Advances in the Use of Targeted Therapies in the Management of Non–Small Cell Lung Cancer

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Stanford Health Care

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Learning Objectives

1. Recall updated clinical practice guidelines regarding genetic testing for targetable mutations in patients with metastatic NSCLC
2. Discuss efficacy and safety data from recent clinical trials of kinase inhibitors targeted against EGFR mutations and ALK rearrangements
3. Comment on best practices for managing side effects associated with EGFR and ALK inhibitors and BRAF
4. Apply recommended procedures for identifying and overcoming the T790M acquired resistance mutation
Financial Disclosure

• Dr. Wakelee has received research support from Genentech/Roche, Novartis, Exelixis, Celgene, BMS, AstraZeneca/Medimmune, Gilead, Pfizer, Xcovery, and Pharmacyclics; and has acted as a consultant for Merck and Novartis.

• Ms. Waxman has nothing to disclose.
Overview

- Tumor genetic testing
- EGFR driver mutations
- EGFR T790M
- ALK
- BRAF
Genomic Driver Mutation in Lung Adenocarcinoma

n = 733 pts
14 institutions
of LCMC
Targeted Approaches

Dimerization inhibitors

Anti-receptor blocking antibodies

Tyrosine kinase inhibitors

Antiligand blocking antibodies

Antibody-toxin conjugates

Adapted from Noonberg and Benz. *Drugs*. 2000;59:753.
Molecular Analysis

• Tumor tissue cancer genomic testing
  • Overview of methods of detection
  • Targeted DNA sequencing panels

• Blood-based cancer genomic testing
  • Sources
  • ctDNA technologies
  • Potential clinical applicability
Methods to Detect Mutations

- DNA sequencing
- Reverse transcriptase polymerase chain reaction (RT-PCR)
- Fluorescence in situ hybridization (FISH)
- Immunohistochemistry (IHC)

Monitoring Disease, Correlation With CT Imaging

EGFR
Case 1

• JH is a 46-year-old woman who notes increasing dyspnea. She eventually gets a CXR and is found to have multiple small pulmonary nodules. A CT scan confirms a “miliary” pattern of nodules. A bronchoscopy confirms adenocarcinoma of the lung, and EGFR results reveal exon 19 deletion.

• She starts therapy with erlotinib at 150 mg and achieves a PR with resolution of dyspnea.

• 13 months later her dyspnea returns and her CT shows regrowth of multiple pulmonary nodules all ~4-7 mm and also growth of an adrenal metastases to 2 cm in size on the left.
A Case: 2nd Line

Would you consider getting a plasma assay for circulating tumor (ct)DNA to test for T790M?
A. Yes
B. No
A Case: 2nd Line (cont.)

A ctDNA assay is obtained which does not show T790M or exon19 deletion in EGFR.
Would you now obtain a tissue biopsy from the adrenal gland?
A. Yes
B. No
A Case: 2nd Line (cont.)

The tissue biopsy of the adrenal confirms the EGFR exon 19 mutation and shows development of T790M; PD-L1 by 22C3 assay is 60%

What would you offer her for treatment now?
A. Osimertinib
B. Platinum/pemetrexed chemotherapy
C. Pembrolizumab
D. Alectinib
E. Dabrafenib
IPASS

Randomization period: March 2006 – October 2007

Patients
• Chemo-naive
• Adenocarcinoma histology
• Never or ex-light smokers*

1:1 randomization

Gefitinib (250 mg/day)

Carboplatin/paclitaxel

End points

Primary
• PFS

Secondary
• RR
• OS
• QoL

Exploratory
• Biomarkers

IPASS: PFS in EGFR Mutation + vs. - Patients

Incidence of EGFR mutation: 261/437 = 59.7%

Treatment by subgroup interaction test, p<0.0001

## Treatment-Naive EGFR\textsuperscript{mut} Patients

### EGFR TKIs vs Chemotherapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>N</th>
<th>Median PFS, mo</th>
<th>Median OS, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maemondo</td>
<td>Gefitinib vs carboplatin / paclitaxel</td>
<td>230</td>
<td>10.8 vs 5.4 (P &lt; .001)</td>
<td>30.5 vs 23.6 (P = .31)</td>
</tr>
<tr>
<td>Mitsudomi</td>
<td>Gefitinib vs cisplatin / docetaxel</td>
<td>177</td>
<td>9.2 vs 6.3 (P &lt; .001)</td>
<td>36 vs 39 (HR: 1.19)</td>
</tr>
<tr>
<td>OPTIMAL</td>
<td>Erlotinib vs carboplatin / gemcitabine</td>
<td>165</td>
<td>13.1 vs 4.6 (P &lt; .001)</td>
<td>HR: 1.065 (P = .65)</td>
</tr>
<tr>
<td>EURTAC</td>
<td>Erlotinib vs platinum-based chemotherapy</td>
<td>174</td>
<td>9.7 vs 5.2 (P &lt; .001)</td>
<td>19.3 vs 19.5 (P = .87)</td>
</tr>
<tr>
<td>LUX-Lung 3</td>
<td>Afatinib vs cisplatin / pemetrexed</td>
<td>345</td>
<td>11.1 vs 6.9 (P = .001)</td>
<td>28.2 vs 28.2 HR 0.88, p.39</td>
</tr>
<tr>
<td>LUX-Lung 6</td>
<td>Afatinib vs cisplatin / gemcitabine</td>
<td>364</td>
<td>11.0 vs 5.6 (P &lt; .001)</td>
<td>23.1 vs 23.5 HR 0.93, p.61</td>
</tr>
</tbody>
</table>

Mechanisms of Resistance to EGFR TKI Therapy: T790M Gatekeeper Mutation in 60%

Osimertinib Single-Agent Activity: 2nd Line+

A) All patients

B) EGFR T790M—Positive

Janne NEJM 2015
Osimertinib Activity by Plasma/Tumor T790M-2nd Line+

A) Tumor T790M Positive (n = 173)
- ORR (95% CI): 62% (54 to 70)
- Plasma T790M Positive
- Plasma T790M Negative
- Plasma T790M unknown

B) Tumor T790M Negative (n = 58)
- ORR (95% CI): 26% (15 to 39)
- Plasma T790M Positive
- Plasma T790M Negative

C) Plasma T790M Positive (n = 164)
- ORR (95% CI): 63% (55 to 70)
- Tumor T790M Positive
- Tumor T790M Negative
- Tumor unknown

D) Plasma T790M Negative (n = 102)
- ORR (95% CI): 46% (36 to 56)
- Tumor T790M Positive
- Tumor T790M Negative
- Tumor unknown

Oxnard JCO 34 (28): 2016
# EGFR Cross-Comparison Plasma Testing

<table>
<thead>
<tr>
<th></th>
<th>Cobas</th>
<th>ARMS (therascreen)</th>
<th>ddPCR</th>
<th>BEAMing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exon 19</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>82%</td>
<td>82%</td>
<td></td>
<td>82%</td>
</tr>
<tr>
<td>Specificity</td>
<td>97%</td>
<td>100%</td>
<td></td>
<td>97%</td>
</tr>
<tr>
<td><strong>L858R</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>87%</td>
<td>78%</td>
<td>90%</td>
<td>87%</td>
</tr>
<tr>
<td>Specificity</td>
<td>97%</td>
<td>100%</td>
<td>100%</td>
<td>97%</td>
</tr>
<tr>
<td><strong>T790M</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>73%</td>
<td>29%</td>
<td>71%</td>
<td>81%</td>
</tr>
<tr>
<td>Specificity</td>
<td>67%</td>
<td>100%</td>
<td>83%</td>
<td>58%</td>
</tr>
</tbody>
</table>

72 plasma samples (65 for T790M)

Non-digital PCR (Cobas)
Therascreen EGFR amplification refractory mutation system (ARMS)
Digital detection droplet PCR (ddPCR)
Beads, emulsion, amplification and magnetics (BEAM)ing dPCR
Plasma, Tissue, and Urine Identify Unique and Overlapping Subsets of T790M-Positive Patients

- 181 samples had matched pretreatment T790M results in plasma, tissue, and urine
  - 7 were T790M-negative or inadequate by all 3 sample types (4%)
  - 174 were T790M-positive by at least 1 sample type (96%)

**T790M-Positive Cases**

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Plasma</th>
<th>Urine</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>18</td>
<td>19</td>
</tr>
<tr>
<td>16</td>
<td>104</td>
<td>5</td>
</tr>
<tr>
<td>8</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

Total positive by tissue: 146 of 181
Total positive by plasma: 145 of 181
Total positive by urine: 144 of 181

104 (57%) were positive by all 3 sample types

Even with multiple tests we can miss some T790M
AURA-3

Patients
- Chemo-naïve
- Activating EGFRmut
- Centrally confirmed T790M
- PD on 1st/2nd gen EGFR TKI

Osimertinib (80 mg / day)
N=279

Platinum / pemetrexed
N=140

End points
Primary
- Investigator assessed PFS

Secondary
- RR
- OS
- QoL

Exploratory
- Biomarkers

Mok/Wu NEJM 2016
# AURA3: Post 1st Gen EGFR TKI

Osimertinib vs Chemotherapy

Mok/Wu NEJM 2016

## Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Osimertinib (N = 279)</th>
<th>Platinum–Pemetrexed (N = 140)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range) — yr</td>
<td>62 (25–85)</td>
<td>63 (20–90)</td>
</tr>
<tr>
<td>Female sex — no. (%)</td>
<td>172 (62)</td>
<td>97 (69)</td>
</tr>
<tr>
<td>Race — no. (%)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>89 (32)</td>
<td>45 (32)</td>
</tr>
<tr>
<td>Asian</td>
<td>182 (65)</td>
<td>92 (66)</td>
</tr>
<tr>
<td>Other</td>
<td>8 (3)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>No history of smoking — no. (%)</td>
<td>189 (68)</td>
<td>94 (67)</td>
</tr>
<tr>
<td>Disease classification — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma histology not otherwise specified</td>
<td>232 (83)</td>
<td>122 (87)</td>
</tr>
<tr>
<td>Metastatic disease</td>
<td>266 (95)</td>
<td>138 (99)</td>
</tr>
<tr>
<td>CNS metastases‡</td>
<td>93 (33)</td>
<td>51 (36)</td>
</tr>
<tr>
<td>Extrathoracic visceral metastases§</td>
<td>145 (52)</td>
<td>80 (57)</td>
</tr>
<tr>
<td>Type of EGFR mutation — no. (%)¶</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T790M</td>
<td></td>
<td>275 (99)</td>
</tr>
<tr>
<td>Exon 19 deletion</td>
<td>191 (68)</td>
<td>87 (62)</td>
</tr>
<tr>
<td>Exon 21 L858R</td>
<td>83 (30)</td>
<td>45 (32)</td>
</tr>
<tr>
<td>G719X</td>
<td>4 (1)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>S768I</td>
<td>1 (-1)</td>
<td>1 (-1)</td>
</tr>
<tr>
<td>Exon 20 insertion</td>
<td>1 (-1)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>No. of previous anticancer regimens for advanced disease — no. (%)**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>269 (96)</td>
<td>134 (96)</td>
</tr>
<tr>
<td>2</td>
<td>9 (3)</td>
<td>6 (4)</td>
</tr>
<tr>
<td>3</td>
<td>1 (-1)</td>
<td>0</td>
</tr>
<tr>
<td>Previous EGFR-TKI therapy — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gefinitib</td>
<td>166 (59)</td>
<td>87 (62)</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>96 (34)</td>
<td>49 (35)</td>
</tr>
<tr>
<td>Afatinib</td>
<td>20 (7)</td>
<td>4 (3)</td>
</tr>
</tbody>
</table>
AURA3: Post 1st gen EGFR TKI
Osimertinib vs Chemotherapy

ORR 71% vs 31%:
Odds ratio 5.39 (3.47-8.48), p<0.001
Grade 3 AEs 23% vs 47%
### AURA3: Toxicity

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Osimertinib (N = 279)</th>
<th>Platinum-Pemetrexed (N = 136)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade ≥3</td>
</tr>
<tr>
<td></td>
<td>number (percent)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>113 (41)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Rash†</td>
<td>94 (34)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Dry skin†</td>
<td>65 (23)</td>
<td>0</td>
</tr>
<tr>
<td>Paronychia†</td>
<td>61 (22)</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>50 (18)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Cough</td>
<td>46 (16)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>45 (16)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>44 (16)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>41 (15)</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>39 (14)</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>35 (13)</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>31 (11)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Back pain</td>
<td>29 (10)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Thrombocytopenia†</td>
<td>28 (10)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>28 (10)</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>28 (10)</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>24 (9)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Neutropenia†</td>
<td>22 (8)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Leukopenia†</td>
<td>22 (8)</td>
<td>0</td>
</tr>
<tr>
<td>Anemia†</td>
<td>21 (8)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>20 (7)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>18 (6)</td>
<td>0</td>
</tr>
<tr>
<td>Alanine transaminase elevation</td>
<td>18 (6)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Aspartate transaminase elevation</td>
<td>14 (5)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Malaise</td>
<td>11 (4)</td>
<td>0</td>
</tr>
</tbody>
</table>
PD-(L)1 Inhibitors and EGFR$^{\text{mut}}$ NSCLC

In KN010, CM057 and OAK, the ONLY subgroup that did not show superior survival with the PD-(L)1 inhibitor vs docetaxel were the patients with EGFR mutations.
OS on 2nd Line Docetaxel vs IO Therapy by EGFR\textsuperscript{mut} Status

### OS on CM057 – Borghaei NEJM 2015

<table>
<thead>
<tr>
<th>EGFR Mutation Status</th>
<th>Censored (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>1.18 (0.69, 2.00)</td>
</tr>
<tr>
<td>Not Detected</td>
<td>0.66 (0.51, 0.86)</td>
</tr>
<tr>
<td>Not Reported</td>
<td>0.74 (0.51, 1.06)</td>
</tr>
</tbody>
</table>

All randomized pts (NIVO, n = 232; DOC, n = 296). HR was not computed for other subasets with less than 10 pts per treatment group.

### OS on OAK – Barlesi ESMO 2016

- **EGFR mutant**: 85 (10%)
- **EGFR wildtype**: 628 (74%)
- **ITT**: 850 (100%)

### OS on Keynote 010 – Herbst Lancet 2016

<table>
<thead>
<tr>
<th>EGFR status</th>
<th>Censored (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutant</td>
<td>0.88 (0.45-1.70)</td>
</tr>
<tr>
<td>Wild type</td>
<td>0.66 (0.55-0.80)</td>
</tr>
</tbody>
</table>

0.1 1 10

Favors Pembrolizumab  Favors Docetaxel
FLAURA Double-Blind Study Design

Key inclusion criteria
• ≥18 years*
• WHO performance status 0 / 1
• Exon 19 deletion / L858R (enrolment by local# or central‡ EGFR testing)
• No prior systemic anti-cancer / EGFR-TKI therapy
• Stable CNS metastases allowed

Stratification by mutation status (Exon 19 deletion / L858R) and race (Asian / non-Asian)

Endpoints
• Primary endpoint: PFS based on investigator assessment (according to RECIST 1.1)
  • The study had a 90% power to detect a hazard ratio of 0.71 (representing a 29% improvement in median PFS from 10 to 14.1 mo) 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

Osimertinib (80 mg p.o. qd) (n=279)

Randomised 1:1

EGFR-TKI SoC§;
Gefitinib (250 mg p.o. qd) or Erlotinib (150 mg p.o. qd) (n=277)

RECIST 1.1 assessment every 6 weeks¶ until objective progressive disease

Crossover was allowed for patients in the SoC arm, who could receive open-label osimertinib upon central confirmation of progression and T790M positivity

*≥20 years in Japan; #With central laboratory assessment performed for sensitivity; ‡cobas EGFR Mutation Test (Roche Molecular Systems); §Sites to select either gefitinib or erlotinib as the sole comparator prior to site initiation; ¶Every 12 wk after 18 mo.

Ramalingam S, et al. ESMO 2017, Abstract LBA2_PR.
### FLAURA: Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Osimertinib (n=279)</th>
<th>SoC* (n=277)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex: male / female</strong></td>
<td>36 / 64</td>
<td>38 / 62</td>
</tr>
<tr>
<td><strong>Age, median (range), years</strong></td>
<td>64 (26–85)</td>
<td>64 (35–93)</td>
</tr>
<tr>
<td><strong>Race: White / Asian / other</strong>#</td>
<td>36 / 62 / 1</td>
<td>36 / 62 / 1</td>
</tr>
<tr>
<td><strong>Smoking status: never / ever</strong></td>
<td>65 / 35</td>
<td>63 / 37</td>
</tr>
<tr>
<td><strong>CNS metastases at study entry‡</strong></td>
<td>19</td>
<td>23</td>
</tr>
<tr>
<td><strong>WHO performance status§: 0 / 1</strong></td>
<td>40 / 60</td>
<td>42 / 58</td>
</tr>
<tr>
<td><strong>Overall disease classification¶: metastatic / advanced</strong></td>
<td>95 / 5</td>
<td>95 / 5</td>
</tr>
<tr>
<td><strong>Histology: adenocarcinoma / other</strong></td>
<td>99 / 1</td>
<td>98 / 2</td>
</tr>
<tr>
<td><strong>EGFR mutation at randomisation</strong>: Exon 19 deletion / L858R</td>
<td>63 / 37</td>
<td>63 / 37</td>
</tr>
</tbody>
</table>

*In the SoC arm, 66% of patients received gefitinib and 34% received erlotinib; #Including Black or African American and American Indian or Alaska Native. Race was missing for 1 patient in the osimertinib arm and 1 patient in the SoC arm; ‡CNS metastases determined programmatically from baseline data of CNS lesion site, medical history, and/or surgery, and/or radiotherapy; §WHO performance status was missing for one patient in the SoC arm; ¶Overall disease classification was missing for one patient in the osimertinib arm; **Local or central test.

Ramalingam S, et al. ESMO 2017, Abstract LBA2_PR.
Tumor Response

Best percentage change in target lesion size is the maximum reduction from baseline or the minimum increase. *Represents imputed values: if it is known that the patient has died, has new lesions or progression of assessments, best change will be imputed as 20%.

By investigator assessment; CI, confidence interval; SD, standard deviation; SoC, standard-of-care.

Ramalingam S, et al. ESMO 2017, Abstract LBA2_PR.
FLAURA
Primary Endpoint: PFS by Investigator Assessment

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

HR 0.46 (95% CI 0.37, 0.57) p<0.0001

Ramalingam S, et al. ESMO 2017, Abstract LBA2_PR.
## FLAURA Safety Summary

<table>
<thead>
<tr>
<th>AE, any cause*, n (%)</th>
<th>Osimertinib (n=279)</th>
<th>SoC (n=277)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>273 (98)</td>
<td>271 (98)</td>
</tr>
<tr>
<td>Any AE Grade ≥3</td>
<td>94 (34)</td>
<td>124 (45)</td>
</tr>
<tr>
<td>Any AE leading to death</td>
<td>6 (2)</td>
<td>10 (4)</td>
</tr>
<tr>
<td>Any serious AE</td>
<td>60 (22)</td>
<td>70 (25)</td>
</tr>
<tr>
<td>Any AE leading to discontinuation</td>
<td>37 (13)</td>
<td>49 (18)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AE, possibly causally related#, n (%)</th>
<th>Osimertinib (n=279)</th>
<th>SoC (n=277)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>253 (91)</td>
<td>255 (92)</td>
</tr>
<tr>
<td>Any AE Grade ≥3</td>
<td>49 (18)</td>
<td>78 (28)</td>
</tr>
<tr>
<td>Any AE leading to death</td>
<td>0</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Any serious AE</td>
<td>22 (8)</td>
<td>23 (8)</td>
</tr>
</tbody>
</table>

*Patients with multiple events in the same category counted only once in that category. Patients with events in more than one category counted once in each of those categories; #As assessed by the investigator. Includes AEs with an onset date on or after the date of first dose and up to and including 28 days following the date of last dose of study medication.
EGFR Overview

- 10% of all cases of NSCLC have an EGFR mutation
- >50% in never-smoking Asian woman with lung cancer
- 5 drugs now available as first-line therapy (1st/2nd gen)
  - Most very expensive >$10,000 per month
- Addition of bevacizumab or ramucirumab may improve outcomes but cost >$10,000 per dose
- Osimertinib: clear superiority vs chemotherapy after 1st/2nd generation EGFR TKI
- Osimertinib new option as first-line EGFR TKI (prolong PFS)
- Checkpoint inhibitors are inferior in EGFRmut NSCLC
EGFR Toxicities

- Dermatologic
- GI
- Ophthalmic
- Cardiac
Toxicity Discussion

EGFR Inhibitors
- Afatinib
- Erlotinib
- Geftinib
- Osimertinib
Incidence of Rash

- Afatinib: 81-89%, 16% grade 3 or 4
- Erlotinib: 75-80%, 13% grade 3 or 4
- Gefitinib: 37-66%, 3% grade 3 or 4
- Osimertinib: 41%, 0.5% grade 3 or 4

Rash: Pathophysiology

EGF

• Found in normal epidermal and follicular keratinocytes
• Primarily serves to regulate differentiation and provide protection from UV rays or other cellular damage
• Can help hasten wound healing and inhibit inflammation
• If inhibited, the skin begins to thin and dry; may result in recruitment of the immune system, leading to a pustular eruption

Clinical Presentation

- Sudden onset of papulopustular eruption
- Usually involves face, scalp, neck, upper chest, back
- Rash may be indicative of clinical benefit
- Low-grade rash affects quality of life

Management: Prophylaxis

• No standard treatment for EGFR skin rash
• MASCC and NCCN guidelines and strategies
• Prophylaxis: daily skin care with thick, alcohol-free emollient to moisturize the skin
• Minimize sun exposure, wear protective clothing, and use sunscreen with SPF 15 or higher.
• Take lukewarm showers, baths
• Avoid perfume- and alcohol-containing skin products

Rash Management

• Depends on severity/grade of rash
• Grade 1: no intervention may be needed. Consider topical steroid/antibiotic ointment, lotion, gel, such as hydrocortisone 2.5%, clindamycin 1%
• Grade 2: hydrocortisone 2.5% plus oral antibiotic, either doxycycline 100 mg BID or minocycline 100 mg BID
• Grade 3/4: same as grade 2, consider methylprednisolone dose pack
Rash Management

Other interventions

• Hold drug and treat rash; consider dose reduction of drug depending on severity of rash and response to interventions
• Refer to dermatology
GI Toxicities: Diarrhea

• Most common GI toxicity associated with EGFR inhibitors
• Due to presence of EGFR in GI mucosa
• Afatinib has the highest incidence of diarrhea (83-95%), often dose limiting/dose reducing
• Ceritinib has the highest incidence of diarrhea for the ALK inhibitors (83%)

Diarrhea Prophylaxis

• Avoid foods that irritate the GI tract: dairy, spicy, greasy foods
• Hydrate
• Good eating habits, healthy diet

Diarrhea

• Usually occurs during first month of starting erlotinib and gefitinib, and within 1 week of starting afatinib
• Rule out other potential causes of diarrhea including *C. diff*, medications (laxatives, antibiotics)

Diarrhea Treatment

- BRAT diet: bananas, rice, applesauce, toast
- Hydrate/electrolyte replacement
- Loperamide
- Diphenoxylate: atropine if loperamide is not effective.
- Intravenous hydration if grade 3 (> 7 episodes/day)
- Consider holding drug, and possible dose reduction
Ophthalmic Issues

- EGFR present on several anatomic sites surrounding and related to the eyes, including: eyelids, eyelash follicles, tear glands, conjunctiva, and cornea.
- Patients on afatinib likely to experience conjunctivitis (11%).
- Conjunctivitis, blepharitis, dry eyes, keratitis (rarely) are associated with gefitinib.
Ophthalmic Issues

- 18% of patients on erlotinib have reported: dry eyes, eyelash growth disturbances (trichomegaly), keratitis
- 19% of patients on osimertinib have experienced: dry eyes, cataracts, keratitis, blurry vision, eye irritation

Ophthalmic Treatment

Refer to ophthalmologist
ALK
Case 2

• RJ is a 47-year-old man who smoked a few cigarettes daily for 10 years. He presents with progressive right-sided chest pain.
• CXR reveals pleural thickening and a mass
• CT reveals right adrenal mass, right lung mass (3 cm), and pleural studding on the right
• Biopsy is c/w adenocarcinoma
• PET/brain MRI show no other areas of disease
• Initially ALK FISH is negative, and rapid EGFR is negative
Case 2 (cont.)

A biopsy is performed of the liver metastases and NGS reveals an ALK rearrangement. He does well with crizotinib for 10 months until disease progression. He then has a biopsy which reveals V1180L ALK resistance mutation.

What do you start?
A. Brigatinib
B. Ceritinib
C. Restart pemetrexed
D. Alectinib
E. Nivolumab or pembrolizumab
F. Lorlatinib or ensartinib or other on trial
# Resistance Mechanisms in ALK+ NSCLC

<table>
<thead>
<tr>
<th></th>
<th>1&lt;sup&gt;st&lt;/sup&gt; gen</th>
<th>2&lt;sup&gt;nd&lt;/sup&gt; gen</th>
<th>3&lt;sup&gt;rd&lt;/sup&gt; gen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td>Alectinib</td>
<td>Brigatinib</td>
</tr>
<tr>
<td>G1123S</td>
<td>Res</td>
<td>Sens&lt;sup&gt;2&lt;/sup&gt;</td>
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</tr>
<tr>
<td>1151Tins</td>
<td>Res</td>
<td>Res&lt;sup&gt;3&lt;/sup&gt;</td>
<td>N/D</td>
</tr>
<tr>
<td>L1152P/R</td>
<td>Res</td>
<td>Sens</td>
<td>N/D</td>
</tr>
<tr>
<td>C1156Y/T</td>
<td>Res</td>
<td>Sens</td>
<td>N/D</td>
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<tr>
<td>I1171T/N</td>
<td>Res</td>
<td>Res&lt;sup&gt;4,5&lt;/sup&gt;</td>
<td>N/D</td>
</tr>
<tr>
<td>F1174C/L/V</td>
<td>Res</td>
<td>Sens</td>
<td>Sens&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td>V1180L</td>
<td>Res</td>
<td>Res&lt;sup&gt;4&lt;/sup&gt;</td>
<td>N/D</td>
</tr>
<tr>
<td>L1196M</td>
<td>Res</td>
<td>Sens&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Sens&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td>L1198F</td>
<td>Sens&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Res&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Res&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>G1202R</td>
<td>Res</td>
<td>Res&lt;sup&gt;3&lt;/sup&gt;</td>
<td>N/D</td>
</tr>
<tr>
<td>S1206C/Y</td>
<td>Res</td>
<td>Sens&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Res&lt;sup&gt;6&lt;/sup&gt;</td>
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<td>F1245C</td>
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<td>N/D</td>
</tr>
<tr>
<td>G1269A/S</td>
<td>Res</td>
<td>Sens</td>
<td>N/D</td>
</tr>
</tbody>
</table>
EML4-ALK Translocations in NSCLC

Identification of the transforming EML4–ALK fusion gene in non-small-cell lung cancer

Manabu Soda1,2, Young Lim Choi1, Munehiro Enomoto1,2, Shuji Takada1, Yoshihiro Yamashita1, Shunpei Ishikawa3, Shin-ichiro Fujiwara1, Hideki Watanabe1, Kentaro Kurashina1, Hisashi Hatanaka1, Masashi Bando2, Shoji Ohno2, Yuichi Ishikawa4, Hiroki Aburatani5, Toshiro Niki1, Yasunori Sohara1, Yukihiro Sugiyama2 & Hiroyuki Mano1,7

EML4-ALK frequency: 
~4% (64/1709) 
Primarily lung adenocarcinoma
Tumor Responses to Crizotinib for Patients With ALK-Positive NSCLC

Primary Endpoint Met: Crizotinib Superior to Pemetrexed-Based Chemotherapy in Prolonging PFS\textsuperscript{a}

Data cutoff: 11/30/13

\textbf{ORR 74\% vs 45\%}

\textbf{OS HR 0.82 (0.54-1.26), NS}

\textsuperscript{a}Assessed by IRR; \textsuperscript{b}1-sided stratified log-rank test.

Next-Generation ALK Inhibitors

- Crizotinib
- Ceritinib
- Ensartinib
- Alectinib
- Brigatinib
- Lorlatinib

Courtesy Solange Peters
ALEX Study Design

KEY ELIGIBILITY
● ALK+ by central IHC testing
● Advanced or metastatic ALK+ NSCLC
● Treatment-naïve
● ECOG PS 0–2
● Measurable disease
● Asymptomatic brain metastases allowed

ENDPOINTS
● Primary
  PFS (RECIST 1.1), by investigator review
● Secondary
  PFS by IRC
  Time to CNS progression
  ORR, DOR
  OS
  Safety and tolerability
  Patient-reported outcomes

Alectinib
600 mg BID PO

Crizotinib
250 mg BID PO

RANDOMIZE

NO CROSSOVER

ALK, anaplastic lymphoma kinase; IHC, immunohistochemistry; NSCLC, non-small cell lung cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; PFS, progression-free survival; IRC, independent review committee; CNS, central nervous system; ORR, objective response rate; DOR, duration of response; OS, overall survival.

Stratification factors:
• ECOG PS (0/1 vs 2)
• Race (Asian vs non-Asian)
• Brain metastases (present vs absent)

ALEX: Objective Response Rate*

<table>
<thead>
<tr>
<th></th>
<th>Crizotinib (N=151)</th>
<th>Alectinib (N=152)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Responders, n (%)</strong></td>
<td>114 (76)</td>
<td>126 (83)</td>
</tr>
<tr>
<td><strong>(95% CI)</strong></td>
<td>(68–82)</td>
<td>(76–89)</td>
</tr>
<tr>
<td><strong>P value</strong></td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td><strong>Complete response, n (%)</strong></td>
<td>2 (1)</td>
<td>6 (4)</td>
</tr>
<tr>
<td><strong>Partial response, n (%)</strong></td>
<td>112 (74)</td>
<td>120 (79)</td>
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<tr>
<td><strong>Stable disease, n (%)</strong></td>
<td>24 (16)</td>
<td>9 (6)</td>
</tr>
<tr>
<td><strong>Median DOR (months)</strong></td>
<td>11.1</td>
<td>NE</td>
</tr>
<tr>
<td><strong>(95% CI)</strong></td>
<td>(7.9–13.0)</td>
<td>(NE)</td>
</tr>
</tbody>
</table>

*Investigator assessment

Primary Endpoint: PFS, Investigator-Assessed

Patients with events, n (%)  
<table>
<thead>
<tr>
<th></th>
<th>Crizotinib (N=151)</th>
<th>Alectinib (N=152)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with events, n (%)</td>
<td>102 (68)</td>
<td>62 (41)</td>
</tr>
</tbody>
</table>

Median PFS, months (95% CI)  
<table>
<thead>
<tr>
<th></th>
<th>Crizotinib</th>
<th>Alectinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>11.1 (9.1–13.1)</td>
<td>NE (17.7–NE)</td>
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</table>

HR (95% CI) P-value (log-rank test)  
<table>
<thead>
<tr>
<th></th>
<th>Crizotinib</th>
<th>Alectinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (95% CI) P-value (log-rank test)</td>
<td>0.47 (0.34–0.65)</td>
<td>P&lt;0.0001</td>
</tr>
</tbody>
</table>

No. at Risk  

<table>
<thead>
<tr>
<th></th>
<th>Crizotinib</th>
<th>Alectinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. at Risk</td>
<td>151 132 104 84 65 46 35 16 5</td>
<td>152 135 113 109 97 81 67 35 15 3</td>
</tr>
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</table>
Secondary Endpoint: OS

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Crizotinib</th>
<th>Alectinib</th>
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</thead>
<tbody>
<tr>
<td>Crizotinib</td>
<td>151</td>
<td>152</td>
</tr>
<tr>
<td>Alectinib</td>
<td>141</td>
<td>142</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients with events, n (%)</th>
<th>40 (27)</th>
<th>35 (23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, months (95% CI)</td>
<td>NE (NE)</td>
<td>NE (NE)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.76</td>
<td>(0.48–1.20)</td>
</tr>
<tr>
<td>P value</td>
<td>P=0.24</td>
<td></td>
</tr>
</tbody>
</table>

ALK Summary

• First-line ALK TKI therapy remains the standard of care for patients with ALK translocations
  • Crizotinib, ceritinib, alectinib approved first-line options
  • 2nd line + ceritinib, alectinib, brigatinib now approved
  • Multiple other ALK inhibitors in development

• Toxicities variable
  • Crizotinib: edema, bradycardia, vision changes, N/V, transaminitis
  • Ceritinib: N/V, fatigue, rash, diarrhea

Costs are >$10,000 per month for all of these agents.
PERHAPS market forces will now start to bring down price?
Toxicity Discussion

ALK inhibitors
- Alectinib
- Brigatinib
- Ceritinib
- Crizotinib
ALK Toxicities

- Dermatologic
- GI
- Ophthalmic
- Cardiac
- Hyperglycemia
Adverse Events, ≥10% in Either Treatment Arm (ALEX Trial)

<table>
<thead>
<tr>
<th>AE</th>
<th>Crizotinib (N=151)</th>
<th>Alectinib (N=152)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>Any grade</td>
<td>Grade 3–5</td>
</tr>
<tr>
<td>Constipation</td>
<td>49 (33)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>72 (48)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>68 (45)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>58 (38)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>42 (28)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>25 (17)</td>
<td>0</td>
</tr>
<tr>
<td>ALT increased</td>
<td>45 (30)</td>
<td>22 (15)</td>
</tr>
<tr>
<td>AST increased*</td>
<td>37 (25)</td>
<td>16 (11)</td>
</tr>
<tr>
<td>Blood bilirubin increased</td>
<td>2 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>21 (14)</td>
<td>0</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>29 (19)</td>
<td>0</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>11 (7)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>3 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>7 (5)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Rash</td>
<td>14 (9)</td>
<td>0</td>
</tr>
<tr>
<td>Visual impairment</td>
<td>18 (12)</td>
<td>0</td>
</tr>
</tbody>
</table>

*AE, adverse event; ALT, alanine aminotransferase; AST, aspartate transaminase.
Ophthalmic Issues

• 61-70% of patients on crizotinib may develop visual changes: common side effect is difficulty with light and dark accommodation
• Visual effects: most common side effect of crizotinib; onset less than 2 weeks
• Shimmering/flashing lights, streamers, strings, floaters, overlapping shadows, afterimages
• No interruption in therapy or dose adjustments
• Baseline ophthalmologic assessment not required, but if visual effects persist, refer to Crizotinib package insert.
Cardiac Toxicities: Sinus Bradycardia

- Retrospective analysis from two studies of patients on crizotinib showed 75.3% of patients experienced sinus bradycardia, heart rate between 50 and 59.
- The average decrease in heart rate was 25 beats/minute.
- Patients with baseline heart rate less than 70 beats/minute were significantly more likely to experience bradycardia.

Cardiac Toxicities: Sinus Bradycardia

- Patients who experienced sinus bradycardia did so after approximately 20 weeks on treatment.
- Patients who did not experience sinus bradycardia had their lowest heart rate near week 12 of treatment.

Cardiac Toxicities: Sinus Bradycardia

- Grade 1: Patient asymptomatic. Majority of patients (83%) had grade 1 sinus bradycardia.
- Grades 2, 3, and 4: Hold drug until recovery of normal heart rate. Review all medications to determine if any contribute to bradycardia.

Cardiac Toxicities: Sinus Bradycardia

• For grade 2 and 3 sinus bradycardia: if no medications are identified as contributing to bradycardia, resume treatment with ALK inhibitor at reduced dose. If medication is identified as contributing to bradycardia, adjust dose of that medication, and resume ALK inhibitor at full dose.

• Grade 4: As above; however, if no medications are identified as contributing to bradycardia, permanently discontinue ALK inhibitor.

Cardiac Toxicities: QT Prolongation

- Crizotinib, ceritinib, and osimertinib all carry boxed warnings for QT prolongation
- Be aware of patient’s PMH and medications
- Baseline and periodic EKGs

Hyperglycemia

- Mainly seen with ceritinib and alectinib
- Due to ability of ALK inhibitors to inhibit insulin-like growth factor receptor

Hyperglycemia

• Treat patients based on current diabetes guidelines
• Hold drug until blood glucose is under control, then resume ALK inhibitor at lower dose
• If the patient’s blood glucose remains uncontrolled, discontinue ALK inhibitor

Other Targets
Genomic Driver Mutation in Lung Adenocarcinoma

N = 733 pts
14 institutions of LCMC
Case 3

- TV is a 58-year-old Asian American woman who notices increasing shortness of breath
- On PE, she has dullness 1/3 up on left lung
- CXR confirms an effusion, and CT reveals a LLL mass and moderate effusion as well as multiple smaller pulmonary nodules bilaterally
- Cytology of effusion is c/w adenocarcinoma
- PET/brain MRI show no other areas of disease
- Cytologic sample is used for rapid EGFR testing and ALK FISH. Both are negative. No tissue remains for further testing.
Case 3

She is started on platinum/pemetrexed and does not tolerate it well. She does not want any further chemotherapy but would consider other options that are available. She has systemic lupus so immune therapy is not an option.

What do you do?

A. Repeat biopsy for NGS
B. Send “liquid biopsy” for NGS
C. Initiate hospice
Case 3: BRAF

A “liquid biopsy” is obtained and reveals BRAF V600E

What do you start?
A. Erlotinib/bevacizumab
B. Osimertinib
C. Dabrafenib/trametinib
D. Alectinib
E. Brigatinib
Case 3: BRAF

Drabrafenib/trametinib was started, and she has had a rapid clinical improvement in symptoms from her pleural effusion. It is well tolerated.
Phase II Dabrafenib (D) + Trametinib (T) in pts With prev Rx BRAF V600E–mut adv NSCLC (BRF113928): N = 57

- BRAF inhibitor combo therapy of dabrafenib (D) + trametinib (T) is active in BRAF V600E-mutant melanoma
- Dosing: D 150 mg po bid + T 2 mg po qd
- Median age 64 yr (range: 41–88); 51% female
- All patients had nonsquamous histology; 73% current/former smokers
- ORR 63% in 52 pts evaluable for efficacy (confirmed response); 50% still with response at the time of analysis
- Safety
  - Most common AEs (> 25%) included pyrexia, nausea, vomiting, diarrhea, asthenia, decreased appetite, dry skin

Response to Cabozantinib in Patients With RET-Rearranged Lung Adenocarcinomas

<table>
<thead>
<tr>
<th>Best Response</th>
<th>% (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PR</strong></td>
<td>44% (7/16)</td>
</tr>
<tr>
<td><strong>confirmed unconfirmed</strong></td>
<td>38% (6/16)</td>
</tr>
<tr>
<td><strong>SD</strong></td>
<td>56% (9/16)</td>
</tr>
</tbody>
</table>

**ORR 38% (95% CI 15%-65%)**

**ORR_{12wks} 36% (95% CI 13%-65%)**
(5 PRs of 14 evaluable at 12 wks)
## RET Inhibitors: Efficacy Summary

<table>
<thead>
<tr>
<th>Agent</th>
<th>RET testing</th>
<th>n</th>
<th>ORR (%)</th>
<th>PFS (months)</th>
<th>OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cabozantinib (Drilon, ASCO 2015)</td>
<td>FISH/NGS</td>
<td>Stage I, 16</td>
<td>38</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Cabozantinib (Gautschi, ASCO 2016)</td>
<td>FISH/NGS/RT-PCR</td>
<td>13</td>
<td>31</td>
<td>3.6</td>
<td>4.9</td>
</tr>
<tr>
<td>Vandetanib (Sato, ASCO 2016)</td>
<td>FISH/RT-PCR</td>
<td>19/17</td>
<td>47/53</td>
<td>4.7</td>
<td>47% 1-year</td>
</tr>
<tr>
<td>Vandetanib (Lee, ASCO 2016)</td>
<td>FISH confirmed</td>
<td>18</td>
<td>17</td>
<td>4.5</td>
<td>11.6</td>
</tr>
<tr>
<td>Vandetanib (Gautschi, ASCO16)</td>
<td>FISH/NGS/RT-PCR</td>
<td>11</td>
<td>18</td>
<td>2.9</td>
<td>10.2</td>
</tr>
<tr>
<td>Sunitinib (Gautschi, ASCO 2016)</td>
<td>FISH/NGS/RT-PCR</td>
<td>9</td>
<td>22</td>
<td>2.2</td>
<td>6.8</td>
</tr>
<tr>
<td>Any RET inhibitor (Gautschi, ASCO 16)</td>
<td>FISH/NGS/RT-PCR</td>
<td>41</td>
<td>23</td>
<td>2.9</td>
<td>6.8</td>
</tr>
</tbody>
</table>

Reckamp KL, discussant ASCO 2016.
MET Exon 14 Splice Variant

- MET exon 14 splice variant ~4% adeno (TCGA)
- 8/18 (44%) pts responded to crizotinib
  - Additional 5/18 (28%) unconfirmed
- Dramatic responses to cabozantinib reported

MET Exon 14 Splice Variant

- MET exon 14 splice variant ~4% adenocarcinoma (TCGA)
- Responses to crizotinib and cabozantinib

HER2-mutant NSCLC

- 69% women, 100% adeno, 50% never-smoker
- ORR 50% and DCR 93% with trastuzumab + chemotherapy
- High RR to afatinib (100% DCR)
- Time to progression relatively short (< 6 mo)

NGS in Patients With “No Genomic Alterations”

**Table:**

<table>
<thead>
<tr>
<th>Genomic alteration with targeted therapy in NCCN guidelines</th>
<th>Tumor from same procedure as tumor subjected to non-NGS testing</th>
<th>Patient’s clinical course</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR G719A, BRAF V600E, SOCS5-ALK, HIP1-ALK, CD74-RSK1, KIF5B-RET, KIF5B-RET, CCDC6-RET</td>
<td>Yes, Yes, Yes, Yes, Yes, No, Yes</td>
<td>Recently started erlotinib, response evaluation pending, Subsequently passed away, Disease shrinkage (&lt;30%) with crizotinib, Partial response to crizotinib, Recently started crizotinib, response evaluation pending, Partial response to cabozantinib, Disease shrinkage (&lt;30%) with cabozantinib, Candidate for cabozantinib after progression on chemotherapy</td>
</tr>
</tbody>
</table>

**Figure 2:**
Clinical NGS and targeted therapy use. The results of NGS of lung adenocarcinomas that harbored no genomic alterations (GA) in 11 genes (EGFR, ERBB2, KRAS, NRAS, BRAF, MAP2K1, PIK3CA, AKT1, ALK, ROSI, and RET) via a focused panel of non-NGS testing in never or ≤15 pack-year smokers are shown. The percentage of patients with results that fall into 1 of 4 categories is depicted in the pie chart.

ctDNA Utility in Undergenotyped NSCLC

**Tissue Genotyping Status**
(n=362 non-squamous NSCLC)

- Tissue Biomarker Positive (n=120)
- Tissue QNS / Partially Genotyped (n=229)
- Tissue NGS, Biomarker Negative (n=13)

**ctDNA NGS Increased Biomarker Yield by 42%**
(51 additional biomarkers identified in tissue QNS/PG cases)

**Biomarker** | **N in Tissue** | **Biomarker** | **N in Tissue**
--- | --- | --- | ---
EGFR | 98 | RET fusion | 1
KRAS | 11 | BRAF^{V600E} | 1
ALK fusion | 5 | MET/ERBB2 amp | 2
ROS1 fusion | 2 | TOTAL | 120

**Biomarker** | **N in ctDNA** | **Biomarker** | **N in ctDNA**
--- | --- | --- | ---
EGFR | 8 | RET fusion | 3
KRAS | 28 | BRAF^{V600E} | 4
ALK fusion | 1 | MET/ERBB2 amp | 7
ROS1 fusion | 0 | TOTAL | 51

*among Tissue QNS/PG

Mack PC. ASCO 2016.
Conclusions

• Promising new EGFR TKIs with T790M+ activity
  • Osimertinib, others

• Promising ALK TKIs with activity 1st/2nd line+

• New insights with recent publications on resistance mechanisms, ongoing combination/sequencing trials

• Multiple other clinically relevant targets with active agents being identified

• Consider repeat testing

• Serum testing: the next step

• Many patients living years in this setting but with medication costs of >$100,000 annually
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If you would like more information about this program, please ask a conference staff member or visit the SMARTIE booth.