Pharmacogenomic markers in EGFR-targeted therapy of lung cancer

Rafal Dziadziuszko, MD, PhD

University of Colorado Cancer Center, Aurora, CO, USA

Medical University of Gdansk, Poland

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Cancer mortality in the European Union; 2004

- LUNG: 20%
- COLON & RECTUM: 12%
- STOMACH: 8%
- BREAST: 8%
- PROSTATE: 5%
- LYMPHOMAS: 4%
- LEUKAEMIAS: 3%
- OTHER: 40%

Boyle et al., Ann Oncol 2005
Rationale for targeted therapy of lung cancer

- Standard chemotherapy provides modest survival benefit at the expense of significant toxicity and costs
- Survival rates from lung cancer almost unchanged for decades
- Significant improvement from targeted therapies in other solid tumors (breast cancer, renal cancer, GIST) and haematologic malignancies
Classes of EGFR inhibitors under clinical development

- Orally available EGFR tyrosine kinase inhibitors (TKIs: gefitinib, erlotinib, lapatinib, canertinib, HKI 272)

- Anti-EGFR monoclonal antibodies (cetuximab, panitumumab, matuzumab, pertuzumab)
Gefitinib and erlotinib: findings from early clinical studies

- Phase I studies: relatively good tolerance; dose limiting toxicities: skin rash and diarrhea

- Phase II monotherapy studies in non-small cell lung cancer (NSCLC): ~10-20% response rates and ~40% disease control rates in pretreated patients
Gefitinib and erlotinib: findings from phase III studies

• No advantage of EGFR TKIs combined with chemotherapy in unselected NSCLC patients in the first-line treatment (four phase III studies; >4,000 patients)

• Significant survival benefit (HR=0.70) with erlotinib monotherapy vs placebo in unselected patients relapsed after one or two lines of chemotherapy (BR.21)

• Insignificant survival benefit (HR=0.89) with gefitinib monotherapy in a similar setting (ISEL)
BR.21: survival

HR=0.70 (0.58–0.85)
Stratified log-rank p<0.001

At risk
Erlotinib 488 255 145 23 4 0
Placebo 243 107 50 9 0 0

Shepherd et al., NEJM, 2005
Clinical markers of increased responsiveness to EGFR TKIs

- Never-smokers (RRs ~ 20-30%)
- Asian ethnicity (RRs ~ 30%)
- Female gender (RRs ~ 15-20%)
- Adenocarcinoma (RRs ~ 10-20%)
BR.21: Forest plot of survival by subsets

Erlotinib:placebo
PS 0–1
PS 2–3
Male
Female
<65 years
≥65 years
Adenocarcinoma
Squamous-cell carcinoma
Other histology
Prior weight loss <5%
Prior weight loss 5–10%
Prior weight loss >10%
Never-smoker
Current/ex-smoker
1 prior regimen
2+ prior regimens

HR

Tsao et al., NEJM, 2005
Biologic selection to EGFR TKIs

*EGFR* gene copy number by FISH

*EGFR* protein expression by IHC

*EGFR* gene mutations
## EGFR FISH

**ISEL STUDY**

<table>
<thead>
<tr>
<th>PATTERN</th>
<th>EGFR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disomy</td>
<td>15.7%</td>
</tr>
<tr>
<td>Low Trisomy</td>
<td>24.1%</td>
</tr>
<tr>
<td>High Trisomy</td>
<td>2.2%</td>
</tr>
<tr>
<td>Low Polysomy</td>
<td>27.3%</td>
</tr>
<tr>
<td>High Polysomy</td>
<td>17.0%</td>
</tr>
<tr>
<td>Gene Amplification</td>
<td>13.8%</td>
</tr>
</tbody>
</table>

*Hirsch et al., J Clin Oncol 2006*
## EGFR TKIs studies: impact of gene copy number by FISH

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Drug</th>
<th>% FISH Positive</th>
<th>RR FISH+ vs. FISH-</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cappuzzo et al.</td>
<td>102</td>
<td>Gefitinib 250 mg/d</td>
<td>32%</td>
<td>36% vs. 3%</td>
<td>0.44* (0.23-0.82)</td>
</tr>
<tr>
<td>Hirsch et al.</td>
<td>82</td>
<td>Gefitinib 500 mg/d</td>
<td>32%</td>
<td>26% vs. 11%</td>
<td>0.50* (0.25-0.97)</td>
</tr>
<tr>
<td>SWOG 0126</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tsao et al.</td>
<td>125</td>
<td>Erlotinib 150 mg/d</td>
<td>45%</td>
<td>20% vs. 2%</td>
<td>0.44** (0.23-0.82)</td>
</tr>
<tr>
<td>BR.21</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hirsch et al.</td>
<td>370</td>
<td>Gefitinib 250 mg/d</td>
<td>31%</td>
<td>16% vs. 3%</td>
<td>0.61** (0.36-1.03)</td>
</tr>
<tr>
<td>ISEL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*HR for FISH+ vs. FISH- subsets; all patients treated with gefitinib

**HR for EGFR TKI vs. placebo in FISH+ patients
Survival according to EGFR gene copy number – BR.21 and ISEL

**ISEL FISH +**

- **Gefitinib**
  - Placebo
  - HR = 0.61 (0.36, 1.04)
  - \( P = .07 \)

- **Erlotinib**
  - Placebo
  - HR = 0.44 (0.23, 0.82)
  - \( P = .008 \)

**ISEL FISH -**

- **Gefitinib**
  - Placebo
  - HR = 1.16 (0.81, 1.64)
  - \( P = .42 \)

**BR.21 FISH +**

- **Gefitinib**
  - Placebo
  - HR = 0.85 (0.48, 1.51)
  - \( P = .42 \)

- **Erlotinib**
  - Placebo
  - HR = 1.16 (0.81, 1.64)
  - \( P = .59 \)

**BR.21 FISH -**

- **Gefitinib**
  - Placebo
  - HR = 0.44 (0.23, 0.82)
  - \( P = .008 \)

- **Erlotinib**
  - Placebo
  - HR = 0.61 (0.36, 1.04)
  - \( P = .07 \)

*ISEL FISH interaction test \( P = .04 \)

*BR.21 FISH interaction test \( P = .10 \)

IHC and EGFR status: scoring system

EGFR POSITIVE: 62/100 pts=62%
## Response according to EGFR protein expression (IHC)

<table>
<thead>
<tr>
<th>EGFR Status</th>
<th>ISEL</th>
<th>IDEAL</th>
<th>BR.21</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ORR (%)</td>
<td>ORR (%)</td>
<td>ORR (%)</td>
<td>ORR (%)</td>
</tr>
<tr>
<td>EGFR +</td>
<td>N=158 13 (8.2%)</td>
<td>N=84 13 (13.4%)</td>
<td>N=106 12 (11.3%)</td>
<td>N=348 38 (10.9%)</td>
</tr>
<tr>
<td>EGFR -</td>
<td>N=69 1 (1.5%)</td>
<td>N=17 1 (5.6%)</td>
<td>N=80 3 (3.8%)</td>
<td>N= 166 5 (3.0%)</td>
</tr>
</tbody>
</table>
BR.21: Survival according to EGFR protein expression

EGFR+

Erlotinib | Placebo
---|---
93 | 48
42 | 24
22 | 14
8 | 3
3 | 0
0 | 0

EGFR–

Erlotinib | Placebo
---|---
117 | 67
71 | 23
43 | 12
5 | 5
5 | 0
0 | 0

Log-rank: $p=0.02$
HR=0.68 (0.49, 0.95)
Log-rank: $p=0.70$
HR=0.93 (0.63, 1.36)

Interaction $P = 0.25$

Tsao et al., NEJM 2005
EGFR gene mutations

- **Ligand binding domain**: GXGXXG
- **Tyrosine kinase domain**: KRHDFFGGXGXXGLLY
- **Autophosphorylation domain**: YYY

Exon:
- 18
- 19
- 20
- 21
- 22
- 23
- 24

Mutations:
- 719
- 747-750
- 757-750
- 858

Paez:
- ▲
- ★★★★★★
- ▲

Lynch:
- ▲
- ★★★★★★
- ▲
- ▲

Pao:
- ★★★★★★
- ▲
- ▲
- ▲

△ Mutacje punktowe
★ Delecje

Pao et al., PNAS 2004
## Retrospective studies: impact of EGFR mutations

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Drug</th>
<th>% Mut+</th>
<th>RR Mut+ vs. Mut-</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitsudomi et al.</td>
<td>59</td>
<td>Gefitinib 250 mg/d</td>
<td>56%</td>
<td>83% vs. 10%</td>
<td>0.34* (0.12-0.99)</td>
</tr>
<tr>
<td>Takano et al.</td>
<td>66</td>
<td>Gefitinib 250 mg/d</td>
<td>59%</td>
<td>82% vs. 11%</td>
<td>0.27* (0.13-0.53)</td>
</tr>
<tr>
<td>Han et al.</td>
<td>90</td>
<td>Gefitinib 250 mg/d</td>
<td>18.9%</td>
<td>64.7% vs. 13.7%</td>
<td>0.16* (0.05-0.52)</td>
</tr>
<tr>
<td>Cappuzzo et al.</td>
<td>89</td>
<td>Gefitinib 250 mg/d</td>
<td>17%</td>
<td>54% vs. 5%</td>
<td>NS</td>
</tr>
<tr>
<td>Cortes-Funes et al.</td>
<td>83</td>
<td>Gefitinib 250 mg/d</td>
<td>12%</td>
<td>60% vs. 8.8%</td>
<td>0.32* (0.12-0.91)</td>
</tr>
</tbody>
</table>

*Mut+ vs. mut- subsets  
NS - non significant
# Prospective studies: impact of EGFR mutations

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Drug</th>
<th>% Mut+</th>
<th>RR Mut+ vs. Mut-</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tsao et al. BR.21</td>
<td>197</td>
<td>Erlotinib 150 mg/d</td>
<td>22.6%</td>
<td>16% vs. 7%</td>
<td>0.77 (0.40-1.50)</td>
</tr>
<tr>
<td>Hirsch et al. ISEL 215</td>
<td></td>
<td>Gefitinib 250 mg/d</td>
<td>12%</td>
<td>37.5% vs. 2.6%</td>
<td>NR</td>
</tr>
<tr>
<td>Bell et al. IDEAL INTACT</td>
<td>79</td>
<td>Gefitinib 250 and 500</td>
<td>18%</td>
<td>46% vs. 10%</td>
<td>NR</td>
</tr>
<tr>
<td>Eberhardt et al. TRIBUTE</td>
<td>228</td>
<td>Erlotinib 150 mg/d</td>
<td>12.7%</td>
<td>53% vs. 18%</td>
<td>NR (NS)</td>
</tr>
</tbody>
</table>

NR – not reported; NS – non significant
BR.21: Survival according to EGFR mutations

Wild-type EGFR

- Erlotinib
- Placebo

Log-rank: p=0.13
HR=0.73 (0.49, 1.10)

Mutant EGFR

- Erlotinib
- Placebo

Log-rank: p=0.45
HR=0.77 (0.40, 1.50)

Interaction test, P= 0.97

Tsao et al., NEJM 2005
Prognostic value of *EGFR* mutations in advanced NSCLC

Bell et al., Clin Cancer Res, 2006
Survival vs. *EGFR* mutation type

![Graph showing survival rates of different *EGFR* mutation types.](image)

**Table: Survival rates and medians**

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>1-yr OS</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exon 19 deletion</td>
<td>22</td>
<td>95%</td>
<td>38 months</td>
</tr>
<tr>
<td>L858R mutation</td>
<td>10</td>
<td>80%</td>
<td>17 months</td>
</tr>
</tbody>
</table>

*Jackman et al., Clin Cancer Res, 2006*
Current status of biomarkers for selection of NSCLC patients to EGFR TKIs

- Several biomarkers identified (gene copy number, EGFR protein expression, EGFR mutations, serum proteomics)
- None routinely used for patient selection
- Clinical trials in selected patient populations or stratified for these markers ongoing
What went wrong with biomarkers in clinical development of EGFR TKIs in NSCLC?

- Poor translational components of clinical studies (none prospectively enriched or stratified for biomarkers)
- Neglecting differences in biology according to demographic and clinical characteristics (i.e. smoking history, ethnicity)
- Poor standarization and validation of technologies for biomarker assessment
EGFR TKI preclinical studies in Colorado

Graph showing the effects of Gefitinib on sensitive and resistant cell lines over time.
Clinical trial design issues

**Prognostic marker**
- Associates with main effect regardless of treatment
- May be used for risk-stratified treatment
- Not suitable for targeted-therapy trial designs

**Predictive marker**
- Interaction with treatment
- Appropriate for targeted-therapy trial designs

Crowley J., Taormina IASLC Meeting, 2006
Targeted therapy clinical trial designs

- **All-comers design**: Randomize everyone, measure marker / stratify by marker

  Register → Measure marker → Randomize

  - A
  - B

- **Targeted design**: Randomize positive patients only

  Register → Measure marker → Randomize M+

  - A
  - B

- **Strategy design**: Randomize to strategy based on marker

  Register → Measure marker → Randomize

  - A or B

*Crowley J., Taormina IASLC Meeting, 2006*
Future directions

- Incorporation of biomarker studies early in preclinical and clinical development
- Understanding of biomarker significance for disease biology (prognostic vs. predictive)
- Better standardization and validation of technologies for biomarker assessment