Targeted Therapies for Advanced NSCLC

Current Clinical Developments

Friday, June 3, 2016

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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.

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.
Previously-Treated Disease

Targeting EGFR and ALK Resistance
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Associate Professor of Medicine
Massachusetts General Hospital Cancer Center
Harvard Medical School
Boston, MA
Disclosures

• I consult for ARIAD, AstraZeneca, Boehringer Ingelheim, Clovis, Merrimack, Novartis, and Taiho
• I am not on any scientific advisory boards
• I am not a member of any speakers’ bureau
TKI-Resistant NSCLC
Type of Disease Progression

What type of progression is the patient having?

Oligoprogession

Diffuse PD

PD=Progressive Disease
TKI-Resistant NSCLC

Oligoprogression

What type of progression is the patient having?

Oligoprogression

Consider RT or surgery with continued TKI

Progression Free Survival (%)

- PFS1: 9.8m
- PFS1 + PFS2: 9.8m + 6.2m

PFS of all patients treated with LAT and continuation of TKI therapy

25 patients, 15 ALK+, 10 EGFR+

TKI-Resistant NSCLC
Oligoprogression – CNS Only

What type of progression is the patient having?

Oligoprogression

Consider RT or surgery with continued TKI

If PD is in CNS only, consider a more CNS-penetrant TKI

PFS of all patients treated with LAT and continuation of TKI therapy

- PFS1: 9.8m
- PFS1 + PFS2: 9.8m + 6.2m

25 patients, 15 ALK+, 10 EGFR+

TKI-Resistant NSCLC

Diffuse Progressive Disease

What type of progression is the patient having?

Oligoprogression

Consider RT or surgery with continued TKI

If PD is in CNS only, consider a more CNS-penetrant TKI

Diffuse PD

Indolent Pace

Treatment Beyond PD
Delaying The Change of Treatment

*Post-Progression Erlotinib*

Baseline: Start erlotinib
3m: Response
14m: PD
18m
24m
30m: Re-biopsy
35m
37m
39m: First dyspnea

Discontinuation of Targeted TKIs

Disease Flare

- Established phenomenon in EGFR mutants
- ~25% of patients with acquired resistance will flare (defined as hospitalization or death) upon TKI d/c
- Median time from drug d/c=8 days

ASPIRATION
Study Design

- Inclusion criteria: patients with confirmed stage IV or recurrent NSCLC with exon 18–21 mutations with measurable disease and ECOG PS 0–2
- Exclusion criteria: T790M mutations, prior chemotherapy, prior treatment with anti-HER agents, uncontrolled systemic conditions, pre-existing lung conditions, and warfarin use
- Primary endpoint: PFS1 (time to RECIST PD or death)
- Secondary endpoints:
  - PFS2 (time to off-erlotinib PD if erlotinib was extended beyond RECIST PD)
  - PFS1 in exon 19 deletion/L858R subsets
  - OS
  - ORR/DCR/BOR
  - Safety

BOR=best overall response; ECOG PS=Eastern Cooperative Oncology Group performance status; DCR=disease control rate; mut+=mutation positive; ORR=objective response rate; OS=overall survival; PFS=progression-free survival

**ASPIRATION**

**PFS1 (Time to RECIST PD or Death)**

- Secondary endpoints, ITT population
  - ORR: 66.2%
  - DCR: 82.6%
  - Median OS: 31.0 months (95% CI, 27.3 - not reached)

- Data cut off - 14 Feb 2014

- N=176 PFS events

![Survival Probability vs Progression-Free Survival Time](chart)

- Survival Probability
- Progression-Free Survival Time (months)

- PFS1 assessed by investigator

- 10.8 months (95% CI, 9.2–11.1)

---

Median PFS 2 (N=93; 79 PD events): 14.1 months (95% CI 12.2-15.9)

Data cut off - 14 Feb 2014
TKI-Resistant NSCLC

Faster Pace Progression

What type of progression is the patient having?

- **Oligoprogression**
  - Consider RT or surgery with continued TKI
  - If PD is in CNS only, consider a more CNS-penetrant TKI

- **Diffuse PD**
  - Indolent Pace
  - Faster Pace

- **Treatment Beyond PD**
  - Switch Therapies
What type of progression is the patient having?

Oligoprogression:
- Consider RT or surgery with continued TKI
  - If PD is in CNS only, consider a more CNS-penetrant TKI

Diffuse PD:
- Indolent Pace
- Faster Pace
  - Treatment Beyond PD
  - Switch Therapies

Beyond PD:
- Faster Pace
  - Switch Therapies
TKI Resistance

General Types

Target Alteration

Mutant and/or amplified TK

- Activated TK
  - PI3K
  - ERK
  - STAT

TKI-naive

- Activated TK
  - PI3K
  - ERK
  - STAT

Bypass Tracks

- Activated TK
  - PI3K
  - ERK
  - STAT

RTK1
RTK2

?
Target Alteration

Majority of Resistance to 1st line EGFR TKIs

Target Alteration

Minority of Resistance to 1st line ALK TKIs

EGFR and ALK TKIs
Approved 2\textsuperscript{nd} line Targeted Therapies

**EGFR**
- Osimertinib: 80 mg daily

**ALK**
- Ceritinib: 750 mg daily
- Alectinib: 600 mg twice daily
Third Generation EGFR TKIs
Irreversible, T790M-Specific, wt-Sparing

IC_{50} (nmol/L)

Wildtype
Del19
T790M

Erlotinib
Afatinib
Rociletinib
Osimertinib
Osimertinib
EGFR T790M-Positive Patients

Best Percentage Change from Baseline in Target-Lesion Size

Response rate = 61%

Osimertinib
AURA Phase I Trial

Number of patients at risk:
- Osimertinib 80 mg

<table>
<thead>
<tr>
<th>Month</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>63</td>
</tr>
<tr>
<td>3</td>
<td>55</td>
</tr>
<tr>
<td>6</td>
<td>48</td>
</tr>
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<td>9</td>
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</tr>
<tr>
<td>24</td>
<td>5</td>
</tr>
<tr>
<td>27</td>
<td>1</td>
</tr>
</tbody>
</table>

Median PFS,* months (95% CI) 9.7 (8.3, 13.6)

Remaining alive and progression-free,† % (95% CI)
- 12 months: 41 (29, 53)
- 18 months: 29 (18, 41)
- 24 months: 17 (8, 30)

Cut off - 4 January 2016; population: safety analysis set; investigator assessed;
Progression events that do not occur within 14 weeks of the last evaluable assessment (of first dose) are censored.
*PFS is the time from date of first dosing until the date of objective disease progression or death
Osimertinib
AURA Pooled Phase II Trial

AURA pooled Ph II data cut off - 1 November 2015; population: full analysis set; assessment: BICR
Progression events that do not occur within 14 weeks of the last evaluable assessment (of first dose) are censored; Tick marks on the Kaplan-Meier plot denote censored observations

*PFS is the time from date of first dosing until the date of objective disease progression or death


**Probabilty of PFS**

<table>
<thead>
<tr>
<th>Month</th>
<th>Osimertinib 80 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>441</td>
</tr>
<tr>
<td>3</td>
<td>332</td>
</tr>
<tr>
<td>6</td>
<td>271</td>
</tr>
<tr>
<td>9</td>
<td>205</td>
</tr>
<tr>
<td>12</td>
<td>161</td>
</tr>
<tr>
<td>15</td>
<td>38</td>
</tr>
<tr>
<td>18</td>
<td>0</td>
</tr>
</tbody>
</table>

Number of patients at risk:

<table>
<thead>
<tr>
<th>Month</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>332</td>
</tr>
<tr>
<td>6</td>
<td>271</td>
</tr>
<tr>
<td>9</td>
<td>205</td>
</tr>
<tr>
<td>12</td>
<td>161</td>
</tr>
<tr>
<td>15</td>
<td>38</td>
</tr>
<tr>
<td>18</td>
<td>0</td>
</tr>
</tbody>
</table>

Median PFS,* months (95% CI) 11 (9.6, 12.4)

Remaining alive and progression-free,† % (95% CI)

<table>
<thead>
<tr>
<th>Time</th>
<th>Osimertinib 80 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 months</td>
<td>48 (42, 53)</td>
</tr>
<tr>
<td>18 months</td>
<td>NC</td>
</tr>
<tr>
<td>24 months</td>
<td>NC</td>
</tr>
</tbody>
</table>
## AURA Pooled Phase II Trial

### Causally-Related AEs

<table>
<thead>
<tr>
<th>Causally-related AEs occurring in ≥15% of patients overall, n (%)</th>
<th>AURA pooled Ph II (80 mg) N=411*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1</td>
</tr>
<tr>
<td>Rash (grouped terms)</td>
<td>146 (36)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>138 (34)</td>
</tr>
<tr>
<td>Dry skin (grouped terms)</td>
<td>116 (28)</td>
</tr>
<tr>
<td>Paronychia (grouped terms)</td>
<td>88 (21)</td>
</tr>
</tbody>
</table>

### Select AEs

<table>
<thead>
<tr>
<th>Select AEs</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade ≥3</th>
<th>Any grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>ILD (grouped terms)†</td>
<td>4 (1)</td>
<td>0</td>
<td>8 (2)</td>
<td>12 (3)</td>
</tr>
<tr>
<td>Hyperglycaemia</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>QT prolongation</td>
<td>7 (2)</td>
<td>3 (&lt;1)</td>
<td>4 (1)</td>
<td>14 (3)</td>
</tr>
</tbody>
</table>

AURA pooled Ph II data cut off - 1 November 2015; population: full analysis set

*Total median treatment duration 13.2 months; †As of June 1, 2015, of more than 1200 patients across all studies dosed with osimertinib, ILD grouped term events were reported in approximately 2.9% of patients (35 events): nine Grade 1, six Grade 2, 18 Grade ≥3, two currently ungraded. Of these, a total of four patients are reported to have died due to ILD (Grade 5).

Rociletinib  
*TIGER-X Updates*

Best response (all doses) in 243 centrally-confirmed tissue EGFR T790M+ pts

<table>
<thead>
<tr>
<th>Dose</th>
<th>n</th>
<th>ORR (%)</th>
<th>DCR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>500 mg BID HBr</td>
<td>48</td>
<td>60%</td>
<td>90%</td>
</tr>
<tr>
<td>625 mg BID HBr</td>
<td>114</td>
<td>54%</td>
<td>84%</td>
</tr>
<tr>
<td>750 mg BID HBr</td>
<td>77</td>
<td>46%</td>
<td>82%</td>
</tr>
<tr>
<td>1000 mg BID HBr</td>
<td>4</td>
<td>75%</td>
<td>100%</td>
</tr>
<tr>
<td>Total</td>
<td>243</td>
<td>53%</td>
<td>85%</td>
</tr>
</tbody>
</table>

ORR, objective response rate; DCR, disease control rate

TIGER-X Updates

Common Treatment-Related AEs

All grades in >10% of pts, n (%)

<table>
<thead>
<tr>
<th>AE</th>
<th>500mg BID (N=119)</th>
<th>625mg BID (N=236)</th>
<th>750mg BID (N=95)</th>
<th>1000mg BID (N=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperglycemia</td>
<td>42 (35)</td>
<td>17 (45)</td>
<td>56 (59)</td>
<td>4 (67)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>39 (33)</td>
<td>94 (40)</td>
<td>28 (30)</td>
<td>4 (67)</td>
</tr>
<tr>
<td>Nausea</td>
<td>23 (19)</td>
<td>79 (34)</td>
<td>35 (37)</td>
<td>3 (50)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>15 (29)</td>
<td>37 (30)</td>
<td>21 (27)</td>
<td>1 (25)</td>
</tr>
<tr>
<td>QTc prolongation</td>
<td>15 (13)</td>
<td>53 (23)</td>
<td>25 (26)</td>
<td>3 (50)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>18 (15)</td>
<td>38 (16)</td>
<td>24 (25)</td>
<td>2 (33)</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>17 (14)</td>
<td>30 (13)</td>
<td>20 (21)</td>
<td>1 (17)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10 (8)</td>
<td>38 (16)</td>
<td>13 (14)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>12 (10)</td>
<td>21 (9)</td>
<td>16 (17)</td>
<td>1 (17)</td>
</tr>
</tbody>
</table>

Grades 3/4 in >10% of pts, N (%)

<table>
<thead>
<tr>
<th>AE</th>
<th>500mg BID (N=119)</th>
<th>625mg BID (N=236)</th>
<th>750mg BID (N=95)</th>
<th>1000mg BID (N=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperglycemia</td>
<td>20 (17)</td>
<td>56 (24)</td>
<td>34 (36)</td>
<td>2 (33)</td>
</tr>
</tbody>
</table>

- No ILD observed in 500mg twice daily dose group
- 7/456 cases overall (1.5%)
- Rociletinib continuation possible with steroid cover
- No fatal ILD in program
- No paronychia or stomatitis observed; trivial rash
- Grade 3 QTc prolongation at 500 mg twice daily=2.5%
- Treatment-related AEs leading to drug discontinuation seen in 2.5% of cases at 500 mg twice daily (4% overall)
- Hyperglycemia readily managed with oral agents
- No contraindication for pre-existing diabetic patients

Rociletinib
NDA Filing Regulatory Update

November 16, 2015

during its regularly scheduled Mid-Cycle Communication Meeting held last week with the U.S. Food and Drug Administration (FDA), the agency requested additional clinical data for use in the efficacy analysis for both the 500mg and 625mg BID dose patient groups for rociletinib. The Company will provide this information in a Major Amendment to the FDA by close of business today.

“We are working hard to meet the FDA’s request,” said P. Peter Woodman, our President and CEO. “In the confirmatory studies, the efficacy analyses were based primarily on unconfirmed responses. This was also true of the Company’s Breakthrough Therapy designation submission. In the Company’s NDA submission, both immature confirmed and unconfirmed response analyses were submitted. As the efficacy data have matured, the number of patients with an unconfirmed response who converted to a confirmed response was lower than expected.

As the rociletinib clinical trials were rapidly enrolling, Clovis presented interim data publicly and at medical meetings and these data therefore included a data set based primarily on unconfirmed responses. This was also true of the Company’s Breakthrough Therapy designation submission. In the Company’s NDA submission, both immature confirmed and unconfirmed response analyses were submitted. As the efficacy data have matured, the number of patients with an unconfirmed response who converted to a confirmed response was lower than expected.

In the intent to treat analysis of the 79 patients in the 500mg dose group, the current confirmed response rate is 28 percent, and 34 percent in the 170 patients in the 625mg dose group, with an encouraging duration of response in both doses. The most frequent reasons that patients’ responses were not confirmed in a subsequent scan were due to progression, often due to brain metastasis, and due to subsequent scans not demonstrating tumor shrinkage greater than 30 percent.

The Company anticipates that the review of this additional information will result in a delay of a potential approval. This additional review could lead to an extension of the Company’s March 30, 2016 Prescription Drug User Fee Act (PDUFA)
Update to Rociletinib Data

**RECIST Confirmed Response Rate**

**Patients with T790M-Positive Disease**

- Reported Response (59%)
- Mature Best Response (45%)

**Dose**
- 1000 mg twice daily
- 750 mg twice daily
- 625 mg twice daily
- 500 mg twice daily
- 900 mg twice daily, free-base formulation

**Patients with T790M-Negative Disease**

- Reported Response (29%)
- Mature Best Response (17%)

**Dose**
- 750 mg twice daily
- 625 mg twice daily
- 500 mg twice daily
- 900 mg twice daily, free-base formulation

Osimertinib

After Disease Progression on Rociletinib

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

EGF816

First-in-Human Phase I/II Study

Best Percentage Change from Baseline in Target Lesions

n/N(%) = 40/53 (75.5%)

Best Percentage Change from Baseline

Treatment Group

75 mg EGF816 QD  150 mg EGF816 QD  225 mg EGF816 QD  300 mg EGF816 QD  350 mg EGF816 QD

# EGF816 Phase I/II Study

## Drug-Related AEs (>10% of Pts)

<table>
<thead>
<tr>
<th>Adverse event, n (%)</th>
<th>All Grades</th>
<th>Grade 3/4</th>
<th>Dose group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3/4</td>
<td>75 mg QD (n=7)</td>
</tr>
<tr>
<td>Maculopapular rash</td>
<td>3 (43)</td>
<td>0</td>
<td>3 (19)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
<td>0</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Dry skin</td>
<td>1 (14)</td>
<td>0</td>
<td>5 (31)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>4 (57)</td>
<td>0</td>
<td>4 (25)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>1 (14)</td>
<td>0</td>
<td>4 (25)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>1 (14)</td>
<td>0</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Dermatitis acneiform</td>
<td>0</td>
<td>0</td>
<td>3 (19)</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (14)</td>
<td>0</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Paronychia</td>
<td>0</td>
<td>0</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (14)</td>
<td>0</td>
<td>1 (6)</td>
</tr>
</tbody>
</table>

Ceritinib in ALK-Rearranged NSCLC Response

Tumor Change

- Prior crizotinib treatment
- No prior crizotinib treatment
- Disease progression or death

PET Scans

Best Change from Baseline (%)

0 -20 -40 -60 -80 -100

Patients

Baseline

After 3.5 weeks

Ceritinib in ALK-Rearranged NSCLC

**PFS**

No. at Risk
NSCLC, no prior crizotinib treatment 34 21 13 4 2 0
NSCLC 114 66 30 9 2 0
NSCLC, prior crizotinib treatment 80 45 17 5 0

### Ceritinib in ALK-Rearranged NSCLC

**Drug-Related Grade 3/4 AEs**

<table>
<thead>
<tr>
<th>Event</th>
<th>Dose group</th>
<th>50-300 mg/day (N=10)</th>
<th>400 mg/day (N=14)</th>
<th>500 mg/day (N=10)</th>
<th>600 mg/day (N=10)</th>
<th>700 mg/day (N=5)</th>
<th>750 mg/day (N=81)</th>
<th>Total (N=130)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any event</td>
<td></td>
<td>2 (20)</td>
<td>4 (29)</td>
<td>3 (30)</td>
<td>5 (50)</td>
<td>4 (80)</td>
<td>46 (57)</td>
<td>64 (49)</td>
</tr>
<tr>
<td>Elevated alanine aminotransferase level</td>
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<td>1 (10)</td>
<td>1 (7)</td>
<td>2 (20)</td>
<td>0</td>
<td>4 (80)</td>
<td>19 (23)</td>
<td>27 (21)</td>
</tr>
<tr>
<td>Elevated aspartate aminotransferase level</td>
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<td>0</td>
<td>1 (7)</td>
<td>0</td>
<td>0</td>
<td>3 (60)</td>
<td>10 (12)</td>
<td>14 (11)</td>
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<tr>
<td>Diarrhea</td>
<td></td>
<td>0</td>
<td>1 (7)</td>
<td>1 (10)</td>
<td>1 (10)</td>
<td>0</td>
<td>6 (7)</td>
<td>9 (7)</td>
</tr>
<tr>
<td>Elevated lipase level</td>
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<td>0</td>
<td>0</td>
<td>1 (10)</td>
<td>0</td>
<td>8 (10)</td>
<td>9 (7)</td>
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<tr>
<td>Nausea</td>
<td></td>
<td>0</td>
<td>0</td>
<td>1 (10)</td>
<td>0</td>
<td>0</td>
<td>6 (7)</td>
<td>7 (5)</td>
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<tr>
<td>Fatigue</td>
<td></td>
<td>0</td>
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<td>1 (10)</td>
<td>0</td>
<td>0</td>
<td>5 (6)</td>
<td>6 (5)</td>
</tr>
<tr>
<td>Vomiting</td>
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<td>0</td>
<td>0</td>
<td>1 (10)</td>
<td>0</td>
<td>5 (6)</td>
<td>6 (5)</td>
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<tr>
<td>Hypophosphatemia</td>
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<td>1 (7)</td>
<td>0</td>
<td>1 (10)</td>
<td>0</td>
<td>2 (2)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Elevated amylase level</td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (10)</td>
<td>0</td>
<td>2 (2)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Elevated blood alkaline phosphatase level</td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (20)</td>
<td>2 (2)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3 (4)</td>
<td>3 (2)</td>
</tr>
</tbody>
</table>

* Adverse events listed here are those that were reported in at least 2% of patients and that were suspected to be related to the study drug. Events were graded according to the Common Terminology Criteria for Adverse Events, version 4.0. Patients who had more than one occurrence of the same event were only counted once within each category. Patients were categorized according to the initial dose received.
**ALK+ NSCLC**

*Sequential Crizotinib and Ceritinib*

- Overall survival: 49.4 months

Alectinib

**ALK+ Crizotinib-Resistant NSCLC**

Systemic best overall response

- **Progressive disease (N=11)**
- **Stable disease (N=22)**
- **Partial response (N=33)**

**Graph**

- **Y-axis**: Sum of longest diameter, maximum decrease, from baseline (%)
- **X-axis**: Patient

Alectinib (cont.)

ALK+ Crizotinib-Resistant NSCLC

PFS as assessed by IRC

Median progression-free survival 8.1 months (95% CI, 6.2-12.6)

Number at risk

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alectinib</td>
<td>87</td>
</tr>
</tbody>
</table>

Alectinib CNS Responses

January 8, 2013
March 8, 2013
January 10, 2013
March 14, 2013

Day -12
Day +23
Day -4
Day +18

#10604
#10605

### Alectinib AF-002JG Phase 1/2 Study

**Common AEs (in >10% Pts)**

<table>
<thead>
<tr>
<th>Grade 3/4 AEs</th>
<th>N=47 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>γ-GT increase</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Neutrophil decrease</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Syncope</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Rash</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Common AEs</th>
<th>N=47 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>14 (30%)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>8 (17%)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>8 (17%)</td>
</tr>
<tr>
<td>Blood CPK increase</td>
<td>7 (15%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>7 (15%)</td>
</tr>
<tr>
<td>ALT increase</td>
<td>6 (13%)</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>6 (13%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>5 (11%)</td>
</tr>
<tr>
<td>Rash</td>
<td>5 (11%)</td>
</tr>
</tbody>
</table>

Brigatinib (AP26113) in ALK+ NSCLC Antitumor Activity

- 72% (41/57) objective response rate (95% CI, 59-83%)

- 100% (6/6) crizotinib-naïve responded (incl. 1 CR)
  - Average time to response: 9.2 wks (+/-3.22 wks)

- 69% (35/51) post-crizotinib responded (95% CI, 54-81%)
  - Response duration: 1.6-14.7 mos (ongoing)
  - Average time to response: 9.3 weeks (+/- 3.72 wks)
  - Median PFS: 10.9 mos (M=49)

Unlike founder mutations, pie charts may not be the best way to conceptualize resistance mutations.
Spectrum of Rociletinib Resistance
Underlying T790M Heterogeneity

T790M+

T790WT

Pre-rociletinib

Response to rociletinib

Acquired Resistance to rociletinib

Conclusions

• New paradigms
  – Treatment beyond progression
  – Local ablative therapy for oligometastatic growth

• New drugs for 2\textsuperscript{nd} line
  – Osimertinib
  – Ceritinib
  – Alectinib
  – More to come

• New technologies – ctDNA

• New hope!
Thank you!

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