Acquired Resistance to EGFR TKIs: Clinical obstacles and recent progress

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Disclosure Slide

• Paid advisory consulting: Clovis, Celgene
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• Thanks to Alice Shaw, Jeff Engelman, Ross Camidge for sharing slides
Before…. …and After
Over 50% of NSCLC have an Identifiable Driver Genotype

KRAS 25%

No Known Genotype

EGFR 13%

ALK 5%

HER2

RET

FGFR1

PIK3CA

MET

Sequist et al, Ann Oncol 2011, adapted
The reality of genotype-directed therapy

- Treatment A
- Treatment B
- Treatment C
- Treatment D

Same diagnosis, same prescription
But responses are short lived

<table>
<thead>
<tr>
<th>Study</th>
<th>Median PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPASS (EGFR mutants, gefitinib)</td>
<td>9.6 months</td>
</tr>
<tr>
<td>NEJ002 (EGFR mutants, gefitinib)</td>
<td>10.4 months</td>
</tr>
<tr>
<td>EURTAC (EGFR mutants, erlotinib)</td>
<td>9.7 months</td>
</tr>
<tr>
<td>LUX Lung 3 (EGFR mutants, afatinib)</td>
<td>13.6 months</td>
</tr>
<tr>
<td>PROFILE 1001, 1005 (ALK, crizotinib)</td>
<td>8-10 months</td>
</tr>
<tr>
<td>Preliminary data ASCO ’12 Shaw (ROS, crizotinib)</td>
<td>Not known but appears similar</td>
</tr>
</tbody>
</table>
Clinical Information

Biopsy

Targeted Therapy

Routine and Molecular Pathology
Two General Classes of TKI Resistance

Target Alteration

- RTK mutation or amplification

Sensitive/TKI-naïve

- Receptor TK

- STAT
- ERK
- PI3K

Bypass Tracks

- Receptor TK

- RTK1
- RTK2

- STAT
- ERK
- PI3K

△ Specific TKI

Slide courtesy of Alice Shaw
37 consecutive samples with paired pre- and post- AR tissue

Comparative analyses for:

- Histology with IHC
- SNaPshot (most common mutations in 13 genes)
- FISH for EGFR and MET amplification
Repeat Biopsies: EGFR mutants with AR to gefitinib, erlotinib

- BRAF (2%)
- EMT (5%)
- PIK3CA (5%)
- SCLC Transformation (14%)

Unidentified Mechanism (22%)

T790M (49%)

With EGFR amp

Sample size now 98, distribution of findings overall stable

Sequist et al Sci Transl Med 2011, adapted; Ohashi et al, PNAS 2012
Waxing/waning resistance in response to TKI selective pressure

<table>
<thead>
<tr>
<th>Histology</th>
<th>Adeno</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Genotype</td>
<td>L858R</td>
<td>L858R</td>
<td>L858R</td>
</tr>
<tr>
<td></td>
<td>TP53</td>
<td>TP53</td>
<td>TP53</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EGFR TKI status</td>
<td>Sensitive</td>
<td>Resistant</td>
<td>Sensitive</td>
</tr>
<tr>
<td>Tumor Burden</td>
<td><img src="image" alt="Graph showing tumor burden changes over time" /></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>Chemo</td>
<td>Erlotinib</td>
<td>Chemo</td>
</tr>
<tr>
<td>Timeline</td>
<td>2007</td>
<td>2008</td>
<td>2009</td>
</tr>
</tbody>
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Sequist et al, Sci Transl Med 2011
Waxing/waning resistance in response to TKI selective pressure

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Sequist et al, Sci Transl Med 2011

High-grade neuroendocrine carcinoma

Adenocarcinoma
EGFR transformed to SCLC is responsive to SCLC chemo

Patient received carboplatin, etoposide and erlotinib
Proof of principle: 63 year old man with an EGFR mutant lung cancer

1/30/08

erlotinib

3/31/08

Developed Resistance

2/25/09

Pre-Rx ‘08

Resistant ‘09

Rx on clinical trial
Irreversible TKIs (Pan-HER Inhibitors): Not highly effective for T790M

- **Neratinib (HKI-272)**
  - RR 2%, PFS 15 weeks in TKI-resistant patients (Sequist, JCO 2010)

- **Afatinib (BIBW-2992)**
  - RR 7%, PFS ~13 weeks in TKI-resistant pts (Miller, Lan Onc ‘12)

- **Dacomitinib (PF-299804)**
  - RR 7% in TKI-resistant patients (Janne, ASCO ’09)

....novel T790M-specific TKIs are entering clinical trials
  - CO-1686
  - AP26113
Afatinib/Cetuximab has been most active treatment, regardless of mechanism of AR

Janjigian YY et al. ASCO 2011;Abstract 7525.
AUY922 (Hsp90): best CT response: **EGFR**-mutant patients (n=25⁺/35)

### EGFR-mutant (n=35)

<table>
<thead>
<tr>
<th>Metric</th>
<th>Value</th>
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<tr>
<td>ORR (any PR)</td>
<td>7 (20%)⁺</td>
</tr>
<tr>
<td>DCR (CR/PR or SD)</td>
<td>20 (57%)</td>
</tr>
<tr>
<td>PFS (18 weeks [95% CI]), %</td>
<td>35.2 (18.7, 52.2)</td>
</tr>
</tbody>
</table>

*Confirmed responses; ⁺Patients with at least one post-baseline scan; ⁺Including one PR not confirmed.

Felip, et al. ESMO ‘12
Treatment Beyond Progression: appealing if PD is slow

Oxnard, et al ASCO’12
Goldberg, et al ASCO ’12 showed RR higher than chemo alone
Ongoing randomized trials in US (Horn) and Asia (Mok)
Disease Relapses on Crizotinib

Baseline

After 8 weeks of crizotinib

After 34 months of crizotinib
Patients with Crizotinib-Resistant ALK+ NSCLC

All patients had acquired TKI resistance

No evidence of SCLC transformation

All evaluable repeat biopsy specimens were ALK+ by FISH

<table>
<thead>
<tr>
<th>Patient</th>
<th>Duration (months)*</th>
<th>Timing (months)+</th>
<th>Histology</th>
<th>ALK fusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>MGH0NZ</td>
<td>20</td>
<td>0</td>
<td>Adeno</td>
<td>Positive</td>
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<tr>
<td>MGH001</td>
<td>4</td>
<td>3.5</td>
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<tr>
<td>MGH010</td>
<td>8</td>
<td>0</td>
<td>Adeno</td>
<td>Positive</td>
</tr>
<tr>
<td>MGH011</td>
<td>34</td>
<td>0</td>
<td>Adeno</td>
<td>Positive</td>
</tr>
<tr>
<td>MGH013</td>
<td>9</td>
<td>0</td>
<td>Adeno</td>
<td>Positive</td>
</tr>
<tr>
<td>MGH016</td>
<td>6</td>
<td>6</td>
<td>Adeno</td>
<td>Positive</td>
</tr>
<tr>
<td>MGH017</td>
<td>23+</td>
<td>0</td>
<td>Adeno</td>
<td>Positive</td>
</tr>
<tr>
<td>MGH018</td>
<td>10</td>
<td>0.5</td>
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</tr>
<tr>
<td>MGH019</td>
<td>8</td>
<td>&lt;0.5</td>
<td>Adeno</td>
<td>Positive</td>
</tr>
<tr>
<td>MGH020</td>
<td>13</td>
<td>0</td>
<td>Adeno</td>
<td>Positive</td>
</tr>
<tr>
<td>MGH021</td>
<td>12</td>
<td>3</td>
<td>Adeno</td>
<td>Positive</td>
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<tr>
<td>MGH022</td>
<td>6</td>
<td>0</td>
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<td>12</td>
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<tr>
<td>MGH024</td>
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<tr>
<td>MGH025</td>
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<td>0</td>
<td>Adeno</td>
<td>NA</td>
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<tr>
<td>MGH027</td>
<td>4</td>
<td>1</td>
<td>Adeno</td>
<td>NA</td>
</tr>
<tr>
<td>MGH028</td>
<td>14</td>
<td>1</td>
<td>Adeno</td>
<td>NA</td>
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<tr>
<td>MGH029</td>
<td>8</td>
<td>0</td>
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Katayama et al. Sci Transl Med 2012;4(120):120ra17
Mechanisms of Crizotinib Resistance

- Unknown Mechanism (27%)
- Target gene alteration (28%)
- Bypass track activation (45%)

Katayama et al. Sci Transl Med 2012;4(120):120ra17
Many Different ALK Resistance Mutations

Lovly and Pao, Sci Transl Med 2012;4(120):120ps2
EGFR Activation in Crizotinib-Resistant NSCLC

## Emergence of Other “Drivers”

<table>
<thead>
<tr>
<th></th>
<th>Doebele et al</th>
<th>Katayama et al</th>
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</table>
| **Addition of other driver mutations** | 1/11 EGFR mt  
2/11 KRAS mt | 0/6 EGFR or KRAS mt |
| **Loss of ALK translocation**   | Absence of ALK = 2/11  
(EGFR mt, unknown) | Absence of ALK = 0/15 |
Marked activity of LDK378 in advanced ALK+ NSCLC

Best % change from baseline
LDK378 400–750 mg PO qd; lung cancer patients only

- Progression or death

Prior crizotinib     Crizotinib-naïve

AUY922: best CT Response: ALK+
Stratum Patients (n=19+/22)

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Felip, et al. ESMO ‘12
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<td>Effective therapies for AR have been challenging to find</td>
<td>ALK can possibly be lost at AR</td>
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<td>LDK378 looks promising for AR</td>
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</table>
Summary and Conclusions

- Genotype-directed therapy paradigm has revolutionized NSCLC landscape
- Treatment of resistance has proven complicated
- Repeat biopsies of patients with AR will continue to greatly supplement lab-based research
- Prevention may be a potent strategy, especially since pre-disposition toward certain mechanisms may be identifiable
- Need less invasive alternatives to biopsies
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And Our Patients!!!