Rediscovering non-small cell lung cancer

-Heterogeneity and more heterogeneity-

D. Ross Camidge, MD PhD
Director, Thoracic Oncology Clinical Program
University of Colorado

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Disclosures (DRC)

- Employment or leadership Position: None
- **Advisory Role: Ad Hoc Advisory Boards/Consultations (most recent contact last 3 years):**
  - 2012: Astellas, Boehringer Ingelheim, Chugai
  - 2011: Ariad, Array Biopharma, Astellas, AstraZeneca, Aveo, Boehringer Ingelheim, Chugai, Clovis, Novartis, Synta
  - 2010: Millenium, Pfizer
- Stock Ownership: None
- **Honoraria: Seminar/Talks to Industry (most recent contact last 3 years).**
  - 2012: Boehringer Ingelheim
  - 2011: Ariad, Array Biopharma, Pfizer
- Speakers Bureau/Talks for Industry: None
- **Research Funding:**
  - 2010: Eli-Lilly (Translational)
- Expert Testimony: None
- Other Remuneration: None
Agenda

• The practical implications of molecular heterogeneity in NSCLC

• Heterogeneity in targeted treatment failure
LCMC 516 analyzed cases: Incidence of Oncogenic Drivers in Adenocarcinoma

Mutation found in 54% (280/516) of Tumors: 97% mutually exclusive

Kris et al, ASCO 2011
Clinical tumor responses in $ROS1^+\text{ NSCLC}$ treated with crizotinib

pre-crizotinib  post-crizotinib (12 weeks)

pre-crizotinib  post-crizotinib (56 days)

Bergethon et al. JCO 2012
Davies et al, AACR 2012
KIF5B-RET fusion detected by FISH

Courtesy of Marileila Varella Garcia
University of Colorado CMOCO Lab
So now we have all the answers?

The practical implications of molecular heterogeneity in NSCLC #1

How do we make testing and treating viable...
Every cancer is an orphan?

Orphan disease status:
- US = Prevalence <200,000 cases
- EU = Prevalence <5/10,000 population

20% lung adenocarcinomas < 20,000 cases/year
1% lung adenocarcinomas < 1000 cases/year
When low biomarker frequency, cost of screening test dominates over cost of drug in cost effectiveness analysis. Lower screening test cost (red line ($500/person) vs blue line ($1500/person screened)) shifts this inflexion point further to the left.

**Take home message:**

Since you can’t change the benefit from the drug in the marker positive population, to be more cost effective either:

1. Reduce cost of drug
2. Reduce price of screening test per Person
3. Screen more enriched populations
Less than or equal to 10 pack years

Adenocarcinoma

EGFR exon 19/21 WT

KRAS WT

≈45% hit rate
### The ‘savings’ and ‘cost’ of enrichment policies

<table>
<thead>
<tr>
<th>Screening Criteria</th>
<th>Predicted proportion of ALK positives</th>
<th>Percentage of total initial population screened</th>
<th>Predicted number of ALK+ cases found per 1000 Initial NSCLC cases</th>
<th>Predicted number of ALK+ cases missed per 1000 Initial NSCLC cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced NSCLC</td>
<td>1.6%</td>
<td>100%</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Advanced stage adenocarcinoma</td>
<td>3.7%</td>
<td>39%</td>
<td>14</td>
<td>2 (13%)</td>
</tr>
<tr>
<td>Advanced stage adenocarcinoma /Never smokers</td>
<td>13.7%</td>
<td>5.80%</td>
<td>8</td>
<td>8 (50%)</td>
</tr>
<tr>
<td>Advanced stage adenocarcinoma /Never smokers /EGFR and KRAS wildtype</td>
<td>35.9%</td>
<td>2.00%</td>
<td>7</td>
<td>9 (56%)</td>
</tr>
</tbody>
</table>

Atherly and Camidge, BJC 2012
When low biomarker frequency, cost of screening test dominates over cost of drug in cost effectiveness analysis. Lower screening test cost (red line ($500/person) vs blue line ($1500/person screened)) shifts this inflexion point further to the left.

**Take home message:**

Since you can’t change the benefit from the drug in the marker positive population, to be more cost effective either:

1. Reduce cost of drug
2. Reduce price of screening test per person
3. Screen more enriched populations
4. Multiplex
Dual ALK/ROS1 testing

normal

Single 3'

3'ALK/5'ALK

Single 3'

3'ROS1/5'ROS1

Courtesy of Marileila Varella Garcia
University of Colorado CMOCO Lab
A view of the future…

• **Next generation sequencing**
  – Sequencing hundreds of regions simultaneously will allow:
    • *Same assay for multiple cancers*
    • *Mutations, rearrangements, copy number*
Multiplex challenges

• Regulatory approval of adding one additional assay to multiplex platform as companion diagnostic (‘revalidation of every component?’)

• Non-actionable, non-standard or non-existent sequence abnormalities as predictive biomarkers – e.g. tumor suppressors, epigenomics, mRNA expression, tumor protein or host immune factors
The practical implications of molecular heterogeneity in NSCLC #2

Conducting clinical research in the era of molecular diversity...
Afatinib/Cetuximab

Maximum percentage decrease from baseline (%)

T790M+  T790M-  No mutation  Uninformative
US Sites participating in afatinib-cetuximab trial
Origin of lung cancer patients (green circles) who participated in afatinib-cetuximab trial at the University of Colorado (red circle) (68% from Colorado, 32% from 6 other US States, (Data to Jan 2012, ongoing).
Origin of lung cancer patients (green circles) who participated in crizotinib clinical trials at the University of Colorado (red circle) (62% from Colorado, 36% from other US States, 2% International (Johannesburg, South Africa; not shown).

West and Camidge, JTO 2012
Have mutation, will travel

- Patients need reliable, up-to-date, useful information
  - e.g. Improve site contact details (direct numbers/maps) on clinicaltrials.gov
  - Use on-line communities (e.g. cancergrace.org)
Have mutation, will travel

- MDs/Pharma/Grants could improve clinical trials/trials support to better address:
  - Remote tumor testing
  - Travel and accommodation re-imbursement
  - Use of local laboratories and phone checks on ‘visit’ days without trial treatment
  - Geographic spread of trial sites (‘trial hubs’)
Heterogeneity in targeted treatment failure #1

Seeing the CNS as a separate place...
### ALK progression on crizotinib within CNS

<table>
<thead>
<tr>
<th>Study</th>
<th>Brain metastases at any point in course of disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shaw et al, TLO 2011*</td>
<td>52% ALK+ crizotinib naive</td>
</tr>
<tr>
<td></td>
<td>47% ALK+ crizotinib treated</td>
</tr>
</tbody>
</table>

### Brain metastases on treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weickhardt et al, Abstract 7526 ASCO 2012*</td>
<td>46% as site of first progression, (85% of whom had CNS as sole site of first progression)</td>
</tr>
<tr>
<td>Costa et al, JCO 2011</td>
<td>At CNS progression: CSF:plasma ratio = 0.0026 (i.e. &lt;0.3% gets into brain)</td>
</tr>
</tbody>
</table>

*Retrospective series, CNS imaging/timing not mandated
EGFR MT disease: CNS progression

<table>
<thead>
<tr>
<th>Patient</th>
<th>Baseline EGFR mutation outside CNS</th>
<th>Sensitizing mutation in CNS at time of acquired resistance</th>
<th>Acquired resistance mutation outside CNS</th>
<th>Acquired resistance mutation in CNS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Exon 19 deletion</td>
<td>Exon 19 deletion</td>
<td>Undetermined</td>
<td>No exon 20 T790M, no MET amplification</td>
</tr>
<tr>
<td>2</td>
<td>Exon 19 insertion</td>
<td>Undetermined</td>
<td>Undetermined</td>
<td>Undetermined</td>
</tr>
<tr>
<td>3</td>
<td>Exon 21 L858R</td>
<td>Exon 21 L858R</td>
<td>Undetermined</td>
<td>No exon 20 T790M</td>
</tr>
<tr>
<td>4</td>
<td>Exon 21 L858R</td>
<td>Exon 21 L858R</td>
<td>Exon 20 T790M</td>
<td>No exon 20 T790M</td>
</tr>
<tr>
<td>5</td>
<td>Exon 19 deletion</td>
<td>Undetermined</td>
<td>Undetermined</td>
<td>No exon 20 T790M</td>
</tr>
<tr>
<td>6</td>
<td>Exon 21 L858R</td>
<td>Exon 21 L858R</td>
<td>Undetermined</td>
<td>No exon 20 T790M</td>
</tr>
<tr>
<td>7</td>
<td>Exon 18 G719S, L861Q</td>
<td>Undetermined</td>
<td>Undetermined</td>
<td>No exon 20 T790M</td>
</tr>
<tr>
<td>8</td>
<td>Exon 19 deletion</td>
<td>Undetermined</td>
<td>Exon 20 T790M, no MET amplification</td>
<td>Undetermined</td>
</tr>
<tr>
<td>9</td>
<td>Exon 21 L858R</td>
<td>Undetermined</td>
<td>Exon 20 T790M, no MET amplification</td>
<td>Undetermined</td>
</tr>
</tbody>
</table>
Treatment of isolated CNS progression and continuation of relevant TKI in oncogene addicted NSCLC is associated with >7 months prolonged disease control.

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>PFS1 (95% CI)</th>
<th>PFS2 (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>10.9 months 7.3–18.3</td>
<td>7.1 months 1.7–11.3</td>
</tr>
</tbody>
</table>
RANO - Addressing brain mets in trials: opinion piece under consideration

- Allow asymptomatic brain mets in trials
- Mandate baseline and follow-up CNS imaging
- Consider allowing systemic Rx to continue if CNS progression can be addressed via add-on local therapy
- Alter trial designs to log CNS progression separately from extra-CNS progression
Antitumor activity of LDK378 in brain metastases at the MTD, 750 mg

Baseline

After 6 weeks on LDK378

Mehra et al, ASCO 2012
Heterogeneity in targeted treatment failure #2

Biological changes selected out by treatment...
EGFR Mutant: acquired resistance mechanisms

Rebiopsy (and reanalysis) of systemic progression

Sequist et al, Science Translational Medicine 2011
Determination of biological resistance mechanisms: analysis of growing lesions following crizotinib failure

Pre-crizotinib

Response

Progression

FFPE tissue

*selected cases

Frozen tissue* → RT-PCR for variant

Fresh tissue* → cell line derivation

ALK Kinase Domain Sequencing

ALK FISH for CNG

EGFR, KRAS and other oncogenes

Doebele et al, ASCO 2012
Systemic resistance to ALK inhibitors

- ALK Mutation: 31%
- Unknown (ALK +): 13%
- Unknown (ALK -): 6%
- ALK CNG: 13%
- ALK Mutation + CNG: 6%
- EGFR Mutation: 12%
- KRAS Mutation: 19%

Doebele et al, ASCO 2012
## Frequency of co-incident ALK fusions and EGFR mutations: baseline samples

<table>
<thead>
<tr>
<th>Publication</th>
<th>Methods</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Koivunen et al, CCR 2008</td>
<td>RT-PCR for EML4-ALK, DS for EGFR</td>
<td>1 of 8 (13%) ALK+ specimens was EGFR mt (exon 19 del)</td>
</tr>
<tr>
<td>Zhang et al, Molecular Cancer 2010</td>
<td>RACE-coupled PCR for EML4-ALK, DS for EGFR</td>
<td>1 of 12 (8%) ALK+ specimens was EGFR mt (exon 19 del)</td>
</tr>
<tr>
<td>Camidge et al, CCR 2010</td>
<td>Break-apart FISH for ALK, DS for EGFR</td>
<td>1 of 13 (8%) ALK+ specimens was EGFR mt (exon 20 S768I)</td>
</tr>
<tr>
<td>Kris et al, ASCO 2011</td>
<td>Break-apart FISH for ALK, SNaPshot or sequenom for EGFR</td>
<td>2 of 38 (5%) ALK+ specimens were EGFR mt (mts not described)</td>
</tr>
<tr>
<td>Sasaki et al, CCR 2011</td>
<td>Break-apart FISH for ALK, DS for EGFR</td>
<td>3 of 50 (6%) ALK+ specimens were EGFR mt (L858R, exon 19 del, exon 20 ins)</td>
</tr>
<tr>
<td>Rimkunas et al., CCR 2012</td>
<td>IHC and FISH for ALK IHC, FISH, RT-PCR for ROS1 IHC for EGFR L858R del19</td>
<td>2/22 (9%) ALK+ (L858R)</td>
</tr>
<tr>
<td>Shaw et al, JCO 2009</td>
<td>Break-apart FISH for ALK, DS for EGFR</td>
<td>0 of 19 ALK+ specimens were EGFR mt</td>
</tr>
</tbody>
</table>

[Shaw et al, JCO 2009]
Choices for acquired resistance approaches…. Doebele et al, ASCO 2012
Drugs for Acquired Resistance (AR): Rapid Deployment Forces vs. Armies of Occupation?

- Adding in/replacing with each new drug at time of AR (e.g. biopsy informed)?
- Or combine up front?
The mechanism of resistance isn’t a single choice for most cancers…

<table>
<thead>
<tr>
<th></th>
<th>Co-incident mechanisms of AR in ALK+ NSCLC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choi et al, 2010</td>
<td>L1196M and C1156Y co-exist as independent</td>
</tr>
<tr>
<td></td>
<td>clones in same patient</td>
</tr>
<tr>
<td>Sasaki et al, 2011</td>
<td>L1152R and increased (?ligand driven) EGFR</td>
</tr>
<tr>
<td></td>
<td>signaling (AR derived cell line) from</td>
</tr>
<tr>
<td></td>
<td>same patient</td>
</tr>
<tr>
<td>Katayama et al, 2012</td>
<td>G1202R and focal amplification of KIT in</td>
</tr>
<tr>
<td></td>
<td>same patient</td>
</tr>
<tr>
<td>Katayama et al, 2012</td>
<td>1151Tins and increased pEGFR compared to</td>
</tr>
<tr>
<td></td>
<td>baseline in same patient</td>
</tr>
</tbody>
</table>
Hypothetically, even if new Rx active against defined resistance mechanism shorter systemic PFS likely in AR setting

Start crizotinib

Dominant crizotinib sensitive population suppressed

Start new drug X with activity against one mechanism of resistance

~10 month PFS to first event (inc CNS only failures) as resistant mechanisms start from low baseline

Shorter PFS in AR setting as 2nd resistant mechanism (resistant to crizotinib AND drug X) has levels already elevated at start of new drug

Clinically detectable level
Giving drug with activity against BOTH baseline (A) and AR (B) forms upfront: PFS A+B or greater than the sum?

Resistant cells continually arise, if total burden of dividing cells is lower for longer may take more time for next resistant form to arise?
Drugs for Acquired Resistance (AR): Rapid Deployment Forces vs. Armies of Occupation?

- Adding in/replacing with each new drug at time of AR (e.g. biopsy informed)?
- Or combine up front?

- **Tolerability of new drug(s)?**
IC50s for EGFR WT, Del 19 and T790M driven cell lines

<table>
<thead>
<tr>
<th>Cell Lines</th>
<th>EGFR Genotype</th>
<th>erlotinib</th>
<th>BIBW2992</th>
</tr>
</thead>
<tbody>
<tr>
<td>A431</td>
<td>WT</td>
<td>297±143</td>
<td>20±4</td>
</tr>
<tr>
<td>H1975</td>
<td>L858R/T790M (Double Mutant)</td>
<td>&gt;5000</td>
<td>196±79</td>
</tr>
<tr>
<td>HCC827</td>
<td>DelE746-A750 (Activating Mutation)</td>
<td>12±6</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>

**Cell Proliferation (Mean GI\textsubscript{50}, nM)**

**Hitting T790M tolerably:**
1. High dose intermittent BIBW2992 (afatinib)?
2. Mutation ‘specific’ drugs?
Making lung cancer a chronic disease

Surfing And Cycling With Stage 4 Lung Cancer

By Colorado Public News and Ann Imse
Left to right:
Andrew Weickhardt, MD PhD
Robert C. Doebele, MD PhD
Marileila Varella-Garcia, PhD
D. Ross Camidge, MD PhD

Molecular Pathology:
Dara L. Aisner, MD PhD
Wilbur A. Franklin, MD

Thoracic Medical Oncology:
Paul A. Bunn, Jr. MD
Ana Oton, MD
Stefani Bender, RN
Dana Gregory, RN
Bethie Jean-Phillipe (Intake)
DeLee Maxson (PRA)

Radiation Oncology:
Brian Kavanagh, MD
Laurie Gaspar, MD

Rebiopsy Team:
Kimi Kondo, DO
Derek Linderman, MD
Steve Malkoski, MD PhD

Phase I Team:
S. Gail Eckhardt, MD
Sarah Eppers (& many more)

Health Economics:
Adam Atherly. PhD

Have Mutation Will Travel:
Jack West, MD
(Swedish Cancer Center, Seattle)

Support:
Bonnie Addario Foundation
CU Lung Cancer SPORE