to **durvalumab**, **durvalumab + tremelimumab** or CT

OS benefit at 24 months with durvalumab vs CT

Durvalumab: 38.3%
(95% CI 30.7–45.7)

Durvalumab + tremelimumab: 35.4%
(95% CI 28.1–42.8)

CT: 22.7%
(95% CI 16.5–29.5)

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

ALK, anaplastic lymphoma kinase; CI, confidence interval; CRT, chemoradiotherapy; CT, chemotherapy; EGFR, epidermal growth factor receptor; HR, hazard ratio; NSCLC, non-small cell lung cancer; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; Pt, platinum; TPS; tumour proportion score.

1. Mok TSK, et al. *Lancet.* 2019;393:1819–30; 2. Paz-Ares L, et al. *Ann Oncol.* 2020;31:798–806; 3. Rizvi NA, et al. *JAMA Oncol.* 2020;6:661–74.

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Future of biomarker testing for ICI use

Emerging biomarkers

Tumour mutation burden
May predict PFS and OS in advanced NSCLC[1,2]

DDR gene alterations
Associated with higher immunity and better clinical outcomes in patients with NSCLC treated with ICIs[1,3]

Circulating tumour DNA
May predict OS in patients with metastatic non-squamous NSCLC[1,4]

TP53
Low-load *TP53* mutations can predict PFS benefit in patients with NSCLC treated with PD-1/PD-L1 inhibitors[1,5]

Tumour microenvironment
May help identify patients with NSCLC who will benefit from treatment with ICIs[1,6]

Gut microbiome
Higher diversity of intestinal flora associated with better ICI efficacy[1,7,8]

Peripheral blood biopsy is gaining popularity:[1]

- **Minimally invasive**
- **Contains DNA, RNA and proteins released by tumour tissues**
- **Reflects dynamic changes in the tumour microenvironment**

DDR, damage response and repair; ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung cancer; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival.

1. Pan Y, et al. *Biomarker Res.* 2022;10:9; 2. Alborelli I, et al. *J Pathol.* 2020;250:19–29; 3. Liu J, et al. *J Thorac Oncol.* 2021;16(Suppl.):S893–4; 4. Assaf ZJ, et al. *J Thorac Oncol.* 2021;16(Suppl.):S905–6; 5. Wang S, et al. *J Thorac Oncol.* 2021;16(Suppl.):S1138–9; 6. Ofek E, et al. *J Clin Oncol.* 2021;39(Suppl.):9045; 7. Jin Y, et al. *J Thorac Oncol.* 2019;14:1378–89; Moon J, Moon H. *J Thorac Oncol.* 2021;16(Suppl.):S709–10.

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Emerging immunotherapy combinations and their potential impact on clinical practice

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Novel agents in combination with immunotherapy

Novel agent	Tiragolumab[1]	Tiragolumab[2]	Eftilagimod alpha[3]	Domvanalimab[4]
Combined ICI	+ atezolizumab	+ atezolizumab	+ pembrolizumab	+ zimberelimab
Comparator arm(s)	Placebo + atezolizumab	Placebo + atezolizumab	None	Zimberelimab alone Zimberelimab + etrumadenant
Study	**SKYSCRAPER-01** Phase III NCT04294810	**CITYSCAPE** Phase II NCT03563716	**TACTI-002** Phase II NCT03625323	**ARC-7** Phase II NCT04262856
Population	Untreated metastatic NSCLC, PD-L1 ≥50% (N=534)	CT-naive recurrent or metastatic NSCLC, PD-L1 ≥1% (N=135*)	Untreated metastatic NSCLC unselected for PD-L1 expression (N=114)	Untreated stage IV squamous or non-squamous NSCLC, PD-L1 ≥50% (N=149†)
Efficacy data	PFS: **Not met** OS: Immature	ORR: 31% PFS: 5.4 months	ORR: 37%‡ DCR: 73% RR: 40%§	ORR: 41% mPFS: 12.0 months

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

*Tiragolumab + atezolizumab, n=67; †Domvanalimab + zimberelimab efficacy population, n=44; ‡In 75 patients with minimum follow-up of 6 months as assessed by iRECIST; §Non-squamous pathology.

CT, chemotherapy; DCR, disease control rate; ICI, immune checkpoint inhibitor; mPFS, median PFS; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; RR, response rate.

1. Brazel D, et al. *Lung Cancer (Auckl).* 2023;14:1–9; 2. Cho BC, et al. *Lancet Oncol.* 2022:23:781–92; 3. Felip E, et al. *J Clin Oncol.* 2022;40(Suppl.):9003; 4. Johnson ML, et al. *J Clin Oncol.* 2022;40(Suppl.):397600.

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Ongoing phase III antibody–drug conjugate + immunotherapy trials

Datopotamab deruxtecan + pembrolizumab

TROPION-Lung08[1,2]

- Untreated, unresectable advanced or metastatic NSCLC, PD-L1 ≥50%
- 1:1 **datopotamab deruxtecan + pembrolizumab** or **pembrolizumab alone**
- PFS and OS

Datopotamab deruxtecan + pembrolizumab

TROPION-Lung07[3]

- Untreated, unresectable advanced or metastatic non-squamous NSCLC, PD-L1 <50%
- 1:1:1 **datopotamab deruxtecan + pembrolizumab + Pt** or **datopotamab deruxtecan + pembrolizumab** or **pembrolizumab + pemetrexed + Pt**
- PFS and OS

Datopotamab deruxtecan + durvalumab

AVANZAR[4]

- Untreated, unresectable locally advanced or metastatic NSCLC
- 1:1 **datopotamab deruxtecan + durvalumab + Pt** or **pembrolizumab + Pt**
- PFS and OS, both in the TROP2-positive population

NSCLC, non-small cell lung cancer; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; Pt, platinum; TROP2, trophoblast cell-surface antigen 2.

1. Levy BP, et al. *J Clin Oncol.* 2022;40(Suppl.):TPS3162; 2. ClinicalTrials.gov. NCT05215340. Available at: www.clinicaltrials.gov/ct2/show/NCT05215340 (accessed 7 June 2023); 3. ClinicalTrials.gov. NCT05555732. Available at: www.clinicaltrials.gov/ct2/show/NCT05555732 (accessed 7 June 2023); 4. ClinicalTrials.gov. NCT05687266. Available at: www.clinicaltrials.gov/ct2/show/NCT05687266 (accessed 7 June 2023).

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