A moving target: Assessing the role of EGFR-TKIs in early-stage NSCLC

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What do the latest data tell us about the role of targeted therapy in early-stage NSCLC?
NSCLC surgery in numbers

Lung cancer is the second most common malignant tumour worldwide¹

Lung cancer is the malignant tumour with the highest mortality¹

NSCLC represents the vast majority of newly diagnosed lung cancers²

Newly diagnosed NSCLC that can receive curative surgery²

25–70% of patients who received surgery for NSCLC experience recurrence due to the presence of preoperative micrometastases²


NSCLC, non-small cell lung carcinoma.
Impact of surgery and adjuvant chemotherapy

Data from the IASLC Lung Cancer Staging Project

Despite surgery and adjuvant therapy, about 10–20% of patients with stage I, 40–50% with stage II, and 60% with stage IIIA die within 5 years.
Adjuvant targeted therapy: ADJUVANT–CTONG1104

Study design: Randomized phase III clinical trial (NCT01405079)

- **N=222**
- At least 18 years of age with NSCLC stage II–IIIA
- Completely resected
- Positive for EGFR–activating mutation

Primary endpoint:
- DFS in the ITT population

Secondary endpoint:
- 3- and 5-year DFS and OS rates

Gefitinib (250 mg once daily) for 24 months

Vinorelbine (25 mg/m², day 1 and day 8) + cisplatin (75 mg/m², day 1) every 3 weeks for 4 cycles

DFS, disease-free survival; EGFR, epithelial growth factor receptor; ITT, intention to treat.


Clinical trial listed by its identifier at ClinicalTrials.gov (accessed 16 February 2021).
Adjuvant targeted therapy: ADJUVANT–CTONG1104

Study outcomes


The DFS advantage did not translate to OS difference
Evolution of EGFR–TKIs

EGFR–TKIs in the advanced/metastatic setting

First generation
- Erlotinib
- Gefitinib

Second generation
- Afatinib
- Dacomitinib

Third generation
- Osimertinib

TKI, tyrosine kinase inhibitor.
Adjuvant targeted therapy: ADAURA

Study design: Randomized phase III clinical trial (NCT02511106)

- N=682
- At least 18 years of age with NSCLC stage IB–IIIA
- Completely resected
- Positive for EGFR-activating mutation
- Patients who received adjuvant chemotherapy were included

1:1

Osimertinib (80 mg once daily) for 3 years

Placebo

Primary endpoint:
- DFS among patients with stage II–IIIA

Secondary endpoint:
- DFS and OS in the overall population (stage IB–IIIA)


Clinical trial listed by its identifier at: ClinicalTrials.gov (accessed 16 February 2021).
Adjuvant targeted therapy: ADAURA

Study outcomes

DFS stages IB–IIIA

- Osimertinib
- Placebo

HR = 0.20 (99.12% CI: 0.14–0.30)
- p < 0.001

CNS DFS

- Osimertinib
- Placebo

HR = 0.18 (95% CI: 0.10–0.33)
Adjuvant targeted therapy: ADAURA

Study outcomes\textsuperscript{1,2}

On 18 December 2020, the FDA approved osimertinib for adjuvant therapy after tumour resection in patients with NSCLC whose tumours have \textit{EGFR} exon 19 deletions or exon 21 L858R mutations\textsuperscript{3}

\begin{table}
\begin{tabular}{|c|c|}
\hline
HR for DFS & \multicolumn{2}{|c|}{
\begin{tabular}{c}
Overall (N=682) \textsuperscript{3} \\
+ chemo (n=352) \\
- chemo (n=118) \\
\end{tabular}
} \\
\hline
& Osimertinib better & Placebo better \\
\hline
& HR=0.20 (99.12% CI: 0.14–0.30) & \\
\hline
\end{tabular}
\end{table}

\begin{table}
\begin{tabular}{|c|c|}
\hline
HR for DFS & \multicolumn{2}{|c|}{
\begin{tabular}{c}
Stage II–IIIA \\
+ chemo (n=166) \\
- chemo (n=70) \\
\end{tabular}
} \\
\hline
& Osimertinib better & Placebo better \\
\hline
& HR=0.15 (95% CI: 0.06–0.32) & \\
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\end{tabular}
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\begin{table}
\begin{tabular}{|c|c|}
\hline
HR for DFS & \multicolumn{2}{|c|}{
\begin{tabular}{c}
Stage IIIA \\
+ chemo (n=186) \\
- chemo (n=48) \\
\end{tabular}
} \\
\hline
& Osimertinib better & Placebo better \\
\hline
& HR=0.10 (95% CI: 0.02–0.29) & \\
\hline
\end{tabular}
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\begin{table}
\begin{tabular}{|c|c|}
\hline
HR for DFS & \multicolumn{2}{|c|}{
\begin{tabular}{c}
Stage IB \\
+ chemo (n=154) \\
\end{tabular}
} \\
\hline
& Osimertinib better & Placebo better \\
\hline
& HR=0.18 (95% CI: 0.06–0.23) & \\
\hline
\end{tabular}
\end{table}

\begin{table}
\begin{tabular}{|c|c|}
\hline
HR for DFS & \multicolumn{2}{|c|}{
\begin{tabular}{c}
Stage II \textsuperscript{2} \\
+ chemo (n=352) \\
- chemo (n=118) \\
\end{tabular}
} \\
\hline
& Osimertinib better & Placebo better \\
\hline
& HR=0.14 (95% CI: 0.08–0.23) & \\
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HR for DFS & \multicolumn{2}{|c|}{
\begin{tabular}{c}
Stage IIIB \\
+ chemo (n=166) \\
- chemo (n=70) \\
\end{tabular}
} \\
\hline
& Osimertinib better & Placebo better \\
\hline
& HR=0.20 (95% CI: 0.07–0.52) & \\
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Stage IIIB \\
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Neoadjuvant targeted therapy: NeoADAURA

Study design: Randomized phase III clinical trial (NCT04351555)

- N=351
- Resectable, stage II–IIIB NSCLC
- Positive for EGFR-activating mutation

Primary endpoint:
- Major pathological response defined as ≤10% residual cancer cells in the lung tumour specimen post-surgery

Enrolment started: December 2020
Primary analysis estimated: Q2 2024

Osimertinib monotherapy
Osimertinib + chemotherapy
Placebo + chemotherapy

## Adjuvant and neoadjuvant immunotherapy

### Ongoing phase III clinical trials for NSCLC

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Neoadjuvant</th>
<th>Neoadjuvant/Adjuvant</th>
<th>Adjuvant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td></td>
<td></td>
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<tr>
<td>Nivolumab</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Pembrolizumab + ipilimumab</td>
<td>CheckMate 816 (NCT02998528)</td>
<td>NADIM-ADJUVANT (NCT04564157)</td>
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<tr>
<td>Nivolumab</td>
<td>CheckMate 77T (NCT04025879)</td>
<td>ALCHEMIST Chemo-IO (NCT04267848)</td>
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</tr>
<tr>
<td>Atezolizumab</td>
<td>IMpower030 (NCT03456063)</td>
<td>IMpower010 (NCT02486718)</td>
<td></td>
</tr>
<tr>
<td>Durvalumab</td>
<td>AEGEAN (NCT03800134)</td>
<td>MERMAID-1 (NCT04385368)</td>
<td>BR31 (NCT02273375)</td>
</tr>
</tbody>
</table>

**Key Points:**
- **CTLA-4, cytotoxic T lymphocyte antigen-4**
- **PD-1, programmed cell death protein 1**
- **PD-L1, programmed death-ligand-1**
Adjuvant and neoadjuvant immunotherapy

Ongoing phase III clinical trials for NSCLC

CTLA-4, cytotoxic T lymphocyte antigen-4; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand-1.


- Pembrolizumab
  - Neoadjuvant
  - Neoadjuvant/Adjuvant
    - KEYNOTE-671 (NCT03425643)
    - ALCHEMIST Chemo-IO (NCT04267848)
    - KEYNOTE-091 - PEARLS (NCT02504372)

- Nivolumab
  - Neoadjuvant
    - CheckMate 816 (NCT02998528)
  - Neoadjuvant/Adjuvant
    - CheckMate 77T (NCT04025879)
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- Atezolizumab
  - Neoadjuvant
    - IMpower010 (NCT02486718)

- Durvalumab
  - Adjuvant
    - AEGEAN (NCT03800134)
    - MERMAID-1 (NCT04385368)
    - BR31 (NCT02273375)
Conclusions

Targeted adjuvant therapy with osimertinib significantly improved DFS in patients with EGFR-mutant early-stage NSCLC, irrespective of prior chemotherapy.

Clinical trials underway to assess safety and efficacy of targeted therapy in the neoadjuvant setting.

Immunotherapy may represent an alternative to targeted therapy and chemotherapy in the adjuvant/neoadjuvant setting in patients with no targetable mutation.
How do recent data impact the future mutation testing guidelines in NSCLC?
Patient’s journey: From diagnosis to adjuvant therapy

NCCN guidelines for NSCLC

Patient’s journey: From diagnosis to adjuvant therapy


CT, computerized tomography; EGFR, epithelial growth factor receptor; FDA, US Food and Drug Administration; MRI, magnetic resonance imaging; NCCN, National Comprehensive Cancer Network; NSCLC, non–small cell lung carcinoma; PET, positron emission tomography.

NCCN guidelines for NSCLC

Part 2 of 2

Surgical resection and lymph node sampling

Margins negative

Recommendation for adjuvant chemotherapy

• High-risk patients with stage IB/IIA disease
• Patients with post-operative pathological stage IIB or higher

Margins positive

Treatment options depending on disease stage

• Reresection
• Radiotherapy
• Chemotherapy
• Chemoradiation
• Reresection + chemotherapy
• Radiotherapy + chemotherapy

Systemic therapy and/or radiotherapy

Assessment for resectability and/or systemic therapy

Initial treatment

Findings at surgery

Adjuvant treatment

December 2020

Osimertinib approved by the FDA as adjuvant therapy in NSCLC

• NSCLC with EGFR exon 19 deletions or exon 21 L858R mutations
Molecular testing to inform adjuvant therapy

Who to treat:
- How to identify patients at high-risk of recurrence

Who to treat:
- Predict response to adjuvant immunotherapy (PD-L1)
- Response to targeted therapy (EGFR/ALK)
Molecular testing to inform adjuvant therapy: Who to treat?

Residual disease: Data from the LUCiD study

- Detection of residual ctDNA in patient plasma
- N=90 patients
- N=350 plasma samples

Pre-treatment

- ctDNA detected in patients with stage I NSCLC (n=32): 38%
- ctDNA detected in patients with stage II/III NSCLC (n=21): 90%

In plasma samples collected post-treatment, ctDNA was detected in close to 50% of cases

cDNA, circulating tumour DNA.
Molecular testing to inform adjuvant therapy: Who to treat?

Minimal residual disease: Study design for MERMAID-1 (NCT04385368, phase III)

Inclusion criteria:
- At least 18 years of age
- Resectable NSCLC stage II–III
- Complete resection of primary NSCLC

Exclusion criteria:
- Evidence of disease recurrence (imaging or biopsy)
- EGFR-mutant and/or ALK-translocation
- Mixed small cell and NSCLC histology
- Any prior adjuvant therapy or exposure to durvalumab

Primary endpoint:
- DFS for patients who show evidence of MRD, tested using a highly sensitive ctDNA assay post-surgery

Study start July 2020
Study completion September 2026
Primary completion December 2024

Adjuvant chemotherapy + durvalumab
Adjuvant chemotherapy + placebo

N=332

DFS, disease-free survival; MRD, minimal residual disease; OS, overall survival.
Clinical trial listed by its identifier at: ClinicalTrials.gov (accessed 6 January 2021).
Molecular testing to inform adjuvant therapy: Who to treat?

TMB as a predictor of response to ICI therapy: Lessons from advanced NSCLC

ICI, immune checkpoint inhibitor; Mb, megabases; NS, not significant; PFS, progression-free survival; TMB, tumour mutational burden.


Clinical trial listed by its identifier at: ClinicalTrials.gov (accessed 6 January 2021).

High TMB

> Neoantigens

> Enhanced tumour immunogenicity

> Response to ICI therapy

CheckMate 227 (NCT02477826)

**Median PFS**

<table>
<thead>
<tr>
<th>TMB (mutations/Mb)</th>
<th>Nivolumab + ipilimumab (n=139)</th>
<th>Chemotherapy (n=160)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High TMB (≥10)</td>
<td>8.0 (p&lt;0.001)</td>
<td>5.6 (NS)</td>
</tr>
<tr>
<td>Low TMB (&lt;10)</td>
<td>5.5</td>
<td>4.2</td>
</tr>
</tbody>
</table>

ICI, immune checkpoint inhibitor; Mb, megabases; NS, not significant; PFS, progression-free survival; TMB, tumour mutational burden.
Clinical trial listed by its identifier at: ClinicalTrials.gov (accessed 6 January 2021).
Molecular testing to inform adjuvant therapy: How to treat?

Lessons from neoadjuvant atezolizumab: LCMC3 (NCT02927301) study design

- N=181
  - Atezolizumab (2 cycles)
  - Surgical resection
  - Surveillance + optional adjuvant atezolizumab (12 months)

Primary endpoint:
- Major pathologic response (<10% viable tumour cells)

Molecular testing to inform adjuvant therapy: How to treat?

Lessons from neoadjuvant atezolizumab: LCMC3 (NCT02927301) outcomes

Major pathologic response

Primary efficacy population (N=144)

- PD-L1 < 50% (n=73): 21%
- PD-L1 ≥ 50% (n=45): 33%

Better pathologic responses correlated with:

- Higher TMB (p=0.047)
- Lack of STK11 mutations (p=0.008)

High PD-L1 expression correlated with major pathologic response in patients treated with neoadjuvant atezolizumab

STK11, Serine/threonine kinase 11.
Molecular testing to inform adjuvant therapy: How to treat?

Molecular testing at enrolment in phase III clinical trials for adjuvant immunotherapy

<table>
<thead>
<tr>
<th>PD-L1 status</th>
<th>EGFR/ALK status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tested</td>
<td>Negative excluded</td>
</tr>
</tbody>
</table>

- **Pembrolizumab**
  - KEYNOTE-671 (NCT03425643)
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- **Nivolumab**
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- **Atezolizumab**
  - IMpower010 (NCT02486718)

- **Durvalumab**
  - MERMAID-1 (NCT04385368)
  - D9106C00001 (NCT03800134)

**PD-1**, programmed cell death protein.
Clinical trials listed by their identifiers at: ClinicalTrials.gov (accessed 6 January 2021).
Molecular testing to inform adjuvant therapy: How to treat?

Molecular testing for driver mutations: Targeted therapy

**Approved in the adjuvant setting**
- Osimertinib

**Active phase III trials for targeted adjuvant therapy include:**
- ALCHEMIST trials:
  - *EGFR* – Erlotinib (NCT02193282)
  - *ALK* – Crizotinib (NCT02201992)
  - NCT03456076:
    - *ALK* – Alectinib

**Approved for advanced disease**
- Osimertinib
- Afatinib
- Dacomitinib
- Erlotinib
- Gefitinib
- Alectinib
- Brigatinib
- Ceritinib
- Crizotinib
- Entrectinib
- Capmatinib
- Lotrectinib
- Dabrafenib
- Trametinib
- Selpercatinib
- Pralsetinib

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*BRAF*, B-Raf proto-oncogene; *MET*, mesenchymal-epithelial transition factor; *NTRK*, neurotrophic tyrosine kinase; *RET*, rearranged during transfection proto-oncogene; *ROS1*, c-ros oncogene 1.

Clinical trials listed by their identifiers at: ClinicalTrials.gov (accessed 6 January 2021).
Molecular testing to inform adjuvant therapy: How to treat?

The potential for EGFR–TKI resistance mutation testing: Lessons from advanced NSCLC

The use of osimertinib as first-line treatment of EGFR–mutant metastatic NSCLC can lead to the development of resistance mutations.\(^1,2\)

- **EGFR C797S mutation**
- **EGFR G724S mutation**
- **MET amplification**
- **Cell cycle gene mutations**

Can molecular testing be used in the adjuvant setting to monitor patients for the development of resistance mutations?
Conclusions

The diagnostic and treatment algorithm for NSCLC needs to identify who will benefit most from different neoadjuvant or adjuvant treatment options.

Markers for tumour mutational burden and minimal residual disease may inform on whether a patient is more likely to benefit from pre- or post-operative therapy.

Markers of response to immunotherapy (PD-L1) or targeted therapy (EGFR, ALK, ROS1, NTRK, RET, BRAF) will aid the selection of optimal adjuvant/neoadjuvant treatment.
How do recent data in early-stage NSCLC impact the current treatment pathway for EGFR-mutant NSCLC?
Multidisciplinary management of early-stage NSCLC

Disease setting
• Patient’s characteristics
• Physiology
• Comorbidities
• Tumour histology
• Stage
• Biomarkers
• Patient’s preference

Rapidly evolving treatment paradigm
• Complex disease staging
• Expanded biomarker testing
• Multimodality treatment algorithms
• Novel therapeutics

Treatment options
• Surgical resection
• Radiation therapy
• Systemic therapy
  • Chemotherapy
  • Immunotherapy
  • Targeted therapy

Multifaceted, collaborative decision making

Optimal treatment process
Multidisciplinary management of early-stage NSCLC

Guidelines on the management of patients with NSCLC highlight the importance of MDT collaborative decision making.
Multidisciplinary management of early-stage NSCLC

Thoracic surgeon
Molecular pathologist
Pathologist
Palliative care specialist
Specialty nurse

Radiation oncologist
Medical oncologist
Pulmonologist
Radiologist
Nuclear medicine specialist
The patient’s journey

MDT involvement in treatment decision

The patient’s journey

MDT involvement in treatment decision\textsuperscript{1,2}


CT, computerized tomography; EGFR, epithelial growth factor receptor; ICI, immune checkpoint inhibitor; MRI, magnetic resonance imaging; NCCN, National Comprehensive Cancer Network; PET, positron emission tomography; TKI, tyrosine kinase inhibitor.

Part 2 of 2

Personalized medicine

Adjuvant therapy

Molecular testing

Prior therapy (neoadjuvant)

Therapy options

• Targeted therapy
• Immunotherapy
• Chemotherapy

Medical oncologist

Thoracic surgeon

Pathologist

Molecular pathologist

Surgical resection and lymph node sampling

Lessons from advanced NSCLC
• Immunotherapy has shown poor results in patients with EGFR-mutant NSCLC\textsuperscript{3,4}
• EGFR-TKI after prior immunotherapy showed poor outcomes with increased toxicity\textsuperscript{4}

Recommendation for adjuvant chemotherapy

Medical oncologist

Pathologist

Molecular pathologist

Findings at surgery

Adjuvant treatment
Conclusions

Each patient’s case should be discussed by the multidisciplinary team/tumour board from diagnosis

The MDT involvement should be considered as a medical intervention in its own right

Effective MDT decision making and optimal patient management requires effective communication among specialties using a common language