Molecular Targets in Lung Cancer

Robert Ramirez, DO, FACP
Thoracic and Neuroendocrine Oncology
November 18th, 2016

Disclosures

• Consulting and speaker fees for Ipsen Pharmaceuticals, AstraZeneca and Merck
Pathologic Evaluation of Lung Cancer

- Non-small cell – 85%
  - Adenocarcinoma
  - Squamous cell carcinoma
  - Large cell carcinoma
  - Mixed histology
- Small cell -15%

Adenocarcinoma by Mutations

- KRAS: 32%
- EGFR: 20%
- ALK: 3%
- ROS1: 3%
- HER2: 3%
- ROS1-HER2: 3%
- Unknown: 34%
Squamous Cell by Mutation

- FGFR1: 20%
- KRAS: 6%
- EGFR: 4%
- DDR2: 3%
- PIK3CA: 2%
- BRAF: 5%
- Not Defined: 60%

Sos, ML et al. Oncogene 2012; 15;31(46):4811

Small Cell by Mutation

- PIK3CA: 10%
- Not Defined: 90%

Bunn, PA. 13th International Lung Cancer Congress 2012
Old Treatment Paradigm (2010)

New Paradigm (2015)

Old Treatment Paradigm (2010)

Metastatic Lung Cancer → 1st Line Chemotherapy → 2nd Line Chemotherapy → 3rd Line Treatment or Hospice → Hospice

New Paradigm (2015)

1. Multidisciplinary discussion to determine optimal procedure for tissue procedure
   2. Biopsy
   3. Morphology
   4. Review of patient and tumor data

Integrated NGS-based assay to detect mutations, amplifications and translocations

EGFR → ALK → ROS → BRAF → Other actionable alterations → No actionable alterations

1. First-line Chemotherapy
2. Second-line (If not EGR positive) - Targeted therapy

Clinical trial of targeted therapies
2. Chemotherapy or (if unavailable, immunotherapy)

Chemotherapy or Immunotherapy

Treatment until response, progressive disease, or unacceptable adverse effects

Therapy switch/completion based on re-biopsies or liquid biopsy

EGFR Therapy

EGFR Targeted Therapy

- Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI)
  - Erlotinib, Gefitinib, Afatinib, Osimertinib
  - Oral agents inhibiting the EGFR downstream pathways leading to proliferation
  - Well tolerated (rash and diarrhea)
  - Used in 2nd and 3rd line treatment (10% RR) or in 1st line treatment in select patients
IPASS

- In prior studies patient who were non-smokers, female, Asian seemed to benefit more from EGFR TKIs
  - These patients had higher frequency of EGFR mutations
- Would TKI be as effective as chemo in front line setting?
  - Primary Endpoint: progression free survival
  - Secondary Endpoints: OS, RR, QOL


IPASS

Advanced NSCLC  
No prior treatment  
Never or former light smoker  
N=1217

Randomize 1:1

Carboplatin/Paclitaxel every 3 weeks

Gefitinib 250mg daily

**IPASS**

- Median OS: 18.6 vs 17.3 months favoring TKI
- RR with TKI:
  - 71% for EGFR mutation positive
  - 1% for mutation negative
- RR with chemo
  - 43.3% for EGFR mutation positive
  - 23.5% for mutation negative
- Improved quality of life with TKI
EURTAC Study Design

- Chemotherapy naïve
- Stage IIIIB/IV NSCLC
- EGFR sensitizing mutation
- ECOG PS 0-2 (n = 174)

Stratification:
- Mutation type
- ECOG PS (0 vs 1 vs 2)

Platinum-based doublet chemotherapy q3wk x 4 cycles

Primary endpoint:
- Progression-free survival
- Interim analysis planned at 88 events

ECOG PS = Eastern Cooperative Oncology Group performance status; PD = progressive disease; R = randomized

EURTAC: Progression-Free Survival

- Erlotinib (n = 88)
- Chemotherapy (n = 87)

HR = 0.37 (0.25 – 0.54)
Log-rank P < .0001

Patients at risk
- Erlotinib: 86, 63, 54, 32, 21, 17, 9, 7, 4, 2, 2, 2, 0
- CT: 87, 49, 20, 8, 5, 4, 3, 3, 1, 0, 0, 0, 0

CT = chemotherapy; PFS = progression-free survival
Rosell R, et al. 2011 Annual Meeting of the American Society of Clinical Oncology
## EGFR TKIs Versus Chemo

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>RR</th>
<th>PFS months (HR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPASS</td>
<td>Gefitinib vs carbo/paclitaxel</td>
<td>71% vs 43%</td>
<td>9.6 vs 6.3 (0.48)</td>
</tr>
<tr>
<td>EURTAC</td>
<td>Erlotinib vs platinum doublet</td>
<td>58% vs 14.9%</td>
<td>9.7 vs 5.2 (0.37)</td>
</tr>
<tr>
<td>OPTIMAL</td>
<td>Erlotinib vs carbo/gem</td>
<td>83% vs 36%</td>
<td>13.1 vs 4.6 (0.16)</td>
</tr>
<tr>
<td>WJTOG 3405</td>
<td>Gefitinib vs cis/docetaxel</td>
<td>62% vs 31%</td>
<td>9.2 vs 6.3 (0.49)</td>
</tr>
<tr>
<td>NEJ 002</td>
<td>Gefitinib vs carbo/paclitaxel</td>
<td>74% vs 31%</td>
<td>10.8 vs 5.4 (0.30)</td>
</tr>
<tr>
<td>LUX-Lung 3</td>
<td>Afatinib vs cisplatin/pemetrexed</td>
<td>56% vs 23%</td>
<td>11.1 vs 6.9 (0.47)</td>
</tr>
<tr>
<td>LUX-Lung 6</td>
<td>Afatinib vs cisplatin/gemcitabine</td>
<td>66% vs 23%</td>
<td>11 vs 5.6 (0.28)</td>
</tr>
</tbody>
</table>

## EGFR Mutations

- Occur in about 15% of general population
- Mutational status should be checked in all non-squamous NSCLCs and some squamous
  - Positive results should prompt initial treatment with EGFR TKI
- Resistance generally develops around 10 months
Overcoming EGFR Resistance

- T790 M is most common mechanism of resistance
- Osimertinib is an oral, irreversible EGFR TKI selective for sensitizing mutations and the T790M resistance mutation
- Phase I Dose expansion study for patients with known EGFR TKI sensitizing mutations OR prior clinical benefit from EGFR TKI with disease progression

Percentage Change in Target Lesion

Progression Free Survival
### Adverse Effects

<table>
<thead>
<tr>
<th>AE %</th>
<th>80mg N=30</th>
<th>160mg N=30</th>
<th>Total N=60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any event grade ≥ 3</td>
<td>33</td>
<td>43</td>
<td>38</td>
</tr>
<tr>
<td>Treatment related AE</td>
<td>97</td>
<td>100</td>
<td>98</td>
</tr>
<tr>
<td>Treatment related AE grade ≥ 3</td>
<td>10</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>Treatment related AE leading to discontinuation</td>
<td>7</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Treatment related SAE</td>
<td>10</td>
<td>3</td>
<td>7</td>
</tr>
</tbody>
</table>

Most common toxicities: skin rash, diarrhea, dry skin, stomatitis (mostly grade 1)

No grade ≥ 3 hyperglycemia, QT prolongation or ILD-like event

---

**ALK Therapy**
Anaplastic Lymphoma Kinase (ALK) Gene Rearrangement

- Occur in about 2-7% of NSCLC
- Genetic alterations lead to increased proliferation

- Crizotinib is a ALK and MET inhibitor
  - Had been shown to decrease proliferation in cell lines
- Phase I trial with expanded cohort

Crizotinib

![Graph showing percent change in tumor burden](image)
Crizotinib

• Well tolerated
  – Elevations in transaminases, nausea, diarrhea, visual disturbances
• In phase III trial crizotinib superior to chemo in 2nd line patients
  – PFS: 7.7 vs 3 months (HR 0.49; 95% CI 0.37–0.64; p < 0.0001)
  – RR: 65% vs 20%; p < 0.0001
  – OS: immature


Shaw, A., et al. ESMO 2012
Crizotinib versus Chemo 2\textsuperscript{nd} Line

A Progression-free Survival

Hazard ratio for progression or death in the crizotinib group, 0.49 (95\% CI, 0.37–0.64)  
P<0.001

<table>
<thead>
<tr>
<th>Months</th>
<th>Crizotinib</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>173</td>
<td>174</td>
</tr>
<tr>
<td>5</td>
<td>93</td>
<td>49</td>
</tr>
<tr>
<td>10</td>
<td>38</td>
<td>15</td>
</tr>
<tr>
<td>15</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>20</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>25</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Crizotinib versus Chemo 1\textsuperscript{st} Line

A Progression-free Survival

Hazard ratio for progression or death in the crizotinib group, 0.45 (95\% CI, 0.35–0.60)  
P<0.001 (two-sided stratified log-rank test)

<table>
<thead>
<tr>
<th>Months</th>
<th>Crizotinib</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>172</td>
<td>171</td>
</tr>
<tr>
<td>5</td>
<td>120</td>
<td>105</td>
</tr>
<tr>
<td>10</td>
<td>65</td>
<td>36</td>
</tr>
<tr>
<td>15</td>
<td>38</td>
<td>11</td>
</tr>
<tr>
<td>20</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>25</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>30</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>35</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>


Mechanisms of Resistance in ALK

- **ALK Mutations**
- **ALK Amplification**
- **Increased EGFR**
- **Change in Driver**
- **KIT Amplification**
- **Unknown**

Camidge, DR et al Nat Rev Clin Onc 2014
Ceritinib

- Oral, small molecule TKI of ALK
- 20 times more potent than crizotinib against ALK
- Does not inhibit MET

- Phase I trial expansion phase evaluation 246 patients with ALK positive NSCLC
  - 163 previously treated
  - 83 naïve

Progression Free Survival

<table>
<thead>
<tr>
<th>Number at risk</th>
<th>Time since start of ceritinib treatment (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALK inhibitor-pretreated</td>
<td>163 108 79 52 29 13 2 1 0 0 0 0 0 0</td>
</tr>
<tr>
<td>ALK inhibitor-naïve</td>
<td>83 50 55 43 32 17 6 2 0 0 0 0 0 0</td>
</tr>
</tbody>
</table>
Duration of Response

![Graph showing duration of response for Alectinib](image)

**Alectinib**

- Highly selective oral ALK and RET inhibitor
- Approximately 5x more potent
- Can inhibit multiple ALK mutations
- Achieves comparable levels in brain tissue as in plasma

Shaw AT et al, Lancet 2015
Alectinib in Crizotinib Resistant Patients

CNS Response
Alectinib vs Crizotinib in ALK inhibitor Naïve Patients J-ALEX Study

### J-ALEX Phase III Study Design

**Key Entry Criteria**
- Stage IIB/IV or recurrent ALK-positive NSCLC
- ALK centralization testing (IHC and FISH or RT-PCR)
- EGFR PS 0-3
- ≥1 measurable lesion assessed by investigator
- Treated/untreated brain metastases allowed
- ≤5 prior chemotherapy

#### Stratification factors:
- Clinical stage (IIB/IV vs. Recurrent)
- Prior chemotherapy (0 vs. 1)
- ECOG PS (0'1 vs. 2)

**Endpoints**
- **Primary**
  - PFS assessed by IRF
- **Secondary**
  - OS
  - ORR
  - PFS
  - CNS PFS
  - Safety

#### Randomization
- 1:1

| Alectinib 300 mg BID PO, 28-day cycle (N=100) | Crizotinib 250 mg BID PO, 28-day cycle (N=100) |

### Safety Overview

<table>
<thead>
<tr>
<th></th>
<th>Alectinib (N=103)</th>
<th>Crizotinib (N=104)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AEs</td>
<td>100 (97.1%)</td>
<td>104 (100.0%)</td>
</tr>
<tr>
<td>Grade 3/4 AEs</td>
<td>27 (26.2%)</td>
<td>54 (51.9%)</td>
</tr>
<tr>
<td>Treatment-related deaths</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>15 (14.6%)</td>
<td>27 (26.0%)</td>
</tr>
<tr>
<td>Discontinuation of study drug due to AEs</td>
<td>9 (8.7%)</td>
<td>21 (20.2%)</td>
</tr>
<tr>
<td>Dose interruptions due to AEs</td>
<td>30 (29.1%)</td>
<td>77 (74.0%)</td>
</tr>
</tbody>
</table>
Alectinib vs Crizotinib

Objective Tumor Response

<table>
<thead>
<tr>
<th>ORR assessed by investigator in ITT population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alectinib (N=103)</td>
</tr>
<tr>
<td>ORR (95% CI)</td>
</tr>
<tr>
<td>CR or PR</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ORR* assessed by IRF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alectinib (n=83)</td>
</tr>
<tr>
<td>ORR (95% CI)</td>
</tr>
<tr>
<td>CR or PR</td>
</tr>
</tbody>
</table>

*In patients with measurable tumor assayed by IRF at baseline

Primary Endpoint: PFS by IRF (ITT Population)

<table>
<thead>
<tr>
<th></th>
<th>Alectinib (N=103)</th>
<th>Crizotinib (N=104)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events (n (%)</td>
<td>47 (46.3)</td>
<td>66 (63.8)</td>
</tr>
<tr>
<td>Median, med (95% CI)</td>
<td>10.2 [8.2 - 12.0]</td>
<td>NR (95% CI)</td>
</tr>
<tr>
<td>Progression-free survival time (months)</td>
<td>8.94 [5.17 - 8.71]</td>
<td>NR</td>
</tr>
</tbody>
</table>

Nokihara H et al 2016 ASCO Annual Meeting
# Other ALK Inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Phase</th>
<th>N</th>
<th>ORR</th>
<th>PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brigatinib</td>
<td>I/II</td>
<td>77</td>
<td>71%</td>
<td>13.4 months</td>
</tr>
<tr>
<td>Lorlatinib</td>
<td>I/II</td>
<td>78</td>
<td>53.1%</td>
<td>n/a</td>
</tr>
</tbody>
</table>

Rosell R et al European Lung Cancer Conference 2016  
Bauer T et al J Thor Oncol 2015

# ROS-1 Therapy
ROS-1 Inhibition with Crizotinib

A Best Response

- Disease progression
- Stable disease
- Partial response
- Complete response

ROS-1 Inhibition with Crizotinib

C Duration of Response

ROS-1 Inhibition with Crizotinib


ROS-1 and Ceritinib?

- Single case report of a patient who progressed on crizotinib and achieved partial response (56% decrease) with ceritinib
- Decrease in thoracic and brain metastasis


V Subbiah et al. Proc Natl Acad Sci USA 2016
### Personalized Medicine in Lung Cancer

<table>
<thead>
<tr>
<th>Genetic Alteration</th>
<th>Targeted Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALK gene rearrangement</td>
<td>Crizotinib, Ceritinib, Alectinib</td>
</tr>
<tr>
<td>EGFR mutation</td>
<td>Erlotinib, Gefitinib, Afatinib, Osimertinib</td>
</tr>
<tr>
<td>HER2 mutation</td>
<td>Traztuzumab, Afatinib</td>
</tr>
<tr>
<td>BRAF</td>
<td>Vemurafenib, Dabrafenib + Trametinib</td>
</tr>
<tr>
<td>MET amplification or MET exon 14 skipping mutation</td>
<td>Crizotinib</td>
</tr>
<tr>
<td>ROS1 gene fusion</td>
<td>Crizotinib, Ceritinib</td>
</tr>
<tr>
<td>RET gene fusion</td>
<td>Vandetanib, sunitinib, sorafenib</td>
</tr>
</tbody>
</table>

---

**Ochsner Health System**

**Ettinger, DS et al. J Natl Compr Canc Netw 2016**

---


---

**Personalized Medicine in Lung Cancer**

![Graph showing survival probability over time for patients with and without targeted therapy.](image)

- **No. at risk**
  - Patients with oncogenic driver: 318
  - No-targeted therapy: 205
  - Targeted therapy: 260
  - Patients with no driver: 360

- **Survival Probability**
  - Years: 0, 1, 2, 3, 4, 5
  - Log-rank P<.001

---

---
Conclusions

• Multiple targets exist for patients with NSCLC
• All non-squamous (some squamous) patients should be tested for mutations
  – And retested
• Newer agents/combinations being developed to overcome resistance
Questions??

robert.ramirez@ochsner.org