Management of EGFR-Mutation Positive Metastatic Non-Small Cell Lung Cancer

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EGFR Mutation in Advanced NSCLC:
NCCN, Florida 2016

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Yale Cancer Center
Chief Medical Officer
Smilow Cancer Hospital
Molecular Targeted Therapy in Cancer

- BCR-ABL: Imatinib, Dasatinib, Nilotinib
- ERBB2 (Her2): Trastuzumab, Lapatinib, Pertuzumab, T-DM1
- EGFR
- ALK
- KRAS: Cetuximab, Panitumumab
- BRAF: Vemurafenib

Personalized Medicine in Lung Cancer

- Certain tumors arise as a result of aberrant activation of a single oncogene and become dependent on this activation.
- This phenomenon is known as oncogenic addiction.
- Identification of actionable oncogenic drivers creates the potential for highly active therapeutic interventions.
- As an example, EGFR TKIs are now considered a standard first-line treatment for patients with mutated tumors.
Molecular Alterations in Lung Adenocarcinoma


Note: Does not include ROS1 or RET

Tumor Profiling at Yale

• Tier 1: Reflex testing using TaqMan platform
  – 5 to 7 days

• Tier 2: Oncomine Cancer Panel (143 genes and >40 translocations/fusions) on Ion Torrent
  – 2 weeks

• Tier 3: Whole exome sequencing with future custom panels per organ system specification
  – 2-3 weeks
EGFR Mutations

- High ORR with EGFR TKIs with exon 19 deletion / exon 21 L858R point mutation
- Most common in never smokers, females, patients with East Asian ethnicity, and adenocarcinomas


The NCCN NSCLC Guidelines Panel strongly endorses broader molecular profiling with the goal of identifying rare driver mutations for which effective drugs may already be available, or to appropriately counsel patients regarding the availability of clinical trials. Broad molecular profiling is a key component of the improvement of care of patients with NSCLC. See Emerging Targeted Agents for Patients With Genetic Alterations (NSCL-H).
Gefitinib vs Carboplatin/Paclitaxel for Clinically Selected Chemotherapy-Naïve Patients With Advanced NSCLC in Asia (IPASS)

Eligibility:
- Chemotherapy-naïve
- Age ≥ 18 years
- Adenocarcinoma
- Never or light ex-smokers
- Life expectancy >12 weeks
- Measurable stage III/IV disease

Gefitinib (G) 250 mg/day
Carboplatin (C) AUC 5 or 6
Paclitaxel (P) 200 mg/m² q3w

Primary endpoint: PFS (noninferiority)
Secondary endpoints: ORR, OS, QOL, disease-related symptoms, safety
Exploratory biomarkers: EGFR mutation, EGFR gene copy number, EGFR protein expression

Endpoints:
<table>
<thead>
<tr>
<th>Endpoint</th>
<th>G N=609</th>
<th>C + P N=608</th>
<th>HR/OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mPFS</td>
<td>5.7 mos</td>
<td>5.8 mos</td>
<td>0.741 (0.65-0.85) P&lt;0.0001</td>
</tr>
<tr>
<td>mOS</td>
<td>18.8 mos</td>
<td>17.4 mos</td>
<td>0.90 (0.79-1.02)  P=0.109</td>
</tr>
<tr>
<td>ORR (%)</td>
<td>43.0</td>
<td>32.2</td>
<td>1.59 (1.25-2.01) P=0.0001</td>
</tr>
</tbody>
</table>

Gefitinib M+ or M- patients upon progression
PC offered to gefitinib patients upon progression

*Limited to maximum of 6 cycles.

IPASS: PFS and OS in EGFR Mutation–Positive and –Negative Patients

Patients at risk excludes censored patients and those who have experienced an event.
### Randomized Trials of EGFR TKI vs CT in 1st Line Rx

<table>
<thead>
<tr>
<th>Study</th>
<th>ORR</th>
<th>PFS (mo)</th>
<th>HR</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>EURTAC</td>
<td>58% vs 15%</td>
<td>9.7 vs 5.2</td>
<td>0.37</td>
<td>ND</td>
</tr>
<tr>
<td>OPTIMAL</td>
<td>83% vs 36%</td>
<td>13.1 vs 4.6</td>
<td>0.16</td>
<td>ND</td>
</tr>
<tr>
<td>NEJ 002</td>
<td>74% vs 31%</td>
<td>10.8 vs 5.4</td>
<td>0.30</td>
<td>ND</td>
</tr>
<tr>
<td>WJTOG 3405</td>
<td>62% vs 31%</td>
<td>9.2 vs 6.3</td>
<td>0.49</td>
<td>ND</td>
</tr>
<tr>
<td>IPASS</td>
<td>71% vs 47%</td>
<td>9.5 vs 5.5</td>
<td>0.19</td>
<td>ND</td>
</tr>
<tr>
<td>LUX LUNG 3</td>
<td>56% vs 23%</td>
<td>11.1 vs 6.9</td>
<td>0.58</td>
<td>ND</td>
</tr>
<tr>
<td>LUX LUNG 6</td>
<td>67% vs 23%</td>
<td>11.0 vs 5.6</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>


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### EURTAC Study

**Patients**
- Chemonaive
- Age ≥18 years
- Known EGFR mutation
  - L858R
  - Del19
- PS 0-2
- Measurable stage IIIB / IV disease

- N= 173

**1:1 randomization**

- Erlotinib (150 mg / day) N=86
- Platinum + docetaxel or gemcitabine* N=87

**Endpoints**

**Primary**
- Progression-free survival

**Secondary**
- Objective response rate
- Overall survival
- EGFR mutation detection from serum

*Investigator could choose cisplatin or carboplatin and also docetaxel vs. gemcitabine

Chemo therapy was given for up to 4 cycles

Rosell et al, Lancet 2012
EURTAC Results

Rosell et al., Lancet 2012

LUX-Lung 3 and 6: design

- Stage IIIIB/IV adenocarcinoma of the lung
- Presence of EGFR mutation in the tumor tissue*
- No prior treatment with chemotherapy for advanced/metastatic disease or EGFR inhibitors
- ECOG PS 0 or 1

Randomization

Stratification by EGFR mutation type: Del19/L858R/other and by race (LUX-Lung 3 only): Asian/non-Asian

Afatinib
40 mg orally once daily

LUX-Lung 3:
Cisplatin + pemetrexed up to 6 cycles

LUX-Lung 6:
Cisplatin + gemcitabine up to 6 cycles

Primary endpoint: PFS (independent review) Secondary end points: ORR, DCR, OS, PRO, safety

*EGFR29: 19 deletions in exon 19, 3 insertions in exon 20, L858R, L861Q, T790M, G719S, G719A and G719C (or G719X), S768I.
Overall Survival with Afatinib by EGFR mutation categories

- **Del19**
  - Afatinib: n=236
  - Chemo: n=119
  - Median, months: 31.7 vs 20.7
  - HR (95% CI): 0.59 (0.45–0.77), p<0.0001

- **L858R**
  - Afatinib: n=183
  - Chemo: n=93
  - Median, months: 22.1 vs 26.9
  - HR (95% CI): 1.25 (0.92–1.71), p=0.1600

Afatinib vs Chemotherapy in the first-line setting:
Combined OS analysis in patients with common EGFR mutations

- Afatinib: n=419
  - Chemo: n=212
  - Median, months: 27.3 vs 24.3
  - HR (95% CI): 0.81 (0.66–0.99), p=0.0374

Yang et al, 2015
LUX-Lung 7 - Study Design

- 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

Gefitinib 250 mg once daily

Primary endpoints: PFS (independent review), TTF, OS

Secondary endpoints: ORR, time to and duration of response, duration of disease control, tumor shrinkage, HRQoL, safety

Stratified by mutation type (Del19 vs L858R) and presence of brain metastases (yes vs no)

*Afatinib is approved in a number of markets, including the EU, Japan, Taiwan and Canada and in the U.S. for use in patients with distinct types of EGFR mutation-positive NSCLC. Registration conditions differ internationally, please refer to locally approved prescribing information. Afatinib is under regulatory review in other countries worldwide.

*Afatinib Gefitinib

Median DoR, months

 Afatinib 112/160

 Gefitinib 89/159

<table>
<thead>
<tr>
<th></th>
<th>Afatinib 112/160</th>
<th>Gefitinib 89/159</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>70%</td>
<td>56%</td>
</tr>
<tr>
<td>Disease control rate (N)</td>
<td>91.3% (146)</td>
<td>87.4% (139)</td>
</tr>
</tbody>
</table>

Objective Response and Disease Control Rates

Park et al. Ann Oncol. 2015;26 (suppl 9; abstract LBA2).
**Common Adverse Events Following Use of EGFR TKIs**

<table>
<thead>
<tr>
<th>Adverse event, %</th>
<th>Afatinib (n=229)</th>
<th>Erlotinib (n=84)</th>
<th>Gefitinib (n=1126)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>Any grade</td>
<td>Grade 3+</td>
<td>Any grade</td>
</tr>
<tr>
<td></td>
<td>96</td>
<td>15</td>
<td>62</td>
</tr>
<tr>
<td>Rash</td>
<td>Any grade</td>
<td>Grade 3+</td>
<td>Any grade</td>
</tr>
<tr>
<td></td>
<td>90</td>
<td>16</td>
<td>85</td>
</tr>
<tr>
<td>Paronychia</td>
<td>Any grade</td>
<td>Grade 3+</td>
<td>Any grade</td>
</tr>
<tr>
<td></td>
<td>58</td>
<td>11</td>
<td>14</td>
</tr>
<tr>
<td>Stomatitis/mucositis*</td>
<td>71</td>
<td>9</td>
<td>18</td>
</tr>
<tr>
<td>Pruritus</td>
<td>Any grade</td>
<td>Grade 3+</td>
<td>Any grade</td>
</tr>
<tr>
<td></td>
<td>21</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>Dry skin</td>
<td>Any grade</td>
<td>Grade 3+</td>
<td>Any grade</td>
</tr>
<tr>
<td></td>
<td>31</td>
<td>0</td>
<td>21</td>
</tr>
<tr>
<td>Skin reactions†</td>
<td>Any grade</td>
<td>Grade 3+</td>
<td>Any grade</td>
</tr>
<tr>
<td></td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Nail disorders††</td>
<td>Any grade</td>
<td>Grade 3+</td>
<td>Any grade</td>
</tr>
<tr>
<td></td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

*Includes acne, acne pustular, dermatitis, dermatitis acneform, dermatitis exfoliatative, drug eruption, dry skin, erythema, exfoliative rash, folliculitis, pruritus, pruritus generalized, rash, rash erythematous, rash generalized, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, rash vesicular, skin exfoliation, skin toxicity, xeroderma
†† Includes ingrowing nail, nail bed infection, nail disorder, nail infection, onychoclastosis, onycholytic, paronychia

*Only includes mucositis for erlotinib

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**PFS by Independent Review**

- **Afatinib vs Gefitinib**
  - Median PFS: Afatinib 11.0 months, Gefitinib 10.9 months
  - HR (95% CI): 0.73 (0.57-0.95)
  - P-value: 0.0165

- **Estimated PFS probability at various timepoints**
  - Afatinib: 27% at 15 months, 18% at 27 months
  - Gefitinib: 15% at 15 months, 8% at 27 months

- **Common Adverse Events**
  - Diarrhea: 96% (Afatinib), 90% (Erlotinib), 58% (Gefitinib)
  - Rash: 90% (Afatinib), 85% (Erlotinib), 14% (Gefitinib)
  - Paronychia: 58% (Afatinib), 14% (Erlotinib)
  - Stomatitis/mucositis*: 71% (Afatinib), 16% (Erlotinib), 7% (Gefitinib)
  - Pruritus: 21% (Afatinib), 0% (Erlotinib)
  - Dry skin: 31% (Afatinib), 21% (Erlotinib)

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*Park et al. Ann Oncol. 2015;26 (suppl 9; abstract LBA2); †*P=0.0176 †. †P=0.0184

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Tumor shrinkage in patients with uncommon mutations

- **De novo T790M (n=14): Response rate = 14%**
- **Exon 20 insertions (n=20): Response rate = 8.7%**
- **Other (n=33): Response rate = 71%**

8 patients were not included due to insufficient data

Progression-free survival and overall survival in patients

- **De novo T790M (n=14)**
  - Median PFS: 2.9 months (range 0.3-13.8)
  - Median OS: 14.9 months (range 1.5-30.5)
- **Exon 20 insertions (n=23)**
  - Median PFS: 2.7 months (range 0.4-11.9)
  - Median OS: 9.4 months (range 0.4-32.2+)
- **Other (n=38)**
  - Median PFS: 10.7 months (range 0.0-35.8+)
  - Median OS: 18.6 months (range 0.0-51.3+)

<table>
<thead>
<tr>
<th>Patient</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.8</td>
<td>8.7</td>
</tr>
<tr>
<td>2</td>
<td>2.6</td>
<td>24.9</td>
</tr>
<tr>
<td>3</td>
<td>6.7</td>
<td>13.2</td>
</tr>
<tr>
<td>4</td>
<td>8.3</td>
<td>30.5</td>
</tr>
<tr>
<td>5</td>
<td>9.6</td>
<td>24.4*</td>
</tr>
<tr>
<td>6</td>
<td>11.0</td>
<td>20.8</td>
</tr>
<tr>
<td>Median</td>
<td>7.5</td>
<td>22.9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.3</td>
<td>8.1</td>
</tr>
<tr>
<td>2</td>
<td>1.2</td>
<td>7.5</td>
</tr>
<tr>
<td>3</td>
<td>3.0</td>
<td>24.6</td>
</tr>
<tr>
<td>Median</td>
<td>1.2</td>
<td>8.1</td>
</tr>
</tbody>
</table>

*Patient data censored; NE = not estimable
Erlotinib +/- Bevacizumab Study Design

**Primary endpoint:**
PFS (RECIST v1.1, independent review)

**Secondary endpoints:**
OS, tumor response, QoL, safety

**Exploratory endpoint:**
biomarker assessment

- Chemotherapy-naïve
- Stage IIIB/IV NSCLC or postoperative recurrence
- Non-squamous
- Activating EGFR mutations*
  - Exon 19 deletion
  - Exon 21 L858R
- Age ≥20 years
- PS 0–1
- No brain metastasis

**Stratification factors:** sex, smoking status, clinical stage, EGFR mutation type

- T790M excluded

**First-Line Erlotinib +/- Bevacizumab**

<table>
<thead>
<tr>
<th></th>
<th>EB</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (months)</td>
<td>16.0</td>
<td>9.7</td>
</tr>
<tr>
<td>HR</td>
<td>0.54 (95% CI: 0.36–0.79)</td>
<td></td>
</tr>
<tr>
<td>P value*</td>
<td>0.0015</td>
<td></td>
</tr>
</tbody>
</table>

*PFS probability vs. Time (months)

- **EB**
- **E**

Number at risk

- EB: 75, 72, 69, 64, 60, 53, 49, 38, 30, 20, 13, 8, 4, 4, 0
- E: 77, 72, 66, 57, 44, 39, 29, 24, 21, 18, 10, 5, 2, 1, 0

**HR**

1.0

0.8

0.6

0.4

0.2

0.0

0

2

4

6

8

10

12

14

16

18

20

22

24

26

28

*PFS probability

**Time (months)**

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Afatinib + Cetuximab at MTD: Responses by T790M mutation

Janjigian et al ESMO ’12

S1403: A randomized phase II/III trial of afatinib plus cetuximab versus afatinib alone in treatment-naïve patients with advanced, EGFR mutation positive NSCLC

Pls: Goldberg; Politi; Lilenbaum
DoR and PFS in osimertinib (AZD9291) first-line cohorts (investigator assessed)

<table>
<thead>
<tr>
<th>Dose</th>
<th>N</th>
<th>Median PFS, months (95% CI)</th>
<th>Maturity</th>
</tr>
</thead>
<tbody>
<tr>
<td>80 mg</td>
<td>30</td>
<td>NC (12.3, NC)</td>
<td>30%</td>
</tr>
<tr>
<td>160 mg</td>
<td>30</td>
<td>NC (11.1, NC)</td>
<td>30%</td>
</tr>
<tr>
<td>Total</td>
<td>60</td>
<td>NC (13.7, NC)</td>
<td>35%</td>
</tr>
<tr>
<td>Maximum PFS, months</td>
<td>19.2+</td>
<td>13.8+</td>
<td>19.2+</td>
</tr>
</tbody>
</table>

Remaining alive and progression-free, % (95% CI)
- 9 months: 83 (64, 93)
- 12 months: 72 (58, 82)

DoR in osimertinib (AZD9291) first-line cohorts

<table>
<thead>
<tr>
<th>Dose</th>
<th>N</th>
<th>Median DoR, months (95% CI)</th>
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<tbody>
<tr>
<td>80 mg</td>
<td>20</td>
<td>NC (9.7, NC)</td>
<td>28%</td>
</tr>
<tr>
<td>160 mg</td>
<td>25</td>
<td>NC (12.3, NC)</td>
<td>31%</td>
</tr>
<tr>
<td>Total</td>
<td>45</td>
<td>NC (11.1, NC)</td>
<td>30%</td>
</tr>
<tr>
<td>Maximum DoR, months</td>
<td>18.0+</td>
<td>12.6+</td>
<td>18.0+</td>
</tr>
</tbody>
</table>

Remaining in response, % (95% CI)
- 9 months: 89 (64, 97)
- 12 months: 71 (58, 82)

**FLAURA Study Design**

- **Enrollment by local or central**
  - EGFR mutation testing of biopsy sample
- **Stratified by:**
  - Asian/ non-Asian
  - Ex19del/ L858R
- Oral osimertinib (80 mg/d)
- RECIST 1.1 assessment every 6 weeks until objective PD
- Patients randomized to standard-of-care arm may receive open-label treatment with osimertinib on central confirmation of both objective disease progression and T790M positive tumor
- Patients randomized to the standard-of-care arm may receive osimertinib after progression

**Primary objective:** efficacy by PFS

*With central laboratory assessment performed for sensitivity; cobas™ EGFR Mutation Test; Sites to select either gefitinib or erlotinib as the sole comparator prior to site initiation; Oral gefitinib (250 mg/d) or oral erlotinib (150 mg/d)


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Conclusions

• Gefitinib, erlotinib, and afatinib are appropriate options
• Afatinib has demonstrated an OS benefit in patients with Del 19 mutations
• Afatinib showed superior ORR, PFS, and TTF in 1st line therapy against gefitinib
• At the current recommended doses, afatinib has a higher rate of toxicity
• Combination of bevacizumab and erlotinib showed better PFS compared to erlotinib alone
• Ongoing studies are evaluating the role of cetuximab in combination with afatinib vs afatinib alone
• Osimertinib is being evaluated in 1st line
Case One

- 64 year old, Caucasian, male former smoker diagnosed with stage IV non-small cell lung cancer, adenocarcinoma histology, positive for EGFR exon deletion 19. He is treated with erlotinib 150 mg daily and after 4 years is found to have progression in a single lung lesion.

What do you recommend?
1. Biopsy the lung lesion
2. Switch to chemotherapy
3. Start on afatinib
4. Start on osimertinib
5. Radiation to the lung lesion

Audience Polling Results

Case One

64 year old, Caucasian, male former smoker diagnosed with stage IV non-small cell lung cancer, adenocarcinoma histology, positive for EGFR exon deletion 19. He is treated with erlotinib 150 mg daily and after 4 years is found to have progression in a single lung lesion.

What do you recommend?
1. Biopsy the lung lesion
2. Switch to chemotherapy
3. Start on afatinib
4. Start on osimertinib
5. Radiation to the lung lesion

68% 4% 9% 1% 17%
Acquired Resistance to EGFR TKIs

- When treated with EGFR TKIs, 70% of patients with activating mutations will have tumor regression and a median PFS of 1 year.

- Once these responding patients progress, they have developed acquired resistance to gefitinib, erlotinib or afatinib.

- In “Acquired Resistance”
  - Oncogene addiction persists
  - Median post-progression survival is 16 months

Criteria for Acquired Resistance

- Previously received treatment with single-agent sensitizing EGFR TKI (gefitinib, erlotinib or afatinib).

- Either of the following:
  - Documented partial response (PR) or complete response (CR) or
  - Durable (>6 months) clinical benefit (stable disease) while on sensitizing EGFR TKI

- Systemic progression of disease while on continuous treatment with sensitizing EGFR TKI during the last 30 days.

- No intervening systemic therapy between cessation of sensitizing EGFR TKI and initiation of new therapy.

Jackman D et al JCO 2009
Acquired Resistance to EGFR TKIs in Lung Cancer

Day 0 4 months 25 months
Growing bone lesion Growing lung lesion

Mechanism of Acquired Resistance to EGFR TKIs

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Type of Progression Drives Therapy: Three PD Subtypes

- **PD-Subtype**
- **Systemic-PD**
- **Oligo-PD**
- **CNS-PD (Sanctuary)**

*Gandara et al., Clinical Lung Cancer 2013*

ASPIRATION: Phase II First-line Erlotinib in Sensitizing EGFR Mutation–Positive NSCLC Continued After Progression – Study Design

- **Primary endpoint:**
  - PFS (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

*Park, et al. Presented at ESMO, 2014 (abstr 1223O)*

BOR=best overall response; ECOG PS=Eastern Cooperative Oncology Group performance status.
**ASPIRATION: PFS1 and PFS2**

- In patients receiving post-PD erlotinib (n=93)
- PFS1 was 11.0 months
- Difference between PFS1 and PFS2 was an additional 3.1 months

**Disease Flare**

Rapid acceleration of disease progression resulting in hospitalization and/or death after discontinuation of gefitinib or erlotinib and before initiation of study drug.

Last day of TKI Off EGFR TKI Resumed TKI

Day 0 Day 21 Day 42
Results

**Flare – progression of disease leading to hospitalization or death during washout

61 protocol eligible patients

14 patients (23%, 95% CI, 14-35%) had a disease flare**

3 patient deaths

3 patients went on to clinical trial treatment

8 patients instructed to restart TKI, removed from trial

47 uneventful washout periods

**Flare – progression of disease leading to hospitalization or death during washout

IMPRESS: Phase III Trial of Gefitinib vs Gefitinib + CT Beyond Progression in Sensitizing EGFR Mutation–Positive NSCLC

Enrollment Period:
March 2012 - December 2013

Primary endpoint: PFS
Secondary endpoints: OS, ORR, DCR, safety, HRQoL
Exploratory endpoint: Biomarkers

*Progressive disease based on radiological evaluation (modified RECIST v1.1) and RECIST version 1.1. Tumor assessments were performed 64 weeks before start of treatment (baseline) and every 6 weeks (±7 days) after randomization until progressive disease.

†Randomization did not include stratification factors; analyses were adjusted for 10 covariates; age (<65 vs ≥65 years) and prior response to gefitinib (SD vs PR+CR).

CRT=chemotherapy; DCR=disease control rate; HRQoL=Health-Related Quality of Life; ORR=objective response rate; PR=partial response; SD=stable disease; WHO PS=World Health Organization performance status.

IMPRESS: PFS (Primary Endpoint; ITT)

**Case Continued**

- He is treated with SBRT to the primary lung lesion but 12 months later develops new disease in the bones and hip pain as well as small bilateral lung nodules.

What do you recommend?
1. Biopsy of a growing lesion
2. Switch to chemotherapy
3. Start on afatinib
4. Start on osimertinib
5. Do something else
Case Continued

He is treated with SBRT to the primary lung lesion but 12 months later develops new disease in the bones and hip pain as well and small bilateral lung nodules.

What do you recommend?
1. Biopsy of a growing lesion
2. Switch to chemotherapy
3. Start on afatinib
4. Start on osimertinib
5. Do something else

Osimertinib (AZD9291)

Primary endpoint
- AURA extension: to investigate the safety, tolerability and efficacy (ORR) of AZD9291 (assessed by BICR).
- AURA2: ORR according to RECIST 1.1 (assessed by BICR).

Key inclusion criteria
- Aged ≥18 (≥20 in Japan).
- Confirmation of tumor EGFR mutation associated with EGFR-TKI sensitivity (including G719X, exon 19 del, L858R, L861Q).
- Measurable disease at baseline.
- WHO performance status 0 or 1.
- Acceptable organ function.
- Stable brain metastases allowed.

For patients second line
- AURA extension: disease progression following at least two lines of prior therapy including at least one EGFR-TKI.
- AURA2: disease progression following at least two lines of prior therapy including both an EGFR-TKI and a platinum-based doublet chemotherapy.

* T790M mutation identified by EGFR Mutation Test.

BICR, blinded independent central review; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumours; TKI, tyrosine kinase inhibitor; WHO, World Health Organization.
Baseline demographics and disease characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>AURA extension (n=201)</th>
<th>AURA2 (n=210)</th>
<th>Total (n=411)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex: male / female</td>
<td>34 / 66</td>
<td>30 / 70</td>
<td>32 / 68</td>
</tr>
<tr>
<td>Age: median (range), years</td>
<td>62 (37–89)</td>
<td>64 (35–88)</td>
<td>63 (35–89)</td>
</tr>
<tr>
<td>Race: White / Asian / other / not reported</td>
<td>38 / 57 / 3 / 2</td>
<td>34 / 63 / 3 / 0</td>
<td>36 / 60 / 3 / 1</td>
</tr>
<tr>
<td>Histology: adenocarcinoma / other</td>
<td>97 / 3</td>
<td>96 / 4</td>
<td>97 / 3</td>
</tr>
<tr>
<td>WHO performance status: 0 / 1 / 2</td>
<td>34 / 66 / 1†</td>
<td>40 / 60 / 0</td>
<td>37 / 63 / 0</td>
</tr>
<tr>
<td>Brain metastases</td>
<td>37</td>
<td>41</td>
<td>39</td>
</tr>
<tr>
<td>Treatment: second line / third line</td>
<td>30 / 70</td>
<td>32 / 68</td>
<td>31 / 69</td>
</tr>
<tr>
<td>EGFR-TKI as last therapy‡</td>
<td>79</td>
<td>75</td>
<td>77</td>
</tr>
<tr>
<td>EGFR mutation type by last test: Exon 19 del / L858R / G719X / S768I / Exon 20 ins</td>
<td>71 / 25 / 2 / 1</td>
<td>65 / 32 / 2 / 1 / 1</td>
<td>68 / 29 / 2 / 1 / 1</td>
</tr>
</tbody>
</table>

*Full analysis set: n=411. Evaluable for response analysis set: n=398; 13 patients did not have measurable disease at baseline by independent central review.
†Protocol deviation: inclusion criteria states patients should have a WHO performance status of 0 or 1
‡Last regimen prior to start of treatment with AZD9291.
EGFR, epidermal growth factor receptor; TKI, tyrosine kinase receptor; WHO, World Health Organization.

Poster #365 presented by Glenwood D. Goss at the ECC 2015 European Cancer Congress.

Response rate

By blinded independent central review. Evaluable for response analysis set (n=398). Mean best percentage change in target lesion size: -45%, standard deviation 28.0 (median best percentage change: -47.6%; range: -100% to +90.8%).

Poster #365 presented by Glenwood D. Goss at the ECC 2015 European Cancer Congress.
Progression-free survival

Median progression-free survival in months: 9.7 (95% CI 8.3, NC), maturity: 39%

By blinded independent central review. Patients with confirmed objective response (n=263), maturity 23%. Blue dotted lines represent 95% CI, confidence interval; NC, not calculated.

Poster #365 presented by Glenwood D. Goss at the ECC 2015 European Cancer Congress.

Most frequent adverse events (all-causality)

<table>
<thead>
<tr>
<th>AE by preferred term occurring in ≥15% of patients overall</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>≥Grade 3</th>
<th>Unknown</th>
<th>Total (n=411)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>147 (36)</td>
<td>21 (5)</td>
<td>4 (1)</td>
<td>2 (1)</td>
<td>174 (42)</td>
</tr>
<tr>
<td>Rash and acnes (grouped terms)</td>
<td>149 (36)</td>
<td>18 (4)</td>
<td>2 (1)</td>
<td>1 (0)</td>
<td>170 (41)</td>
</tr>
<tr>
<td>Dry skin</td>
<td>88 (21)</td>
<td>7 (2)</td>
<td>0</td>
<td>0</td>
<td>95 (23)</td>
</tr>
<tr>
<td>Paronychia</td>
<td>52 (13)</td>
<td>20 (5)</td>
<td>0</td>
<td>0</td>
<td>72 (18)</td>
</tr>
<tr>
<td>Nausea</td>
<td>58 (14)</td>
<td>9 (2)</td>
<td>2 (1)</td>
<td>0</td>
<td>69 (17)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>49 (12)</td>
<td>13 (3)</td>
<td>3 (1)</td>
<td>0</td>
<td>65 (16)</td>
</tr>
<tr>
<td>Constipation</td>
<td>50 (12)</td>
<td>8 (2)</td>
<td>1 (0)</td>
<td>3 (1)</td>
<td>62 (15)</td>
</tr>
<tr>
<td>Select AEs of interest</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ILD and pneumonitis</td>
<td>4 (1)</td>
<td>0</td>
<td>7 (2)</td>
<td>0</td>
<td>11 (3)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>3 (1)</td>
<td>1 (0)</td>
<td>1 (0)</td>
<td>0</td>
<td>5 (1)</td>
</tr>
<tr>
<td>QT prolongation</td>
<td>9 (2)</td>
<td>3 (1)</td>
<td>5 (1)</td>
<td>0</td>
<td>17 (4)</td>
</tr>
</tbody>
</table>

AE, adverse event; ILD, interstitial lung disease
Poster #365 presented by Glenwood D. Goss at the ECC 2015 European Cancer Congress.
Rociletinib (CO-1686): Best response in Phase 1 and early Phase 2 expansion cohort patients

Centrally confirmed T790M+ patients within therapeutic dose range (N=40)

Change from Baseline (%)

ORR to date: 58%


Adverse events

<table>
<thead>
<tr>
<th>Treatment-related adverse events* occurring in &gt;10% of CO-1686 patients (N=72) treated at efficacious doses, % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred term</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Hyperglycemia and IGT</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Vomiting</td>
</tr>
<tr>
<td>Decreased appetite</td>
</tr>
<tr>
<td>Myalgia</td>
</tr>
<tr>
<td>QTc prolonged</td>
</tr>
</tbody>
</table>

*Excluding malignancy-related adverse events (eg, disease progression)

4% (3) patients with any form of rash, all Grade 1

Sequist et al., ASCO 2014
ASP8273: Preliminary Results:
Phase 1/2 Study in Asian Subjects
(Phase 2 Part)

Best Change (%) from Baseline of Target Lesions in
T790M+ Subjects

Preliminary ORR:
• 64% (n=45/70)
• Both confirmed and unconfirmed responses
• Investigator assessment

‡ Indicates unconfirmed response in target lesions, but ORR is progressive disease based on new or non-target lesions
* Subject was withdrawn from the study with unconfirmed stable disease in target lesions;


ASP8273 Preliminary Results:
US Phase 1 Study

Antitumor activity has been observed at doses of ≥ 100 mg:
ORR: 36.8% (25/68)
• T790M+: 40.9% (18/44)
• 50% (1/2) exon 20 insertion

Preliminary Results: US Phase 1 Study
Treatment Emergent AE’s (> 10%)

- 95 patients received a dose of ASP8273 (25 – 500mg)
- Table reflects doses which will be utilized in future studies and events which occurred in at least 10% of pts

<table>
<thead>
<tr>
<th>Treatment-Emergent Adverse Events Occurring in ≥10% of the Total Population, n (%)</th>
<th>100 mg (n=12)</th>
<th>200 mg (n=12)</th>
<th>300 mg* (n=48)</th>
<th>Total (N=72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>Overall</td>
<td>1 (8)</td>
<td>2 (17)</td>
<td>17 (35)</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>0</td>
<td>0</td>
<td>1 (2)</td>
<td>1 (5.4)</td>
</tr>
<tr>
<td>Nausea</td>
<td>Overall</td>
<td>3 (25)</td>
<td>4 (33)</td>
<td>10 (21)</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>1 (8)</td>
<td>0</td>
<td>0</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Overall</td>
<td>3 (25)</td>
<td>2 (17)</td>
<td>6 (13)</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>Overall</td>
<td>2 (17)</td>
<td>5 (25)</td>
<td>6 (13)</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>Overall</td>
<td>2 (17)</td>
<td>2 (17)</td>
<td>6 (13)</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>1 (8)</td>
<td>1 (8)</td>
<td>4 (8)</td>
<td>7 (10)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Overall</td>
<td>2 (17)</td>
<td>0</td>
<td>7 (15)</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>1 (8)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>Overall</td>
<td>1 (8)</td>
<td>3 (25)</td>
<td>7 (15)</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>0</td>
<td>0</td>
<td>1 (2)</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>Paraesthesia</td>
<td>Overall</td>
<td>0</td>
<td>0</td>
<td>5 (10)</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cough</td>
<td>Overall</td>
<td>1 (8)</td>
<td>2 (17)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>


Lux Lung 1

- Randomized Phase II/III comparing afatinib to placebo in patients who had progressed following at least 12 weeks of gefitinib or erlotinib (EGFR mutation not required)
- RR was 7% for afatinib vs. 1% for placebo
- 141 patients had tumors available for molecular testing
  - 96 patients: sensitizing EGFR mutation positive, 76 (79%) had common mutations,
  - Median PFS was 3.3 months for afatinib vs. 1.1 months placebo (HR 0.38; p < 0.0001) in patients with sensitizing EGFR mutation positive NSCLC
  - Median PFS was 1.8 months for both afatinib and placebo in patients negative for sensitizing EGFR mutations
- Median overall survival was 10.3 months for afatinib vs. 12.0 months for placebo (HR 1.08; p = 0.74)

Miller et al., Lancet Oncology 5:528 (2012)
**Phase Ib Study: Afatinib+ Cetuximab**

- Phase Ib, open-label, multicenter trial in the US and The Netherlands
- Primary endpoints: RECIST 1.1 Response and PFS, with imaging at Week 4, 8, 12, and every 8 weeks thereafter
- Key eligibility criteria:

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathologically confirmed NSCLC</td>
<td>Prior treatment with EGFR targeting antibodies</td>
</tr>
<tr>
<td>Presence of EGFR drug-sensitizing mutations or RECIST response, or SD ≥6 months on prior EGFR TKI</td>
<td>Symptomatic brain metastases or disease progression only in CNS</td>
</tr>
<tr>
<td>Gefitinib/erlotinib as last systemic treatment</td>
<td>Disease progression on treatment with erlotinib or gefitinib within 30 days</td>
</tr>
<tr>
<td>Disease progression on treatment with erlotinib or gefitinib within 30 days</td>
<td>Biopsy (available) at time of acquired resistance</td>
</tr>
<tr>
<td>Biopsy (available) at time of acquired resistance</td>
<td>ECOG PS 0–2</td>
</tr>
</tbody>
</table>

SD = stable disease; i.v. = intravenous; RECIST = Response Evaluation Criteria in Solid Tumors.

**Afatinib + Cetuximab at MTD: Responses by T790M mutation**

- Overall PFS 4.7 mos

Janjigian et al., Cancer Discover 2014
### Most Frequent Adverse Events

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Grade ≥3 n (%)</th>
<th>All Grades n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>5 (8)</td>
<td>53 (87)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3 (5)</td>
<td>40 (66)</td>
</tr>
<tr>
<td>Xerosis</td>
<td>1 (2)</td>
<td>34 (56)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2 (3)</td>
<td>31 (51)</td>
</tr>
<tr>
<td>Skin fissures</td>
<td>29 (48)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>27 (44)</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>2 (3)</td>
<td>25 (41)</td>
</tr>
<tr>
<td>Paronychia</td>
<td>1 (2)</td>
<td>18 (30)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (2)</td>
<td>18 (30)</td>
</tr>
</tbody>
</table>

### Blood-Based Testing (cfDNA) in detection of biomarkers

Blood-Based Testing in TIGER-X Trial: Sensitivity and Specificity of cfDNA Analysis

Plasma Testing for T790M has Good Sensitivity and Likely Good Specificity

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Positive</th>
<th>Negative</th>
<th>Inadequate Tissue</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma</td>
<td>155</td>
<td>37</td>
<td>12</td>
<td>194</td>
</tr>
</tbody>
</table>

- When inadequate tissue specimens are factor in, plasma testing identifies as many patients as T790M+ as tissue testing
- T790M tissue/plasma* are not false positives - T790M confirmed in plasma on subsequent testing in 5/7 samples

*patients at all times

Tissue as reference: T790M
Positive percent agreement: 81% (155/192)
Activating mutations: 87% (193/221)


Blood-Based Testing in TIGER-X: ORR by Tumor or cfDNA Analysis

T790M Plasma Testing is a Viable Alternative to Tissue Testing

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Plasma T790M</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>55% (72/130)</td>
</tr>
<tr>
<td>-</td>
<td>25% (17/71)</td>
</tr>
</tbody>
</table>

- Similar ORR observed when detecting T790M in either tissue or plasma
- Not all patients with progression on first-line TKI are candidates for tissue re-biopsy

**NCCN Guidelines Version 4.2016**

**Non-Small Cell Lung Cancer**

### Sensitizing EGFR Mutation Positive

**First-Line Therapy**
- **EGFR mutation discovered prior to first-line chemotherapy**
  - Erlotinib (category 1) or Afatinib (category 1) or Gefitinib (category 1)
  - Progression

**EGFR mutation discovered during first-line chemotherapy**
- Interrupt or complete planned chemotherapy, followed by Erlotinib or Afatinib or Gefitinib
  - Progression

---

### Sensitizing EGFR Mutation Positive

**Subsequent Therapy**
- **Asymptomatic**
  - Osimertinib or Continue Erlotinib or Afatinib or Gefitinib
  - Consider local therapy and Continue Erlotinib or Afatinib or Gefitinib
  - See NCCN Guidelines for CNS Cancers
  - Progression

- **Symptomatic**
  - Isolated lesion
    - Osimertinib or Continue Erlotinib or Afatinib or Gefitinib
  - Multiple lesions
    - Osimertinib or See First-line therapy options for Adenocarcinoma (NSCL-19) or Squamous cell carcinoma (NSCL-20)
  - Progression

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**NSCL-17**

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(Images and text from the NCCN Guidelines, version 4.2016, National Comprehensive Cancer Network.)
Conclusions

• In patients with sensitizing EGFR mutation positive NSCLC who progress on a first or second generation EGFR TKI, the type of progression determines treatment option
• All patients should have a biopsy to evaluate for T790M prior to switching systemic therapy
• In patients where a tissue biopsy is not possible, a serum based test for T790M is reasonable
• Osimertinib is approved for patients who are T790M positive (with more agents on the way)