Collaborative Practice in the Management of Patients With Cancer

Targeted Therapies in Advanced Non-Small Cell Lung Cancer
Program Chair

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Disclosures

Faculty

Ms. Eaby-Sandy has acted as a consultant for AstraZeneca and Clovis; she has served on speakers bureaus for Amgen, Celgene, Eisai, and Merck.

Planning Committee

Moshe C. Ornstein, MD, MA, Cleveland Clinic Taussig Cancer Institute (Reviewer) has nothing to disclose. Alana Brody, Terry Logan, Lynn Rubin, and Wendy Smith (MEI) have nothing to disclose. Sandra Leatherman, Annamarie Luccarelli, and Jessica Tamasi (APSHO) have nothing to disclose. Claudine Kiffer and Annie Yueh (Harborside Press) have nothing to disclose.
Learning Objectives

• Demonstrate a foundational understanding of how to interpret imaging studies that are used in the management of NSCLC
• Choose relevant molecular/biomarker tests to identify the most appropriate therapy for the patient with NSCLC (e.g., targeted or immunotherapy)
• Use appropriate management strategies for toxicities associated with targeted therapies
• Differentiate between the various treatment options available for NSCLC: Comparing mechanisms of action, toxicity profiles, and monitoring
• Manage toxicities associated with different agents used to treat NSCLC
• Demonstrate an understanding of the science behind immune checkpoint inhibition and how this drug category differs from other available and evolving options for NSCLC, including cytotoxic chemotherapy
Objectives

• Discuss biomarkers and their role in NSCLC treatment
• Review of clinical trial data for drugs that target EGFR, ALK, ROS1, T790M
• Review of side-effect profiles and management of toxicities
Why Do Molecular Biomarkers Matter in NSCLC?

• PFS with standard chemotherapy regimens in NSCLC
  – Pemetrexed/cisplatin: 5 months
  – Paclitaxel/carboplatin/bevacizumab: 6 months
• PFS with EGFR-mutated NSCLC receiving EGFR targeted therapy
  – Gefitinib: 9.5 months
  – Erlotinib: 9.7 months
  – Afatinib: 11.0 months
• PFS with ALK-positive NSCLC receiving ALK inhibitor
  – Crizotinib: 9.7 months
Genetic Biomarkers for NSCLC

- KRAS (24%)
- EGFR (sensitizing) (17%)
- ALK (rearrangement) (8%)
- EGFR (other) (4%)
- ERBB2 (2%)
- BRAF (2%)
- V600E
- PIK3CA
- MET
- NRAS
- G719X
- L861Q
- Non-V600E
- MEK1
- UNKNOWN ≤ 1%

## Molecular Abnormalities in NSCLC With Current FDA-Approved Implications

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Details</th>
</tr>
</thead>
</table>
| **EGFR**    | Transmembrane receptor  
              Level of expression varies widely  
              Mutations in this domain (10-15% of pts) result in activation of the tyrosine kinase domain with significantly better response to erlotinib or gefitinib or afatinib  
              Mutations: highest incidence in never-smokers, adenocarcinoma, women, and patients with Asian ethnicity |
| **EML4-ALK**| Incidence of EML4-ALK translocation: 2-7%  
              Estimated prevalence of EML4-ALK in lung cancer: 6,000 pts/yr US; up to 40,000 pts/yr globally  
              Three drugs approved to treat: crizotinib, ceritinib, alectinib  
              EML4-ALK rarely coexists with EGFR, HER2, or KRAS mutations, indicating it is a distinct disease subtype |
| **ROS1**    | About 1-2% of patients with NSCLC  
              Most common in younger, never-smokers  
              Detected via FISH test  
              Crizotinib approved to treat ROS1+ patients |
| **T790M**   | EGFR resistance mutation  
              About 60% patient develop post failure of EGFR TKI  
              Osimertinib FDA approved to treat |

FISH = fluorescence in situ hybridization.

NCCN. Non-Small Cell Lung Cancer. V.2.2010. Available at http://www.nccn.org;
## Molecular Abnormalities of Interest

| **BRAF mutations** | • 4% NSCLC  
  • Most common is *V600E*  
  • Drugs in trials: dabrafenib, vemurafenib, dasatinib, |
|--------------------|---------------------------------------------------------------|
| **RET rearrangements** | • 1-2% NSCLC  
  • Highly associated with young, never-smokers  
  • Drugs in trials: vandetanib, cabozantinib, sunitinib, ponatinib |
| **MET amplification** | • Drugs in trials: crizotinib, tivantinib, onartuzumab, MET inhibitors |
| **HER2 mutations** | • Drugs in trials: trastuzumab, afatinib, dacomitinib, neratinib |
| **KRAS mutations** | • 25-30% NSCLC, most common mutation  
  • MEK, PI3K, FAK inhibitors |

Case Study #3

- Mrs. DD is a 64-year-old female who had surgery 2 years ago for a stage IIB NSCLC but refused adjuvant chemotherapy.

- She is a never-smoker, only smoked less than 20 cigarettes in her life, all while in high school.

- She comes in now with a routine CT chest showing new pulmonary nodules and some mediastinal adenopathy and a small pleural effusion.

- Her surgical tissue 2 years ago tested positive for an EXON 19 deletion EGFR mutation.
**EGFR Mutation +**

- **Most common types:** Exon 19 deletion and Exon 21 point mutation (L858R)
  - 42% never-smokers + EGFR mutations\(^1\)
  - 63% Asian female never-smokers + EGFR mutation\(^2\)

- **Uncommon mutations:** Exon 18, 20 and others have been associated with decreased response to EGFR TKIs in some cases, though some can respond\(^3\)

- **Approved agents** are afatinib 40 mg daily, erlotinib 150 mg daily, gefitinib 250 mg daily (all oral TKIs)

\(\text{TKIs} = \text{tyrosine kinase inhibitors.}\)

Epidermal Growth Factor-Induced Signal Transduction and Tumorigenesis

Epidermal growth factor receptor (EGFR) is a tyrosine kinase growth factor receptor
Activated by binding of natural ligands
  – TGF-α
  – EGF
Activation of EGFR linked with
  – Increased cell proliferation
  – Angiogenesis
  – Metastasis
EGFR expression correlates with
  – Poor response to treatment
  – Disease progression
  – Poor survival

Important Large Clinical Trials

Demonstrating Improvement in PFS With First-Line Treatment With an EGFR TKI vs. Chemotherapy

• LUX-LUNG 3
• EURTAC
• IPASS
LUX-Lung 3 Study Design

Stage IIIB (wet)/IV lung adenocarcinoma (AJCC version 6)
EGFR mutation in tumor
(central lab testing; Therascreen EGFR29* RGQ PCR)

Randomization 2:1
Stratified by:
EGFR mutation (Del19/L858R/other)
Race (Asian/non-Asian)
N = 345

Afatinib 40 mg/day†
Cisplatin + Pemetrexed
75 mg/m² + 500 mg/m² IV
q21 days, up to 6 cycles

Primary endpoint: PFS (RECIST 1.1, independent review)‡
Secondary endpoints: ORR, DCR, DoR, tumor shrinkage, OS, PRO§, safety, PK

*EGFR29:19 deletions in exon 19, 3 insertions in exon 20, L858R, L861Q, T790M, G719S, G719A and G719C (or G719X), S768I.
†Dose escalated to 50 mg if limited AE observed in cycle 1. Dose reduced by 10-mg decrements in case of related G3 or prolonged G2 AE.
‡Tumor assessments: q6 weeks until week 48 and q12 weeks thereafter until progression/start of new therapy.
§Patient-reported outcomes: Q-5D, EORTC QLQ-C30 and QLQ-LC13 at randomization and q3 weeks until progression or new anti-cancer therapy.

EURLTAC Study Design

Erlotinib vs platinum-based chemotherapy in EGFR M+ NSCLC patients

- Stage IIIB (with pleural effusion) or IV NSCLC
- Activating mutation of the EGFR gene detected prospectively using DNA sequencing (Sanger), confirmed by
  - Exon 19 deletion (n = 115) (length analysis after PCR amplification in an ABI prism 3130 DNA analyzer)
  - Exon 21 (L858R) (n = 58) (TaqMan assay)
- No prior CT for metastatic disease or prior treatment with EGFR-targeted therapies
- ECOG PS 0–2 (strata)
- European Population (France, Italy, Spain)
  \[ N = 173 \]

Randomization
(strata: mutation type, ECOG status)

Erlotinib until disease progression (150 mg/day)

4 cycles of platinum-doublet CT:
- Cis (75 mg/m²) + Doc (75 mg/m²)
- Cis (75 mg/m²) + Gem (1,250 mg/m²; day 1 + 8)
- Carbo (AUC 6) + Doc (75 mg/m²)
- Carbo (AUC 5) + Gem (1,000 mg/m²; day 1 + 8)

Primary endpoint: PFS (Investigator review confirmed by independent review)
Secondary endpoints: RR, OS, EGFR mutation analysis in serum

Carbo = carboplatin; Cis = cisplatin; CT = chemotherapy; Doc = docetaxel; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EGFR = epidermal growth factor receptor; Gem = gemcitabine; NSCLC = non-small cell lung cancer; OS = overall survival; PCR = polymerase chain reaction; PFS = progression-free survival; RR = response rate.

IPASS (Iressa Pan-Asia Study) Study Design

**Gefitinib vs paclitaxel/carboplatin in light/never-smoking Asian NSCLC**

- Stage IIIIB or IV adenocarcinoma NSCLC
- Light or never-smokers
- No previous chemotherapy or biologic or immunologic therapy
- WHO Performance scale: 0–2
- Including sub-population with EGFR mutation detected retrospectively using ARMS and DxS EGFR 29 mutation-detection kit (29 mutations screened)
  - Exon 19 deletion (n = 140)
  - Exon 20 (T790M) (n = 11)
  - Exon 21 (L858R) (n = 111)
  - Other mutations (n = 10)
- N = 1,217
- n = 261 EGFR-M+ (pre-specified subgroup)

**Randomization**
(dynamic balancing/strata: WHO PS, smoking status, sex, center)

- Gefitinib until disease progression (250 mg/day)
- Up to 6 cycles of carboplatin/gemcitabine
  - Carboplatin (AUC 5/6) + Paclitaxel (200 mg/m² day 1) q3wk

**Primary endpoint:** PFS (Investigator review)

**Secondary endpoints:** OS, ORR

## LUX-Lung 3, EURTAC, IPASS: PFS and ORR

**First-Line Reversible EGFR-TKI in EGFR M+ NSCLC**

<table>
<thead>
<tr>
<th>Trial</th>
<th>CT</th>
<th>Mutations</th>
<th>ORR</th>
<th>PFS</th>
<th>Hazard ratio (95% CI)</th>
<th>Primary Endpoint Assessment</th>
</tr>
</thead>
</table>
| **LUX-Lung 3**
N = 345              | Pem/Cis x 6 vs afatinib          | EGFR            | 56 vs 23 | 11.1 vs 6.9 | 0.58 (0.43, 0.78)    | Independent                |
|                     | Del19/L858R (89%)                |                 | 61 vs 22 | 13.6 vs 6.9 | 0.47 (0.34, 0.65)    |                           |
|                     | EGFR                             |                 | 69 vs 44 | 11.1 vs 6.7 | 0.49 (0.37, 0.65)    | Investigator               |
| **EURTAC**
2,3 N = 173        | Cis (Carbo) + Doc/Gem x 4 vs erlotinib | Del19/L858R (100%) | 10.4 vs 5.4 | 0.47 (0.28, 0.78) | Independent |
|                     | Del19/L858R (100%)               |                 | 58 vs 15  | 9.7 vs 5.2  | 0.37 (0.25, 0.54)    | Investigator               |
| **IPASS**
4 N = 1,217        | Carbo/Pac x 6 vs gefitinib       | EGFR            | 71 vs 47  | 9.5 vs 6.3  | 0.48 (0.36, 0.64)    | Investigator               |
|                     | Del19/L858R (96%)                |                 | NR       | NR         |                       |                            |

LUX-Lung 3 and LUX-Lung 6: Median OS in Del19+ Tumor Subgroup

Only 68% of patients in the chemotherapy arm went on to receive EGFRI therapy post-progression

# LUX-Lung 3, EURTAC, IPASS: Most Frequently Reported Adverse Events

First-line reversible EGFR-TKI in EGFR M+ NSCLC

<table>
<thead>
<tr>
<th></th>
<th>LUX-Lung 3&lt;sup&gt;1&lt;/sup&gt; Afatinib N = 229 %</th>
<th>EURTAC&lt;sup&gt;2&lt;/sup&gt; Erlotinib N = 84 %</th>
<th>IPASS&lt;sup&gt;3&lt;/sup&gt; Gefitinib N = 607 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>96.1 14.8</td>
<td>57 5</td>
<td>46.6 3.8</td>
</tr>
<tr>
<td>Rash/acne*</td>
<td>90.0 16.2</td>
<td>80 13</td>
<td>66.2 3.1</td>
</tr>
<tr>
<td>Stomatitis/mucositis*</td>
<td>73.4 8.7</td>
<td>NR  NR</td>
<td>17 0.2</td>
</tr>
<tr>
<td>Paronychia</td>
<td>56.8 11.4</td>
<td>NR  NR</td>
<td>13.5 0.3</td>
</tr>
<tr>
<td>Dry skin</td>
<td>30.1 0.4</td>
<td>NR  NR</td>
<td>23.9 0.0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>28.8 4.4</td>
<td>31 0</td>
<td>21.9 1.5</td>
</tr>
<tr>
<td>Pruritus*</td>
<td>20.1 0.4</td>
<td>NR  NR</td>
<td>19.4 0.7</td>
</tr>
<tr>
<td>Nausea</td>
<td>25.3 1.3</td>
<td>NR  NR</td>
<td>16.6 0.3</td>
</tr>
<tr>
<td>Fatigue*</td>
<td>27.1 3.1</td>
<td>57 6</td>
<td>16.8 0.3</td>
</tr>
<tr>
<td>Vomiting</td>
<td>22.7 4.4</td>
<td>NR  NR</td>
<td>12.9 0.2</td>
</tr>
<tr>
<td>Alopecia</td>
<td>12.7 0</td>
<td>14 0</td>
<td>11 0</td>
</tr>
</tbody>
</table>

*Group term at least in one of the trials included in the table

EGFR = epidermal growth factor receptor; NR = not reported; TKI = tyrosine kinase inhibitor
Case Study #3 (continued)

Mrs. DD was prescribed erlotinib 150 mg daily, however, developed grade 3 rash requiring dose reduction after 2 weeks on therapy.
EGFR Inhibitor Rash

• Most common “toxicity” associated with EGFR inhibitors
• Tends to appear on the face and chest but can be seen on any part of the body
• Can range from mild to severe
• Often described as a “papulopustular eruption”
Why Does EGFR Inhibitor Rash Occur?

- The epidermis relies on EGF
- The keratinocytes located in the basal layers of the epidermis express elevated level of EGF
- Inhibition of EGF will result in negative effects on cell growth in this layer of the epidermis
- This results in thinning, which decreases ability of skin to hold in moisture
- The damage also causes recruitment of the immune system response and thus, a pustular eruption

Adapted from Lacouture, 2006
# Incidence and Severity of Rash

<table>
<thead>
<tr>
<th>Agent</th>
<th>All Rash Incidence</th>
<th>Grade 3/4 Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetuximab</td>
<td>87% (70% in FLEX trial)</td>
<td>17% (10% in FLEX trial)</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>85%</td>
<td>14%</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>Rash 43%, Acne 25%</td>
<td>0% (only reported ≥5%)</td>
</tr>
<tr>
<td>Afatinib</td>
<td>90%</td>
<td>16%</td>
</tr>
</tbody>
</table>

Cetuximab full prescribing information; Pirker R, et al. *Lancet.* 2009;373:1525-1531; Erlotinib full prescribing information; Gefitinib full prescribing information; Afatinib full prescribing information.
Rash and Overall Survival (TOPICAL Study)

- 670 patients in the UK
  - Stage IV NSCLC
  - Unsuitable for chemotherapy
  - Randomly assigned erlotinib or placebo
- If rash in first 28-d cycle, significant improvement in OS/PFS
  - OS in rash group seen in EGFR mutants as well as EGFR wild type
  - All EGFR mutants developed rash
- Discontinue erlotinib if no rash? Controversial...

OS = overall survival; PFS = progression-free survival; HR = hazard ratio; CI = confidence interval.
Meta-Analysis of EGFR Rash and Clinical Benefit

Liu and colleagues (2013) reviewed 33 studies of EGFR TKIs that reported rash and clinical benefit

– Rash was a significant predictor of clinical benefit for NSCLC patients receiving EGFR inhibitor therapy

– Rash predicted ORR, longer PFS, and longer OS

<table>
<thead>
<tr>
<th>Rash acneiform*</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papules and/or pustules covering &lt;10% BSA, which may or may not be associated with symptoms of pruritus or tenderness</td>
<td>Papules and/or pustules covering 10-30% BSA, which may or may not be associated with symptoms of pruritus or tenderness</td>
<td>Papules and/or pustules covering &gt;30% BSA, which may or may not be associated with symptoms of pruritus or tenderness</td>
<td>Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness</td>
<td>Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness</td>
<td>Death</td>
</tr>
<tr>
<td>Associated with psychosocial impact</td>
<td>Limiting to instrumental ADL</td>
<td>Limiting self-care ADL</td>
<td>Associated with extensive superinfection, with IV antibiotics indicated</td>
<td>Associated with local superinfection, with oral antibiotics indicated</td>
<td>Lead to life-threatening consequences</td>
</tr>
</tbody>
</table>

*A disorder characterized by an eruption of papules and pustules, typically appearing on face, scalp, upper chest, and back

BSA = body surface area; ADL = activities of daily living.

Strategies to Prevent Dermatologic Toxicities: Preemptive

STEPP trial in panitumumab-containing regimens in 95 metastatic colorectal patients:

- Showed significant improvement in EGFR rash and quality of life (QOL) with preemptive doxycycline and topical hydrocortisone cream

- Skin toxicities of ≥ grade 2 were reduced by more than 50% at 6 weeks in the preemptive arm

NCCN Recommendations for Prophylactic/Mitigating Treatments

• Prophylactic/mitigating treatments (i.e., to decrease the severity of rash)
  – Tetracycline antibiotics: minocycline, doxycycline, tetracycline

• Reactive treatments (based on anecdotal or non-randomized studies)
  – Retinoids: isotretinoin (problem with paronychia), acitretin

• Reactive treatment for infection
  – Importance of bacterial culture, especially around nose, abscesses, and pustules on body
  – Antistaphylococcal antibiotics: cephalexin, dicloxacillin
  – Antimethicillin-resistant *Staphylococcus aureus* antibiotics: sulfamethoxazole/trimethoprim, linezolid

### MASCC Recommendations for Treatment

<table>
<thead>
<tr>
<th></th>
<th>Recommended</th>
<th>Not Recommended</th>
<th>Level of Evidence</th>
<th>Recommendation Grade</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Topical</strong></td>
<td>Alclometasone 0.05% cream</td>
<td>Vitamin K1 cream</td>
<td>IV</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fluocinonide 0.05% cream twice daily</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clindamycin 1%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Systemic</strong></td>
<td>Doxycycline 100 mg twice daily</td>
<td>Acitretin</td>
<td>IV</td>
<td>C</td>
<td>Photosensitizing agents</td>
</tr>
<tr>
<td></td>
<td>Minocycline 100 mg daily</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Isotretinoin at low doses 20–30 mg/d</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Other Cutaneous Toxicities

• Alopecia/scalp rash
• Paronychia
• Hypertrichosis
• Fissures

Images courtesy of Beth Eaby-Sandy, MSN, CRNP, OCN®
Conclusions for EGFRIs

• 3 drugs approved with similar response rates
• Only drug to show OS is afatinib in the deletion 19 population only, though many did not get crossover EGFRi
• Toxicity profiles vary among approved agents, but can be managed for patient to remain on therapy
Case Study #3 (continued)

- After 2 years of responding to erlotinib, Mrs. DD developed disease progression on CT chest.
Liquid Biopsy for Molecular Analysis

• Using a blood test for DNA sequencing to detect molecular abnormalities in a variety of solid tumors

• 80% sensitivity for EGFR mutations in blood serum samples assessing circulating tumor cells or circulating free DNA

• Obvious benefit over attempting invasive procedure for tissue, though not 100% accurate

• Mrs. DD is found to have a T790M mutation, otherwise known as an EGFR resistance mutation.
• She is enrolled in a clinical trial with rociletinib.
T790M Mutation in EGFR Mutation+ NSCLC

- Rarely can be de novo mutation; however, generally occurs as a resistance mutation in EGFR mutation+ patients upon disease progression
- Need a new biopsy, whether tumor tissue or blood sample for liquid biopsy
- Occurs in about 60% of EGFR mutation+ NSCLC patients post progression on EGFR1 therapy
- Recent approval of osimertinib to treat T790M+ patients
Osimertinib

- Dose is 80 mg taken daily (with or without food)
- Accelerated FDA approval in late 2015 based on response rates
- RR 57% and 61% in 2 clinical trials (AURA studies not published to date)
Key Inclusion Criteria:
• Aged $\geq 18$ years ($\geq 20$ in Japan)
• Confirmation of tumor EGFR mutation associated with EGFR-TKI
• At least 1 lesion suitable for accurate repeated measurements
• WHO performance status 0 or 1
• Acceptable organ function
• Stable brain metastases allowed

Confirmed EGFRm locally advanced or metastatic NSCLC who have progressed following prior therapy with an approved EGFR-TKI

Central T790M mutation testing of biopsy sample collected following confirmed disease progression

T790M Positive (n = 210)

T790M negative

Osimertinib 80 mg once daily

Not eligible for enrollment

Primary Objective:
To investigate efficacy of osimertinib (AZD291) by assessment of ORR

## AURA2: Results

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR by BICR</td>
<td>71%</td>
</tr>
<tr>
<td>Median DOR</td>
<td>7.8 mo</td>
</tr>
<tr>
<td>Range of DOR</td>
<td>1.3-8.4 mo</td>
</tr>
<tr>
<td>Median PFS</td>
<td>8.6 mo</td>
</tr>
<tr>
<td>Follow-up for PFS</td>
<td>6.7 mo</td>
</tr>
</tbody>
</table>

### Drug-Related Adverse Events

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade ≥ 3</td>
<td>11%</td>
</tr>
<tr>
<td>Any AE leading to discontinuation</td>
<td>3%</td>
</tr>
<tr>
<td>Any serious AE</td>
<td>5%</td>
</tr>
</tbody>
</table>

AURA3 is an ongoing phase III study of osimertinib vs. platinum-based doublet chemotherapy in patients with EGFRm and T790M positive advanced NSCLC with disease progression following prior EGFR-TKI therapy

- Primary objective: PFS
- Estimated enrollment: 410 patients

AE = adverse event; BICR = blinded independent central review; DOR = duration of response; ORR = objective response rate; PFS = progression-free survival.

Osimertinib Toxicity

Warnings in PI:

- ILD/pneumonitis: 3.3%
- DC’d drug
- QTc interval prolongation
- Cardiomyopathy: 1.4%
  - Recommend to evaluate LVEF at baseline and Q3 mo
- Embryo-fetal toxicity

Table 2: Adverse Reactions (>10% for all NCI CTCAE Grades or >2% for Grades 3-4) in Study 1 and Study 2

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>42</td>
<td>1.0</td>
</tr>
<tr>
<td>Nausea</td>
<td>17</td>
<td>0.5</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>16</td>
<td>0.7</td>
</tr>
<tr>
<td>Constipation</td>
<td>15</td>
<td>0.2</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Skin disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>41</td>
<td>0.5</td>
</tr>
<tr>
<td>Dry skin</td>
<td>31</td>
<td>0</td>
</tr>
<tr>
<td>Nail toxicity</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Eye Disorders</td>
<td>18</td>
<td>0.2</td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>14</td>
<td>0.2</td>
</tr>
<tr>
<td>General</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>14</td>
<td>0.5</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>13</td>
<td>0.7</td>
</tr>
<tr>
<td>Central Nervous System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>10</td>
<td>0.2</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>4</td>
<td>2.2</td>
</tr>
<tr>
<td>Vascular events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>7</td>
<td>2.4</td>
</tr>
</tbody>
</table>

* NCI CTCAE v4.0.
EML4-ALK GENE TRANSLOCATION
Case Study #4

• MB is a 48-year-old African American female who presented with headaches and mental status changes to the ER.
• She is a never-smoker and otherwise has no PMH.
• She was found to have brain mets and a CT chest found a lung lesion, liver, and bone mets.
• She underwent craniotomy followed by WBXRT and her tumor in the brain was found to be positive for an EML4-ALK gene translocation.
• She started crizotinib twice a day.
3 Drugs Approved to Treat EML4-ALK + NSCLC

- Crizotinib 250 mg orally twice a day, first line
- Ceritinib 5 tablets (150 mg each) orally once daily on an empty stomach
  - Approved second line after failure of crizotinib
- Alectinib 600 mg twice a day with food, approved December 2015
  - Approved second line after failure of crizotinib
Response to ALK Inhibition: Crizotinib

- RR 57%
- SD 33%
- 8-week DCR 87%
- PD 7%

Progression-Free Survival

A  Progression-free Survival

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

B  Progression-free Survival with Crizotinib vs. Pemetrexed or Docetaxel

Hazard ratio for progression or death, 0.59 (95% CI, 0.43-0.80)  
P<0.001 (vs. pemetrexed)

Hazard ratio for progression or death, 0.30 (95% CI, 0.21-0.43)  
P<0.001 (vs. docetaxel)

No. at Risk
Crizotinib  173  93  38  11  2  0
Chemotherapy  174  49  15  4  1  0

Crizotinib Toxicity

Warnings

Hepatoxicity
- ILD/pneumonitis
- QT prolongation
- Bradycardia
- Severe vision loss
- Embryo-fetal toxicity

Common Toxicities
- Visual changes 71%
  - Light and dark accommodation, recommend no driving at night in beginning
- Vomiting 46%
- Diarrhea 61%
- Edema 49%
Case Study #4 (continued)

• Mrs. MB had significant disease improvement on crizotinib and remained on drug for 2 years.
• She did develop asymptomatic sinus bradycardia, HR in the low 50s. Saw cardiology and nothing more to do.
• For first month on crizotinib, did experience the light accommodation, however, has subsided after time on drug.
• She is now developing disease progression and is a candidate for either ceritinib or alectinib treatment.
ASCEND-1 Trial: Ceritinib in Patients With ALK-Rearranged NSCLC

- Updated analysis of phase I, open-label, multicenter trial
- Patients ≥ 18 years with ALK-rearranged locally advanced or metastatic NSCLC
  - Disease progression despite standard therapy
  - At least 1 measurable lesion at baseline
- Primary objective: maximum tolerated dose
- 255 pts enrolled (246 with ALK-rearranged NSCLC) and received at least 1 dose of ceritinib 750 mg/day
- At data cutoff (Apr 2014), median follow-up 11.1 mo and 147 pts had discontinued treatment

<table>
<thead>
<tr>
<th>Outcome</th>
<th>ALK Inhibitor-Naïve</th>
<th>ALK Inhibitor-Pretreated</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>60/83 (72%)</td>
<td>92/163 (56%)</td>
</tr>
<tr>
<td>Median DOR</td>
<td>17 mo</td>
<td>8.3 mo</td>
</tr>
<tr>
<td>Median PFS</td>
<td>18.4 mo</td>
<td>6.9 mo</td>
</tr>
<tr>
<td>Intracranial disease*</td>
<td>15/19 (79%)</td>
<td>49/75 (65%)</td>
</tr>
</tbody>
</table>

- Most common grade 3/4 laboratory AEs: Increased ALT (30%) and AST (10%)
- Most common grade 3/4 non-laboratory AEs: Diarrhea (6%) and nausea (6%)

*Of 94 patients with retrospectively confirmed brain metastases and ≥ 1 post-baseline MRI or CT tumor assessment.

ORR = objective response rate; DOR = duration of response; PFS = progression-free survival.
Ceritinib in ALK+ NSCLC

- NSCLC patients with ALK rearrangement
- Dose escalation phase (n = 59)
  - Ceritinib 50 → 750 mg QD
- Dose expansion phase (n = 130)
- Primary objective: MTD of ceritinib
- ORR 58% in pts who received ceritinib ≥400 mg/day (n = 114)
- ORR 56% in pts previously treated with ceritinib (n = 80)
- PFS 7.0 mo in pts who received ceritinib ≥400 mg/day
- Median DOR 8.2 mo
- Most common AEs: nausea, diarrhea, vomiting, fatigue, increased ALT levels

Alectinib

Warnings in PI
- Hepatotoxicity
- ILD in 0.4% of patients
- Bradycardia
- Severe myalgia/CPK elevation
- Embryo-fetal toxicity

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>Study 1 N=87</th>
<th>Study 2 N=138</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRC* Assessment</td>
<td>Investigator Assessment</td>
<td>IRC* Assessment</td>
</tr>
<tr>
<td>ORR (95% CI)</td>
<td>38% (28, 49)</td>
<td>46% (35, 57)</td>
</tr>
<tr>
<td>Number of Responders</td>
<td>33</td>
<td>40</td>
</tr>
<tr>
<td>DOR (median in months [95% CI])</td>
<td>7.5 (4.9, NE)</td>
<td>NE (4.9, NE)</td>
</tr>
</tbody>
</table>
# Recent Studies of Alectinib

<table>
<thead>
<tr>
<th>Drug/Study</th>
<th>N</th>
<th>Dose</th>
<th>Outcomes</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alectinib(^1)</td>
<td>138</td>
<td>600 mg BID</td>
<td>• 122 evaluable</td>
<td>27.5% pts had grade 3-5 AEs (most commonly dyspnea and pulmonary embolism)</td>
</tr>
<tr>
<td>Phase II, single-arm,</td>
<td>ALK+</td>
<td></td>
<td>• ORR 49.2%</td>
<td></td>
</tr>
<tr>
<td>open-label, multicenter</td>
<td>NSCLC pts</td>
<td></td>
<td>• DCR 79.5%</td>
<td></td>
</tr>
<tr>
<td>with PD on crizotinib</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alectinib(^2)</td>
<td>87</td>
<td>600 mg BID</td>
<td>• 69 evaluable</td>
<td>31% pts had grade 3-5 AEs (most commonly increased blood CPK, increased</td>
</tr>
<tr>
<td>Phase II, single-arm,</td>
<td>ALK+</td>
<td></td>
<td>• ORR 47.8%</td>
<td>ALT, increased AST)</td>
</tr>
<tr>
<td>open-label, multicenter</td>
<td>NSCLC pts</td>
<td></td>
<td>• DCR 79.7%</td>
<td></td>
</tr>
<tr>
<td>with PD on crizotinib</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PD = progressive disease; BID = twice daily; ORR = objective response rate; DCR = disease control rate; CPK = creatine phosphokinase; ALT = alanine aminotransferase; AST = aspartate aminotransferase.

Recent Study of Brigatinib (Not FDA Approved)

<table>
<thead>
<tr>
<th>Drug/Study</th>
<th>N</th>
<th>Dose</th>
<th>Outcomes</th>
<th>Adverse Events</th>
</tr>
</thead>
</table>
| Brigatinib (AP26113) Update of a phase I/II ongoing trial in advanced malignancies | 137 79 ALK+ NSCLC pts 52 (66%) had CNS metastases at BL | 90 mg, 90→180 mg, or 180 mg | • 78 evaluable ALK+ NSCLC pts  
• 58 (74%) responded  
–50 pretreated with crizotinib  
–8 crizotinib-naive  
• Median PFS 13.4 mo  
(pretreated with crizotinib) | Most common: Nausea 52%  
Fatigue 42%  
Diarrhea 40% |

Other Drugs That Target ALK

• Second-generation ALK Inhibitors
  X-396 (ensartinib)
  PF-06463922 (lorlatinib)

• HSP90 Inhibitors
  AUY992
  STA9090
ROS1 in NSCLC

- Rare, only about 1% of patients with NSCLC
- Most common in never-smokers and younger patients
- Crizotinib is only approved therapy, at same dose, 250 mg twice a day
Tumor Responses to Crizotinib in ROS1-Rearranged NSCLC

- 50 patients with ROS1-rearranged lung cancer
- RR 72%
- Median duration of response was nearly 18 mo

SQUAMOUS CELL CARCINOMA IN NSCLC: ANY TARGETS?
S1400: MASTER LUNG-1: Squamous Lung Cancer- 2nd Line Therapy

Multiple Phase II-III Arms with "rolling Opening & Closure"

- PI3K
  - TT A
  - CT*
  - Endpoint (Interim PFS) OS
  - GDC094

- CDK 4/6
  - TT B
  - CT*
  - Endpoint (Interim PFS) OS
  - Pablociclib

- FGFR
  - TT C+CT
  - CT*
  - Endpoint (Interim PFS) OS
  - AZD4547

- HGF
  - TT D+E
  - E*
  - Endpoint (Interim PFS) OS
  - AMG102

CT* = Anti-PDL1: MEDI 4736

TT=Targeted therapy, CT=chemotherapy (docetaxel or gemcitabine), E=erlotinib

PI: V. Papadimitrakopoulou (SWOG)
Summary: Targeted Therapy in NSCLC

• There are several molecular targets that have been identified with corresponding targeted agents FDA approved that show superior clinical benefit vs chemotherapy.

• There remain other molecular targets for which clinical trials are ongoing to evaluate drug efficacy to treat.

• Toxicity profiles vary widely and there are several different management strategies.

• Squamous cell carcinoma less likely to exhibit molecular targets; however, in a nonsmoker, would be reasonable to test. Clinical trial S1400 Master Lung Protocol looking for biomarkers and responses to treatment.