Clinical Considerations in EGFR Mutation–Positive NSCLC: Does Treatment Sequence Matter?

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Faculty Disclosure

- Honoraria: AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Merck, Novartis, Pfizer
Choosing the Sequence in *EGFR*-Mutant NSCLC

TKIs are standard up front but they are not equal

Evidence #1

Mutational subgroup/resistance pattern determines treatment choice

Evidence #2

Sequence affects survival

Evidence #3

NSCLC = non–small cell lung cancer; TKI = tyrosine kinase inhibitor.
Choosing the Sequence in *EGFR*-Mutant NSCLC

Evidence #1

TKIs are standard up front but they are not equal
First-, Second-, and Third-Generation EGFR TKIs Are Not Equal: Activity Against EGFR Mutations

First- and Second-Generation EGFR TKIs Are Not Equal: LUX-Lung 7

LUX-Lung 7: Afatinib vs gefitinib as first-line treatment of patients with EGFR mutation-positive NSCLC: a phase 2B, open-label, randomised controlled trial

PFS = progression-free survival; HR = hazard ratio; CI = confidence interval.

First- and Second-Generation EGFR TKIs Are Not Equal: ARCHER 1050

ARCHER 1050: Dacomitinib vs gefitinib as first-line treatment of patients with EGFR mutation–positive NSCLC: a phase 3, open-label, randomised trial (excluding CNS metastases)

- Advanced NSCLC with EGFR-activating mutation(s)
- No prior systematic treatment of advanced NSCLC
- No CNS metastasis
- No prior EGFR TKI or other TKI
- ECOG PS 0, 1

Dacomitinib 45 mg PO QD (n=227)

Gefitinib 250 mg PO QD (n=225)

R 1:1 (N=452)

Primary end point PFS by blinded independent review
- ≥256 PFS events
- PFS HR ≤0.667 (50%↑)
- 90% power
- 1-sided α=0.025
- mPFS: 14.3 vs 9.5 months

Events, n (%)
- Dacomitinib: 136 (59.9%) vs Gefitinib: 179 (79.6%)
- Median PFS (95% CI): Dacomitinib: 14.7 (11.1-16.6) vs Gefitinib: 9.2 (9.1-11.0)
- HR (95% CI): 0.59 (0.47-0.74) P<0.0001

PFS rate 30.6% vs 9.6%

No. at risk
- Dacomitinib: 227
- Gefitinib: 225

Months

CNS = central nervous system; ECOG PS = Eastern Cooperative Oncology Group performance status; R = randomised; PO = orally; QD = once daily; mPFS = median progression-free survival; ITT = intent-to-treat.

First- and Second-Generation EGFR TKIs Are Not Equal: FLAURA

**FLAURA**: Osimertinib vs erlotinib or gefitinib as first-line treatment of patients with *EGFR* mutation‒positive NSCLC: a phase 3, double-blind, randomised trial

**Primary endpoint: PFS (By investigator assessment)**

Date cut-off 12 Jun 2017. Tick marks indicate censored data. "For statistical significance, *P*-value of less than 0.0015, determined by O'Brien Planning approach was required.

CI = confidence interval; DCO = data cut-off; HR = hazard ratio; NS = not significant; PFS = progression-free survival.

First-, Second-, and Third-Generation EGFR TKIs Are Not Equal: Safety

Second- or Third-Generation TKIs vs First-Generation TKIs

<table>
<thead>
<tr>
<th></th>
<th>LUX-Lung 7¹,²</th>
<th>ARCHER 1050³</th>
<th>FLAURA⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Afatinib (n=160)</td>
<td>Gefitinib (n=159)</td>
<td>Dacomitinib (n=227)</td>
</tr>
<tr>
<td>Treatment</td>
<td>6%</td>
<td>6%</td>
<td>10%</td>
</tr>
<tr>
<td>discontinuation</td>
<td>discontinuation</td>
<td>discontinuation</td>
<td>discontinuation</td>
</tr>
<tr>
<td>rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Most common</td>
<td>Diarrhoea, 12%</td>
<td>Liver enzyme</td>
<td>Acne, 14%</td>
</tr>
<tr>
<td>grade ≥3 AEs</td>
<td>Rash/acne, 9%</td>
<td>elevation, 9%</td>
<td>Diarrhoea, 8%</td>
</tr>
<tr>
<td></td>
<td>Rash/acne, 3%</td>
<td>9%</td>
<td>Paronychia, 7%</td>
</tr>
</tbody>
</table>

AE = adverse event.
Dose Reduction of Afatinib Reduced Drug-Related AEs Without Compromising Efficacy

Treatment-Related AEs in Patients Who Had a Dose Reduction From 40 mg (n=63)

- **Before Reduction (≥40 mg)**
  - Any: 100.0%
  - Diarrhoea: 63.5%
  - Rash/acne: 95.2%
  - Stomatitis: 81.0%
  - Nail effect: 60.3%

- **After Reduction (<40 mg)**
  - Any: 90.5%
  - Diarrhoea: 61.9%
  - Rash/acne: 52.4%
  - Stomatitis: 27.0%
  - Nail effect: 33.3%

PFS in Patients Who Received a Dose Reduction Within the First 6 Months of Treatment

- **Before Reduction (≥40 mg)**
  - Median, mo: 12.8
  - HR (95% CI): 1.34 (0.90-2.00)
  - *P* value: 0.1440

- **After Reduction (<40 mg)**
  - Median, mo: 11.0

Choosing the Sequence in *EGFR*-Mutant NSCLC

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TKIs are standard up front but they are not equal

**Evidence #2**

Mutational subgroup/resistance pattern determines treatment choice

Girard. *Future Oncol.* 2018;14:1117.
First-Line: PFS Efficacy of TKIs Is Different in EGFR del19/L858R Mutations

- Impact of specific EGFR mutations and clinical characteristics on outcomes after treatment with EGFR TKIs vs chemotherapy in EGFR M+ lung cancer: a meta-analysis

<table>
<thead>
<tr>
<th>Trial</th>
<th>HR</th>
<th>95% CI</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Exon 19 deletion</td>
<td></td>
<td>Exon 21 L858R substitution</td>
</tr>
<tr>
<td>ENSURE</td>
<td>0.20</td>
<td>0.12-0.33</td>
<td>0.54</td>
<td>0.32-0.91</td>
</tr>
<tr>
<td>EURTAC</td>
<td>0.27</td>
<td>0.17-0.43</td>
<td>0.53</td>
<td>0.29-0.97</td>
</tr>
<tr>
<td>LUX-Lung 3</td>
<td>0.28</td>
<td>0.18-0.44</td>
<td>0.73</td>
<td>0.46-1.16</td>
</tr>
<tr>
<td>LUX-Lung 6</td>
<td>0.20</td>
<td>0.13-0.32</td>
<td>0.32</td>
<td>0.19-0.54</td>
</tr>
<tr>
<td>NEJ002</td>
<td>0.24</td>
<td>0.15-0.38</td>
<td>0.33</td>
<td>0.20-0.54</td>
</tr>
<tr>
<td>OPTIMAL</td>
<td>0.13</td>
<td>0.07-0.24</td>
<td>0.26</td>
<td>0.14-0.48</td>
</tr>
<tr>
<td>WJTOG 3405</td>
<td>0.42</td>
<td>0.26-0.66</td>
<td>0.69</td>
<td>0.44-1.07</td>
</tr>
<tr>
<td>All</td>
<td>0.24</td>
<td>0.20-0.29</td>
<td>0.48</td>
<td>0.39-0.58</td>
</tr>
</tbody>
</table>

First-Line: OS Efficacy of TKIs Is Different in \textit{EGFR} del19/L858R Mutations

<table>
<thead>
<tr>
<th>Agent</th>
<th>Study</th>
<th>HR (95% CI)</th>
<th>Del19</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Del19</td>
<td>L858R</td>
</tr>
<tr>
<td>Afatinib</td>
<td>LUX-Lung 3</td>
<td>0.53 (0.36-0.79)</td>
<td>1.30 (0.80-2.11)</td>
<td>1.25 (0.91-1.71)</td>
</tr>
<tr>
<td></td>
<td>LUX-Lung 6</td>
<td>0.64 (0.44-0.94)</td>
<td>1.22 (0.81-1.83)</td>
<td>1.20 (0.81-1.83)</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>0.59 (0.45-0.77)</td>
<td></td>
<td>1.25 (0.91-1.71)</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>ENSURE</td>
<td>0.79 (0.48-1.30)</td>
<td>1.05 (0.60-1.84)</td>
<td>1.00 (0.56-1.79)</td>
</tr>
<tr>
<td></td>
<td>EURTAC</td>
<td>0.94 (0.57-1.54)</td>
<td>1.00 (0.56-1.79)</td>
<td>0.92 (0.55-1.54)</td>
</tr>
<tr>
<td></td>
<td>OPTIMAL</td>
<td>1.52 (0.91-2.52)</td>
<td></td>
<td>0.98 (0.72-1.35)</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>1.04 (0.71-1.51)</td>
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<td></td>
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<tr>
<td>Gefitinib</td>
<td>IPASS</td>
<td>0.86 (0.61-1.22)</td>
<td>1.40 (0.91-2.15)</td>
<td>1.11 (0.81-1.54)</td>
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<td></td>
<td>NEJ002</td>
<td>0.83 (0.52-1.34)</td>
<td>0.82 (0.49-1.38)</td>
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<tr>
<td></td>
<td>WJTOG3405</td>
<td>1.19 (0.65-2.18)</td>
<td>1.11 (0.60-2.05)</td>
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<tr>
<td></td>
<td>Total</td>
<td>0.90 (0.70-1.17)</td>
<td></td>
<td>1.11 (0.81-1.54)</td>
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</tbody>
</table>

OS = overall survival.
LUX-Lung 3 and LUX-Lung 6: OS in Del19 Subgroup (Prespecified Endpoint)

LUX-Lung 3

<table>
<thead>
<tr>
<th></th>
<th>Afatinib (n=112)</th>
<th>Cis/Gem (n=57)</th>
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<tbody>
<tr>
<td>Median, mo</td>
<td>33.3</td>
<td>21.1</td>
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<tr>
<td>HR (P)-value</td>
<td>0.54 (0.36–0.79)</td>
<td>(P=0.0015)</td>
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LUX-Lung 6

<table>
<thead>
<tr>
<th></th>
<th>Afatinib (n=124)</th>
<th>Cis/Gem (n=62)</th>
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</thead>
<tbody>
<tr>
<td>Median, mo</td>
<td>31.4</td>
<td>18.4</td>
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<tr>
<td>HR (P)-value</td>
<td>0.64 (0.44–0.94)</td>
<td>(P=0.0229)</td>
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No. at risk:

<table>
<thead>
<tr>
<th></th>
<th>Afatinib</th>
<th>Cis/Gem</th>
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<tbody>
<tr>
<td>LUX-Lung 3</td>
<td>Afatinib</td>
<td>Cis/Gem</td>
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<tr>
<td>No. at risk</td>
<td>112</td>
<td>57</td>
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<td>Months</td>
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<td>105</td>
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No. at risk:

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<tr>
<th></th>
<th>Afatinib</th>
<th>Cis/Gem</th>
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<tbody>
<tr>
<td>LUX-Lung 6</td>
<td>Afatinib</td>
<td>Cis/Gem</td>
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<tr>
<td>No. at risk</td>
<td>124</td>
<td>62</td>
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<tr>
<td>Months</td>
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<td>8</td>
<td>3</td>
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<tr>
<td></td>
<td>1</td>
<td>0</td>
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</table>
First-Line: Afatinib Is Effective for Uncommon EGFR Mutations

- Clinical activity of afatinib in patients with advanced NSCLC harbouring uncommon EGFR mutations: a combined post hoc analysis of LUX-Lung 2, 3, and 6

![Graph showing response rate and PFS for different mutation types]

<table>
<thead>
<tr>
<th>Mutation Type</th>
<th>Group 1 (n=33)</th>
<th>Group 2 (n=14)</th>
<th>Group 3 (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exon 18-21: G719X, L861Q</td>
<td>120%</td>
<td>100%</td>
<td>80%</td>
</tr>
<tr>
<td>Exon 18-21: T790M mutations</td>
<td>60%</td>
<td>40%</td>
<td>20%</td>
</tr>
<tr>
<td>Exon 18-21: G719X, L861Q, S768I</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

- **Response rate (%)**
  - T790M (n=14): 14.3
  - Exon 20 Ins (n=23): 8.7
  - Mut/Dup Exon 18-21 (n=38): 71.1
  - G719X (n=18): 77.8
  - L861Q (n=16): 56.3
  - S768I (n=8): 100.0

- **PFS (mo)**
  - T790M (n=14): 2.9
  - Exon 20 Ins (n=23): 2.7
  - Mut/Dup Exon 18-21 (n=38): 10.7
  - G719X (n=18): 13.8
  - L861Q (n=16): 8.2
  - S768I (n=8): 14.7

- **OS (mo)**
  - T790M (n=14): 19.4
  - Exon 20 Ins (n=23): 26.9
  - Mut/Dup Exon 18-21 (n=38): 17.1
  - G719X (n=18): NE
  - L861Q (n=16): NE
  - S768I (n=8): NE

Note: A patient may be presented in more than 1 category.

Choosing the Sequence in \textit{EGFR}-Mutant NSCLC

Evidence #1

TKIs are standard up front but they are not equal

Evidence #2

Mutational subgroup/resistance pattern determines treatment choice
Molecular Mechanisms of Acquired Resistance to First- and Second-Generation EGFR TKIs

- 155 EGFR-mutant NSCLC, acquired resistance after TKI
- Molecular analyses on rebiopsy specimen

AURA 3: Osimertinib Standard of Care for T790M+ Acquired Resistance to First- and Second-Generation EGFR TKIs

Biopsy or Plasma May be Used to Determine EGFR T790M Status

- **Acquired resistance to first-/second-generation EGFR TKI**
  - Biopsy/plasma assay
    - T790M+\(^a\)
    - T790M\(^b\)

- **Acquired resistance to third-generation EGFR TKI**
  - Biopsy/plasma assay
    - C797S, MET amplification, HER2

**Third-generation EGFR TKI**
- Around 75% of patients acquiring T790M are Del19+

**Chemotherapy**
- In case of negative plasma assay, tissue biopsy testing is recommended

- **Trial inclusion**

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Girard. *Future Oncol.* 2018;14:1117.
OS in *EGFR*-Mutant NSCLC: ARCHER 1050 Trial (Excluding Brain Metastases)

- Third-generation *EGFR* TKIs were used as a first subsequent therapy in 22 patients (9.7%) in the dacomitinib arm and in 25 patients (11.1%) in the gefitinib arm.

- Median OS in patients subsequently treated with third-generation TKIs was **36.7** (95% CI: 30.1-NR) months in the dacomitinib arm.

NR = not reported.
**OS in \textit{EGFR}-Mutant NSCLC: LUX-Lung 3 Trial**

- **Common Mutations**
  - **Afatinib** (n = 203)
  - **Cis/Pem** (n = 104)
  - Median, \text{mo} 31.6, 28.2
  - HR (95\% CI) 0.78 (0.58-1.06)

- **Estimated OS Probability**
  - **No. at risk:**
    - Afatinib: 203, 197, 188, 181, 171, 162, 143, 133, 121, 108, 101, 90, 58, 49, 32, 9, 1, 0
    - Cis/Pem: 104, 98, 92, 86, 81, 71, 63, 55, 52, 47, 40, 35, 26, 20, 10, 5, 1, 0

- OS was up to **41.5 months** in del19 patients in countries with a **universal healthcare reimbursement** policy

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OS in Patients in LUX-Lung 3, 6, and 7 Treated Subsequently With Osimertinib

• 71% of patients received subsequent therapy
• Median follow-up = 4.7 years

OS in Patients Treated With First-Line Osimertinib

FLAURA OS DATA ARE IMMATURE (25% MATURITY)

NC = not calculable.
Treatment Sequences in *EGFR*-Mutant NSCLC After First-Line *EGFR* TKI

**First-/Second-Generation TKI**

- **T790M+**
  - Osimertinib
  - Chemotherapy

- **T790M-**
  - Chemotherapy
  - Other
  - MET/HER2 inhibitor

**Osimertinib**

- Chemotherapy

Except if molecular target

**NEED MATURE OS AND TREATMENT SEQUENCES FROM FLAURA and AURA 3**

Girard. *Future Oncol.* 2018;14:1117.
How Do We Optimise Sequence?

Clinical factors

- CNS disease and progression
  - Data for afatinib and osimertinib show delay in onset and progression of CNS metastases
- Loss of patients from one line to another
- Treatment of oligoprogression, treatment beyond PD

Optimisation of treatments

- Antiangiogenics
- Anti-EGFR antibodies
- Chemotherapy + TKI

Understanding of biology

- *EGFR* mutational subgroups (eg, del19, L858R, uncommon mutations) determine treatment choice
- Resistance mechanisms impact subsequent therapy choice
Choosing the Sequence in \textit{EGFR}-Mutant NSCLC

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Sequence makes survival