New Developments in Lung Cancer Treatment

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Outline

• Biomarkers/Genomics  
  – EGFR  
  – ALK  
  – ROS  
  – Others  
• Immune Therapy  
  – Checkpoint Inhibitors – antibodies to PD1 and PDL1

Lung Cancer is Complicated

Somatic Mutation Frequencies


Cost per Genome

Author: Wetterstrand KA
Between 2009 and 2012, 14 centers enrolled 1000 patients to test for 10 oncogenic drivers:
- Lung adenocarcinomas, metastatic, ECOG 0-2
- Oncogenic driver found in 64% of testable samples
- KRAS, EGFR, ALK, ERBB2, BRAF, PIK3CA, METamp, NRAS, MEK, AKT

LCMC Results:
- 733 patients had all 10 assays completed
- 466 (64%) had identifiable driver alteration
- Results used to select targeted therapy in 275 of 1007 patients (28%)
  - Median survival of 3.5 years for those with genotype directed therapy
  - Median survival of 2.4 years for those with oncogenic driver but no genotype directed therapy

What strategy for testing?

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sequential, gene specific (KRAS, then EGFR, then ALK, then others)</td>
<td>Identify most common mutation first, most &quot;expeditious&quot; use of material</td>
</tr>
<tr>
<td>- Time delay, consumption of precious resources</td>
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<tr>
<td>Next Generation Sequencing (Ion Torrent, Illumina)</td>
<td>Comprehensive analysis of multiple genes</td>
</tr>
<tr>
<td>- Time delay (3-4 weeks for completion/validation of results)</td>
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<tr>
<td>Screening selected genes, then NGS (&quot;Combination&quot; strategy)</td>
<td>Quick evaluation of &quot;first line&quot; actionable mutations</td>
</tr>
<tr>
<td>- EGFR sizing assay – already CLIA certified</td>
<td></td>
</tr>
<tr>
<td>- ALK FISH (or IHC in some labs)</td>
<td>Two step process, 7 Concerns re billing for same result twice (for example EGFR by sizing and NGS)</td>
</tr>
</tbody>
</table>
Summary of mutations in the TK domain of EGFR in NSCLCs

EGFRi vs Chemo

- Seven + phase III first line studies
- In mutation positive patients (exon 19 deletion, L858R)
  - Superior response (~ 60-70% vs ~ 30%)
  - Superior PFS (~10-12 mos vs ~ 5-6 mos)
  - Similar OS
  - Improved QoL

Subsequent Treatment

<table>
<thead>
<tr>
<th>Study (n= mutation pts)</th>
<th>TKI/Chemo</th>
<th>2nd line after TKI</th>
<th>2nd line after chemo</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPASS* (n=261 EGFRmt)</td>
<td>Gefitinib / PC</td>
<td>39% to PC 10% other</td>
<td>40% EGFR TKI 14% other</td>
</tr>
<tr>
<td>NEJSG^ (Maemondo n=230)</td>
<td>Gefitinib / PC</td>
<td>66% PC 21% other</td>
<td>95% gefitinib</td>
</tr>
<tr>
<td>EURTAC # (n=174)</td>
<td>Erlotinib / Cis or Carbo + Gem or Docetaxel</td>
<td>37% cis/carbo 22% EGFR TKI</td>
<td>76% erlotinib</td>
</tr>
</tbody>
</table>

**Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer**

- Echinoderm microtubule-associated protein-like 4 (EML4) becomes fused with the anaplastic lymphoma kinase (ALK)
- Inversion within chromosome 2p
- First identified in 2007 from a resected lung adenocarcinoma specimen
- Clinical evaluation
  - Young
  - Never/light smokers
  - Male predominance
  - Adenocarcinoma histology

*Nature* 448, 561-566 (2 August 2007)

**Diagnostic Studies**

- A) FISH Breakapart
- B) H&E
- C) Sequencing
- D) IHC

**Updated Phase I Results**

- Additional follow up of 149 patients
  - 60.8% ORR (77% Asian, 55% non-Asian)
  - Median time to response 7.9 weeks
  - Median PFS 9.7 months
- 69 pts with disease progression
  - 39 continued crizotinib beyond progression (for > 2 weeks)
  - 10 brain, 5 lung, 3 liver


**Treatment Upon Progression**

- Mechanism of progression
  - Pharmacokinetic – Brain
  - Genetic resistance
- “Oligo”-progressive disease
  - Consider stereotactic radiation (brain or elsewhere)
- Diffuse metastatic progression
  - Chemotherapy
  - Clinical trials
Second Generation ALKi

LDK 378 Preliminary Results

- Potent activity seen at doses ≥ 400 mg/day
  - ORR 58% in 114 NSCLC pts
  - ORR 56% in Criz treated pts
  - Median PFS 7 months
- Significant activity seen in CNS
- Activity seen regardless of resistance mechanism
- Most frequent toxicities GI
  - Nausea, vomiting, diarrhea

ROS1 Translocations

- ROS1 receptor tyrosine kinase of insulin receptor family
  - Translocations described in GBM (with FIG gene)
  - Targeted by crizotinib (and others)

<table>
<thead>
<tr>
<th></th>
<th>All pts (n=1073)</th>
<th>ROS1 (+) (n=18)</th>
<th>ALK (+) (n=31)</th>
<th>ROS(-) (n=1055)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median)</td>
<td>62</td>
<td>49.8</td>
<td>51.6</td>
<td>82.3</td>
</tr>
<tr>
<td>Sex % (M/F)</td>
<td>49/51</td>
<td>39/61</td>
<td>55/45</td>
<td>49/51</td>
</tr>
<tr>
<td>Smoking % (Never-Eve)</td>
<td>28/8/57</td>
<td>84/11/6</td>
<td>45/10/45</td>
<td>27/66/7</td>
</tr>
<tr>
<td>Ethnicity %</td>
<td>4/8/8</td>
<td>28/72</td>
<td>6/58/35</td>
<td>4/8/8</td>
</tr>
<tr>
<td>Pathology %</td>
<td>65/19</td>
<td>100/0</td>
<td>52/3/45</td>
<td>64/19</td>
</tr>
</tbody>
</table>

ROS1 mutant

- In vitro sensitivity to crizotinib
- 50 patients enrolled on standard crizotinib dosing (on original phase I protocol expansion cohort)
- ORR 72% (3 CR, 33 PR)
- Duration of response 17.6 mos
- PFS 19.2 mos
### Other Molecular Markers

- EGFR – atypical mutations, Exon 20, others
- MET amplification or mutations – ASCO 2014
- BRAF - < 5% of NSCLC patients, ~ 50% of the mutations seen are V600E
- ERBB2 mutations
- FGFR mutations and amplifications
- Other tumors – Squamous?
  - SWOG 1400 “Master Protocol”

### Conclusions

- Molecular Directed Medicine is the current standard of care for patients with “Driver Mutations”
- Clinical Trials needed to confirm the preliminary activity seen in MET amp, BRAF, ERBB2 mutant cancers and others
- Expansion of mutation testing to non-adenocarcinoma lung cancers needed

### Immune Therapy

- Attempts for 30+ years
  - Interferons
  - IL-2
  - Vaccines
- Activity seen in Renal Cell Cancer and Melanoma with Interferons and IL-2
- Sipuleucel-T recently approved for prostate cancer
- Disappointment for NSCLC

### Checkpoint Inhibitors

- Recent improved understanding of mechanisms of immune suppression in cancer
  - Immune tolerance induced by tumor expression of PDL1 which binds to PD1 on immune (T-cells)
  - When PD1 binds to PDL1, T cells become anergic, blockade of this interaction (with antibodies to PD1 or PDL1) may activate the T-cell
**Checkpoint Inhibitors**

![Diagram showing the interaction between Tumor Cell, T cell, and Dendritic Cell with PD1, PD-L1, CTLA4, and PDL1 inhibitors.](image)

**NEJM 2012 Results**

- Phase I studies – both humanized antibodies against PD1 or PDL1
  - 207 patients (PDL1 antibody)
    - NSCLC, Melanoma, Colorectal, Renal Cell, Ovarian, Pancreatic, Gastric, Breast cancer
  - 296 patients (PD1 antibody)
    - Melanoma, NSCLC, Prostate, Renal, Colorectal Cancer
- Toxicity
  - Well tolerated
  - Immune related toxicity including Pneumonitis (in PD1 antibody)

**Responses in Phase I**

- PD1 Antibody (Nivolumab)
  - NSCLC – 18% (14 of 76 response evaluable pts)
  - Melanoma – 28% (26 of 94)
  - Renal Cell Cancer – 27% (9 of 33)
- Durability of responses
  - 20 of 31 responses lasted a year or more (in those patients with a year or more of follow up)
**Phase II Study of Nivolumab**

- Phase II study – 3rd line setting (after two prior chemotherapy regimens)
  - 3 mg/kg every two weeks
  - 117 treated patients
    - Median 6 doses
    - OS 6.1 months
    - Time to Response 3 months
  - Toxicity mild – fatigue, diarrhea, pneumonitis
- Response Rate by PDL1 expression
  - 20% in PDL1 positive tumors
  - 9.8% in PDL1 negative tumors

**Immune Therapy Conclusions**

- Checkpoint blockade is promising
- Predictive biomarkers unclear
  - PDL1 expression not great at predicting response
- Toxicity is modest and different
  - Autoimmune side effects typical with this class of agents – manageable with steroids
- Duration of response may be most interesting aspect

**Targeted Therapy in NSCLC**

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**Case 1**

- 52 yo man, never smoker
- Presented to PCP with 6 months of non-resolving cough
- Medical History – HTN
- Imaging studies were ordered
### Baseline scans – spring 2012

Innumerable small lung nodules throughout both lungs at baseline.

### Pathology, Staging, and Treatment

- Lung, left lower lobe, biopsy:
  - Primary lung adenocarcinoma
  - Positive for EGFR Exon 19 short-in-frame deletion mutation
- Staging demonstrated bone metastases, brain metastases (7 – all < 1 cm)
- Started Erlotinib 150 mg July 2012
- Brain metastases improved with erlotinib – no brain radiation to date.

### Imaging January 2015

Patient on erlotinib alone over 2 years with near complete response.

### Case 2

- 56 yo woman, never smoker
- Presented with 12/2012, w/ symptoms of SOB, non-productive cough and chest tightness. She was treated with antibiotics, but the symptoms did not improve.
- In 1/2013 she noted an enlarged L neck lymph node (supraclavicular).
Case 2

• 2/2013: Neck CT was performed which revealed a superior mediastinal mass w/ necrosis, as well as a R lung apex lung mass. Bilateral supraclavicular lymph nodes were also seen.
• 2/2013: CT c/a/p: numerous pulmonary nodules throughout both lungs; bulky LAD in the R paratracheal region w/ enlarged LNs in the prevascular space, azygoesophageal recess and lower neck.

Baseline imaging – spring 2013

Large mediastinal mass as well as multiple bilateral lung nodules at baseline

Pathology, Staging, and Treatment

• Mediastinal lymph node biopsy: Metastatic adenocarcinoma.
• FISH testing for ALK performed outside – positive for rearrangement
• Started Crizotinib 250 mg BID 3/2013
  – Mild transaminitis in first 4 weeks, resolved without dose adjustment
  – Enrolled in clinical trial after response 8 weeks into therapy

Imaging January 2015

Mediastinal mass has resolved. Minimal residual lung nodules. Patient did develop new brain metastases – treated with radiation. She has been started on second generation ALK inhibitor – ceritinib – due to progressive brain disease not amenable to further radiation.
Case 3

- 51 yo man – 30+ pack year tobacco user - with recurrent metastatic NSCLC
- Initial surgical resection for 2/2012 - he was found to have adenocarcinoma 3.5 cm - T2N0. No adjuvant chemotherapy was given. KRAS mutation positive.
- January 2013 – Mediastinal recurrence

Case 3

- Treatment History:
  - Spring 2013: Concurrent chemoradiation with carboplatin-paclitaxel
  - Fall 2013: New contralateral lung nodules
  - Fall 2013: Carboplatin-gemcitabine – stopped due to progressive disease
  - Spring 2014: Pemetrexed – stopped due to progression
- Evaluated at OSU for clinical trial – PDL1 positive

Baseline Imaging April 2014

Progression after chemoradiation and 2 lines of chemotherapy – multiple growing lung nodules

Imaging August 2015

Partial response to treatment after starting anti-PDL1 therapy on clinical trial. Remains on trial as of January 2015 with sustained response > 8 months. No drug-related toxicity observed to date
Conclusions

• Targeted therapy can produce durable and clinically meaningful responses which translate into improved quality of life and survival for our patients.