Targeted Therapies for Advanced NSCLC

Current Clinical Developments

Moderator
Pasi A. Jänne, MD, PhD
Lowe Center for Thoracic Oncology
Dana Farber Cancer Institute
Boston, MA

Panelists
Tony S.K. Mok, BMSc, MD, FRCPC
The Chinese University of Hong Kong
Hong Kong, China

Lecia V. Sequist, MD, MPH
Harvard Medical School
Massachusetts General Hospital Cancer Center
Boston, MA

Tom Stinchcombe, MD
University of North Carolina at Chapel Hill
Chapel Hill, NC
Learning Objectives

1) Review the molecular pathology of lung cancer and examine its relevance for clinical practice.

2) Outline the safety and efficacy of first-line therapies for advanced NSCLC, including first-generation EGFR and ALK inhibitors.

Learning Objectives (cont.)

3) Evaluate treatment approaches used to overcome EGFR and ALK resistance in advanced NSCLC, including the safety and efficacy of second- and third-line therapies and recommended molecular testing.

4) Appraise emerging concepts with EGFR TKIs and ALK inhibitors, including their role in adjuvant therapy, combination therapies, and other evolving data.
### Lung Cancer
**CAP/IASLC/AMP Guideline**

**Molecular Testing Guideline for Selection of Lung Cancer Patients for EGFR and ALK Tyrosine Kinase Inhibitors**

“The major recommendations are to use testing for **EGFR** mutations and **ALK** fusions to guide patient selection for therapy with an epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) inhibitor, respectively, in all patients with advanced-stage adenocarcinoma, regardless of sex, race, smoking history, or other clinical risk factors, and to prioritize **EGFR** and **ALK** testing over other molecular predictive tests.”


### Metastatic NSCLC
**NCCN Guidelines Version 4.2016**

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

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

**TESTING**
- **EGFR** mutation testing (category 1)
- **ALK** testing (category 1)
- **EGFR** and **ALK** testing should be conducted as part of broad molecular profiling

**TESTING RESULTS**
- Sensitizing **EGFR** mutation positive
  - **ALK** positive
  - See First-Line Therapy (NSCL-17)
- Both sensitizing **EGFR** mutation and **ALK** are negative or unknown
  - See First-Line Therapy (NSCL-18)
- Sensitizing **EGFR** mutation positive
  - **ALK** positive
  - See First-Line Therapy (NSCL-19)
- **EGFR** and **ALK** testing especially in never smokers or small biopsy specimens, or mixed histology
  - **EGFR** and **ALK** testing should be conducted as part of broad molecular profiling
  - See First-Line Therapy (NSCL-20)

NSCLC With Genetic Alterations
Emerging Targeted Agents

<table>
<thead>
<tr>
<th>Genetic Alteration (eg, driver event)</th>
<th>Available Targeted Agents with Activity Against Driver Event in Lung Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BRAF V600E mutation</strong>*</td>
<td>vemurafenib</td>
</tr>
<tr>
<td></td>
<td>dabrafenib</td>
</tr>
<tr>
<td></td>
<td>dabrafenib + trametinib</td>
</tr>
<tr>
<td>High level <em>MET</em> amplification or MET</td>
<td>crizotinib</td>
</tr>
<tr>
<td>exon 14 skipping mutation</td>
<td></td>
</tr>
<tr>
<td><strong>RET rearrangements</strong></td>
<td>cabozaatinib</td>
</tr>
<tr>
<td><strong>ROS1 rearrangements</strong></td>
<td>crizotinib</td>
</tr>
<tr>
<td><strong>HER2 mutations</strong></td>
<td>trastuzumab (Category 2B)</td>
</tr>
<tr>
<td></td>
<td>afatinib (Category 2B)</td>
</tr>
</tbody>
</table>

*Non-V600E mutations have variable kinase activity and response to these agents


NSCLC
Currently Available EGFR TKIs

<table>
<thead>
<tr>
<th>TKIs</th>
<th>Reversible vs irreversible</th>
<th>EGFRm binding</th>
<th>EGFRwt binding</th>
<th>HER2 [ErbB2] and ErbB4 binding</th>
<th>T790M binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gefitinib, Erlotinib</td>
<td>Reversible</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Afatinib</td>
<td>Irreversible</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Osimertinib</td>
<td>Irreversible</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>++</td>
</tr>
</tbody>
</table>

LUX-Lung 7 Phase IIb Trial
Afatinib vs Gefitinib

- Stage IIIB/IV adenocarcinoma of the lung
- *EGFR* mutation (Del19 and/or L858R) in the tumor tissue*
- No prior treatment for advanced/metastatic disease
- ECOG PS 0/1

Randomization

1:1

Afatinib 40 mg once daily (n=160)

Gefitinib 250 mg once daily (n=159)

Primary endpoints: PFS (independent review), TTF, OS
Secondary endpoints: ORR, time to and duration of response, duration of disease control, tumor shrinkage, HRQoL, safety

Treatment beyond progression allowed if deemed beneficial by investigator


---

LUX-Lung 7 Phase IIb Trial
PFS by Independent Review

<table>
<thead>
<tr>
<th></th>
<th>Afatinib</th>
<th>Gefitinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>160</td>
<td>159</td>
</tr>
<tr>
<td>Median PFS (months)</td>
<td>11</td>
<td>10.9</td>
</tr>
<tr>
<td>HR (95%CI)</td>
<td>0.73 (0.57–0.95)</td>
<td>.0165</td>
</tr>
<tr>
<td><em>P</em>-value</td>
<td><em>0.0176</em></td>
<td><em>0.0184</em></td>
</tr>
</tbody>
</table>

### LUX-Lung 7 Phase IIb Trial

**ORR and DCR**

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>Afatinib (n=160)</th>
<th>Gefitinib (n=159)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>70%</td>
<td>56%</td>
<td>0.0083 (OR=1.87)</td>
</tr>
<tr>
<td>DCR</td>
<td>91%</td>
<td>87%</td>
<td>0.24 (OR=1.55)</td>
</tr>
<tr>
<td>ORR Exon 19 (n=186)</td>
<td>73%</td>
<td>66%</td>
<td></td>
</tr>
<tr>
<td>ORR Exon 21 L858R (n=133)</td>
<td>66%</td>
<td>42%</td>
<td></td>
</tr>
</tbody>
</table>

DCR=disease control rate; OR=odds ratio; ORR=overall response rate


### LUX-Lung 7 Phase IIb Trial

**Select Drug-Related AEs**

<table>
<thead>
<tr>
<th>AE category</th>
<th>Afatinib</th>
<th>Gefitinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>78%</td>
<td>12%</td>
</tr>
<tr>
<td>Rash/acne</td>
<td>79%</td>
<td>9%</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>60%</td>
<td>4%</td>
</tr>
<tr>
<td>Paronychia</td>
<td>54%</td>
<td>2%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>15%</td>
<td>6%</td>
</tr>
<tr>
<td>Nausea</td>
<td>15%</td>
<td>1%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>11%</td>
<td>3%</td>
</tr>
<tr>
<td>AST/ALT increased</td>
<td>10%</td>
<td>16%</td>
</tr>
<tr>
<td>ILD</td>
<td>0%</td>
<td>1%</td>
</tr>
</tbody>
</table>

Drug-related AE leading to dose reduction: afatinib 39% doses reduced to 30 mg daily, 13% reduced to 20 mg

PROFILE 1014 Phase III Study
First-line Crizotinib vs Chemotherapy

Key Entry Criteria
- ALK-positive by central FISH testing
- Locally advanced, recurrent, or metastatic non-squamous NSCLC
- No prior systemic treatment for advanced disease
- ECOG PS 0–2
- Measurable disease
- Stable treated brain metastases allowed

Endpoints
- Primary
  - PFS (RECIST 1.1, independent radiologic review [IRR])
- Secondary
  - ORR
  - OS
  - Safety
  - Patient-reported outcomes (EORTC QLQ-C30, LC13)

Crossover to crizotinib permitted after progression


PROFILE 1014 Phase III Study
PFS as Assessed by IRC

<table>
<thead>
<tr>
<th></th>
<th>Crizotinib n=172</th>
<th>Chemo n=172</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>100 (58)</td>
<td>137 (80)</td>
</tr>
<tr>
<td>Median, months</td>
<td>10.9</td>
<td>7</td>
</tr>
<tr>
<td>HR (95%CI)</td>
<td>0.45 (0.35–0.60)</td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>74%</td>
<td>45%</td>
</tr>
<tr>
<td><em>p</em>-value</td>
<td>&lt;.0001</td>
<td></td>
</tr>
</tbody>
</table>

J-ALEX Phase III Study
Alectinib vs Crizotinib

- ALK + NSCLC
- ALK Treatment naive
- ALK positive by central testing
- PS 0-2

Primary end-point: PFS by IRR
Secondary end-point: OS, ORR, CNS progression, HRQoL

<table>
<thead>
<tr>
<th></th>
<th>Alectinib (n=103)</th>
<th>Crizotinib (n=104)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR* in ITT population [95%CI]</td>
<td>85.4% [78.6 – 92.3]</td>
<td>70.2% [61.4 – 79.0]</td>
</tr>
<tr>
<td>CR or PR</td>
<td>88</td>
<td>73</td>
</tr>
</tbody>
</table>


Choosing The First-Line TKI
Things to Consider

- Aim for the therapy that can be effective not just for the 28 days but for months, if not years.
- If starting with afatinib (40 mg), inform a patient that they may need to go down on the dose due to toxicities.
  - Alternatively, start with 30 mg
- Consider first-generation TKIs, especially in a patient who is frail, unlikely to tolerate rash, diarrhea, and mucositis.
  - If necessary, start with lower dose (eg, erlotinib 100 mg).

Consider each patient as an individual
JO25567 Phase II Trial
Erlotinib +/- Bevacizumab

- Stage IIIIB/IV NSCLC
- EGFR exon 19 deletion or exon 21 L858R
- No brain metastases

Primary end-point: PFS by IRC
Secondary end-points: OS, ORR. DCR, QoL

Erlotinib 150 mg daily (n=77)
Erlotinib 150 mg daily + bevacizumab 15 mg/kg every 3 weeks (n=75)


## JO25567 Phase II Trial

### Safety Data

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Erlotinib + Bevacizumab (n=75)</th>
<th>Erlotinib (n=77)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td>Rash</td>
<td>25%</td>
<td>0%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Paronychia</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>Dry skin</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Liver tests</td>
<td>7%</td>
<td>1%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>60%</td>
<td>0%</td>
</tr>
<tr>
<td>Hemorrhagic event</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>8%</td>
<td>0%</td>
</tr>
</tbody>
</table>


## Erlotinib and Bevacizumab

### Potential Mechanism of Interaction

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>Erlotinib</th>
<th>Bevacizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism</td>
<td>Inhibits tumor cell growth and blocks synthesis of angiogenic proteins (eg, bFGF, VEGF, TGF-α) by tumor cells</td>
<td>Inhibits endothelial cells from responding to the angiogenic protein VEGF</td>
</tr>
</tbody>
</table>

**NEJ026 Phase III Trial**  
*Erlotinib +/- Bevacizumab*

- Non-sq NSCLC Previously untreated  
  Age 20 or above  
  EGFR M+  
  N=214

- Erlotinib + Bevacizumab  
  Recommend Pem/Platinum

- Erlotinib  
  Recommend Pem/Platinum + Bevacizumab

**Primary endpoint:** PFS  
**Secondary endpoint:** OS, RR, Safety

**RELAY Phase III Trial**  
*Erlotinib +/- Ramucirumab*

- Age >18  
- Stage IV NSCLC  
- EGFR exon 19/21  
- Measurable disease  
- N=462

- Ramucirumab 10mg/kg every 2 weeks + Erlotinib 150mg daily  
  Primary endpoint: PFS

- Placebo + Erlotinib 150mg daily

**Started in May 2015**

ClinicalTrials.gov Identifier: NCT02411448.
**ALK-Rearranged NSCLC**

**Current and Emerging ALK inhibitors**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Study (reference)</th>
<th>Previous crizotinib</th>
<th>Crizotinib-naive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crizotinib</td>
<td>Phase I (PROFILE 1001)</td>
<td>67/143 (46.6%)</td>
<td>9.7</td>
</tr>
<tr>
<td></td>
<td>Phase II (PROFILE 1005)</td>
<td>158/259 (61.8%)</td>
<td>8.1</td>
</tr>
<tr>
<td></td>
<td>Phase III 2nd line (PROFILE 1007)</td>
<td>119/173 (68.6%)</td>
<td>7.7</td>
</tr>
<tr>
<td></td>
<td>Phase III 1st line (PROFILE 1014)</td>
<td>126/172 (72.4%)</td>
<td>10.9</td>
</tr>
<tr>
<td>Ceritinib (LDK378)</td>
<td>Phase I (ASCEND-1)</td>
<td>92/136 (59%)</td>
<td>9.4</td>
</tr>
<tr>
<td></td>
<td>Phase II (ASCEND-2)</td>
<td>35/55 (64%)</td>
<td>5.7</td>
</tr>
<tr>
<td></td>
<td>Phase II (ASCEND-3)</td>
<td>70/124 (58.7%)</td>
<td>11.1</td>
</tr>
<tr>
<td>Alectinib (CH542480)</td>
<td>Phase II (AF-003-1F)</td>
<td>59/111 (53.8%)</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Phase III (AF-003-0G)</td>
<td>24/44 (54.5%)</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Phase II (NP29701)</td>
<td>33/69 (48%)</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Phase II (NP23673)</td>
<td>51/122 (42%)</td>
<td>10.3</td>
</tr>
<tr>
<td>Brigatinib (AP26113)</td>
<td>Phase II (77, phase II portion)</td>
<td>60/70 (71%)</td>
<td>13.4</td>
</tr>
<tr>
<td></td>
<td>(NCT01404461)</td>
<td>8/8 (100%)</td>
<td>Not reached</td>
</tr>
<tr>
<td>Lorlatinib (PF06403922)</td>
<td>Phase II (76, dose escalation)</td>
<td>17/32 (53.1%)</td>
<td>2/2 (100%)</td>
</tr>
<tr>
<td></td>
<td>(NCT01370865)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Entrectinib (RX-101)</td>
<td>Phase II (78, dose escalation)</td>
<td>9/4 (60%)</td>
<td>NA</td>
</tr>
</tbody>
</table>


---

**Targeted Therapies in NSCLC**

**Unanswered Questions**

- What is the optimal TKI sequence?
  - What is the value of moving the second-line therapy up?
- What is the mechanism of resistance?
  - G1202R (alectinib, ceritinib)
  - C797S (gefitinib, erlotinib, afatinib, osimertinib)
  - In case of other resistance mechanisms, is salvage with existing agents a possibility?
**Osimertinib**

*After Disease Progression on Rociletinib*

Longitudinal response for each patient who transitioned directly from rociletinib to osimertinib

Osimertinib
After Disease Progression on Rociletinib

- Early data warrant heightened vigilance and caution with regard to the attendant toxicities.
  - Sometimes uncommon and unexpected toxicities are seen.
  - It is uncertain at this point how general or drug-specific some of these toxicities are.
- Patient population that is likely to benefit from the TKI/immunotherapy combinations may not be defined well at this point.

CTONG1104 Phase III Trial

**Design**

1:1 randomization

- Adjuvant gefitinib (24 months)
- Adjuvant vinorelbine plus platinum chemotherapy (4 cycles)

**Primary:**
- Disease Free Survival

**Secondary:**
- OS
- DDFS
- Safety
- QoL

FPI: Sept 15, 2011

- Sample size was estimated to be 220 when HR of DFS; the primary endpoint was estimated to be 0.6; the enrollment period was to be 2 years; the period of follow-up after the final enrollment was to be 5 years; statistically significant level (α) was to be 0.05; the statistical power was to be 80%; the estimated total events is 122 from 208 analysed patients.

24 sites, 41 patients randomized (9/2012)

ClinicalTrials.gov Identifier: NCT01405079.

---

WJOG6410L, IMPACT Phase III Trial

**Design**

Assumptions:
- DFS for chemo 28 months
- HR=0.65
- Alpha=0.0025 (one sided), beta=0.2
- Necessary DFS events=169
- Registration 3y, f/u 5y
- Sample size=217

**Patients**
- Completely resected, stage II-III NSCLC
- EGFR mutation (exon 19 del or L858R)
- NO T790M

**Stratification**
- Institution
- Stage
- Gender
- Age

**Endpoints**
- 1^ Disease free survival
- 2^ OS Safety Recurrence Pattern

**Gefitinib**
- 250 mg/day for 2 years

**Cisplatin**
- 80 mg/m² d1
- Vinorelbine 25 mg/m² d1,8 every 3 weeks X 4 courses

**ALCHEMIST Phase III Trial (A081105)**

**Design**

- Resected NSCLC tissue tested on ALCHEMIST Screening Trial
- Patients with tumors with an EGFR mutation

Randomize

1 cycle = 21 days

- Erlotinib 150 mg po daily x 2 years → Long Term Follow-up
- Placebo po daily x 2 years → Long Term Follow-up

Primary endpoint is overall survival

ClinicalTrials.gov identifier: NCT02193282.

---

**ADAURA Phase III Trial**

**Design**

- Stage IB-IIIA Primary NSCLC
- EGFR mutation positive including the atypical mutations
- WHO PS 0,1 Completed resection and adjuvant chemotherapy

Randomize

- Osimertinib 2:1 2 year treatment period
- Placebo

- Primary endpoint: Disease-free survival (DFS)
- Secondary endpoints: OS; DFS and OS in patients with del19/L858R

ClinicalTrials.gov identifier: NCT02511106.
Liquid Biopsy
Potential Clinical Applications

- Screening and early detection of cancer
  - EGFR mutations in ctDNA
  - CTC counts
- Stratification and therapeutic intervention
- Real time monitoring of therapy
- Therapeutic targets and resistance mechanisms
- Risk for metastatic relapse (prognosis)
  - CTC counts in solid tumors

AURA Phase I Study
Plasma EGFR Genotyping

```
Sensitivity

<table>
<thead>
<tr>
<th>Allele Fraction (%)</th>
<th>19 del</th>
<th>L858R</th>
<th>T790M</th>
</tr>
</thead>
<tbody>
<tr>
<td>N/D</td>
<td>n = 136</td>
<td>n = 73</td>
<td>n = 158</td>
</tr>
<tr>
<td></td>
<td>92.9%</td>
<td>88.9%</td>
<td>70.5%</td>
</tr>
</tbody>
</table>

Specificity

<table>
<thead>
<tr>
<th>Allele Fraction (%)</th>
<th>19 del</th>
<th>L858R</th>
<th>T790M</th>
</tr>
</thead>
<tbody>
<tr>
<td>N/D</td>
<td>n = 190</td>
<td>n = 143</td>
<td>n = 518</td>
</tr>
<tr>
<td></td>
<td>97.8%</td>
<td>96.8%</td>
<td>69.0%</td>
</tr>
</tbody>
</table>
```

Use of Plasma EGFR Genotyping

New Paradigm

Acquired resistance to EGFR TKI

- FDA-approved plasma assay for T790M and sensitizing mutations
  - T790M+
    - Skip biopsy, start 3rd gen EGFR TKI
  - T790M-
    - Biopsy, FDA approved FFPE assay for T790M
      - T790M+
        - 3rd gen EGFR TKI
      - T790M-
        - Chemo


Osimertinib

Select Combination Trials

- NCT02143466 (TATTON)
  - Selumetinib (MEK inhibitor)
  - Savolitinib (MET inhibitor)
  - Durvalumab (anti-PD-L1 mAb)
- NCT02496663: Necitumumab (anti-EGFR mAb)
- NCT02520778: Navitoclax (Bcl-xL, Bcl-2, and Bcl-w inhibitor)

Lung Adenocarcinoma
Progress in Identifying Genomic Alterations

Key Take Home Points

• There has been a lot of progress and the future seems bright.
  – We have developed a number of sophisticated tools and targeted agents, and now we need to figure out how best to use them, and in what context.

• As we continue making progress, molecular testing is going to be more and more important.
  – Learning from the tumors, learning from our patients, not just what happens at diagnosis, but during the course of the therapy will help us guide our therapies moving forward.
Thank you for participating in this activity.

Abbreviations

- AE = Adverse event
- ALK = Anaplastic lymphoma kinase
- ALT = Alanine aminotransferase
- ASCO = American Society of Clinical Oncology
- AST = Aspartate aminotransferase
- CAP/IASLC/AMP = College of American Pathologists/International Association for the Study of Lung Cancer/Association for Molecular Pathology
- CI = Confidence interval
- DCR = Disease control rate
- DFS = Disease free survival
- ddPCR = Droplet digital PCR
- ECOG = Eastern Cooperative Oncology Group
- EGFR = Epidermal growth factor receptor
- FISH = Fluorescence In Situ Hybridization
- HR = Hazard ratio
Abbreviations (cont.)

- HRQoL = Health-Related Quality of Life
- ILD = Interstitial lung disease
- IRC = Independent review committee
- IRR = independent radiologic review
- KRAS = V-Ki-ras2 Kristen rat sarcoma
- NSCLC = Non-small cell lung cancer
- OR = Odds ratio
- ORR = Objective response rate or overall response rate
- OS = Overall survival
- PFS = Progression free survival
- PS = performance status
- QOL = Quality of life
- RECIST = Response Evaluation Criteria in Solid Tumors
- TKI = Tyrosine-kinase inhibitor
- TTF = Time to treatment failure