Navigating the Landscape of Molecular Testing and Treatments With Targeted Therapies for Patients With Non–Small Cell Lung Cancer
Navigating the Landscape of Molecular Testing and Treatments With Targeted Therapies for Patients With Non–Small Cell Lung Cancer

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Emory University
Financial Disclosure

- Dr. Padda
  - Consultancy: Clovis Oncology

- Dr. Harvey
  - Research funding to institution: Bristol-Myers Squibb, Merck, AstraZeneca, Novartis
  - Advisor: Bristol-Myers Squibb
Learning Objectives

1. Discuss evidence-based guidelines for the biopsy, histology, and molecular testing for diagnostic/prognostic markers
2. Identify which patients with advanced NSCLC should undergo mutation testing and understand how these results impact the selection of therapy
3. Describe scientific updates and key practice changes in the management of lung cancer, focusing on targeted therapies, including both new and investigational biologic therapies
4. Identify the common disease symptoms and/or side effects encountered in the management of NSCLC and detail the best management strategies utilized by advanced practitioners (APs) in oncology
5. Describe collaboration between various members of the health-care team (including but not limited to physician, AP, and pharmacist) in the care of NSCLC
Diagnostic Workup
Case 1

- A 40-year-old nonsmoking Asian woman has a persistent cough

- Chest x-ray
  - Increased interstitial markings in the right lower lung, and the right hemidiaphragm is partially obscured

- CT chest
  - Right 4-cm infrahilar mass with associated small pleural effusion
  - Multiple bilateral pulmonary ground-glass nodules
  - Extensive hilar and mediastinal lymph nodes
  - < 1 cm liver metastases
  - Multiple foci of osseous metastases (largest in scapula)
What do you do next for this patient?

A. Thoracentesis of small right pleural effusion  JL341
B. Bronchoscopy and endobronchial biopsy of 4-cm infrahilar mass  JL342
C. CT guided–core biopsy of 4-cm right infrahilar mass  JL343
D. Endobronchial ultrasound and fine-needle aspiration of mediastinal lymph node  JL344
E. Biopsy of large scapular bone lesion  JL345

Tissue Is Always the Issue

- When thinking about acquiring tissue, think:
  - Safest
  - Effective
  - Efficient
  - Least invasive

- Sufficient tissue is needed
  - **Histologic diagnosis** (i.e., squamous, adenocarcinoma, large cell neuroendocrine NSCLC vs. small cell lung cancer)
  - **Immunohistochemistry** (adenocarcinoma TTF-1$^+$ or napsin A$^+$; squamous p63$^+$ or p40$^+$; neuroendocrine chromogranin$^+$ or synaptophysin$^+$)
  - **Molecular markers** (i.e., gene mutation testing, EGFR, ALK, etc.)

Multidisciplinary Approach Key in Acquiring Tissue for Lung Cancer

Case 1 (cont)

- Patient has a bronchoscopy
  - Bronchial washings show atypical cells suspicious for lung adenocarcinoma
  - Endobronchial biopsy of the right infrahilar mass confirms **lung adenocarcinoma**; immunohistochemistry stains TTF-1 positive

- PET-CT and brain MRI reveal no other sites of disease except for those mentioned. Patient is **asymptomatic** except for a persistent mild cough.
Audience Response Question

What do you do next?

A. Test tumor for *KRAS* mutation  JL346
B. Test tumor for *EGFR* mutation and *ALK* rearrangement  JL347
C. Test tumor for *EGFR* mutation, *ALK* rearrangement, and *ROS1* rearrangement  JL348
D. Send for comprehensive next-generation sequencing (i.e., Foundation Medicine)  JL349
E. Start platinum-based therapy immediately  JL350
Transition From Histology → Genomic Driver Mutations

Histology + Molecular Testing Matters

Non-Small Cell Lung Cancer

SYSTEMIC THERAPY FOR METASTATIC DISEASE

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

HISTOLOGIC SUBTYPE

- Adenocarcinoma
- Large Cell
- NSCLC not otherwise specified (NOS)

TESTING

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

- Consider EGFR mutation and ALK testing especially in never smokers or small biopsy specimens, or mixed histology
- EGFR and ALK testing should be conducted as part of broad molecular profiling

Metastatic Disease

Squamous cell carcinoma

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EGFR-/ALK- Nonsquamous NSCLC

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Squamous NSCLC


NO BEVACIZUMAB (safety) OR PEMETREXED (efficacy)

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Summary

Biopsy, Histology, and Molecular Testing

- Acquiring tumor tissue for diagnosis of lung cancer requires a multidisciplinary approach
- Histology matters, certain agents not effective (i.e., pemetrexed in squamous) or not safe (i.e., bevacizumab in squamous)
- Molecular testing critical for patients with metastatic non-squamous NSCLC, particularly EGFR and ALK, as it can change first-line treatment
The patient has testing for *EGFR* mutation status and *ALK* status by FISH testing (fluorescence in situ hybridization)

- *EGFR* mutation detected exon 21 L858R substitution (FISH: *ALK*-negative)
Audience Response Question

What do you do next?

A. Start erlotinib JL351
B. Start gefitinib JL352
C. Start afatinib JL353
D. Start carboplatin, paclitaxel, bevacizumab JL354
E. Enroll in clinical trial with third-generation EGFR TKI, i.e., rociletinib/CO-1686 or osimertinib AZD-9291 JL355
EGFR-Mutated NSCLC
EGFR Mutated

NCCN Guidelines Version 1.2016 Non-Small Cell Lung Cancer

SENSITIZING EGFR MUTATION POSITIVE

FIRST-LINE THERAPY

EGFR mutation discovered prior to first-line chemotherapy

- Erlotinib (category 1)
- Afatinib (category 1)
- Gefitinib (category 1)

EGFR mutation discovered during first-line chemotherapy

- Interrupt or complete planned chemotherapy, followed by erlotinib or afatinib or gefitinib

Interrupt or complete planned chemotherapy due to progression

SECOND-LINE THERAPY

- Continue erlotinib or afatinib or gefitinib
- Consider local therapy and continue erlotinib or afatinib or gefitinib

SUBSEQUENT THERAPY

- Adenocarcinoma NSCL-19 or Squamous cell carcinoma NSCL-20

GEFITINIB NOW FDA APPROVED (AGAIN) BUT FOR THIS NARROWER INDICATION: EGFR-MUTATED NSCLC

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**EGFR Tyrosine Kinase Inhibitors: Clinical Pharmacology Points**

<table>
<thead>
<tr>
<th></th>
<th>Erlotinib</th>
<th>Afatinib</th>
<th>Gefitinib</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose</strong></td>
<td>150 mg PO daily</td>
<td>40 mg PO daily</td>
<td>250 mg PO daily</td>
</tr>
<tr>
<td><strong>Interactions</strong></td>
<td>CYP3A4 inducers, inhibitors, smoking (induces CYP1A2 goal = 300 mg PO daily)</td>
<td>High-fat meal decreases exposure by 39% compared with fasted state</td>
<td>Systemic exposure may be increased in CYP2D6 poor metabolizers</td>
</tr>
<tr>
<td><strong>Common AEs</strong></td>
<td>Rash, diarrhea, weakness</td>
<td>Rash, weight loss, diarrhea</td>
<td>Rash, diarrhea, weakness</td>
</tr>
<tr>
<td><strong>Administration</strong></td>
<td>Empty stomach, avoid PPIs, H2 antagonists</td>
<td>Take at least 1 hour before or 2 hours after meals</td>
<td>No food effect</td>
</tr>
<tr>
<td><strong>Strengths</strong></td>
<td>25-, 100-, 150-mg tablets</td>
<td>20-, 30-, 40-mg tablets</td>
<td>250-mg tablet</td>
</tr>
</tbody>
</table>
Erlotinib and Smoking

**EGFR-Sensitizing Mutations Predict for Response to EGFR TKI Therapy (IPASS Gefitinib Study)**

Incidence of \( \text{EGFR} \) mutation: 261/437 = 59.7%  
Most common: \( \text{EGFR} \) exon 21 L858R and exon 19 deletion  
Treatment by subgroup interaction test, \( p < .0001 \)

## Treatment-Naive *EGFR*-Mutated Lung Cancer: EGFR TKIs Beat Chemotherapy (RR, PFS)

<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>NEJ002</td>
<td>Gefitinib vs. carboplatin/paclitaxel</td>
<td>230</td>
<td>10.8 vs. 5.4</td>
<td>27.7 vs. 26.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(p &lt; .001)</td>
<td>(p = .48)</td>
</tr>
<tr>
<td>WJTOG-3405</td>
<td>Gefitinib vs. cisplatin/docetaxel</td>
<td>172</td>
<td>9.2 vs. 6.3</td>
<td>34.8 vs. 37.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(p &lt; .0001)</td>
<td>(HR: 1.25)</td>
</tr>
<tr>
<td>OPTIMAL</td>
<td>Erlotinib vs. carboplatin/gemcitabine</td>
<td>165</td>
<td>13.1 vs. 4.6</td>
<td>22.7 vs. 28.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(p &lt; .0001)</td>
<td>(p = .69)</td>
</tr>
<tr>
<td>EURTAC</td>
<td>Erlotinib vs. platinum-based chemotherapy</td>
<td>174</td>
<td>10.4 vs. 5.2</td>
<td>22.9 vs. 19.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(p &lt; .0001)</td>
<td>(p = .68)</td>
</tr>
<tr>
<td>LUX-Lung 3</td>
<td>Afatinib vs. cisplatin/pemetrexed</td>
<td>345</td>
<td>11.1 vs. 6.9</td>
<td>28.2 vs. 28.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(p = .001)</td>
<td>(p = .38)</td>
</tr>
<tr>
<td>LUX-Lung 6</td>
<td>Afatinib vs. cisplatin/gemcitabine</td>
<td>364</td>
<td>11.0 vs. 5.6</td>
<td>23.1 vs. 23.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(p &lt; .0001)</td>
<td>(p = .61)</td>
</tr>
</tbody>
</table>

Combined Lux-Lung 3 and 6 Afatinib Data Showed Overall Survival Benefit With EGFR TKI Therapy

Mutation Subtype Appears to Matter for EGFR TKI Therapy: Exon19del > Exon21 L858R

Case 1 (cont)

- Patient starts **erlotinib 150 mg oral daily dosing**, and her cough resolves within 2 weeks. She develops a bothersome acneiform rash on her face, chest, and back and grade 2 diarrhea. She is started on oral doxycycline and topical steroids, which improves the rash. The diarrhea is controlled after the initiation of loperamide.

- She does well on therapy for approximately 8 months before she has progressive disease with diffuse new metastases, and she is symptomatic with fatigue and cough. Brain MRI is stable.
What do you do next?

A. Repeat biopsy of an accessible tumor lesion  JL356
B. Switch to carboplatin, pemetrexed, bevacizumab  JL357
C. Enroll in clinical trial with third-generation EGFR TKI, i.e., rociletinib/CO-1686 or osimertinib/AZD-9291  JL358
D. Start afatinib and cetuximab  JL359
E. Add platinum-based chemotherapy to erlotinib  JL360
F. Liquid biopsy with circulating tumor DNA  JL361
Mechanisms of Resistance to EGFR TKI Therapy: T790M Gatekeeper Mutation in 60%

Plasma Genotyping:

“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></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>155</td>
<td>23</td>
<td>12</td>
<td>190</td>
</tr>
<tr>
<td>Negative</td>
<td>37</td>
<td>12</td>
<td>8</td>
<td>57</td>
</tr>
<tr>
<td>Total</td>
<td>192</td>
<td>35</td>
<td>20</td>
<td>247</td>
</tr>
</tbody>
</table>

* patients at all doses

- When inadequate tissue specimens are factored 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

Tissue as reference:
Positive percent agreement

<table>
<thead>
<tr>
<th>Mutation</th>
<th>T790M</th>
<th>Activating mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>81% (155/192)</td>
<td>87% (193/221)</td>
</tr>
</tbody>
</table>

Third-Generation EGFR TKIs Have Activity at Time of Acquired Resistance (e.g., AZD-9291 and CO-1686)

AZD-9291/osimertinib ORR
- EGFR T790M+ 61%
- EGFR T790M- 21%

CO-1686/rociletinib ORR
- EGFR T790M+ 53%
- EGFR T790M- 35%*

### Summary: Third-Generation EGFR TKIs

<table>
<thead>
<tr>
<th>“3rd” gen</th>
<th>N</th>
<th>RR* T790M-</th>
<th>RR T790M+</th>
<th>PFS</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rociletinib</td>
<td>256</td>
<td>35%</td>
<td>53%</td>
<td>~8.0 mo</td>
<td>Hyperglycemia</td>
</tr>
<tr>
<td>(CO-1686)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AZD-9291</td>
<td>253</td>
<td>21%</td>
<td>61%</td>
<td>~8.2 mo</td>
<td>Diarrhea/rash</td>
</tr>
<tr>
<td>(osimertinib)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HM61713</td>
<td>62</td>
<td>29%**</td>
<td>55%</td>
<td>NR</td>
<td>Diarrhea/rash</td>
</tr>
<tr>
<td>(800 mg)</td>
<td></td>
<td>(300 mg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EGF816X*</td>
<td>53</td>
<td>–</td>
<td>60%</td>
<td>NR</td>
<td>Rash</td>
</tr>
<tr>
<td>ASP8273*</td>
<td>47</td>
<td>~33%</td>
<td>67%</td>
<td>NR</td>
<td>Hyponatremia/diarrhea</td>
</tr>
</tbody>
</table>

*T790M- subgroups are very small

**12% T790M+

Multiple other agents earlier in development

Modified slide courtesy of Heather A. Wakelee, ASCO 2015 discussant.

Third-Generation EGFR TKIs Being Tested in First-Line Setting

Response Rate in First-line Cohorts by Dose

12 mo: 75% ongoing response
12 mo PFS: 72%

AZD-9291

<table>
<thead>
<tr>
<th>Dose</th>
<th>Objective response ratea (%)</th>
<th>Disease control rateb (%)</th>
<th>Best objective response</th>
</tr>
</thead>
<tbody>
<tr>
<td>80 mg N=30</td>
<td>63% (95% CI 44, 80)</td>
<td>93% (95% CI 78, 99)</td>
<td>0</td>
</tr>
<tr>
<td>160 mg N=30</td>
<td>83% (95% CI 65, 94)</td>
<td>100% (95% CI 88, 100)</td>
<td>19</td>
</tr>
<tr>
<td>Total N=60</td>
<td>73% (95% CI 60, 84)</td>
<td>97% (95% CI 89, 100)</td>
<td>43</td>
</tr>
</tbody>
</table>

Other Methods to Overcome Resistance: Afatinib + Cetuximab (T790M+/-)

ORR 29% (n = 37/126)
- T790M-positive: 32%
- T790M-negative: 25%

mPFS: 4.7 mo (4.3–6.4)
mDOR: 5.7 mo (1.8–24.4)

Other Methods to Overcome Resistance: IMPRESS: Continue EGFR TKI Beyond Progression and Add Chemotherapy

Gefitinib (n = 133) vs. Placebo (n = 132)

<table>
<thead>
<tr>
<th>Time of randomisation (months)</th>
<th>Patients at risk: Gefitinib</th>
<th>Patients at risk: Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>133</td>
<td>132</td>
</tr>
<tr>
<td>2</td>
<td>110</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>88</td>
<td>85</td>
</tr>
<tr>
<td>6</td>
<td>40</td>
<td>39</td>
</tr>
<tr>
<td>8</td>
<td>25</td>
<td>17</td>
</tr>
<tr>
<td>10</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>12</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>14</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Median PFS, mo

Gefitinib: 5.4 mo  vs. Placebo: 5.4 mo

Number of events, n (%)

Gefitinib: 98 (73.7%) vs. Placebo: 107 (81.1%)

HR$^a$ (95% CI) = 0.86 (0.65, 1.13); $p = .273$

HR < 1 implies a lower risk of progression with gefitinib.

Med OS: 14.8 mo (G) vs. 17.2 mo (P)

HR 1.62, $p = .029$ but 33% of events

$^a$Primary Cox analysis with covariates

Mok T, et al. ESMO 2014 (abstract LBA2).
Continuing EGFR TKI Therapy Post Progression to Delay Second-Line Therapy

-28 (66%) continued single-agent erlotinib after PD
-21 (50%) were able to delay a change in systemic therapy for > 3 months
Case 1 (cont)

Patient has a repeat bronchoscopic endobronchial tumor biopsy, which demonstrates a T790M mutation. She enrolls on a clinical trial with a third-generation EGFR TKI and has a partial response, with significant improvement in symptoms.
Summary

*EGFR-Mutated NSCLC*

- 3 options for first-line treatment of *EGFR* mutated NSCLC: afatinib, erlotinib, or gefitinib
  - All individual trials comparing *EGFR* TKI to chemotherapy showed no improvement in OS (only PFS and RR)
  - *EGFR* exon 19 del do better than *EGFR* exon 21 L858R with *EGFR* TKI therapy

- Most patients develop resistance to *EGFR* TKI at a median of ~9-12 months
  - *EGFR* T790M gatekeeper mutation most common mechanism of resistance
  - Plasma genotyping emerging
  - Clinical trials with 3rd generation *EGFR* TKIs (target T790M) show significant promise
Case 2

- A 63-year-old African-American woman who has smoked 1 pack/day for 35 years and has a history of multifocal ground-glass opacities with 3 separate foci of stage I lung adenocarcinomas last resected 5 years prior, develops dysphagia.

- **CT**: 5-cm right lower lobe lung mass abutting the esophagus

- Bronchoscopy and left hilum fine-needle aspiration: lung adenocarcinoma TTF-1 positive. EGFR, ROS1 (FISH), and ALK (FISH) analysis negative

- **PET**: multiple bilateral pulmonary masses, pleural metastases, liver metastases, and bony metastases. Brain MRI negative.

- She was started on **carboplatin and pemetrexed** and had an impressive **partial response**, with resolution of multiple lesions. She was on maintenance pemetrexed for 1 year prior to widespread disease progression. She is asymptomatic.
Audience Response Question

What would you do next?

A. Send archival tissue for repeat molecular testing with Foundation Medicine or comparable next-generation sequencing platform JL362

B. Switch to docetaxel chemotherapy, unlikely to have mutation since former smoker (35 pack-years) JL363

C. Repeat fresh biopsy and send for EGFR and ALK testing JL364
The patient is asymptomatic, and the archival tissue is sent for next-generation sequencing. It reveals an \textbf{ALK rearrangement}. What do you do next?

A. Start crizotinib JL367
B. Start ceritinib JL368
C. Start alectinib (on clinical trial) JL369
D. Restart pemetrexed since patients with \textit{ALK} rearrangements have good outcomes with pemetrexed JL370
ALK-Rearranged NSCLC
### ALK Inhibitors: Clinical Pharmacology Points

<table>
<thead>
<tr>
<th></th>
<th>Crizotinib</th>
<th>Ceritinib</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose</strong></td>
<td>250 mg po bid</td>
<td>750 mg PO daily</td>
</tr>
<tr>
<td><strong>Interactions</strong></td>
<td>CYP3A4 inducers, inhibitors</td>
<td>CYP3A4 inducers, inhibitors</td>
</tr>
<tr>
<td></td>
<td>High-fat meal decreases exposure by</td>
<td></td>
</tr>
<tr>
<td></td>
<td>39% compared to fasted state.</td>
<td></td>
</tr>
<tr>
<td><strong>Common AEs</strong></td>
<td>Vision disorders, edema, elevated transaminases,</td>
<td>Diarrhea, nausea, vomiting, elevated transaminases, fatigue, rash, hyperglycemia</td>
</tr>
<tr>
<td></td>
<td>nausea, diarrhea</td>
<td></td>
</tr>
<tr>
<td><strong>Administration</strong></td>
<td>No food effect (avoid grapefruit)</td>
<td>Fat may increase exposure. Take on an empty stomach (2 hours before or after a meal)</td>
</tr>
<tr>
<td><strong>Strengths</strong></td>
<td>200-, 250-mg tablets</td>
<td>150-mg tablet</td>
</tr>
<tr>
<td><strong>Hepatic dysfunction</strong></td>
<td>Study ongoing (NCT01576406)</td>
<td>Study ongoing (NCT01950481)</td>
</tr>
</tbody>
</table>

Primary Endpoint Met: First-Line Crizotinib Superior to PT-Pemetrexed-Based Chemotherapy in Prolonging PFS (PROFILE1014)


- **Progression-free Survival**
  - Hazard ratio for progression or death in the crizotinib group, 0.45 (95% CI, 0.35–0.60)
  - P<0.001 (two-sided stratified log-rank test)

- Median, 10.9 mo vs. 7.0 mo
- ORR 74% vs. 45%
Ceritinib

ASCEND-1

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients</th>
<th>ORR</th>
<th>mDOR</th>
<th>mPFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCEND-1</td>
<td>Both crizotinib-naive and prior crizo</td>
<td>58% (48–67)</td>
<td>8.2 mo (6.9–11.4)</td>
<td>7.0 mo (5.6–9.5)</td>
</tr>
<tr>
<td>Ph I, n=114</td>
<td></td>
<td>(56% prior crizo)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASCEND-2</td>
<td>Chemo and ALKi refractory</td>
<td>38.6% (30.5–47.2)</td>
<td>9.7 mo (7–11.1)</td>
<td>5.7 mo (5.4–7.6)</td>
</tr>
<tr>
<td>Ph 2, n=140</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASCEND-3</td>
<td>ALKi naive (prior chemo)</td>
<td>63.7% (54.6–72.2)</td>
<td>9.3 mo (9.1–NE)</td>
<td>11.1 mo (9.3–NE)</td>
</tr>
<tr>
<td>Ph 2, n=124</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Alectinib**

*Chemotherapy-naive patients
Updated analysis cut-off 8 Jan 2015

**Systemic BOR:**

- **PD** (n=22)
- **SD** (n=35)
- **PR** (n=61)

**Trial** | **Patient** | **ORR** | **mDOR** | **mPFS**
--- | --- | --- | --- | ---
AF-001JP ph 1/2, n = 46 | ALKi naive but not treatment naive | 93.5% (82–98.6) | NA | NR estimated > 29 mo

NP28673 ph 2, n = 122 | ALKi resistant (chemo naive and resistant) | 50.0% (40.8–59.1) | 11.2 mo (9.6–NE) | 8.9 mo (5.6–11.3)

prior chemo: 44.8% vs. none: 69.2%

NP28761 ph 2, n = 67 | ALKi resistant (chemo naive and resistant) | 52.2% (39.7–64.6) | 13.5 (6.7–NE) | 8.1 mo

Patient switches to crizotinib and achieves a partial response for 7 months. She develops widespread systemic progression and multiple tiny (< 1 cm) brain metastases, except for one in left frontal lobe that is ~1.5 cm. She is asymptomatic. What do you do next?

A. Stereotactic radiosurgery to left frontal lobe 1.5 cm brain met JL365
B. Whole-brain radiation and continue crizotinib JL366
C. Switch to ceritinib JL371
D. Enroll on clinical trial with alectinib JL372
E. Whole-brain radiation followed by docetaxel chemotherapy JL373
CNS Metastases Major Issue in ALK+ NSCLC, Particularly as Form of Relapse After Crizotinib
## CNS Relapse Issue With Crizotinib

<table>
<thead>
<tr>
<th>Drug</th>
<th>Intracranial response</th>
<th>Intracranial DCR</th>
<th>Intracranial TTP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crizotinib (PROFILE1014)</td>
<td>N/A treated brain mets</td>
<td>12 wk: 85% (vs. 45% chemo)</td>
<td>NR (vs. 17.8 mo); HR 0.60 (0.34–1.05), ( p = .069 )</td>
</tr>
<tr>
<td>Ceritinib/ASCEND-2 n = 33</td>
<td>39.4% (22.9–57.9)</td>
<td>84.8% (68.1–94.9)</td>
<td>–</td>
</tr>
<tr>
<td>Alectinib/NP28673 n = 35</td>
<td>57.1% (39.4–53.7)</td>
<td>85.7% (69.7–95.2)</td>
<td>–</td>
</tr>
<tr>
<td>Brigatinib Ph 1, n = 15</td>
<td>53%</td>
<td>87%</td>
<td>–</td>
</tr>
</tbody>
</table>

Case 2 (cont)

Patient switches to ceritinib. After some difficulty managing GI side effects, she has a systemic partial response, with disease control of brain metastases at first follow-up scan.
Summary

**ALK Rearranged NSCLC**

- Crizotinib: 1st line treatment (FDA approved)
- Ceritinib: 2nd line treatment (FDA approved)
- Many other ALK inhibitors in clinical trials, including those with enhanced intracranial activity (i.e., alectinib granted Priority Review from FDA Sep 8, 2015)
ROS1 and Other Genomic Targets
• **72% ORR** (95% CI, 58%–84%; 3 CRs)
• 64% (23/36) ongoing responses
• **Median DOR 17.6 mo** (95% CI, 14.5–not reached [NR])
• **mPFS of 19.2 mo** (95% CI 14.4–NR)

Other Genomic Targets

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Drug(s)</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRAF V600E</td>
<td>*Dabrafenib</td>
<td>Blanchard D. ESMO 2014</td>
</tr>
<tr>
<td></td>
<td>*Dabrafenib + trametinib</td>
<td>Johnson BE. ASCO 2015 (8006)</td>
</tr>
<tr>
<td>RET fusion</td>
<td>Cabozantinib</td>
<td>Drilon AE. ASCO 2015 (8007)</td>
</tr>
<tr>
<td>MET exon 14 splice mutation</td>
<td>Cabozantinib or crizotinib</td>
<td>Paik PK. ASCO 2015 (8021)</td>
</tr>
</tbody>
</table>

Immunotherapy
Case 3

A 71-year-old man with stage IIIB squamous NSCLC s/p concurrent chemoradiotherapy relapses 6 months later. He progressed on carboplatin/gemcitabine chemotherapy after only 2 cycles, with worsening cough and fatigue.
Audience Response Question

What do you do next?

A. Docetaxel chemotherapy JL374
B. Docetaxel + ramucirumab JL375
C. Nivolumab JL376
D. Pembrolizumab if tumor PD-L1+ JL378
E. Afatinib or erlotinib JL406
Immunologic Synapse: Costimulatory and Inhibitory Signals Fine-Tune the Immune Response

**PD-1/PD-L1:** taking the brakes off the immune system

---

B7-CD28 family

- B7H1/B7DC
- B7RP-1
- B7-1/B7-2
- B7H3
- B7H4/X
- MHC/pep

TNFR/ligand family

- 4-1BBL
- 4-1BB
- CD27L
- OX40L
- LIGHT

Signal 1

**T cell**

- B7H1/B7DC
- PD-1
- CD28
- CTLA-4
- ICOS
- BTLA
- MHC/pep

**TOPALIAN, WEINER, AND PARDO**

---

Nivolumab Improves Overall Survival vs. Docetaxel in Squamous Cell NSCLC

Benefit independent of PD-L1 expression (IHC); FDA & NCCN approved

18-mo PFS rate: 17% (N) vs. 2.7% (D)
ORR: 20% (N) vs. 9% (D), p = .0083

Nivolumab Improves Overall Survival vs. Docetaxel in Nonsquamous NSCLC


- **Benefit dependent on PD-L1 expression (IHC);**
- **FDA & NCCN approved**

mDOR: 17.2 (N) vs. 5.6 mo (D)
Pembrolizumab FDA Approved for 2L+ NSCLC With Companion Diagnostic (PD-L1 IHC)


**PFS**
- All: 3.7 mo
- PD-L1+: 6.3 mo (12.5 mo if untreated)

**OS**
- All: 12.0 mo
- PD-L1+: NR

ORR: 19.4% (all), 45.2% (PD-L1+)
# Clinical Development of Checkpoint Blockade in NSCLC

<table>
<thead>
<tr>
<th>Target</th>
<th>Antibody</th>
<th>Molecule</th>
<th>Development stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-1</td>
<td>Nivolumab (BMS-936558)</td>
<td>Fully human IgG4</td>
<td>Phase III FDA approved; PD-L1 (IHC) “complementary” diagnostic</td>
</tr>
<tr>
<td></td>
<td>Pembrolizumab (MK-3475)</td>
<td>Humanized IgG4</td>
<td>Phase III FDA approved; PD-L1 (IHC) “companion” diagnostic</td>
</tr>
<tr>
<td>PD-L1</td>
<td>BMS-936559</td>
<td>Fully human IgG4</td>
<td>Phase I</td>
</tr>
<tr>
<td></td>
<td>Durvalumab MEDI4736</td>
<td>Fully human IgG1</td>
<td>Phase III</td>
</tr>
<tr>
<td></td>
<td>Atezolizumab (MPDL3280A)</td>
<td>Engineered human IgG1</td>
<td>Phase III FDA fast track</td>
</tr>
<tr>
<td></td>
<td>Avelumab (MSB0010718C)</td>
<td>Fully human IgG1</td>
<td>Phase III</td>
</tr>
</tbody>
</table>

Multiple others!
Case 3 (cont)

The patient starts on nivolumab 3 mg/kg IV every 2 weeks and develops worsening shortness of breath after 6 weeks on therapy. He is also mildly hypoxic now. He does not have fevers. Physical exam reveals bibasilar crackles.
Audience Response Question

What do you do next?

A. Start antibiotics, since he most likely has an infection JL377
B. Start furosemide, since he is most likely fluid overloaded JL379
C. Perform CT with low threshold to start high-dose steroids JL380
Case 3 (cont)

CT findings are shown below. Patient is diagnosed with pneumonitis and started on high-dose steroids, with symptomatic improvement.

Be Cautious of Autoimmune Adverse Events, Early Steroids Necessary (eg. nivolumab)

Table 3. Treatment-Related Adverse Events Reported in at Least 5% of Patients.

<table>
<thead>
<tr>
<th>Event</th>
<th>Nivolumab (N=131)</th>
<th>Docetaxel (N=129)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3 or 4</td>
</tr>
<tr>
<td>Any event</td>
<td>76 (58)</td>
<td>9 (7)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>21 (16)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>14 (11)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>13 (10)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>12 (9)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10 (8)</td>
<td>0</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>7 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>6 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>6 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>5 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>3 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Myalgia</td>
<td>2 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>2 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Alopecia</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Summary

**Immunotherapy**

- Nivolumab (PD-1 inhibitor) approved for treatment of squamous and non-squamous NSCLC 2L+
  - PD-L1 (IHC) is a “complementary” diagnostic, may assist in clinical use of drug but not required (PD-L1 IHC 28-8 pharmDx test)
- Pembrolizumab (PD-1 inhibitor) approved for treatment of squamous and non-squamous NSCLC 2L+
  - PD-L1 (IHC) is a “companion” diagnostic, required for clinical use of drug (PD-L1 IHC 22C3 pharmDx test)
- Predictive biomarkers (other than PD-L1 IHC) being explored for PD-1/PD-L1 immunotherapy
- Several other immune checkpoints being examined for cancer immunotherapy