Improving Therapy for EGFR-Mutant Lung Cancers

Zosia Piotrowska, MD
Instructor, Harvard Medical School
Massachusetts General Hospital Cancer Center
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Objectives

• Review the current understanding of resistance to third-generation EGFR inhibitors and the role of cancer heterogeneity in the development of resistance.

• Define potential treatment strategies to overcome resistance to EGFR-targeted therapy.
Classifying NSCLC in 2017

- Adenocarcinoma - 50%
- Squamous Cell Carcinoma - 30%
- Other - 20%

- KRAS* - 25%
- EGFR (sensitizing)** – 17%
- ALK** - 9%
- EGFR (other)* - 4%
- Her2* - 3%
- PIK3CA* - 1%
- NRAS - 1%
- MEK1 - <1%
- MET amp* - 1%
- MET exon 14 skipping*, ~5%
- NTRK1 Rearrangements*, <1%
- ROS1 Rearrangements**, 1-2%
- RET1 Rearrangements*, 1-2%
- No oncogene driver detected - 35%

Others...**

1. Kris et al, JAMA 2014
2. Gainor and Shaw, Oncologist 2013
3. Heist et al, Oncologist 2016
4. Farago et al, JTO 2015

** FDA-approved targeted therapy available
* Off-label or clinical trial targeted options
The Concept of Oncogene Addiction

**EGFR-Addicted**

- EGFR
- gefitinib
- PI3K
- P42/44
- MAPK
- Jak/Stat
- Apoptosis

**Non-addicted case**

- IGFR
- EGFR
- K-Ras
- PTEN
- PI3K
- MAPK
- Jak/Stat

EGFR mutant cancers are “simple”-one RTK controls all downstream signaling.

Slide courtesy of Lecia V Sequist
EGFR-mutant NSCLC: 2004 to 2017

**EGFR mutations described as oncogenic drivers of NSCLC**

2003

**ERLOTINIB**

FDA approved for NSCLC after failure of ≥ 1 prior therapy

2004

**GEFITINIB**

Accelerated FDA approval for NSCLC after failure of docetaxel (later lost full approval for this indication)

2005

**T790M Resistance Mutation described**

2009

**ERLOTINIB and AFATINIB**

FDA approval for 1st-line EGFRm+ NSCLC

2013

**iPASS**

2014

**OSIMERTINIB**

FDA approval for second-line, T790M+ EGFRm+ NSCLC

2015

**PLA05**

Ph1 studies of T790M-specific 3rd gen EGR TKIs start (osimertinib, rociletinib)

2016

**OSIMERTINIB**

FDA approved as companion diagnostic for erlotinib (activating EGFR mutations)

2017

**FLAURA**

First-line Osimertinib

2018

**OSIMERTINIB**

FDA approval for second-line, T790M+ EGFRm+ NSCLC

**WHAT’S NEXT?**

- Defining resistance to osimertinib
- Combination therapies
- Further improvement in first-line therapy

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Treatment of EGFR-mutant NSCLC

iPASS (Mok T, et al. NEJM 2009)

Stage IIIIB/IV disease
Chemo-naïve
Adenocarcinoma
Never/light-smokers
ECOG PS 0-2

GEFITINIB 250 mg QD
CARBOPLATIN (AUC 5/6)
PACLITAXEL 200mg/m2
IV q21 days (x6)

1:1

ENDPOINTS
1º: PFS
2º: ORR, OS,
Symptoms, QoL

*Patients were not selected based on EGFR status, but factors that enriched for EGFR+ disease
**EGFR status was analyzed post-hoc
EGFR inhibitors improve PFS among EGFR-mutants, but not among those without EGFR mutations. Molecular testing is key to selecting therapy.

Mok et al, NEJM 2009
<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Arms</th>
<th>Response Rate (%)</th>
<th>Med PFS (mo)</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPASS NEJM ‘09</td>
<td>261</td>
<td>Gefitinib Carbo/taxol</td>
<td>71% 47%</td>
<td>9.6 6.3</td>
<td>0.48 (.36, .64)</td>
</tr>
<tr>
<td>WJTOG 3405</td>
<td>228</td>
<td>Gefitinib Cis/docetaxel</td>
<td>62% 31%</td>
<td>9.2 6.3</td>
<td>0.49 (.35, .71)</td>
</tr>
<tr>
<td>LUX-Lung 3</td>
<td>345</td>
<td>Afatinib Cis/pem</td>
<td>69% 44%</td>
<td>11.1 (13.6)</td>
<td>0.58 (.43,.78)</td>
</tr>
</tbody>
</table>

Despite significant advances, the median PFS for all three EGFR TKIs (erlotinib, gefitinib, afatinib) used in the first line setting remains between 9-13 months.
Management of EGFR-mutant NSCLC

Initial Diagnosis

EGFRm+ NSCLC
- Exon 19 deletion
- L858R
- Other (G719X, S768I)

First-Line Therapy

Erlotinib
Gefitinib
Afatinib

mPFS 9-13 mo

Second-Line Therapy

?
A personalized approach to overcoming resistance to targeted therapy
Resistance mechanisms observed upon initial resistance to EGFR TKI therapy (n=258)

- **T790M - 44%** (1 with PIK3CA)
- **No Identified Mechanism - 23%**
- **T790M + EGFR Amp - 15%** (1 w/ PIK3CA, 2 w/ HER2 Amp)
- **EGFR Amp - 4%**
- **MET Amp - 5%** (2 w/ PIK3CA, 3 w/ EGFR Amp 1 w/ EGFR + HER2 Amp)
- **SCLC Transformation - 3%** (4 with PIK3CA)
- **PIK3CA - 2%**
- **BRAF - 1%**
- **Not tested/Insufficient - 3%**

Overall T790M-positive: 59%
103 patients with 2 post-resistance biopsies

- 103 patients had 2 biopsies performed during their post-resistance course.
- 56/103 (54%) had variations in the resistance mechanisms identified between biopsy 1 and 2.
- 24% patients “lost” T790M between biopsy 1 and 2, while 11% “gained” T790M.
- Of the 25 pts who lost T790M, 7 had a new resistance mechanism identified on the second biopsy
  - 1 patient had an acquired *BRAF* V600E mutation on biopsy two
  - 5 patients developed *MET* amplification on biopsy two
  - 1 patient developed SCLC transformation on biopsy two
T790M “positive” tumors can be heterogeneous

<table>
<thead>
<tr>
<th>T790M Status</th>
<th>Total Clones</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wild-type</td>
<td>3 of 8 (38%)</td>
</tr>
<tr>
<td>Mutant</td>
<td>5 of 8 (62%)</td>
</tr>
</tbody>
</table>

Targeting T790M - Osimertinib

### AURA Ph I

**Confirmed ORR**
- 71% (95% CI 57, 82)

**Disease control rate**
- 93% (95% CI 84, 98)

### AURA pooled Ph II

**Confirmed ORR**
- 66% (95% CI 61, 71)

**Disease control rate**
- 91% (95% CI 88, 94)

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*Note:
- AURA pooled Ph II data cut-off 1 November 2015; population: evaluable for response set; assessment: BICR.
- *Represents imputed values: if it is known that the patient has died, has new lesions or progression of non-targeted 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%.
- †Complete response, partial response, stable disease ≥6 weeks.
- ORR, objective response rate; CI, confidence interval.
AURA3 - Osimertinib vs. Platinum-Pemetrexed

**A Patients in Intention-to-Treat Population**

<table>
<thead>
<tr>
<th>Month</th>
<th>Osimertinib</th>
<th>Platinum-pemetrexed</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>279</td>
<td>140</td>
</tr>
<tr>
<td>3</td>
<td>240</td>
<td>93</td>
</tr>
<tr>
<td>6</td>
<td>162</td>
<td>44</td>
</tr>
<tr>
<td>9</td>
<td>88</td>
<td>17</td>
</tr>
<tr>
<td>12</td>
<td>50</td>
<td>7</td>
</tr>
<tr>
<td>15</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>18</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Median Progression-free Survival**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of Patients</th>
<th>Median Survival (mo, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osimertinib</td>
<td>279</td>
<td>10.1 (8.3–12.3)</td>
</tr>
<tr>
<td>Platinum-pemetrexed</td>
<td>140</td>
<td>4.4 (4.2–5.6)</td>
</tr>
</tbody>
</table>

Hazard ratio for disease progression or death: 0.30 (95% CI, 0.23–0.41), P<0.001

Mok TS, et al, NEJM 2016
Resistance mechanisms observed upon initial resistance to EGFR TKI therapy (n=258)

Overall T790M-positive: 59%
Overcoming non-T790M resistance

• **MET amplification (~5%)**:
  - Erlotinib + Crizotinib
  - Clinical trials
    - Osimertinib + Savolitinib (AZD6094) – TATTON (NCT02143466)
    - EGF816 + Capmatinib (INC280) - NCT02335944

Overcoming non-T790M resistance

- **Histologic transformation to SCLC**
  - SCLC Transformed cancers lose expression of/dependence upon EGFR
  - Genetic loss of Rb1, which appears to be necessary but not sufficient to cause the transformation
  - Patients can respond to **Platinum + Etoposide chemotherapy**

Niederst, Nat Comm 2015
Management of EGFR-mutant NSCLC

Initial Diagnosis
EGFRm+ NSCLC
- Exon 19 deletion
- L858R
- Other (G719X, S768I)

First-Line Therapy
Erlotinib
Gefitinib
Afatinib

Second-Line Therapy
T790M+ : Osimertinib
METamp : EGFR + MET TKI
SCLC: Platinum/Etoposide
Other: Carboplatin/Pemetrexed

Third-Line Therapy
?
Resistance to 3rd generation EGFR TKIs

Table 1. Reported Mechanisms of Resistance to Third-Generation EGFR TKIs

<table>
<thead>
<tr>
<th>Resistance Mechanism</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No. of patients</td>
<td>35</td>
</tr>
<tr>
<td>C797S/T790M</td>
<td>8 (23)</td>
</tr>
<tr>
<td>T790M Maintained</td>
<td>12 (34)</td>
</tr>
<tr>
<td>Loss of T790M</td>
<td>10 (29)</td>
</tr>
<tr>
<td>MET Amp/T790-wt</td>
<td>1 (3)</td>
</tr>
<tr>
<td>ERBB2(HER2) Amp/T790-wt</td>
<td>1 (3)</td>
</tr>
<tr>
<td>SCLC/T790-wt</td>
<td>3 (9)</td>
</tr>
</tbody>
</table>

Abbreviations: Amp, amplification; SCLC, small cell lung cancer; T790-wt, T790 wild-type.

Others:
- BRAF V600E mutations
- FGFR3
- KRAS

Heterogeneity Plays an Important Role in Development of Resistance

Heterogeneity may play an increasing role in resistance

Overlapping resistance mechanisms to rociletinib detected in ctDNA

Longitudinal ctDNA analysis reveals distinct evolution of heterogeneous resistant subclones

Liver Biopsy: 
**EGFR Del19, T790M**

Liver biopsy + ablation: 
**EGFR Del19, BRAF V600E** (No EGFR T790M/C797S)

ctDNA: 
**EGFR Del19, T790M/C797S** (No BRAF V600E)
EGFR C797S mediates resistance to osimertinib
Potential Strategies to Overcome *EGFR C797S*

**Brigatinib (EGFR/ALK Tyrosine Kinase Inhibitor) + EGFR mAb**


**EAI045 (Allosteric EGFR Inhibitor) + EGFR mAb**

Management of EGFR-mutant NSCLC

Initial Diagnosis
- NSCLC in 2016
  - EGFRm+ NSCLC
    - Exon 19 deletion
    - L858R
    - Other (G719X, S768I)

First-Line Therapy
- Erlotinib
- Gefitinib
- Afatinib

Second-Line Therapy
- T790M+ : Osimertinib
- METAMP : EGFR + MET TKI
  - SCCL: Platinum/Etoposide
  - Other: Carboplatin/Pemetrexed

Third-Line Therapy
- Chemotherapy
- Clinical Trials
- Afatinib/Cetuximab
Management of EGFR-mutant NSCLC

**Initial Diagnosis**
- EGFRm+ NSCLC
  - Exon 19 deletion
  - L858R
  - Other (G719X, S768I)

**First-Line Therapy**
- Erlotinib
- Gefitinib
- Afatinib

**Second-Line Therapy**
- T790M+ : Osimertinib
  - MET
  - MET+ : EGFR + MET TKI
  - SCLC: Platinum/Etoposide
  - Other: Carboplatin/Pemetrexed

**Third-Line Therapy**
- Chemotherapy
- Clinical Trials
- Afatinib/Cetuximab

**2016 Initial Diagnosis**

**EGFRm+ NSCLC**
- Exon 19 deletion
- L858R
- Other (G719X, S768I)

**Osimertinib ?**
Improving front-line therapy for EGFR-mutant NSCLC

**FLAURA DOUBLE-BLIND STUDY DESIGN**

- **Key inclusion criteria**
  - 21 years or older
  - WHO performance status 0/1
  - Exon 19 deletion / L858R (locally or central EGFR testing)
  - No prior systemic anti-cancer / EGFR-TKI therapy
  - Stable CNS metastases allowed

- **Randomised 1:1**
  - Osimertinib (80 mg p.o. qd) (n=279)
  - EGFR-TKI SoC

- **OSDST**
  - Gefitinib (250 mg p.o. qd) or
  - Erlotinib (150 mg p.o. qd) (n=277)

- **RECIST 1.1 assessment every 6 weeks until objective disease**

- **Endpoints**
  - **Primary endpoint**: PFS based on investigator assessment (according to RECIST 1.1)
    - The study had 90% power to detect a hazard ratio of 0.71 (representing a 29% improvement in median PFS from 10 months to 14.1 months) at a two-sided alpha-level of 5%.
  - **Secondary endpoints**: objective response rate, duration of response, disease control rate, depth of response, overall survival, patient reported outcomes, safety

- **PRIMARY ENDPOINT: PFS BY INVESTIGATOR ASSESSMENT**

  - **342 events in 556 patients at DCO: 62% maturity; osimertinib: 136 events (49%), SoC: 206 events (74%)**

  - **Median PFS, months (95% CI)**
    - Osimertinib: 18.9 (15.2, 21.4)
    - SoC: 10.2 (8.6, 11.1)

  - **HR 0.48**
    - (95% CI 0.37, 0.57)
    - p<0.0001

Front-line combination therapy

- Combination therapy with gefitinib (1\textsuperscript{st} gen) and EGF816 (3\textsuperscript{rd} gen) EGFR TKIs may induce more durable responses than either drug alone
- Resistance to the combination would require EGFR T790M and C797S in \textit{cis} configuration
- NCT03292133/DFHCC 17-291 is a phase 2, investigator initiated trial of EGF816 and gefitinib for newly-diagnosed EGFR-mutant NSCLC
Conclusions

- The eventual development of resistance is universal among patients treated with EGFR TKIs.
- Repeat biopsies at the time of resistance are critical to understanding resistance mechanisms and selecting optimal post-resistance therapy. Repeat biopsies (or liquid biopsies) should be considered when selecting subsequent lines of post-progression therapy.
- Resistance to third-generation EGFR inhibitors can be mediated by loss of T790M, C797S, bypass pathway activation and can be heterogeneous
- New approaches will be required to overcome resistance to third-generation EGFR inhibitors
- Moving next-generation EGFR TKIs and combination treatment strategies to the front-line setting may minimize cancer heterogeneity and induce more durable remissions.
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