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.
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

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
Case 1 (cont)

- 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**

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 *EGFR* mutation: 261/437 = 59.7%

Most common: *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
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>155</td>
<td>23</td>
<td>12</td>
<td>190</td>
</tr>
<tr>
<td>Pos</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></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%

Sequist LV, et al. *J Clin Oncol*. 2015;33 (suppl; abstract 8001);
Wakelee HA. MINI03.10. WCLC 2015.
### 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 (CO-1686)</td>
<td>256</td>
<td>35%</td>
<td>53%</td>
<td>~8.0 mo</td>
<td>Hyperglycemia</td>
</tr>
<tr>
<td>AZD-9291 (osimertinib)</td>
<td>253</td>
<td>21%</td>
<td>61%</td>
<td>~8.2 mo</td>
<td>Diarrhea/rash</td>
</tr>
<tr>
<td>HM61713 (800 mg)</td>
<td>62</td>
<td>29%**</td>
<td>55%</td>
<td>NR</td>
<td>Diarrhea/rash</td>
</tr>
<tr>
<td>(300 mg)</td>
<td></td>
<td></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

AzD-9291

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

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

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

Mok T, et al. ESMO 2014 (abstract LBA2).

Med OS: 14.8 mo (G) vs. 17.2 mo (P)
HR 1.62, p = .029 but 33% of events

**Probability of PFS**

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

**Number of events, n (%)**

<table>
<thead>
<tr>
<th></th>
<th>Gefitinib (n=133)</th>
<th>Placebo (n=132)</th>
</tr>
</thead>
<tbody>
<tr>
<td>98 (73.7)</td>
<td></td>
<td>107 (81.1)</td>
</tr>
</tbody>
</table>

**Median PFS, mo**

<table>
<thead>
<tr>
<th></th>
<th>Gefitinib (n=133)</th>
<th>Placebo (n=132)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.4</td>
<td></td>
<td>5.4</td>
</tr>
</tbody>
</table>

HR<sup>a</sup> (95% CI) = 0.86 (0.65, 1.13); p = .273

**Other Methods to Overcome Resistance:** IMPRESS: Continue EGFR TKI Beyond Progression and Add Chemotherapy.
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.
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.
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 **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 **ALK** rearrangements have good outcomes with pemetrexed  JL370
ALK-Rearranged NSCLC
ALK-Rearranged NSCLC

First-Line Therapy:
- Crizotinib (category 1)

Subsequent Therapy:
- Continue crizotinib or switch to ceritinib

Symptomatic systemic progression after local therapies and/or after switching to ceritinib. See First-line therapy options for Adenocarcinoma NSCL-19 or Squamous cell carcinoma NSCL-20

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**ALK Inhibitors: Clinical Pharmacology**

<table>
<thead>
<tr>
<th>Points</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></td>
<td>High-fat meal decreases exposure by 39% compared to fasted state.</td>
</tr>
<tr>
<td><strong>Common AEs</strong></td>
<td>Vision disorders, edema, elevated transaminases, nausea, diarrhea</td>
<td>Diarrhea, nausea, vomiting, elevated transaminases, fatigue, rash, hyperglycemia</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)

- 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 PFS, 10.9 mo vs. 7.0 mo
- ORR 74% vs. 45%

## Ceritinib

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

**Alectinib**

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

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patient</th>
<th>ORR</th>
<th>mDOR</th>
<th>mPFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>AF-001JP</td>
<td>ALKi naive but not treatment naive</td>
<td>93.5% (82–98.6)</td>
<td>NA</td>
<td>NR estimated &gt; 29 mo</td>
</tr>
<tr>
<td>NP28673</td>
<td>ALKi resistant (chemo naive and resistant)</td>
<td>50.0% (40.8–59.1) prev chemo: 44.8% vs. none: 69.2%</td>
<td>11.2 mo (9.6–NE)</td>
<td>8.9 mo (5.6–11.3)</td>
</tr>
<tr>
<td>NP28761</td>
<td>ALKi resistant (chemo naive and resistant)</td>
<td>52.2% (39.7–64.6)</td>
<td>13.5</td>
<td>8.1 mo</td>
</tr>
</tbody>
</table>

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
B. Whole-brain radiation and continue crizotinib
C. Switch to ceritinib
D. Enroll on clinical trial with alectinib
E. Whole-brain radiation followed by docetaxel chemotherapy
CNS Metastases Major Issue in ALK+ NSCLC, Particularly as Form of Relapse After Crizotinib

Slide courtesy of Dr. Ignatius Ou
## 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</td>
<td>39.4% (22.9–57.9)</td>
<td>84.8% (68.1–94.9)</td>
<td>–</td>
</tr>
<tr>
<td>Alectinib/NP28673</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>

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
Crizotinib Activity in ROS1

- **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 + trameitinib</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.
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

Dendritic cell or tumor cell

TNFR/ligand family

T cell

Signal 1

B7H1/B7DC
B7H4/X
B7RP-1
B7H3
MHC/pep
CD27L
OX40L
LIGHT
4-1BBL
CD40
CD40L
CD27
OX40
LIGHT-R
4-1BB
4-1BBL
B7-1/B7-2
B7-1/B7-2
B7H1/B7DC
PD-1
CD28
CTLA-4
ICOS
BTLA
Activated DCs

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.
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>Any event</td>
<td>76 (58)</td>
<td>111 (86)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>21 (16)</td>
<td>42 (33)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>14 (11)</td>
<td>25 (19)</td>
</tr>
<tr>
<td>Anemia</td>
<td>13 (10)</td>
<td>18 (14)</td>
</tr>
<tr>
<td>Nausea</td>
<td>12 (9)</td>
<td>30 (23)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10 (8)</td>
<td>26 (20)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>7 (5)</td>
<td>9 (7)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>6 (5)</td>
<td>10 (8)</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>6 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>5 (4)</td>
<td>8 (6)</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>3 (2)</td>
<td>12 (9)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>2 (2)</td>
<td>13 (10)</td>
</tr>
<tr>
<td>Anemia</td>
<td>2 (2)</td>
<td>28 (22)</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>1 (1)</td>
<td>15 (12)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>1 (1)</td>
<td>8 (6)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1 (1)</td>
<td>42 (33)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>0</td>
<td>14 (11)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>0</td>
<td>29 (22)</td>
</tr>
</tbody>
</table>

*number of patients with an event (percent)*
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
NAVIGATING THE LANDSCAPE OF MOLECULAR TESTING AND TREATMENTS WITH TARGETED THERAPIES FOR PATIENTS WITH NON–SMALL CELL LUNG CANCER

SUKHMANI K. PADDHA, MD  Dr. Harvey and I hope to offer you an exciting hour as the last session of the day. Thank you for staying. We’re going to be discussing Navigating the Landscape of Molecular Testing and Treatments with Targeted Therapies for Patients with Non–Small Cell Lung Cancer. These are our disclosures.

There are a lot of learning objectives for the next one hour. We want to ensure that you understand the evidence-based guidelines for biopsy, histology, and very importantly molecular testing. And most of all, identify which patients with advanced non–small cell lung cancer should undergo mutation testing and why that’s so important. And then of course to describe key updates. It literally feels like every other month there is a new FDA approval for the treatment of lung cancer, which is fabulous for our patients. And then, of course, understand the side effects of some of these compounds and the collaboration of how we can work together to improve the care of our patients.

So first we’re going to discuss the diagnostic workup. Let’s start with a case. So we have a 40-year-old nonsmoking Asian woman. She has a persistent cough. Chest x-ray is abnormal, shows increased interstitial markings in the right lower lung, and the right hemidiaphragm is partially obscured. CT chest is also highly abnormal. Right four-centimeter infrahilar mass. There is a small pleural effusion there, multiple bilateral nodules, extensive hilar and mediastinal lymph nodes, also liver metastases although they’re quite small, and then multiple foci
of osseous metastases with the largest one in the left scapula. So what do you do next for this patient? It looks like majority of you chose bronchoscopy and endobronchial biopsy of the four-centimeter infralilar mass.

So this is a really good question because tissue is critically important for the management of our lung cancer patients. So when we’re thinking about acquiring tissue, for example, in the last case, we’re thinking about what’s the safest way to get tissue for this patient, what’s the most effective way, and which way will give us all the answers that we need in a time-efficient manner. So sufficient tissue is needed for multiple reasons. There’s a lot of testing that goes on, on this tissue. So first of all is obviously the histologic diagnosis. We want to know, are we dealing with a small cell lung cancer or non–small cell lung cancer because the treatment paradigms there are very different. And then with a non–small cell lung cancer, you want to decide what subtype. Are you dealing with squamous, adenocarcinoma, large cell neuroendrocine? All of those have different implications for treatment.

And then the pathologist will run a variety of immunohistochemistry protein testing, and you want to ensure that you tell the pathologist that you are concerned that this patient has a diagnosis of lung cancer because in situations you don’t need to use that many markers to actually come up with a diagnosis because everything you test for costs tissue. So, for example, for adenocarcinoma, TTF-1 or napsin A can answer that question; for squamous p63 or p40; for neuroendocrine chromogranin or synaptophysin. So it’s just important to keep that conversation open with the pathologist. And then of course most
importantly—which really changes the treatment for our patients—is molecular markers.

One of the answer choices for the last question was a bone biopsy. Actually bone biopsies are pretty difficult to run molecular testing on, so if we can avoid it in lung cancer, we do if there is a better option. So this is just to emphasize the multidisciplinary approach that is key in acquiring tissue for lung cancer. Frequently we do discuss these cases in a tumor board because we have our radiologist there to tell us what’s the most successful lesion. We have all our surgeons, our interventional pulmonologists in the same room, and also our pathologists there to say, you know, once we get tissue, let’s focus on getting the molecular testing and spending as little tissue as we need on the immunohistochemistry.

This is case one continued. So she did have a bronchoscopy. She had an endobronchial biopsy. It did show lung adenocarcinoma, positive for TTF-1. She had other staging workup and no other sites of disease except those that I mentioned previously, and the patient is asymptomatic except for a persistent mild cough. So what do you do next? It looks like majority of people in the room want to test for at least EGFR and ALK rearrangement. There are also a subset who want to test in addition for ROS1, and a smaller subset to send for comprehensive next-generation sequencing. I’ll let Dr. Harvey kind of take us through the molecular testing and why histology is important also.

**R. Donald Harvey, PharmD, FCCP, BCOP** Thanks, Dr. Padda. I want to thank the organizers for inviting me. It’s fun to be a pharmacist here in a group
full of advanced practice providers. Our lung cancer program at Emory is fairly large and works in consort with a variety of others and we actually participated in a number of these studies of genetic testing. If you think about lung cancer as a whole, it’s important to go from this traditional view of histology alone to really at least a functional perspective after the diagnosis of non–small cell is made that it’s really squamous and non-squamous. And the squamous population has a certain pathway of treatment. The non-squamous population has a different pathway of treatment and a growingly diverse number of options for therapy in the non-squamous group.

You can see here that from two pie charts of likelihood of genetic abnormalities based on squamous and non-squamous disease, just checking the squamous we still don’t know a lot about some of the molecular abnormalities that drives squamous cell, non–small cell lung cancer. But there are many there and you can see there a few holy grails in both of them. One of them is KRAS. KRAS is not druggable right now but there are currently ongoing therapies or at least attempts to drug KRAS. If one can get a drug for KRAS-positive disease, it could have a large impact on a number of cancers. But you can see here that a number of them are certainly druggable, and specifically we’ll focus in on EGFR, ALK, and ROS1.

You can see the proportion of patients that are EGFR-mutated in the adeno population is about 11 percent. Across all non-small cell, that range is anywhere from 15 to 20 percent. There are a few specific lesions that are there. You’ll see a few others that you might recognize. HER2 is occasionally seen in
some non-squamous histology patients. Usually that’s not particularly druggable and not a big driver in many of them. And you can see as well that there are drugs like BRAF mutations. One might consider a BRAF mutation inhibitor in certain patients and certain select instances. But for the most part, we’ll focus in on the ROS1, EGFR, and ALK-positive patients.

So this is our NCCN Guidelines that help us to decide what therapeutic options to pursue in patients with non-small cell, and really again the first cut point is do you have squamous histology or do you not? If you do not have squamous histology, there needs to be a knee jerk reaction to then send tissue, as Dr. Padda mentioned, for molecular testing. And there are a few key things that are there and they’re listed here. EGFR mutation should be done. That should be done first. Again, she also mentioned that tissue is the issue, but tissue is also at a premium, meaning that you may or may not be able to go back and get more tissue from patients, which is often encouraged whenever you can because patients may have converted from non-small cell to small cell if they have a long smoking history, for example.

But sometimes you can’t do that, and if you can’t you have to think about your sequence of testing and how you will use that tissue for the best outcome. The most common abnormality is EGFR mutation testing, so that should be done first. ALK testing should follow that, and usually they’re done concurrently on the same tissue. But if they’re not, then that should be broad molecular profiling testing as well. So that’s really the non-squamous histology approach. You can consider doing that in squamous cell patients, particularly in those patients who
perhaps never smoked if there’s some reason, although it would be very odd, that they were classified as squamous and in reality they’re non-squamous. But in general, EGFR and ALK testing usually isn’t very fruitful in patients that are squamous histology patient but can be part of a much larger, broad look by next-gen sequencing like Foundation Medicine or other approaches.

So when one sees the patient with non-squamous histology cancer, if they are negative, if both tests for EGFR and ALK come back and they are clearly negative, then you have to consider chemotherapeutic approaches and these are fairly similar but are also growing in diversity between adeno or non-squamous and squamous patients. Everybody should get a platinum-based regimen whether you are non-squamous or squamous. The question is which platinum and which combination. So looking at the non-squamous EGFR-negative, ALK-negative patient, doublet chemotherapy with platinum-containing drug as a backbone is important.

Certainly carboplatin and pemetrexed, for example, or platinum pemetrexed-based regimens have much data which we won’t go to a lot during this presentation. There’s also the combination of bevacizumab, carboplatin, and paclitaxel if specific criteria are met. There are fears of bleeding with bevacizumab, particularly for patients who may have a central lesion that’s more commonly in the squamous population, but you have to have other clinical criteria that have to be met as well. A key thing in this population is to look at disease response after four or six cycles. So generally most people, at least I believe the data is strong, four cycles is enough and then restage at that point to
see what your decisions are. Some people go as long as six and that’s the data with bevacizumab.

But at that four- or six-cycle period, you have to look and see, all right, did they progress. If they progress, you obviously then move on to other therapies or second line therapies. If they have not progressed or optimally have had a partial response or in rare instance in complete remission, then you go on to maintenance therapy and that’s listed there as well. There’s continuation maintenance if the patient received bevacizumab initially. They may receive bevacizumab alone for maintenance treatment after that. A more common approach at least in our institution is maintenance pemetrexed, so continuation maintenance after that initial four or six cycles of platinum and pemetrexed. And then rarely one might consider switch maintenance or a different drug, really a pretty unusual scenario.

Now, if they have progressed and they have good performance status, and performance status is certainly critical here, good performance status should be thought of initially for treatment but then at the time of progression as well. And so changing up therapy if they’ve not already received immune checkpoint inhibitors which we’ll talk a little bit about here. They’ve certainly been, I suspect, a large part of this meeting, will continue to be a large part of this meeting, and will also continue to be a large part of general cancer therapy. There are new options there, nivolumab and pembrolizumab. Other options are listed there and are more historical but still established. Docetaxel, pemetrexed if they didn’t get it
before, for example. So that’s kind of a broad brush look at the EGFR-negative, ALK-negative patient population.

Now, if you look at squamous cell cancer, this is kind of easy and a little bit like it’s been for a long time, and that’s platinum-based regimens. Now, one thing that’s been learned is that you surely should not use bevacizumab nor should you use pemetrexed. Bevacizumab for safety concerns, pemetrexed for efficacy concerns. There was a randomized trial comparing platinum pemetrexed with platinum gemcitabine. Platinum gemcitabine was actually superior in the squamous population, moderately superior, whereas the pemetrexed combination was superior in the non-squamous population. So platinum-based regimen, again four or six cycles in the same idea.

If they have had a response or stable disease, continuation maintenance is a very reasonable approach if patients can tolerate it, and that’s certainly an important point to consider, or a therapy holiday if their performance status is declined but they still have stable disease or better. Again, if they progress, performance status of zero to two, one should consider systemic immune checkpoint inhibitors as well, nivolumab and pembrolizumab, or another systemic therapy which is more historical. So you can see that there’s been a landscape change in both subtypes, both histologies, that PD-1 inhibition is now moved into preferred category for the second line treatment of patients who progress.

So again, in summary, tissue really is the issue, making sure you have adequate tissue, that it’s sent for the right testing is important, that there’s a multidisciplinary approach to it, that histology does matter only a way to kind of
serve as a guidepost for how patients should be managed, following, and tested further, following on initial histological assessment, and then molecular testing is certainly critical as it can very much change first line therapy. So let’s continue our case that was presented earlier. The patient has testing for an EGFR mutation and ALK status by FISH, fluorescence in situ hybridization, and an EGFR mutation was detected in exon 21 at the L858R substitution pattern as a single-nucleotide polymorphism and FISH was ALK-negative.

So what do you do next in your practice, in your thoughts? Do you start erlotinib as a first line agent; gefitinib as a first line agent; afatinib as a first line agent; start conventional carboplatin, paclitaxel, and bevacizumab; or enroll in a clinical trial with the Clovis compound or the AstraZeneca compound, AZD-9291 or CO-1686? I still know most drugs by letters and numbers. Okay, so let’s take a look and see where people are coming through. There are multiple answers to this. So most individuals chose or are choosing to start erlotinib overall.

So this is the NCCN Guidelines slide for those patients who are EGFR-mutated. So if you discover they have one of the two more common EGFR mutations, then you would consider one of these three agents, and all of them have category one data now. Erlotinib, afatinib, and gefitinib. You may remember a few important historical points about these drugs. One is that gefitinib was approved and then removed from market. Secondly, the erlotinib was approved for second or third line treatment only for EGFR expression, not for mutation. So you can use erlotinib in third line lung cancer in patients who don’t have EGFR
mutation. You will get it paid for. It's not very effective but it is out there and is part of the label.

People will realize then that it's not that just EGFR is there, but that EGFR is activated. You can have a room full of TVs that are plugged in, but if none of them are actually turned on then they don't work. The same idea is true in EGFR. You have to have a mutation that then says this is going to be an effective drug based on the mutational status. Gefitinib is again FDA approved after doing a confirmatory trial but it is approved only specifically for EGFR-mutated non-small cell. Erlotinib has a much more broad approval, but the reality is most people are only using erlotinib in EGFR-mutated disease.

So when you think about these drugs, there are a few clinical points that become important from a pharmacology perspective. These are doses listed across the three. There are on-target side effects that occur with these drugs that are clear and relevant and would be seen in many if not all patients. One is diarrhea. So diarrhea certainly is an on-target effect of EGFR inhibition. Patients need to be counseled. You may have this as soon as a few hours after you take the drug based on absorption patterns. You need to have Lomotil or Loperamide at home for that diarrhea. It can be a little bit self limiting, it can be more than self limiting, but again patients can take anti-diarrheal to manage, and for the most part it is something that patients become either acclimated to or treated well with supportive medications.

And secondly is the rash, and I'll tell you that people will have many thoughts on how you should manage EGFR and related rash. Candidly, there's
really no one optimal way because it is a drug-related effect, it is there, it is supportive, it’s an acneiform rash, it looks like you’re 14 again or worse in some instances, so patients can find it quite debilitating but in the end there is no optimal way. Really things like minocycline, topical minocycline have been used. There are other things that have been used but there is really no optimal way other than supportive standard washes that might be helpful. From a counseling perspective as well, there are a few things that are important. I’ll touch a little bit on smoking and the effects on erlotinib. But some of these drugs, many of these drugs are metabolized through the cytochrome P450 system.

There are only a few drugs that really are major problems. Reach out to your local pharmacist, hopefully you have one, who can help you understand a little bit more about what the clinical relevance of some of these things are. CYP1A2 is an enzyme system that’s responsible for a lot of erlotinib metabolism and is induced by smoking. Afatinib, a high fat meal can decrease exposure so you want to tell patients to take it in a fasted state if they can tolerate it. If not, a light meal, a light breakfast might be best. And all of these drugs should optimally be taken in the morning because who wants to have diarrhea overnight, right? So most of the time it’s a 12 to 18-hour period of diarrhea. And then finally there are some issues that come up.

Now, one thing that comes up often in discussions is acid environment and absorption of erlotinib. Optimally patients shouldn’t be on H2 antagonists for PPIs because it does reduce the absorption. But the reality is that even if you have two-thirds absorption of 150 mg of erlotinib, that’s probably enough to treat
the cancer, to be honest. So it’s certainly something to counsel patients on but these days you can walk outside here and I bet there’s an omeprazole sales person standing there. You can find these drugs anywhere. Patients are going to take them, so you want to counsel them not to, but then what do you do if they need them and it does become a bit more challenging? Optimally you avoid them or at least space them out enough that you’re not going to have an issue with absorption, specifically H2 antagonists. Afatinib should be again on a fasted stomach, and there is no food effect with gefitinib.

So this is just a quick slide on erlotinib and smoking. You can see it in an old study in ’06 if you do suspect smoking. And this is clinically irrelevant because if you have a patient who you’ve placed on erlotinib and you know that they have an EGFR mutation and they either don’t respond when you’re looking for a response, you might just consider this. This is not a reason to start a smoker on 300. This is simply showing you that if smokers, meaning one and a half packs per day or more are continuing to smoke while taking the drug, it’s an issue. But the reality is the majority of patients who have EGFR-mutated disease actually are nonsmokers although some still are. So with that, I’ll turn it back over to Dr. Padda.

**DR. PADDA** Thank you, Dr. Harvey, for going through that. So now I’m going to spend some time on why the NCCN Guidelines have afatinib, erlotinib, and gefitinib as sort of category one recommendations for the first line treatment. I saw that a lot of people also chose platinum-based chemotherapy, carbo/Taxol, bevacizumab in this setting. I don’t think that’s wrong in a case where you have a
patient who is very symptomatic where you cannot wait for molecular testing because sometimes depending on the institution or the send out, it can take a couple weeks, and maybe a couple weeks you don’t have at that time. So in that scenario it’s okay to start platinum-based chemotherapy because you can reserve the EGFR TKI for later.

So Dr. Harvey mentioned this previously; the first study with gefitinib was a massive study in Asia called IPASS, and at that time they had no idea about the EGFR mutation. But once it was discovered, they went back and tested patients' tumor samples at that time. The incidence of EGFR mutation was very high in this population, over 60 percent. It’s not totally surprising because they enriched for this patient population. So we know that EGFR mutation associated with East Asian, non-smoker, or light smokers, and those were some of the eligibility criteria for this trial.

So what you can see, very interestingly there on the left panel, is the EGFR mutation negative subset and you’re looking at progression-free survival curves. And what you’re seeing if the patient does not have an EGFR mutation in the first line, they should receive platinum-based chemotherapy. You see there the progression-free survival is worse if they get gefitinib. However, the vice versa is true. On the right panel you see the EGFR mutation-positive cohort. Gefitinib improves progression-free survival in patients who have an EGFR mutation. So I will just note that there are two most common activating mutations of EGFR and they are in all the FDA approved indications for these EGFR TKI therapies. One is exon 19 deletion, and the other is exon 21 L858R substitution.
So this was landmark. This really changed the way we began to think of lung cancer.

As you can see from this very busy table, there are many other trials that looked at the EGFR TKI in the first line versus a platinum based chemotherapy in the EGFR mutation subset. And what you can see from the median progression free survival is that EGFR TKIs beat platinum chemotherapy for that. So the median progression free survival for any of these EGFR TKIs is somewhere between nine months to twelve months. But if you look at the far right column in terms of median overall survival, none of these particular trials on an individual basis have been able to show an overall survival benefit. So this is all coming, progression free survival usually has better response rates. So that’s just important to note.

I will mention one caveat. There were two trials involving afatinib. This is one of our second generation EGFR TKIs. It’s irreversible. It binds EGFR in addition to other members of the HER family. And when they combined two trials that had similar designs, they saw maybe a little bit of improvement in overall survival there with a hazard ratio of 0.81 in favor of afatinib. But again, no individual single trial on its own has been able to show an overall survival benefit. So what’s increasingly been clear, and that’s why I mentioned the two most common activating mutations, is that the subtype of EGFR mutation does appear to matter.

So reports as of 2006 were coming out that maybe exon 19 deletions do better than exon 21 L858R mutations with EGFR TKI therapy. And what you’re
seeing in that top panel is another trial involving afatinib versus platinum-based chemotherapy. On the left you have exon 19 deletion. You see a very nice separation. These are overall survival curves. So this was a preplanned analysis in the subset, and afatinib improved the overall survival in this exon 19 deletion cohort. However, on the right panel you see in the exon 21 L858R substitution, the curves don’t separate as nicely and this is not a statistically significant improvement for afatinib.

Down below is another example from the European trial involving erlotinib versus platinum-based chemotherapy. They went back and they looked at this particular question and again they saw that exon 19 deletions do better than exon 21 L858R mutations in terms of overall survival. We don’t know what exactly is happening here. Is this just something that’s simply prognostic? Is there some interesting interaction going on with the drug and the specific type of mutation? Is there some difference in terms of the resistance patterns that emerge in these subsets?

Let’s continue with our case. It’s drawn out of our many slides so I hope you remember. So our patient with EGFR mutation, she does go on to start erlotinib at the standard dosing of 150 mg. Her cough results within two weeks, she has a fabulous partial response on her first interval scan. She has classic side effects from the on-target effect of erlotinib including acneiform rash and also some diarrhea. She is started on oral antibiotics, doxycycline and topical steroids which improves her rash. And the diarrhea is well controlled with Loperamide. So she does well on therapy for eight months before she has
progressive disease with diffuse new metastases, and she is now symptomatic with a fatigue and cough. Re-imaging of her brain reveals still no brain metastases. What do you do next? And again, there’s not one right answer.

All right. So about a third of you want to repeat biopsy of a tumor lesion. I think that’s reasonable. A third of you want to switch to chemotherapy, also reasonable. And 20 percent of you want a clinical trial with either one of these third generation EGFR TKIs want to do that. So I think all of those are reasonable and I’ll take you through it. So unfortunately, despite these amazing therapies for our EGFR mutated lung cancer, resistance develops usually at an average of nine to twelve months. And a lot of groups study what is the mechanism of resistance to these therapies? So in 60 percent it’s T790M mutations. This is a second site mutation that develops in EGFR while on EGFR TKI therapy that prevents the drug from binding as well. This is the major mechanism, but you can see from the pie chart there that there are other mechanisms that are currently being explored.

So a lot of you chose repeat tumor biopsy. For patients we know that’s very difficult. A lot of times for these patients when they progress, it’s devastating news especially since they feel so good when they’re on the first line EGFR TKI. And for lung cancer patients it’s not always easy to find an easily-accessible lesion that’s going to be safe to undergo biopsy, so a lot of smart people are looking at the potential of testing circulating tumor DNA to identify the mutation in the blood. This slide is actually from one of the third generation EGFR TKI compounds rociletinib which I will discuss in another slide or two, and they
looked at the agreement of detecting the T790M mutation in the blood versus the issue, and you can see down below that it had pretty good agreement at 81 percent for detecting T790M mutation and also 87 percent for detecting activating mutations. So this is a stay tuned thing. This is definitely going to come our way. I think right now there are some companies that do offer plasma ctDNA testing, so I think we can believe a positive result, but I think we should question potentially a negative result especially if you’re suspicious. But a lot of nice data coming out showing pretty good agreement between what we detect in plasma and what we detect in the tumor.

So these compounds are very, very cool. We had the discovery of the most common resistance mechanisms in EGFR, and then very smart people got together and started designing drugs that target this mutation. These are our third generation EGFR TKIs. Probably the front runners right now who have FDA breakthrough designation include rociletinib and osimertinib so you’ll definitely be hearing more about those compounds. They target T790M, they target the original activating mutation, and they’re also designed to spear EGFR wild type so you have less of those problems with diarrhea and rash.

And what you’re looking at, at the top panel is a cohort of T790M mutated patients who were treated with osimertinib. And what’s amazing is the response rate is 61 percent. So this is like resetting the clock for the patients with T790M mutation. There’s also activity in patients who don’t have a T790M mutation so we don’t know totally what’s going on there. Rociletinib is the bottom panel with the waterfall plot. You can see that’s a lot of responses there, again resetting the
clock. Overall response rate of 53 percent in patients with a T790M mutation; and still some activity in those who don’t, 35 percent. So these drugs are also coming our way and the FDA is aware of them.

There are many others in development. This table is just to show you that. They all have some activity in T790M-negative. The majority of the activity is T790M-positive. And I think where the distinctions are going to come for these medications is in their side effect profile. For example, rociletinib has an unusually side effect of hyperglycemia, so you get to learn your hyperglycemia management again. And osimertinib still does have some issues with diarrhea and rash although it does spear EGFR wild type more than some of the original drugs, and there are many others coming.

Of course when something works well at the time of acquired resistance, we want to test it at the time of first diagnosis. This is just one of the phase I cohorts for patients who are EGFR TKI naïve who were treated with osimertinib. You can see the response rates at this time seem to be relatively similar to what we see with our first generation and second generation EGFR TKIs of 73 percent. And these particular compounds are now going head to head with current first line EGFR TKI therapy like erlotinib and gefitinib so we’ll see how they compare against our current standard of care.

There are other methods. Afatinib and cetuximab. This is quite a toxic regimen because you are hitting EGFR from two ways, but still a pretty good overall response rate in both T790M-positive and negative patients. It can be a little bit difficult to get insurance authorization for the cetuximab but it is
something to think of for your patients. And then the question is once someone has progression, should you continue the EGFR TKI and add chemotherapy. And a lot of groups were doing that but then we had this IMPRESS study which was looking at gefitinib and then adding pemetrexed-based chemotherapy and there actually was no difference in progression free survival, just more toxicity when you continue the EGFR TKI with the chemotherapy.

Then sometimes the progression is relatively mild, so the patient is feeling well, maybe one of their tumors is growing. And you can get away. This was a retrospective cohort study looking about 92 patients, and 66 percent were continued beyond progression and 50 percent were able to delay therapy for an additional three months. So just because you see something growing a little bit on a scan, you want to look at the overall picture, look at how the patient is doing, and see maybe we can continue the same therapy with close follow up and CT imaging. So the patient does have a repeat tumor biopsy, as many of you selected, demonstrates T790M mutation. She enrolls on a clinical trial with third-generation EGFR TKI and has a partial response with significant improvement in symptoms.

In summary, we have three options. First line for EGFR mutated lung cancer: afatinib, erlotinib, gefitinib. All of them improved progression free survival compared to platinum-based chemotherapy. None of them had been able to show an improvement in overall survival. Exon 19 deletions do better than exon 21 L858R substitutions. Resistance is a problem. Develops at nine to twelve months. The T790M is the most common mechanism of resistance. We have the
ability to potentially plasma genotype our patients in the future. And the clinical trials with the newer generation of therapy shows significant promise. So take it on, Dr. Harvey.

**DR. HARVEY** All right. Thanks. So we got our second case. A 63-year-old African American woman who is a past smoker for 35 years and multifocal ground-glass opacities with three foci of stage I adenocarcinomas resected five years ago. She has a history of known adenocarcinomas stage one that’s been resected. She now presents with dysphagia. She has a CT of five centimeter right lower lobe mass abutting the esophagus. She gets bronched, and then it shows from a histological perspective she’s TTF-1 positive, but EFGR, ROS1 by FISH, and ALK by FISH are all negative. She has a PET scan, which shows multiple pulmonary masses, pleural metastases, liver metastases, and bony metastases but luckily has a negative brain MRI. She was started on carboplatin and pemetrexed with an impressive response in resolution of many of those lesions described on PET scans. She was on maintenance pemetrexed for a year prior to widespread disease progression. So again, history stage I resected, new disease, placed on carbo/pem with pem maintenance, lasted for a year prior to disease progression and is otherwise asymptomatic.

So in this patient, what would consider doing next? Sending archival tissue for repeat deep sequencing with next-gen sequencing through, for example, Foundation Medicine; switch to docetaxel chemotherapy as she’s unlikely to have a mutation since she is a former smoker; or repeat a fresh biopsy and send for EFGR and ALK testing? Okay. So we have repeat biopsy and
archival tissue as thoughts. We’ll talk about those a little bit, and less commonly switch to docetaxel. These days I feel badly for docetaxel.

The patient is asymptomatic and the archival tissue is sent for next-gen sequencing and has an ALK rearrangement. So that’s the idea that these deeper sequencing next-gen sequencing can determine changes that may not be seen on initial FISH testing. So that’s an important point. We’re moving towards next-gen sequencing more and more. There’s a big question in not only lung cancer but many other cancers which are the driver mutations, which are the passenger mutations, which might be part of the patient, meaning the germline versus part of the cancer. Those are the more rare mutations, things that we don’t know as much about yet. However, there are certainly druggable, actionable mutations. So she’s ALK rearranged. What do you do? Do you start crizotinib, ceritinib, or others, or alectinib or restart pemetrexed?

We have a large majority who are loving crizotinib. So let’s move on and talk about it. So this is the ALK-positive algorithm for non-small cell lung cancer that is ALK mutated or ALK rearranged. Crizotinib is the category one recommendation. This is easy. One rearrangement, one drug, and then move on. If patients progress, that’s where it gets a little more interesting. If they progress and are asymptomatic, then you might consider continuing crizotinib or switching to ceritinib, a second-generation ALK inhibitor. This is an area that is actually quite exciting for next molecules.

So some of the clinical pharmacy points around these drugs, crizotinib and ceritinib. Crizotinib is an important drug. For those of you who have used
crizotinib, the number one thing patients will complain about is visual changes seen early in the development of the drug. Most commonly it’s a light to dark transition that bothers patients. They may also see floaters, rarely double vision. It’s something that patients tend to acclimate to over time, but certainly if they don’t know about it, they’re going to freak out appropriately. So counseling is important for visual changes that might occur.

Patients can have transaminitis with this drug too, so measuring LFTs for the first maybe every one or two weeks for the first four to six weeks or so, ensuring that they’re not elevated. That’s the time frame they’re more likely to be elevated. And then moving on from there, there is a hepatic dysfunction study that’s finishing up and should be published in the next year or so. There is a CYP3A4 substrate. Crizotinib is, and so thinking about points around CYP3A4 inducers and inhibitors and those drugs are out there. One thing I want to point out because it’s a little bit of a pet peeve of mine is that there is an issue with grapefruit juice with CYP3A4, and there’s an issue with sort of exotic citrus, things like blood oranges for example. It’s not an issue with navel oranges, with lemons, with limes, with other citrus. Patients don’t need to avoid all citrus. They need to avoid grapefruit and they need to avoid the stuff that you can get at specialty markets. Otherwise, everything else is fine. You can eat an orange if you’re taking crizotinib. I’m sure the Florida citrus growers are thanking me right now.

Ceritinib is a little bit of a different drug, a little harder drug in many ways. High fat can decrease the exposure compared to fasting. It’s got a few more side
effects than crizotinib, a little tougher to handle on patients. It is a second line
drug for the most part, but it is effective on those patients who have failed

crizotinib. Fat may increase exposure and there is also an ongoing hepatic
dysfunction study. So with that, I'll turn it back over to Dr. Padda.

DR. PADDA Thank you, Dr. Harvey. So now we're going to go through
the data of why the NCCN Guidelines are the way they are. So this is a
PROFILE1014 study. This looked at first line crizotinib in ALK rearranged non—
small cell lung cancer compared to platinum pemetrexed chemotherapy. The
partner here pemetrexed is actually really important because there are several
reports now that ALK rearranged lung cancer patients do extremely well with
pemetrexed as you saw from this case, had complete resolution of a lot of their
lesions and also had a long time on therapy. So even with that, crizotinib here,
you can see beat this chemotherapy in terms of progression free survival, the
hazard ratios here were 0.45 with a median PFS of 10.9 months versus seven
months, and overall response rates are also improved. So this is why we use
crizotinib first line for patients with ALK rearranged non-small cell lung cancer.

Then for second line, Dr. Harvey mentioned that we use ceritinib for
patients with ALK rearranged non—small cell lung cancer, and it actually came
from this very large phase I study called ASCEND-1. That's what you're seeing in
the top picture there, that's a waterfall plot. Each of those bars which represent
patients are color coded. So all the blue indicates patients who have received
prior crizotinib and now have gone on to treatment with ceritinib. And the yellow
bars are those who have never received any sort of ALK targeted treatment. And
what you can see is ceritinib works in both of these populations. So that’s why ceritinib is approved after crizotinib because it has activity after crizotinib failure.

And then what you’re seeing in the table below are other trials that have gone with ceritinib including ASCEND-2. These are patients who have both received ALK inhibitor and chemotherapy. The overall response rate maybe isn’t as impressive at around 38 percent, whereas in ASCEND-3 where they’re ALK inhibitor naïve but have received prior chemotherapy, the overall response rate is a little bit higher at 63 percent. So this is why we use ceritinib after crizotinib per NCCN Guidelines. So crizotinib is what we call a first-generation ALK inhibitor. The story of crizotinib is actually very interesting because it was developed as a Met inhibitor. And just fortuitously like a lot of things in medicine it was also found to have activity in ALK.

So now second-generation ALK inhibitors are being developed, and the advantages of them is that they target ALK better, they tend to penetrate the blood brain barrier better. So if you have brain metastases, you can get some control of them without having to use things like radiation. And then unlike EGFR where there is a dominant mechanism of resistance, in ALK the mechanisms of resistance are very heterogeneous. So these second-generation ALK inhibitors are attempting to target a variety of those, so those are the three main advantages of these drugs coming through. Alectinib actually filed for FDA priority review in September, meaning they will be reviewed by the FDA in approximately six months from that date.
What you can see in that top figure is a waterfall plot looking at patients who have previously received crizotinib but may or may not have received chemotherapy which are all those stars there, indicate they have received chemotherapy. And you can see this drug works extremely well at producing responses in this patient. The overall response rate here was 50 percent. For those who had never received chemotherapy it was as high as 70 percent, and for prior chemotherapy is 45 percent. And if you look at the table, that top clinical trial, that Japanese trial is being performed in ALK inhibitor naïve patients but not treatment naïve, but they are right now with 46 patients at their last updated stated an overall response rate of 93.5 percent.

So these drugs are very exciting. We’ll have to see where alectinib runs in this landscape. I think part of the question is going to be how do we sequence these drugs, what is the best way to do it. Is crizotinib first best? Is ceritinib second best? And where are all these other drugs going to fit in which have clear activity? Our patient with detected ALK, on next-generation sequencing, switches to crizotinib. She achieves a partial response for seven months, but then she develops wide-spread progression and multiple tiny brain metastases. There’s one in the left frontal lobe that is 1.5 centimeters but she’s otherwise asymptomatic. She only got the brain MRI really for restaging purposes. So what do you do? About a third of you want to switch -- oh, 40 percent, switch to ceritinib. Some people want to take local action with stereotactic radio surgery in the brain or whole brain radiation and continue the crizotinib.
So I think switching to ceritinib is very reasonable. I wouldn’t continue the crizotinib in this situation because the patient had widespread systemic progression. I think it is good to note, however, if the patient does have brain-only progression, you can radiate the brain and then continue crizotinib, which would be reasonable in that situation. Maybe you start to get worried about the 1.5 centimeter brain met, but she is asymptomatic and it’s in a location of the brain that may not cause any problems. So let’s talk about why we asked you this question.

So CNS metastases are a major issue in ALK rearranged lung cancer, particularly as a form of relapse. This slide is courtesy of Dr. Ou. And what you can see there at the top is that those are patients who are treatment naïve or ALK inhibitor naïve, and we know that metastatic lung cancer patients unfortunately suffer from brain mets at a rate about 30 to 40 percent, and that’s what we’re seeing. But at the bottom half of that figure, what you’re seeing is after they’ve received crizotinib therapy, the rates of brain metastases becomes higher, so on the order of 60 to 70 percent. And that’s because crizotinib is just not that great at crossing the blood brain barrier.

As I mentioned, the second-generation ALK inhibitors are attempting to have better activity in the brain since this is an issue with crizotinib. A lot of times for patients on crizotinib, even if they’re asymptomatic you may want to perform a brain MRI on some sort of routine basis whether that’s every six months or something like that just because the rates of this occurring is so high. And you can see here with the second generation ALK inhibitors at the bottom, ceritinib,
alectinib, brigatinib is another one under FDA breakthrough designation, is that although these patient numbers are small, they do give us an indication that these drugs do have activity in the brain with an intracranial response rate of somewhere between 40 percent, upwards of 50 percent, and a very high disease control rate in the high 80s.

So patient does switch to ceritinib. She doesn’t get any local therapy for the brain. After some difficulty managing GI side effects, as Dr. Harvey alluded to, she does have a systemic partial response and does have disease control of brain metastases at first follow-up scan, so we were able to avoid radiation. So in summary, ALK rearranged lung cancer, first line treatment: Crizotinib. Second line treatment: Ceritinib. Many other ALK inhibitors, as you have seen, are in clinical trials including those with enhanced intracranial activity, so stay tuned. And will be interesting to see how we use those. So I’ll pass is on to Dr. Harvey.

**DR. HARVEY** So there a few other genomic targets including ROS1 and a few others that we want to go through quickly. Crizotinib also has activity in ROS1 disease, and so this is something that should be a part of routine panels now as well as a mutation that demonstrates activity to crizotinib with the presence of the mutation. You can see here very similar to ALK rearrangement, ROS1 activity is quite good with over 70 percent overall response rates. Duration of responses is in the 18-month range, and PSF is up to 19 months or so. That’s quite impressive for again this subset of patients with ROS1.

Other genomic targets are listed here. Again we mentioned some of the V600E, the BRAF mutations. MET mutations are getting more and more activity.
The group at Colorado is doing a lot of work with MET, and there are a few other mutations that are coming along that are going to be likely druggable, EGFR as well as a few others. And so MET mutations, RET fusions, these are some ideas that if you get that Foundation Medicine report back, often times they will say, you know, you might consider this drug or that drug but it really needs to be looked at with ultimately your molecular group, if you have that, or at least your pathologist to consider what’s important and what might you do because some of these combinations that come may not have actually been evaluated fully in clinical trials. So you have to think carefully about some of these things. But if they are good rationale and ability to get paid for, you could do it.

We'll move in immunotherapy briefly because I’m sure this place is packed with immunotherapy but we have to say something about it I think. Case three, 71-year-old man with stage IIIB squamous, after concurrent chemorads relapses six months later, progresses on carbo/gem after only two cycles with worsening cough and fatigue. So rapid progression. What do you do next? Docetaxel alone, docetaxel with ramucirumab, the VEGF or pan-VEGF inhibitor, monoclonal antibody; nivolumab; pembrolizumab if the tumor is PD-L1-positive; and afatinib or erlotinib as the last choice. Clearly the majority of folks chose nivolumab and we’ll go through a little bit of that data here lately. Immunotherapy is certainly taken off here as well as in melanoma. Be on the lookout for bladder, head, neck, Hodgkin’s lymphoma. I think all those approvals are coming. Certainly renal is probably the next approval for these drugs based on where things are. There are about six different compounds in development now.
So immunotherapy: you’ve probably seen all those slides with all the three-letter pathways. Immunotherapy is going to now add to that. There’s a lot out there. CTLA-4, ipilimumab is already almost dead despite only being approved a few years ago. Combination strategies would appear important, but by itself it’s really probably not ever going to be used again. The combination strategies that are important are certainly more toxic than single agents, but this is just a list of everything that one might consider. OX40 is probably the next on the list. 4-1BBL is also another target for solid tumors that appears to be promising. And then of course PD-1 or others. The bottom line of all these is that they unleash the hounds. They take the negative signal away from T cells. The T cells are then upregulated and go after the cancer in a somewhat nonspecific fashion.

**DR. PADDIA** Let’s talk about why these therapies are now approved. In summary, we have two approvals for the treatment of both squamous and non-squamous non–small cell lung cancer. One is nivolumab, PD-1 inhibitor, and the other is pembrolizumab and we’ll talk about a little bit of difference there. So this is a trial in squamous non–small cell lung cancer. This looked at nivolumab versus docetaxel, and you can see here that the primary end point is overall survival. And look how nicely those survival curves separate, very early on. So nivolumab here beats docetaxel for overall survival. The median overall survival is 9.2 months versus six months, one year overall survival of 42 percent versus 24 percent. This was super exciting because we have been waiting a long time for a new approval in squamous cell non–small lung cancer, so this was it.
One of the biomarkers of response that is emerging to these therapies is PD-L1 expression by immunohistochemistry, and in this particular trial it didn’t matter for patients if the tumor expressed PD-L1 or didn’t. They all received benefit. So now this is recommended by the FDA and the NCCN. This is looking at the non-squamous non–small cell lung cancer population of nivolumab versus docetaxel. You can see there’s a little bit of crisscross in the overall survival curves there, but in the end nivolumab wins out against docetaxel, the median overall survival of 12.2 versus 9.4 months.

And here actually they showed a very significant interaction with PD-L1 expression. Patients who had PD-L1-positive tumors benefited more from this kind of therapy. Maybe that’s why we’re seeing some of those crisscross and those curves. There are clearly some patients with non-squamous non–small cell lung cancer who don’t benefit from these therapies. So that’s still being worked out. And nivolumab has a complementary diagnostic. That was the first time I had heard of that. You basically can send it on the tumor sample and it can assist you in your decision whether or not to use nivolumab but it’s not required.

Pembrolizumab is also a PD-L1 inhibitor. Instead of giving IV every two weeks like nivolumab, it’s given every three weeks. This had accelerated approval, and what you’re looking at is progression free survival stratified by the level of PD-L1 expression on the left and overall survival on the right. And you can see the patients who benefit most from this therapy are patients who have the most staining of PD-L1 in their tumors. So PS greater than 50 percent, that means that 50 percent of the tumor cells within the sample you have tested have
stained for PD-L1. So this test, this particular compound has been approved with a companion diagnostic meaning PD-L1 expression has to be present in order to give this drug.

This is just to tell you there are multiple other PD-1 and PD-L1 inhibitors in development. You can see atezolizumab down there has an FDA fast track so we may be seeing more of that. And so our patient starts on nivolumab, squamous cell, and given therapy every two weeks, develops worsening shortness of breath after six weeks, also mildly hypoxic. He doesn’t have fevers and physical exam reveals bibasilar crackles. What do you do next? I think that’s our last question. Oh, good. That’s a great answer. 93 percent CT low threshold to start high dose steroids. So this was the CT findings. It was pneumonitis. They did respond to high-dose steroids. Anything with -itis can occur with these drugs. I know you have a whole lecture tomorrow about immunotherapy and lung cancer so I won’t spend time on it since we’re over.

In summary, for immunotherapy, nivolumab is approved for the treatment of squamous and non-squamous non-small cell lung cancer second line. PD-L1 is a complementary diagnostic. Pembrolizumab is approved for the treatment of squamous and non-squamous lung cancer second line, only if the tumor is PD-L1 positive. Many other predictive biomarkers are being explored because there’s a lot of complexity with the PD-L1 immunohistochemistry biomarker. And like Dr. Harvey mentioned, this is just the tip of the iceberg. There’s going to be several other immune checkpoints that are going to be examined and probably
approved and brought to practice. So that's the end, and I think you have some post-test questions and then we'll open for questions.

SPEAKER  Okay. Do we have any questions for Dr. Padda and Dr. Harvey here?

DR. PADD A  So the question was regarding immunotherapy and pseudo progression. This was actually first described by our melanoma colleagues when they first started using CTLA-4 inhibitors, meaning that sometimes immunotherapies don't have the conventional responses that we see with chemotherapy or targeted therapy. Sometimes it takes much longer to have a response. Sometimes it appears that there may be progression before there is a response. So a lot of times if the patient is feeling well and it looks like they progressed on their scan with nivolumab, you can have that discussion with the patient, make sure they feel comfortable with it, and then repeat a CT in about six weeks to see if you confirm it or don't confirm it. I think originally at least in lung cancer we overestimated how much this occurs. I think it occurs probably less than we think it does, so probably less than 10 percent. But it's still something to be aware of because it's a new therapy in this disease that we have never had to deal with before. So great question.

SPEAKER  In an ALK-positive patient that presents with brain mets up front after that's been treated, would you go ahead and use afatinib in that patient?

DR. PADD A  For ALK rearranged lung cancer with brain metastases, the question is would you use crizotinib up front in that patient. So part of it depends
on the brain metastases, how symptomatic the patient is. So it depends on preference a little bit. Some investigators are physicians. They feel comfortable if the brain metastases is not in a critical location and the patient is asymptomatic, that you can try crizotinib. It doesn't have zero activity in the brain but you have to be very cautious because it's not fabulous. And some other practitioners will prefer to deal with the brain metastases first with stereotactic radiosurgery, something like that, and then use crizotinib. So some people are more comfortable starting crizotinib without treating the brain, but I prefer to treat the brain before crizotinib.

**DR. HARVEY** It's all going to be symptom-driven so you can actually resect brain mets as well, depending on neurosurgical approaches and their ability to do that and then control visceral disease. We're moving into lung cancer a little bit like breast cancer has been. You get great control of visceral disease and relapse in the brain and so hopefully our targeted therapies will get to that paradigm sooner rather than later.

**SPEAKER** Could you please explain again the mechanism of resistance to crizotinib?

**DR. PADD** There are many. I can't remember all the acronyms. There is a gatekeeper mutation for ALK like there is for EGFR. It's L1196M, but there are literally dozens of ALK resistance mutations.

**DR. HARVEY** Okay. Thank you.

**SPEAKER** Thank you both very much again for a wonderful presentation.