Genomic Profiling of Lung Cancer
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GENOMIC PROFILING OF LUNG

Disclosures:
- Consultant Genentech Inc. 2012-2013
- No Current disclosures.

Treatment Selection in Advanced Lung Cancer

- The OLD Way
  - Empiric
  - Comparison of RR, PFS, and OS only in randomized, controlled trials
  - Best numbers = Standard of care

- The NEW Way
  - Rational
  - Emphasis on “targeted therapy”
  - Molecular targets
  - Histology guides therapeutic options

With Molecular Targeted Therapy…

- How do we know that a switch is there?
- How do we know that we hit the switch?
- How do we measure the clinical benefit?
- How do we know if it stops working?

Why Does genomic profiling matter?

- Predictive of treatment efficacy & drug toxicity
  - Pemetrexed: improved outcomes in non-squamous NSCLC
  - Bevacizumab: increased toxicity in patients with squamous histology
  - EGFR TKIs
  - EML4-Alk: Crizotinib
  - Informative about resistance mechanism

- Prognostic

Tumors are functionally heterogeneous…

Discovery of Sensitizing EGFR Mutations

- Adenocarcinoma
- Non-smokers
- Women
- Asian ethnicity

57 year old with adenocarcinoma and worsening shortness of breath over 24 hours

Clinical trial of first-line gefitinib for patients with EGFR mutations

MULTIFOCAL ADENOCARCINOMA WITH BAC FEATURES

COMPLETE REMISSION 1.5 MONTHS AFTER STARTING GEFTINIB

Evolution of Identification of Genomic Alterations in Lung Adenocarcinoma
**Targeted Therapy in NSCLC: Understanding and Overcoming Resistance**

**EML4-alk translocation**

- Translocation of genes on chromosome 2
- Clinical characteristics somewhat similar to **EGFR** mutation
  - 141 tumors screened
  - 19 EML4-alk mutants found (13%)
    - 18/19 were adenocarcinoma histology; 1 adenosquamous
    - 14/19 (74%) were never smokers. The remaining 5 were light smokers
    - 11/19 (58%) were male

**Mechanisms of Resistance to EGFR kinase inhibitors in EGFR mutant NSCLC**

**Tumor Responses to PF-02341066 for Evaluable NSCLC ALK Patients**

Two patients had clinical progression and discontinued without radiographic confirmation.
**Immunotherapy in NSCLC: Most Promise in Anti-PD1 Therapy**

- Clinical evaluation
- Mechanisms of relative tumor immunity and immunity

**Oncogene Mutations Current and Clinical Trial Agents**

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Mutation Prevalence</th>
<th>Targeted Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR</td>
<td>Asians (30-40%)</td>
<td>Erlotinib + OSI 906 (IGF1R)</td>
</tr>
<tr>
<td></td>
<td>Whites (10-20%)</td>
<td>Erlotinib + MM 121 (HER3)</td>
</tr>
<tr>
<td>KRAS</td>
<td>Asians (10%)</td>
<td>Trametinib + Erlotinib</td>
</tr>
<tr>
<td></td>
<td>Whites (30%)</td>
<td>Trametinib + Erlotinib</td>
</tr>
<tr>
<td>EML4-ALK</td>
<td>1-7% (no clear ethnicity diff)</td>
<td>Crizotinib</td>
</tr>
<tr>
<td>ROS1</td>
<td>1.7% (higher in Asians?)</td>
<td>Crizotinib</td>
</tr>
<tr>
<td>HER2</td>
<td>Higher in Asians?</td>
<td>Afatinib</td>
</tr>
<tr>
<td>MET Amp</td>
<td></td>
<td>GSK1120212</td>
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<tr>
<td>MEK1</td>
<td></td>
<td>GSK2118434</td>
</tr>
<tr>
<td>BRAF (V600E)</td>
<td></td>
<td>GSK1120212</td>
</tr>
<tr>
<td>BRAF (not V600E)</td>
<td></td>
<td>GSK1120212</td>
</tr>
<tr>
<td>PIK3CA</td>
<td></td>
<td>BKM120</td>
</tr>
</tbody>
</table>

**FDA-Approved Targeted Therapies**

- **EGFR**
  - Erlotinib
  - Afatinib
- **EML4-ALK**
  - Crizotinib

**Molecular Markers With Targeted Therapies in Clinical Trials**

- KRAS
- MET Amplification
- MEK1
- BRAF (V600E)
- BRAF (not V600E)
- HER2
- PIK3CA
- AKT1
- ROS1

**Overview of Testing Methods**

- Sanger sequencing
- PCR-based sequencing
- FISH
- IHC
- Snapshot
- NextGen Sequencing

**Types of Biopsy**

- Pulmonology: EBUS
- Radiology: CT-guided
- FNA vs Core biopsies
  - FNA, how many passes
  - Core, how many passes
    - Size gauge
    - FNA and Core
    - Adverse events
Benefits of the Cell Block

- Provide cellular detail:
  - intercellular bridges between squamous cells
  - architectural patterns in adenoc: lepidic, papillary, micropapillary
- Provide multiple slides in concentrated format for IHC
  - 87% of 44 cases of NSCLC-NOS had sufficient tissue for IHC
  - 85% of these histologic sampling was possible
- FFPE tissue for DNA mutation & FISH
  - risk of false positives with FFPE samples

Genomic Profiling of Non-Small Cell Lung Cancer (NSCLC) for Personalized Targeted Therapy Using CT-guided Transthoracic Needle Biopsy (TTNB) ASCO 2012

Ritu R. Gill, Stephanie Cardarella, Beow Y. Yeap, Neal I. Lindeman, Mohit Butaney, Michael S. Rabin, David M. Jackman, Passi A. Jänne, Bruce E. Johnson

- 78% of patients had sufficient tissue for genomic profiling.
- The number of samples obtained ranged from 1-5 (2 cm 18G)
- 40/52 (77%) patients with pre-procedure PET/CT had adequate tissue for genomic profiling compared with 37/47 (78%) without PET/CT.
- The smallest lesion successfully profiled was 1.2 cm.
- The least amount of tissue needed for successful molecular profiling was a 2 cm 18G core biopsy.
- Rates of pneumothorax were higher with 18G needles [26/34 (76%),] in smokers [24/34 (71%),] and in patients >60 years [16/34 (53%),] 86% of pneumothoraces were <10%; only 3% required chest tubes and 12% required hospital admission.

Genome-wide Approach to Characterize Lung Cancer

Re-biopsy After Progression Or With Treatment?

- Re-biopsy only on progression, especially for those with a known mutation since other agents might be available for treatment.
- Mixed response with trend towards overall progression.
- This is a re-biopsy and re-sequence, again cost?
- Many trials need target confirmation now, so re-biopsy is more likely for targeted therapies

Molecular Profiling and Therapeutic Decision Making for Advanced NSCLC General Guidelines for 2013

- Who to test: patients with NSCLC and adenocarcinoma component
- What to test for: EGFR mutation and ALK fusion (+ others?)
- When to test: at the time of diagnosis (not just when treatment decision needed)
- What specimen: core needle biopsy (or multi-pass FNA), cytology cell block, surgical biopsy (bone biopsy problematic)
- How to test: concurrently (not sequentially test-by-test)
- How long a turnaround time is acceptable?: 2 weeks or less
- When to re-test: after a targeted therapy intervention (to assess for tumor evolution in the molecular profile)

Adapted from: CAP/IASCL/AMP Guidelines

CAP/IASCL/AMP Guidelines

- Who to test: All patients with advanced adenocarcinoma or mixed NSCLC with an adenocarcinoma component, regardless of clinical characteristics
  - If an adenocarcinoma component cannot be excluded (e.g. limited specimen), may pursue EGFR and ALK testing but clinical criteria may be useful in selecting samples for testing
- What to test: Prioritize EGFR and ALK testing over other molecular predictive tests
CAP/IASCL/AMP Guidelines (cont’d)

- What specimen:
  - Primary tumors or metastatic lesions equally suitable
  - FFPE, fresh, frozen, or alcohol-fixation OK
    - Heavy metals interfere with PCR
    - Decal, unbuffered formalin degrade DNA
    - Avoid prolonged fixation (>48 hours)
    - If cytologic sample, cell block preferred
    - Use cytology in conjunction with small biopsies
      - Cytology or core biopsy alone rates of NSCLC NOS = 10-30% of cases
      - Used together, this diagnosis drops to <5% of cases
  - How rapidly: Results within 10 working days of receiving the specimen in the testing laboratory

Lindeman, JTO 2013; Travis, JTO 2011
Patient with right perihilar mass, right adrenal and bone metastases

Answer: Right adrenal nodule is most likely to yield adequate tumor material with least amount of complication.

Communication is Key for optimal genomic profiling

- Intradepartmental
  - Educating the technical staff on specimen handling
  - Educating colleagues who may not regularly engage with molecular diagnostics
- Interdepartmental
  - Clearly labeled requisitions
  - Standardized indication terminology
  - Active lines of email or phone communication

Early-Stage Lung Cancer Patients Have Poor Outcomes

- 35%-50% recurrence rates even in patients with no nodal or other metastatic involvement at time of surgery
- No proven benefit of adjuvant chemotherapy in stage IA patients
- One controversial study suggests adjuvant chemotherapy provides benefit in Stage IB patients >4cm
- Defined need for objective information to identify early-stage patients at greater or less risk of mortality

Role of genomic profiling in early stage lung cancer

- Inoperable early stage lung cancer, due to comorbidities, patient preference and advanced age can help personalize therapy.
- Prognostic information can be acquired and can guide management post surgery.

Conclusion

- The promise of molecular medicine demands close collaboration between multiple different specialties to advance the field of cancer prevention, diagnosis, and therapy.
- Genomic profiling of lung cancer is a rapidly evolving field, radiologists play a key role in diagnosis and management.
Thanks