Use of Genomics To Assign Therapy in Lung Cancer

The Lung Cancer Oncogenome Group: Bedside to Bench and Beyond

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Agenda

• Bench
  – Rationale for development of anti-EGFR therapies

• Bedside
  – Clinical experience with EGFR TKIs

• Bench
  – Can we identify molecular predictors of sensitivity or resistance?
  – Can we determine why patients develop acquired resistance?

• Bedside
  – New trials based upon bench findings
MSK Strategy to Improve Outcomes Beyond Chemotherapy in NSCLC

Disrupt cellular pathways that cause or maintain lung cancer
The EGFR Pathway for Thoracic Oncologists

From J. Mendelsohn 1985
Why Target EGFR in NSCLC?

- Using IHC, EGFR expressed in from 32%-93% of resected primary tumors ...overexpressed in 45%
- Measuring mRNA, EGFR expressed in 100%
- EGFR shed ectodomain found in urine in 50%
- TGFα expressed in 82%, overexpressed in 61% of surgical specimens
- Mechanism of EGFR overexpression unknown
EGFR Hypothesis in NSCLC

Block EGFR-mediated effects

Arrest those non-small cell lung cancers dependent upon EGFR signaling (the more “addicted” the cell – the susceptible)
Gefitinib and Erlotinib – Related Quinazoline EGFR-TKIs

ZD1839
Gefitinib

OSI-774
Erlotinib

ATP
Gefitinib Phase II Trials—NSCLC
The Mystery Begins

<table>
<thead>
<tr>
<th>Sites</th>
<th>Japan *</th>
<th>Europe *</th>
<th>United States **</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entered</td>
<td>111</td>
<td>104</td>
<td>216</td>
</tr>
<tr>
<td>Radiographic</td>
<td>28%</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>Response Rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptom</td>
<td>39%</td>
<td>39%</td>
<td>39%</td>
</tr>
<tr>
<td>Improvement Rate</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Fukuoka et al JCO 2003
**Kris et al JAMA 2003
Factors Predicting Gefitinib Sensitivity
MSK Single Agent Studies

- 1997-2002, 140 Patients, 21 partial responses (15%)
- Univariate Prognostic Factors
  - Never Smokers vs Former/Current –36% vs 8%, p<0.001
  - AdenoCa vs Other Histologies -21% vs 0%, p<0.001
  - Bronchioloalveolar vs Other AdenoCa –37% vs 15%, p<0.001
  - Female Gender -19% vs 8%, p=0.14
- Multivariate Prognostic Factors
  - Never Smokers vs Former/Current (p=0.005)
  - Bronchioloalveolar vs Other AdenoCa (p=0.007)

Miller J Clin Oncol 2004
Factors Predicting Gefitinib Sensitivity
Iressa™ Package Insert

<table>
<thead>
<tr>
<th></th>
<th>Overall Response Rate</th>
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</thead>
<tbody>
<tr>
<td>Women</td>
<td>18%</td>
</tr>
<tr>
<td>Men</td>
<td>5%</td>
</tr>
<tr>
<td>Never Smokers</td>
<td>29%</td>
</tr>
<tr>
<td>Current/Former Smokers</td>
<td>5%</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>12%</td>
</tr>
<tr>
<td>Other NSCLC</td>
<td>7%</td>
</tr>
</tbody>
</table>
Results with Gefitinib 250 mg Daily

6 FEB 2002

11 FEB 2002
TURNING ON A MUTANT KRAS PROTO-ONCOGENE CAUSES LUNG CANCERS THAT REGRESS WHEN KRAS IS TURNED OFF.
RAPID DISAPPEARANCE OF LUNG CANCERS

KRAS ON

NO THERAPY

GEFITINIB DAY 5

KRAS OFF

DAY 1

HUMAN XRAY

DAY 9

MOUSE MRI

6 FEB 2002

11 FEB 2002
Exon 19 Deletion Found in a Patient with Long-term Response to Gefitinib

07.01.2002 07.29.2002 10.23.2003

K Y Y Y TM EGF binding Tyrosine kinase Auto-phos

PVAIKELREATSPKAN

ATP-binding site

Exon 19

6 aa del

December '03
EGFR Mutations Associated with Sensitivity to Gefitinib/Erlotinib

Lynch et al ’04; Paez et al ‘04; Pao et al ‘04
# Predictors of Response to Gefitinib/Erlotinib

<table>
<thead>
<tr>
<th>Clinical Predictors</th>
<th></th>
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<tbody>
<tr>
<td>NSCLC</td>
<td>10%</td>
</tr>
<tr>
<td>Female</td>
<td>18%</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>12%</td>
</tr>
<tr>
<td>Never smoker</td>
<td>30%</td>
</tr>
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</table>

## Molecular Predictors

<table>
<thead>
<tr>
<th>molecular predictor</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>KRAS mutn</td>
<td>1%</td>
</tr>
<tr>
<td>EGFR mutn</td>
<td>75%</td>
</tr>
</tbody>
</table>
Week 4 On Gefitinib Regression

Milton J Clin Oncol 2006

Exon 19 del

Exon 19 del

Pretreatment
Week 8 Off Gefitinib Growth
Exon 19 del

Week 12 On Gefitinib Regression
Exon 19 del

Milton J Clin Oncol 2006
Week 12 On Gefitinib
Regression

Exon 19 del

Week 54 On Gefitinib
Growth

Exon 19 del

Milton J Clin Oncol 2006
Disease Response and Progression

Day 0 4 months 25 months

Growing bone lesion Growing lung lesion

Growing bone lesion Growing lung lesion
Erlotinib and T790

Courtesy of Nikola Pavletich
Erlotinib and T790M

Courtesy of Nikola Pavletich
Week 54 On Gefitinib
Growth
Exon 19 del + T790M

Week 12 On Gefitinib
Regression
Exon 19 del

Milton J Clin Oncol 2006
Mice Expressing Mutant EGFR\textsuperscript{L858R+T790M} Do Not Respond to Erlotinib

Regales et al ‘07
What About Other Mechanisms of Acquired Resistance?

- Array CGH
- 244K Agilent chips
- 12 patients, 12 samples with acquired resistance
- Compare to aCGH data (44K chips) from 38 patients -- all EGFR mutant never treated with TKI

Bean et al, submitted
Genomic Profiles of *EGFR* Mutant Lung Adenocarcinomas

Acquired resistance samples (n=12; Agilent 244K; 6.4 kb SR)

Untreated samples (n=38; Agilent 44K; 35 kb SR)

- Data from untreated set provided by William Gerald, Marc Ladanyi
- Analysis by Cameron Brennan
Differentially Altered Genomic Loci

<table>
<thead>
<tr>
<th>Cytoband</th>
<th>MCR (MB)</th>
<th>Max CNA</th>
<th># samples above threshold</th>
<th># refseq genes</th>
<th>Likely target gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>5p15.2 - 15.3</td>
<td>8.2 - 14.6</td>
<td>&gt;8</td>
<td>2</td>
<td>7</td>
<td>unknown</td>
</tr>
<tr>
<td>7p11-12</td>
<td>53.8 – 55.5</td>
<td>&gt;8</td>
<td>3</td>
<td>4</td>
<td>EGFR</td>
</tr>
<tr>
<td>7q31.2</td>
<td>114.8 - 116.4</td>
<td>&gt;12</td>
<td>2</td>
<td>6</td>
<td>MET</td>
</tr>
</tbody>
</table>

Genomic loci significantly differentially altered between 12 EGFR mutant tumor samples from patients with acquired resistance and 38 EGFR mutant tumor samples from untreated patients.

- *MET* amplification is rare in lung adenocarcinomas – in 371 primary lung adenocarcinomas, *MET* amplification was not found (Weir et al, submitted)

Cameron Brennan
Focal Amplifications at \textit{EGFR} and \textit{MET}

\textbf{Sample 5} (no T790M)

\textbf{Sample 6} (no T790M)

\textbf{Sample 10a} (T790M)

\textbf{Sample 10b} (no T790M)

Cameron Brennan
Summary

- Second-site EGFR mutations are found in ~50% of cases of acquired resistance to EGFR inhibitors.

- The type and nature of kinase inhibitor resistance mutations may be influenced by both mode of binding to the target kinase and by anatomical site:
  - Inactive (ABL, CKIT - imatinib) vs. active (EGFR - gefitinib/erlotinib)
  - Visceral sites vs. brain

- MET amplification found in ~20% of cases of acquired resistance:
  - 40% of patients with MET amplification also have the T790M EGFR resistance mutation.

- MET inhibitors may have a role in treating acquired resistance:
  - Similar data reported by Engelman et al '07 using a different approach.
Potential Drugs to Overcome Acquired Resistance

- **Next-generation EGFR inhibitors**
  - HKI-272 Wyeth
  - XL-647 Exelixis
  - BIBW2992 Boerhinger-Ingelheim
  - PF00299804 Pfizer

- **MET inhibitors**
  - **Small molecule inhibitors**
    - ARQ-197 ArQule
    - PF2341066 Pfizer
    - SGX-523 SGX
    - XL-880 Exelixis
    - XL-184 Exelixis
  - ** Antibodies**
    - AV-299 anti-HGF Aveo/Xoma
    - AMG-102 anti-HGF Amgen
    - Anti-MET Genentech
Use of Genomics To Assign Therapy

Examples of Clinical Trials and Plans of Care Based on EGFR and KRAS Mutation Status
In patients with non-small cell lung cancer, the proportion with a mutation in exon 19 or 21 of \textit{EGFR} will be higher in individuals with a radiographic response following gefitinib.
cStage I or II NSCLC
-- BAC Features and/or
-- <15 Pack Year Smoker
Measurable Lesion
Operable and Resectable

Chest CT
Needle Biopsy for
EGFR Mutation
Testing in exons 18-24

Gefitinib 250 mg
PO daily for at least 21 days

Repeat Chest CT

Surgery
Repeat EGFR
Mutation Testing in
exons 18-24
Tumor Banking

Continue Gefitinib for 2 years if CT
Response or EGFR
exon 19 or 21
Mutation Present
**EGFR Mutations and Gefitinib Sensitivity**

**Results: Primary Study Endpoint**

<table>
<thead>
<tr>
<th>Observed Results as of 1 AUGUST 07</th>
<th><strong>EGFR</strong> Exon 19 or 21 Mutation</th>
<th><strong>EGFR</strong> Wild Type *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response</td>
<td>12 (77%)</td>
<td>3 (11%)</td>
</tr>
<tr>
<td>No Response</td>
<td>3</td>
<td>25</td>
</tr>
</tbody>
</table>

* No mutation in *EGFR* exons 18-24

Fisher’s exact test: two tailed P value < 0.0001
EGFR Mutations and Gefitinib Sensitivity

Results – 43 Completed Patients

- Pretreatment core needle biopsies adequate for mutation testing in 17/18 (94%)
- Mutations in EGFR in 35% and in KRAS in 9%.
- Mutation results identical in 17/17 paired pretreatment core needle biopsies and post-treatment surgical specimens
- 42/43 (98%) completed preoperative gefitinib
- Response, defined as $\geq 25\%$ reduction by WHO after 21 days, 15/43 (35% observed, 95% CI 19-50%)
- No increase in perioperative complications
EGFR Mutations and Gefitinib Sensitivity

Response with Gefitinib after 21 days

WHO (Bidimensional) Criteria

-100%
-75%
-50%
-25%
0%
25%
50%

EGFR mutant

KRAS mutant

EGFR and KRAS wild type

- EGFR and KRAS wild type
- EGFR mutant
- KRAS mutant

12C
12D
19
21
Specific Aims

• Primary
  To determine the feasibility of obtaining paired biopsy specimens and serial imaging studies in patients with advanced non-small cell lung cancer treated with erlotinib.

• Secondary
  To develop a profile of early imaging and molecular events in patients sensitive and resistant to erlotinib as assessed by:
  – Selected markers of proliferation (Ki67), apoptosis (activated caspase 3), and EGFR kinase activity (p-AKT).
  – Changes in volumetric CT and FDG PET.
Identifying Early Markers of Erlotinib Sensitivity and Resistance in Patients with Advanced NSCLC

Eligibility

- Adenocarcinoma of the Lung
- Metastatic (Stage IIIB/IV)
- \( \leq 15 \) Pack Year History of Cigarette Smoking
- Measurable Indicator Lesion (RECIST)
- No prior treatment with an EGFR TKI
- No \( KRAS \) mutation. If KRAS status not available a biopsy will be performed before study entry.
Identifying Early Markers of Erlotinib Sensitivity and Resistance in Patients with Advanced NSCLC

Study Plan

Erlotinib Treatment

CT
PET/CT
& Biopsy

CT
PET/CT
& Biopsy
(Day 7±2)

Ki67
Caspase
pAKT

CT
PET/CT
(Day 29)

Ki67
Caspase
pAKT
### Improved Curability With Adjuvant Chemotherapy in Resected NSCLC

<table>
<thead>
<tr>
<th># Pts</th>
<th>↑ 5 yr (%)</th>
<th>HR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meta95 1394</td>
<td>5</td>
<td>0.87</td>
<td>0.74-1.02</td>
<td>0.08</td>
</tr>
<tr>
<td>1209</td>
<td>3</td>
<td>0.96</td>
<td>0.81-1.13</td>
<td>0.59</td>
</tr>
<tr>
<td>1867</td>
<td>4</td>
<td>0.86</td>
<td>0.76-0.98</td>
<td>0.03</td>
</tr>
<tr>
<td>482</td>
<td>15</td>
<td>0.70</td>
<td>0.52-0.92</td>
<td>0.01</td>
</tr>
<tr>
<td>344</td>
<td>2</td>
<td>0.80</td>
<td>0.60-1.07</td>
<td>0.10</td>
</tr>
<tr>
<td>840</td>
<td>8</td>
<td>0.79</td>
<td>0.66-0.95</td>
<td>0.01</td>
</tr>
<tr>
<td>Meta06 4584</td>
<td>4</td>
<td>0.89</td>
<td>0.82-0.96</td>
<td>0.005</td>
</tr>
</tbody>
</table>

JNCI 03; NEJM 04; NEJM 05; Proc ASCO 06; Lancet Oncol 06
<table>
<thead>
<tr>
<th>ERCC1 status</th>
<th>EGFR mutation</th>
<th>KRAS mutation</th>
<th>EGFR and KRAS Wildtype</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERCC1 positive</td>
<td>Docetaxel + Vinorelbine ↓ Erlotinib</td>
<td>Docetaxel + Vinorelbine ↓ KRAS vaccine</td>
<td>Docetaxel + Vinorelbine</td>
</tr>
<tr>
<td>ERCC1 negative</td>
<td>Cisplatin + Vinorelbine ↓ Erlotinib</td>
<td>Docetaxel + Vinorelbine ↓ KRAS vaccine</td>
<td>Cisplatin + Vinorelbine</td>
</tr>
</tbody>
</table>
## MSKCC Adjuvant and Neoadjuvant Studies for NSCLC

### Neoadjuvant
For all patients with resectable Stage I – III NSCLC

<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>BEACON (05-052)</td>
<td>For high-risk stage IB-IIIA, ≥ 15 pack-year smoker</td>
</tr>
<tr>
<td>POPP (04-071)</td>
<td>For low-risk stage I, &lt; 15 pack-year smoker</td>
</tr>
<tr>
<td>ECON (07-103)</td>
<td>For high-risk stage IB-IIIB, &lt; 15 pack-year smoker</td>
</tr>
</tbody>
</table>

### Adjuvant
For all patients with R0 resected IB – IIIB NSCLC not enrolled in POPP, ECON or BEACON

<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
</tr>
</thead>
</table>
| VIN-Doc (under review) | ERCC1 Positive or ineligible for cisplatin  
Phase II vinorelbine, docetaxel, bevacizumab  
Endpoint: vinorelbine delivery |
|                 | ERCC1 Negative and eligible for cisplatin  
Cisplatin plus vinorelbine (BR.10 – Winton et al) |

### Consolidation
IA - IIIB NSCLC, not enrolled in ECON or POPP, who have completed all therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
</tr>
</thead>
</table>
| POSTER (under review) | EGFR mutation +  
Phase II erlotinib trial  
Endpoint: erlotinib delivery |
| RASVAX (under review)  | KRAS mutation +  
Ph 2 GI-4000 trial  
Endpoint: mutation specific immune response |
07-110 Phase II Study of Salirasib in Advanced NSCLC

**Treatment:** salirasib (S-trans, trans-farnesyl thiosalicylic acid), an inhibitor of prenylated protein methyltransferase, prevents binding of KRAS to cell membrane  **Dose:** 800 mg bid

**Patients:** Patients with mutated *KRAS* and stage IIIB/IV NSCLC

**Endpoints:**
1. rate of non-progression at 10 weeks (CR+PR+SD)
2. response rate, response duration, time to progression, overall survival, and safety
Use of Genomics To Assign Therapy
Conclusions

• Translational research is an iterative process. Be ready to listen (esp. to patients) and revise plans.

• Tissue collection/analysis from select populations of patients can be very informative.

• *EGFR* and *KRAS* mutations are the critical drivers in one-third of lung adenocarcinomas.
  – These mutations are predictive markers for EGFR tyrosine kinase inhibitors.

• Current technology permits their precise and rapid detection in tumor samples.
Lung Cancer 2007 – USA
213,000 New Cases

Small Cell Lung Cancer (13%)

EGFR mutated (10% of NSCLC)

KRAS mutated (25% of Adenocarcinoma)

Other NSCLC

Relative Yearly Incidence of Some Oncogene Related Cancers

KRAS-mutated NSCLC
36,000 cases/year

EGFR-mutated NSCLC
18,000 cases/year

CML
4500 cases

GIST
3000 cases
Targeted Therapies for Lung Cancer

**Thoracic Medical Oncology**
- Jerry Azzoli
- Jorge Gomez
- Lee Krug
- Vincent Miller
- Naiyer Rizvi
- Herbert Oettgen
- Gregory Riely

**Surgery**
- Valerie Rusch
- Bhuvanesh Singh

**Biostatistics and Bioinformatics**
- Ennadapam Venkatraman
- Alex Lash

**Radiology**
- Robert Heelan
- Larry Schwartz
- Michelle Ginsberg
- Binsheng Zhao
- George Getrajdman

**Pathology**
- Maureen Zakowski
- Mark Ladanyi
- William Gerald
- William Travis

**Nuclear Medicine**
- Timothy Akhurst
- Steven Larson

**Clinical Trials Office**
- Jessica Jones

**Research Nursing**
- Barbara Pizzo
- Leslie Tyson
- Megan Dunne

**SKI and HOPP Laboratories**
- Harold Varmus
- Neal Rosen
- David Solit
- Joan Massague