Treatment algorithm for EGFR-M+ NSCLC: Where do the 3\textsuperscript{rd} Generation EGFR TKIs fit in?

Carlos Barrios
POTENTIAL CONFLICTS OF INTEREST

• **Clinical Research**: Pfizer, Novartis, Amgen, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Roche/Genentech, Lilly, Sanofi, GlaxoSmithKline, Taiho Pharmaceutical, Mylan, Merrimack, Merck, Abbvie, Astellas Pharma, Biomarin, Bristol-Myers Squibb, Daiichi Sankyo, Abraxis BioScience, AB Science, Asana Biosciences, Medivation, Daiichi Sankyo, Exelixis, ImClone Systems, LEO Pharma, Millennium

• **Academic Research Projects**: CPO, PUCRS, LACOG, GBECAM, INCA-Brazil.

• **Advisory Boards and Consulting**: Boehringer-Ingelheim, GSK, Novartis, Pfizer, Roche/Genentech, Eisai, Bioepis.

• No financial conflicts to declare.
Key Questions: How to maximise the survival benefit from 1st-line treatment and delay the occurrence of resistance

• Multiple drugs available in EGFR-M+ NSCLC
  → EGFR-TKI 1\textsuperscript{st}, 2\textsuperscript{nd}, 3\textsuperscript{rd} generation
  → Platinum-based chemotherapy: current role?
  → Emerging role for immune checkpoint inhibitors?

• Resistance to treatment to 1\textsuperscript{st} and 2\textsuperscript{nd} generation TKI occurs within 9 to 16 months
  → is there an optimal sequence of drugs use?
  → is EGFR-TKI re-introduction a good option?
NCCN and Advanced NSCLC

**SYSTEMIC THERAPY FOR METASTATIC DISEASE**
- Establish histologic subtype$^a$ with adequate tissue for molecular testing (consider rebiopsy if appropriate)
- Smoking cessation counseling
- Integrate palliative care$^c$ (See NCCN Guidelines for Palliative Care)

**Metastatic Disease**

**HISTOLOGIC SUBTYPE**
- Adenocarcinoma
- Large Cell
- NSCLC not otherwise specified (NOS)

**EGFR mutation testing$^a$ (category 1)$^a$**
- ALK testing (category 1)$^a$
- EGFR and ALK testing should be conducted as part of multiplex/next generation sequencing$^{hh}$

**TESTING RESULTS**
- Sensitizing EGFR mutation positive
- ALK positive
- Both sensitizing EGFR mutation and ALK are negative or unknown$^{kk}$

**Squamous cell carcinoma**
- Consider EGFR mutation and ALK testing$^{ii}$ especially in never smokers or small biopsy specimens, or mixed histology$^{ii}$
- EGFR and ALK testing should be conducted as part of multiplex/next generation sequencing$^{hh}$

Both sensitizing EGFR mutation and ALK are negative or unknown$^{kk}$
LCMC: Median Survival of Patients According to Driver Mutation

**ALK**
OS 4.25 (2.92-NA)

**EGFR**
OS 3.97

**EGFR (o)**
OS 2.70

**KRAS**
OS 2.41

Two drivers
OS 2.03

Different Mutations – Different Biology – Different Results

Table 1  \(\textit{EGFR}\)-activating and resistance mutations in adenocarcinoma of the lung

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Frequency in (\textit{EGFR})-mutant lung adenocarcinoma (%)</th>
<th>Response rate to EGFR TKIs</th>
<th>Clinical properties</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>%</td>
<td>Reference</td>
</tr>
<tr>
<td>Exon 19 deletions</td>
<td>45</td>
<td>82.8</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>84.8</td>
<td>170</td>
</tr>
<tr>
<td></td>
<td></td>
<td>63</td>
<td>171</td>
</tr>
<tr>
<td></td>
<td></td>
<td>64</td>
<td>172</td>
</tr>
<tr>
<td></td>
<td></td>
<td>70</td>
<td>173</td>
</tr>
<tr>
<td></td>
<td>L858R (exon 21)</td>
<td>67.3</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>60.9</td>
<td>170</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50(^a)</td>
<td>171</td>
</tr>
<tr>
<td></td>
<td></td>
<td>62</td>
<td>172</td>
</tr>
<tr>
<td></td>
<td>Exon 20 insertions</td>
<td>2–9</td>
<td></td>
</tr>
</tbody>
</table>
|                    | The variable response to EGFR TKIs is thought to be related to the effect of varying insertion length on the drug-binding pocket\(^d\). Median OS of 16 months\(^e\) in one series and 4 years in another\(^f\).
| G719X              | 3                                                         | -50                       | 178                | 8.1        | 179       | 16.4    | 179     |
| L861X              | 2                                                         | 60                        | 179                | 6          |           | 15.2    |         |
| Exon 19 Insertions | 1                                                         | 0.5–3 (in some case series) |                    |            |           |         |         |
| T790M              | 6                                                         | 179                        | 80                  | 6          |           |         |         |

\(^{a}\)\(P = 0.39\) compared to exon 19 deletions in this series. \(^{b}\)\(P = 0.075\) compared to exon 19 deletions in this series. \(^{c}\)\(P = 0.65\) compared to exon 19 deletions in this series. PFS, progression-free survival; OS, overall survival.

Women, benefit was 27% greater (HR, 0.33; 95% CI, 0.28 to 0.38) than men (HR, 0.45; 95% CI, 0.36 to 0.55; treatment-sex interaction P < 0.02).

Never-smokers, benefit was 36% greater (HR, 0.32; 95% CI, 0.27 to 0.37) than current or former smokers (HR, 0.50; 95% CI, 0.40 to 0.63; P interaction 0.001).

Exon 19 deletions, benefit was 50% greater (HR, 0.24; 95% CI, 0.20 to 0.29) than exon 21 substitutions (HR, 0.48; 95% CI, 0.39 to 0.58; P interaction 0.001).

Women, benefit was 27% greater (HR, 0.33; 95% CI, 0.28 to 0.38) than men (HR, 0.45; 95% CI, 0.36 to 0.55; treatment-sex interaction P < 0.02).
A Tumor’s Molecular Profile Should be Expected to Change Overtime

Natural progression due to genetic instability
Natural selection due to treatment pressure

As tumors evolve, tumor profile in metastases does not necessary correlate to the one in primary tumor

Spatial and Temporal Heterogeneity

How can we adequately evaluate the complexity of a tumor’s genomic landscape through the analysis of a single biopsy at one point in time?

Come to think about this, it is surprising we have gone this far!
Schematic representation of main EGFR-TKIs resistance mechanisms

A EGFR variant III is constitutively phosphorylated in a ligand-independent manner.
B Mutation at threonine 790 (T790M), and other resistance mutations.
C Oncogenic shift to other RTKs (including MET, AXL and IGF-1R).
D Downregulation of the IGF-binding proteins IGFBP3 and IGFBP4
E Mutations in Ras
F Mutations in PTEN
G Increased VEGF production
H VEGFR1 signaling
Mechanisms of Acquired Resistance to Afatinib

- Preclinical and clinical data show that resistance mechanism on afatinib are similar to those of first generation TKIs.
- T790M is the major acquired resistance mechanism.

- 42 pts had tissue specimen after acquired resistance to afatinib
  - T790M+ : n=20 (47.6%)
    - T790M rate was similar between first-generation EGFR TKI-naïve patients (50%) and first-generation EGFR TKI-treated patients (46.4%).
  - No other second-site EGFR mutations were detected.
  - No small cell or squamous NSCLC transformations
  - A few cases of Met-amplification are described
  - Other genetic mutations were not identified in PIK3CA, BRAF, HER2, KRAS, NRAS, MEK1, AKT2, LKB1 and JAK2

The Challenge of Resistance Development

Importance of Repeat Biopsy in the Multi-line Strategy

- EGFR-mutant NSCLC (n=135)
- Re-biopsy after EGFR-TKI failure between 2009 and 2015
- T790M mutation: 68 re-biopsy cases (50%) after EGFR-TKI failure

- Duration from initial diagnosis to re-biopsy significantly affected the frequency of T790M mutation
- Trend was the same irrespective of stage of NSCLC
- Repeated re-biopsy may be important after some interval, despite T790M-negative status in earlier biopsy

Need to Recognize Different Patterns of Progression

Therapeutic Alternatives for Progressing EGFR-M+ Patients

- Chemotherapy
- Targeted therapy beyond progression
- Combination Chemotherapy + Targeted therapy
- Local therapy
- Re-challenging after drug holiday

- Second and third generation agents
- Immunotherapy
- Targeting alternate bypass networks
Therapeutic Alternatives for Progressing EGFR-M+ Patients

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EGFR-TKI post-progression in EGFR-M+ Advanced NSCLC

• A significant proportion of patients treated in 1st L with 1st and 2nd gen EGFR TKIs were re-challenged in phase 3 trials

✔ EURTAC: 22%
✔ NEJ002: 47%
✔ LUX-Lung 3: 40%
✔ LUX-Lung 6: 23%

EGFR-TKI reintroduction is a strong option in clinical practice

Feasibility of EGFR-TKI Treatment Beyond Progression

- Stage IV NSCLC
- ≥18 years
- *EGFR* exon 18–21 mutation (except T790M)

**ASPIRATION phase II trial**

→ Oligoprogression and slow progression


Erlotinib

**PFS 1**

**PD (RECIST)**

**PFS 2**

**PD (physician assessment)**

PFS probability

Time (months)

$\Delta 3.1$ months

11.0 months

14.1 months

ASPIRATION phase II trial → Oligoprogression and slow progression

**Third Generation Agent - Osimertinib - AURA**

**Phase 1 escalation**
Not preselected by T790m status

**Phase 1 expansion**
Enrollment by local testing followed by central laboratory confirmation§ of T790M status or by central laboratory testing alone

- **Tumor biopsy**

**Phase 2 extension**
Enrollment by central laboratory confirmation§ of T790M status

- **175 T790M+ ≥second-line patients who have received prior EGFR-TKI therapy**

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Janne P, et al.
DOI: 10.1056/NEJMoa1411817
All patients
PR 51% confirmed

T790M+
ORR 61%

T790M-
21% ORR

Janne P, et al.
DOI: 10.1056/NEJMoa1411817
Tumor response by independent central review

Best percentage change from baseline in target lesion – all patients

<table>
<thead>
<tr>
<th>Confirmed objective response</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, † % (95% CI)</td>
<td>71 (64, 77)</td>
</tr>
<tr>
<td>Complete response, ‡ n (%)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Partial response, ‡ n (%)</td>
<td>139 (70)</td>
</tr>
<tr>
<td>Stable disease ≥ 6 weeks, § n (%)</td>
<td>41 (21)</td>
</tr>
<tr>
<td>Progressive disease, n (%)</td>
<td>15 (8)</td>
</tr>
<tr>
<td>DCR, % (95% CI)</td>
<td>92 (87, 95)</td>
</tr>
</tbody>
</table>

NOTE: Investigator-assessed ORR was also 71% (95% CI 64, 77)
Data cut-off: May 1, 2015. Population evaluable for response set (n=199). *Represents imputed values: if it is known that the patient has died, has new lesions or progression of non-target lesions, has withdrawn due to disease progression, and has no evaluable target lesion (before or at progression) assessments, best change will be imputed as 20%. †ORR defined as the number (%) of patients with at least one visit response of complete response or partial response that was confirmed at least 4 weeks later; ‡Response required confirmation after 4 weeks; §Stable disease ≥6 weeks included the RECIST visit window (17 days) CI, confidence interval; DCR, disease control rate (complete response + partial response + stable disease)
Progression-free Survival With Osimertinib

**AURA Ph I**
- Osimertinib 80 mg
- Number of patients at risk: 63
- Median PFS, months (95% CI): 9.7 (8.3, 13.6)

**AURA pooled Ph II**
- Osimertinib 80 mg
- Number of patients at risk: 411
- Median PFS, months (95% CI): 11.0 (9.6, 12.4)

Tumour Response to Osimertinib in EGFR-M+ First-line Cohorts (Investigator Assessed)

Best percentage change from baseline in target lesion size (%)

<table>
<thead>
<tr>
<th></th>
<th>1st line 80 mg</th>
<th>1st line 160 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>80 mg</strong></td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td><strong>160 mg</strong></td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>D</td>
<td>D</td>
</tr>
</tbody>
</table>

**Confirmed ORR**

- **80 mg**
  - n=30
  - 67% (95% CI 47, 83)
- **160 mg**
  - n=30
  - 87% (95% CI 69, 96)
- **Total**
  - N=60
  - 77% (95% CI 64, 87)

**Disease control rate**

- **80 mg**
  - 93% (95% CI 78, 99)
- **160 mg**
  - 100% (95% CI 88, 100)
- **Total**
  - 98% (95% CI 89, 100)

PFS in Osimertinib EGFR-M+ First-line Cohorts (Investigator Assessed)

Number of patients at risk:
- 1st line 80 mg: 30, 26, 23, 22, 20, 16, 14, 7, 0, 0
- 1st line 160 mg: 30, 29, 27, 23, 20, 19, 7, 0, 0

Month

Probability of PFS survival

Median PFS, months (95% CI)
- 80 mg, n=30: NC (12.3, NC)
- 160 mg, n=30: 19.3 (11.1, 19.3)
- Total, N=60: 19.3 (13.7, NC)

Mutation of C797S in EGFR is a novel mechanism of acquired resistance to third-generation TKIs.

## Mechanisms of Acquired Resistance to Osimertinib

<table>
<thead>
<tr>
<th>Resistance mechanism</th>
<th>Frequency</th>
<th>Treatment option</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of T790M</td>
<td>27% (4/15)</td>
<td>Driver mutation unknown No established targeted treatment option</td>
</tr>
<tr>
<td>Retained T790M</td>
<td>33% (5/15)</td>
<td>Driver mutation unknown No established targeted treatment option Rechallenge with 3rd gen might be beneficial</td>
</tr>
<tr>
<td>Gained C797S</td>
<td>40% (6/15)</td>
<td>Depending on the allelic context:</td>
</tr>
<tr>
<td>C797S and T790M in trans</td>
<td></td>
<td>Cells will be resistant to 3rd-gen TKIs, but will be sensitive to a combination of TKIs</td>
</tr>
<tr>
<td>Mutations are in cis</td>
<td></td>
<td>No EGFR TKIs alone or in combination can suppress activity</td>
</tr>
<tr>
<td>T790M wt</td>
<td></td>
<td>Cells are resistant to 3rd-gen TKIs, but retain sensitivity to 1st-gen TKIs</td>
</tr>
</tbody>
</table>

- Acquired resistance to EGFR-TKI is a dynamic process and biopsies and cDNA analysis should be repeated.
- Sequencing biopsy samples from patients whose tumours have progressed on 3rd gen EGFR TKIs and determining if the C797S mutation is in cis or trans with T790M should be a priority going forward.

Designing a treatment strategy that can suppress triple-mutant EGFR may soon be needed.
Targeting a genetic defect (mutation) with a personalized or precise strategy using a “single targeted agent” is limited by the high degree of intra-tumor heterogeneity, adaptation of the different cellular networks and the high somatic mutation rates of cancer.
**PD-L1 in EGFR mutant NSCLC**

**In vitro data:**
- Decrease expression of PD-L1 after EGFR-TKI (EGFR-mutant cell lines)
- Inhibition of PD-1/PD-L1 axis before EGFR TKI use may be more effective than the reverse strategy or the combined administration.

To Recap…

- EGFR-TKIs are the standard in first-line EGFR-M+ NSCLC
- Not all mutations are the same…
- EGFR-TKIs could be used beyond RECIST-progression
- Repeated biopsies and/or cDNA analysis should be performed for optimal targeting of molecular alterations
- Third generation EGFR-TKI are indicated in EGFR-M+ NSCLC with T790M mutation
- The role of immunotherapy is not yet well defined in this oncogenic addicted model
Treatment Algorithm for EGFR-M+ Advanced NSCLC

EGFR-M+ NSCLC

EGFR-TKI 1st-2nd generation

T790M+
EGFR-M+ NSCLC

EGFR-TKI 3rd generation

Progression

T790M−
EGFR-TKI

Progression

Chemotherapy or other strategy

PFS 1 + PFS 2 > PFS (?); impact on OS (?)

FLAURA study

Chemotherapy or other strategy
Conclusions

• We are making (slow) progress… in spite of significant **limitations** in our understanding of cancer.

• Recently developed technology is allowing us to unravel the **bewildering heterogeneity** underlying lung cancer.
Conclusions

• Significant (more definitive) progress will only be possible with the persistent search for the 
  molecular alterations that explain the incredibly diverse biology and clinical behavior we see in our patients.

• Our main goal, whenever possible, would be the rational application of this new information in the design of trials generating smarter and more effective treatment alternatives.
Treatment algorithm for EGFR-M+ NSCLC: Where do the 3rd Generation EGFR TKIs fit in?

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Mechanisms of Acquired Resistance to EGFR-TKI