Lung Cancer Treatment Updates

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Oct 28th, 2016

Objectives

- Briefly review general treatment strategies for non-small cell lung cancer (NSCLC)
- Identify tyrosine kinase inhibitors (TKIs), anaplastic lymphoma kinase (ALK) inhibitors, and program cell death protein/ligand (PD-1/PD-L1) antibodies available for the treatment of NSCLC
- Evaluate the clinical benefits of targeted therapies in NSCLC patients

Targeted Therapies for NSCLC

<table>
<thead>
<tr>
<th>Year</th>
<th>Drugs</th>
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<tbody>
<tr>
<td>2003</td>
<td>Gefitinib</td>
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<tr>
<td>2004</td>
<td>Erlotinib</td>
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<td>2011</td>
<td>Crizotinib</td>
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<tr>
<td>2013</td>
<td>Afatinib</td>
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<td>2014</td>
<td>Ceritinib</td>
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<td>Ramucirumab</td>
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<td>2015</td>
<td>Nivolumab</td>
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<td></td>
<td>Pembrolizumab</td>
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<td>Osimertinib</td>
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<td>Necitumumab</td>
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<td></td>
<td>Alectinib</td>
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<td>2016</td>
<td>Atezolizumab</td>
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</tbody>
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Disclosure

- Many of these slides were created and presented previously by Erin Kelley, PharmD. She has approved presenting.
- Consultant for Lilly and Medical Exchange International (MEI)
- Speaker for Grifols

Lung Cancer – Fast Facts

- Leading cause of cancer death in US
  - Est. 224,390 new cases, 158,080 deaths in 2016
  - 17.4% overall 5 year survival
  - NSCLC accounts for ~85% of lung cancer cases
  - Further divided into non-squamous and squamous

Risk Factors

- Smoking tobacco
  - 85-90% of cases caused by cigarette smoking
  - Increased risk with increased pack-year history
  - Secondhand smoke also increases risk
  - Carcinogen exposure – asbestos, arsenic
  - Family history

Tumor, nodes, metastases (TNM) system
- 16% confined to primary site at diagnosis
- 57% diagnosed after metastasis

Staging

Predictive and Prognostic Biomarkers

Predictive Biomarkers
- Indicative of therapeutic efficacy – predicts response to certain agents
  - Examples: ALK gene rearrangements, EGFR mutations

Prognostic Biomarkers
- Indicative of patient survival, independent of treatment received
  - Example: KRAS oncogene, predicts poor survival

NSCLC Treatment – Early Stage

- Surgery = best chance of cure for stage 1-2
- Radiation if ineligible for or refusing surgery
- Adjuvant (post-operative) chemotherapy
  - Improves survival in stage 2 disease
  - Does not appear to improve survival in stage 1
  - May be considered for high-risk, stage 1B patients

NSCLC Treatment – Stage 3

- Ongoing debate re: which to use and in what order
  - Chemoradiation preferred to radiation alone for unresectable disease
    - Concurrent chemoradiation preferred to sequential chemoradiation
  - All three treatment modalities utilized

NSCLC – Stage 4

- Systemic therapy recommended
  - If epidermal growth factor receptor (EGFR) mutation positive, EGFR TKI
  - If anaplastic lymphoma kinase (ALK) rearrangement positive, ALK TKI
  - If ROS1 positive crizotinib
  - If PDL-1 positive pembrolizumab

NSCLC - Stage 4

- No sensitizing mutations and performance status (PS) 0-2 → chemo
  - PS: measure of general well being
    - 0 is best, 5 is deceased
  - Platinum doublets common for PS 0-1
  - May use single agent for PS ≥2
  - Brain metastases are common – may be treated with radiation or surgery

Common Abbreviations

- OS: overall survival
- PFS: progression-free survival
- CR: complete response
- PR: partial response
- ORR: objective response rate

Targeted Therapies (Oral)

- Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs)
  - Gefitinib
  - Erlotinib
  - Afatinib
  - Osimertinib
- Anaplastic lymphoma kinase (ALK) inhibitors
  - Crizotinib
  - Ceritinib
  - Alectinib

EGFR Mutations

- Exon 18, 19, and 21 mutations associated with response to EGFR TKIs
  - These mutations are examples of predictive biomarkers
  - Sensitizing mutations occur in up to 10% of Caucasian and 50% of Asian patients
- More common in:
  - Never-smokers
  - Non-squamous histology
  - Female patients

EGFR TKIs: Erlotinib, Gefitinib, Afatinib

- MOA
  - Compete with ATP for binding to intracellular domain of EGFR
  - Inhibit phosphorylation of EGFR and downstream signaling
- Overall effects: reduced cancer cell proliferation, metastasis, and angiogenesis

EGFR TKIs: Dosing

- Erlotinib
  - 150 mg daily
- Gefitinib
  - 250 mg daily
- Afatinib
  - 40 mg daily

EGFR TKIs: Place in Therapy

- Erlotinib and gefitinib: recommended as first-line therapy for advanced, recurrent, or metastatic non-squamous NSCLC for patients with known sensitizing mutations
- Afatinib recommended first-line for metastatic disease
- Can be given regardless of PS
**Why are TKIs first line?**

- When compared to traditional chemotherapy:
  - Improved response rates and PFS
  - Fewer severe adverse effects

**IPASS trial**

- Gefitinib vs. Paclitaxel/Carbo
  - 12-mo PFS:
    - 24.9% w/ gefitinib
    - 6.7% w/ carbo/paclitaxel
  - Grade 3-4 adverse events:
    - 28.7% w/ gefitinib
    - 62% w/ standard chemotherapy

**EURTAC trial**

- Erlotinib vs. Platinum/Docetaxel or Gemcitabine
  - PFS:
    - 9.4 mo w/ erlotinib
    - 5.2 mo w/ standard chemotherapy
  - Grade 3-4 adverse events:
    - 45% w/ erlotinib
    - 67% w/ standard chemotherapy

**EGFR TKIs: Adverse Effects**

- Most common: diarrhea and rash
  - Often dose limiting
  - May also cause nausea, anorexia
- Diarrhea occurs in ~60% of patients
  - Manage with loperamide
  - Hold for ≥7 loose stools per day
- Drug/food interactions:
  - CYP450 interactions (3A4 and others)
  - Take on empty stomach
  - Avoid drugs that raise GI pH (PPIs, H2RAs)

**Acneiform rash**

- Occurs in up to 90% of patients
  - Common on face, shoulders, back, chest
- May lead to erythema, edema, sensory disturbances

**Treatment:**

- Topical corticosteroids and/or antibiotics
- Systemic antibiotics
  - Minocycline
  - Doxycycline
- Avoid acne products

**Progression on EGFR TKIs**

- Most patients eventually develop EGFR TKI resistance and disease progression

<table>
<thead>
<tr>
<th>Options after progression on an EGFR TKI:</th>
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<tbody>
<tr>
<td>Asymptomatic</td>
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<tr>
<td>Symptomatic Brain mets</td>
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<tr>
<td>Symptomatic Single systemic met</td>
</tr>
<tr>
<td>Symptomatic Multiple systemic mets</td>
</tr>
<tr>
<td>Treatment</td>
</tr>
<tr>
<td>Osimertinib or continue EGFR TKI</td>
</tr>
<tr>
<td>Consider local therapy and continue EGFR TKI</td>
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<tr>
<td>Osimertinib or Local therapy + continue EGFR TKI</td>
</tr>
<tr>
<td>Osimertinib or Chemotherapy</td>
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</tbody>
</table>

**EGFR TKI Resistance**

- Resistance often occurs between 9-13 months
- Multiple proposed mechanisms
  - Activation of alternate pathways
  - Development of secondary mutations
    - T790M is most common resistance mechanism
    - T790M is found in 60% of patients with EGFR TKI resistance
- EGFR mutations → constitutive activation of EGFR signaling

**Osimertinib**

- Approved Nov 2015 for metastatic, T790M mutation positive NSCLC
- Must confirm mutation status before starting
- Dosing:
  - 80 mg daily
### Osimertinib - MOA
- The T790M mutation changes the conformation of the EGFR receptor
- Osimertinib has the ability to bind to mutant forms of EGFR


### Clinical Trial Data - Osimertinib
- **AURA extension and AURA2: Open-label, single arm design in patients with T790M+ metastatic NSCLC**
- **All patients previously treated with EGFR TKI(s)**

**AURA Extension Trial**
- 57% objective response rate
- 113/115 responders had ongoing response at data cutoff

**AURA-2 Trial**
- 61% objective response rate
- 120/126 responders had ongoing response at data cutoff

Center for Drug Evaluation and Research: medical and statistical reviews. Application 208065.

### Targeted Therapies
- **Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs)**
  - Gefitinib
  - Erlotinib
  - Afatinib
  - Osimertinib
- **Anaplastic lymphoma kinase (ALK) inhibitors**
  - Crizotinib
  - Ceritinib
  - Alectinib

### Anaplastic Lymphoma Kinase (ALK) Rearrangements
- ALK rearrangements occur in 2-7% of patients with NSCLC
- These are also predictive biomarkers
- ALK is a transmembrane tyrosine kinase
- ALK signaling contributes to cell survival and proliferation
- Certain chromosomal rearrangements lead to activation of ALK


### ALK Rearrangements
- Like sensitizing EGFR mutations, ALK rearrangements are more likely in non-smokers and adenocarcinoma histology
- More likely in men than EGFR mutations
- Patients with ALK rearrangements don't respond to EGFR TKIs
- ALK inhibitors are recommended for patients with ALK rearrangements


### ALK inhibitors: Crizotinib, Ceritinib, Alectinib
- **MOA**
  - Crizotinib, ceritinib, and alectinib inhibit ALK signaling
  - End effect: decreased cell survival and proliferation

**ALK Inhibitors: Dosing**

- Crizotinib
  - 250 mg BID
- Ceritinib
  - 750 mg daily
- Alectinib
  - 600 mg BID

**ALK Inhibitors: Place in Therapy**

- Crizotinib - recommended first-line for advanced, metastatic, or recurrent ALK+ NSCLC
  - Also recommended for subsequent therapy in patients who progressed on chemotherapy

<table>
<thead>
<tr>
<th>Crizotinib vs chemotherapy in ALK+ lung cancer</th>
<th>Median PFS</th>
<th>ORR</th>
<th>1Y Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crizotinib</td>
<td>10.9 mo</td>
<td>74%</td>
<td>84%</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>7 mo</td>
<td>45%</td>
<td>79%</td>
</tr>
</tbody>
</table>

- Crizotinib also associated with improved QOL compared to chemotherapy

**Ceritinib & Alectinib: Place in Therapy**

- Ceritinib and alectinib are recommended for patients who progress on or are intolerant to crizotinib
  - 56% of patients who had previously received crizotinib responded to ceritinib
    - Median PFS was 7 mo
  - Response rates of 48% and 50% to alectinib in patients who had already received crizotinib

**Progression on ALK Inhibitors**

<table>
<thead>
<tr>
<th>Options after progression on an ALK inhibitor (crizotinib):</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
</tr>
<tr>
<td>Continue crizotinib or switch to ceritinib or alectinib</td>
</tr>
<tr>
<td>Symptomatic Brain mets</td>
</tr>
<tr>
<td>Consider local therapy and continue ALK inhibitor or switch to ceritinib or alectinib</td>
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<td>Ceritinib or alectinib</td>
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</table>

**Brain Metastases in ALK+ NSCLC**

- ~7.4% of NSCLC patients have brain metastases at diagnosis
- 20-30% will develop brain mets at some point

- Treatment:
  - Possible resection
  - Whole-brain radiation therapy
  - Chemotherapy?

**ALK Inhibitors for CNS Disease**

- Crizotinib: little data available
- Ceritinib:
  - Responses seen in central nervous system
- Alectinib:
  - Disease control rate of 83% in 84 patients with brain mets
    - 27% achieved CNS CR
  - Median CNS duration of response: 10.3 mo
**ALK Inhibitors: Adverse Effects**

- Visual disturbances
  - Visual impairment, blurry vision, photophobia
- Elevated transaminases
- Fatigue
- Edema
- GI effects
  - Nausea, constipation

**Targeted Therapies**

- Program cell death protein/ligand (PD-1/PD-L1) antibodies
  - Pembrolizumab
  - Nivolumab
  - Atezolizumab

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**PD-1 and PDL-1 Expression**

- Anti-PD-L1 IHC may be a biomarker used to select NSCLC pt more likely to respond
  - Concerns regarding variety of therapeutics, with a different Anti-PD-L1 IHC assay
  - Definition of + test results varies on biomarker assay used

**PD-1/PD-L1 MOA**

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**Indication in Lung Cancer**

- **Pembrolizumab**
  - Metastatic NSCLC and PD-L1 expression (Tumor Proportion Score [TPS]) greater than or equal to 1% as determined by an FDA-approved test with progression after platinum, EGFR+ or ALK+ therapy
  - **Oct 25, 2016** metastatic NSCLC whose tumors have high PD-L1 expression (Tumor Proportion Score [TPS]) greater than or equal to 50% as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, and no prior systemic chemotherapy treatment for metastatic NSCLC

- **Nivolumab**
  - Metastatic NSCLC with progression after platinum, EGFR+ or ALK+ therapy

- **Atezolizumab**
  - Metastatic NSCLC with progression after platinum, EGFR+ or ALK+ therapy

**Dosing**

- **Pembrolizumab**
  - 200mg IV every 3 weeks

- **Nivolumab**
  - 240mg IV every 2 weeks

- **Atezolizumab**
  - 1200mg IV every 3 weeks

- No premedications needed (DO NOT use steroids prior to dose)
**PD-1/PD-L1 Warnings**

<table>
<thead>
<tr>
<th>Immune-Related</th>
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<tbody>
<tr>
<td>Pneumonitis</td>
<td>Nephritis</td>
</tr>
<tr>
<td>Colitis</td>
<td>Skin reactions</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>Encephalitis</td>
</tr>
<tr>
<td>Endocrinopathies</td>
<td>Pancreatitis</td>
</tr>
</tbody>
</table>

- Infusion-Related reactions
- Embryofetal toxicity

**PD-1/PD-L1 Monitoring**

- CMP, TSH + free T4, signs and symptoms
- Dose adjustments
  - varies on adverse reaction type and severity
  - Most "itis", dose is held and corticosteroids administered. If Grade 3 or 4 permanently discontinue
    - Exception: hypo/hyperthyroidism treat with appropriate therapy

**Nivolumab Update**

**FDA Announces Nivolumab Dose Change for RCC, NSCLC, Metastatic Melanoma**

<table>
<thead>
<tr>
<th>Date</th>
<th>September 28, 2016</th>
<th>Renal Cell Carcinoma, Genitourinary Cancers, Kidney Cancer</th>
<th>By Leigh Lawrence</th>
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</thead>
</table>

The US Food and Drug Administration (FDA) announced a modification to the recommended dosage regimen for nivolumab (Opdivo) for renal cell carcinomas (RCC), metastatic melanomas, and non-small-cell lung cancer (NSCLC). Nivolumab was originally approved at a single dose of 3 mg/kg intravenously IV every 2 weeks. For all three diseases, the new dosage is 240 mg IV every 2 weeks until disease progression or intolerable toxicity.

**Pembrolizumab 1st line Therapy**

- Open-label, phase 3, randomized trial of 305 patients
  - Received pembrolizumab or platinum-based therapy
  - Median PFS of 10.3 months versus 6.0 months (P <0.001)
  - Overall survival at 6 months of 80.2% vs 72.4% (P=0.005)

**Atezolizumab New Indication**

**FDA Approves Atezolizumab for Lung Cancer**

- All patients had disease that progressed on prior chemotherapy or PD-L1 as measured on tumor cells (TC) and tumor-infiltrating immune cells (IC) by Roche’s investigational PD-L1 test. An IHC score of TC2 or IC3 was the inclusion criteria established by the trial design.

- Phase 3 study looked at atezolizumab versus docetaxel in patients with NSCLC
- Results demonstrated that patients treated with atezolizumab lived 4.2 months longer on average compared to patients on docetaxel

**Summary**

<table>
<thead>
<tr>
<th>Drugs</th>
<th>EGFR TKIs</th>
<th>EGFR TKI (for T790M)</th>
<th>ALK inhibitors</th>
<th>PD-1/PD-L1</th>
</tr>
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<tr>
<td>Erlotinib</td>
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<td>Matuzavib</td>
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<td>Pembrolizumab</td>
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<table>
<thead>
<tr>
<th>Indication</th>
<th>Advanced, metastatic, or recurrent EGFR mutation + NSCLC</th>
<th>Metastatic T790M mutation + NSCLC</th>
<th>Advanced, metastatic, or recurrent ALK rearrangement + NSCLC</th>
<th>P: 1st line metastatic NSCLC ALL: metastatic NSCLC post platinum, EGFR or ALK</th>
</tr>
</thead>
</table>