Targeting EGFR and ALK in the treatment of NSCLC: What is the next?

Christian Rolfo, MD, PhD
Oncology Department
Antwerp University Hospital
“If it were not for the great variability among individuals, medicine might as well be a science and not an art.”

Sir William Osler
1849 -1919
NSCLC

Non-small cell lung cancer (NSCLC) (80%)

Squamous cell carcinomas (25–30%)

Non-squamous cell carcinomas (70–75%)

Classic adenocarcinoma (75–90%)

Carbone, Semin Oncol 1997
Historical context: chemotherapy reached a therapeutic plateau in early 2000s

<table>
<thead>
<tr>
<th>Decade</th>
<th>Therapy</th>
<th>Median Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1970s</td>
<td>BSC</td>
<td>2–5</td>
</tr>
<tr>
<td>1980s</td>
<td>Single-agent platinum</td>
<td>6–8</td>
</tr>
<tr>
<td>1990s</td>
<td>Platinum doublets</td>
<td>8–10</td>
</tr>
<tr>
<td>2000s</td>
<td>Cisplatin/pemetrexed</td>
<td>11</td>
</tr>
</tbody>
</table>

Recent milestones in NSCLC

How do we translate these advances from clinical trials into daily practice?

Changing landscape in advanced NSCLC treatment: slow but real improvement

<table>
<thead>
<tr>
<th></th>
<th>80's</th>
<th>90's</th>
<th>2000</th>
<th>2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st line</td>
<td>Questioned</td>
<td>Confirmed</td>
<td>Confirmed</td>
<td>Cost-effective</td>
</tr>
<tr>
<td>2nd line</td>
<td>No</td>
<td>Doubtful</td>
<td>Confirmed</td>
<td>Confirmed</td>
</tr>
<tr>
<td>3rd line</td>
<td>No</td>
<td>No</td>
<td>Selected subsets</td>
<td>Feasible</td>
</tr>
<tr>
<td>Maintenance</td>
<td></td>
<td>Questioned</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>Response rate</td>
<td>15%</td>
<td>25%</td>
<td>35%</td>
<td>45%</td>
</tr>
<tr>
<td>Median survival</td>
<td>7 m</td>
<td>10 m</td>
<td>12 m</td>
<td></td>
</tr>
<tr>
<td>1 year survival</td>
<td>25%</td>
<td>40%</td>
<td>45-50%</td>
<td></td>
</tr>
</tbody>
</table>
NSCLC is the first epithelial neoplasm that could be treated with single agent targeted therapy in first line treatment.
# Review of First-line Chemotherapy for Advanced NSCLC

<table>
<thead>
<tr>
<th>Treatment</th>
<th>E1594 (^1) (Phase III) Schiller</th>
<th>E4599 (^2) (Phase III) Sandler</th>
<th>AVAiL (^3-4) (Phase III)</th>
<th>IPASS (^5) (Phase III)</th>
<th>JMDB (^6) (Phase III)</th>
<th>EURTAC (^7) Phase III Rosell GECP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Paclitaxel + Cisplatin (P/C)</strong></td>
<td>Paclitaxel + Cisplatin + Placebo</td>
<td>Gemcitabine + Cisplatin + Placebo</td>
<td>Gefitinib</td>
<td>Gemcitabine + Cisplatin (G/C)</td>
<td>Paclitaxel-carboplatin</td>
<td>Erlotinib Vs Platinun –based chemotherapy</td>
</tr>
<tr>
<td><strong>Gemcitabine + Cisplatin (G/C)</strong></td>
<td>Paclitaxel + Carboplatin + Placebo</td>
<td>Gemcitabine + Cisplatin + Bevacizumab (7.5 mg/kg)</td>
<td></td>
<td>Gemcitabine + Cisplatin (G/C)</td>
<td>Pemetrexed + Cisplatin(P/C)</td>
<td></td>
</tr>
<tr>
<td><strong>Docetaxel + Cisplatin (D/C)</strong></td>
<td>Paclitaxel + Carboplatin + Bevacizumab (15 mg/kg)</td>
<td>Gemcitabine + Cisplatin + Bevacizumab</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Paclitaxel + Carboplatin (P/Cb)</strong></td>
<td></td>
<td>Gemcitabine + Cisplatin + Bevacizumab</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gemcitabine + Cisplatin + Placebo</strong></td>
<td></td>
<td></td>
<td>Gefitinib</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Median OS (months)

<table>
<thead>
<tr>
<th><strong>OS (CI: 95%)</strong></th>
<th><strong>13.6 vs 13.1</strong> (low dose; (p = 0.42))</th>
<th><strong>HR=0.93 95%CI (0.78-1.11)</strong></th>
<th><strong>18.6 vs 17.3</strong> HR = 0.91 95% CI 0.76-1.10</th>
<th><strong>10.3 vs 10.3</strong> HR = 0.94 95% CI 0.84-1.05</th>
<th><strong>No mature Considerer Crossover</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>7.8 (7.0-8.9); 8.1 (7.2-9.4); 7.4 (6.6-8.8); 8.1 (7.0-9.5)</td>
<td>10.3 vs 12.3 HR=0.79 95%CI (0.67-0.92) ((p = 0.003))</td>
<td>13.4 vs 13.1 (high dose; (p = 0.76)) HR=1.03 95%CI (0.86-1.23)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Median PFS (months)

<table>
<thead>
<tr>
<th><strong>PFS (months)</strong></th>
<th><strong>6.7 vs 6.1</strong> (low dose; (p = 0.003))</th>
<th><strong>HR=0.75 95%CI (0.62-0.91)</strong></th>
<th><strong>5.7 vs 5.8</strong> HR = 0.74 95% CI 0.65-0.85 ((p &lt; 0.001))</th>
<th><strong>4.8 vs 5.1</strong> HR: 1.04 (0.94–1.15)</th>
<th><strong>9.4 m vs 5.2m (HR 0.47)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>3.4 (P/C) vs 4.2 (G/C) ((p = 0.001))</td>
<td>4.5 vs 6.2 HR=0.66 95%CI (0.57-0.67) ((p &lt; 0.001))</td>
<td>6.5 vs 6.1 (high dose; (p = 0.03)) HR=0.82 95%CI (0.68-0.98)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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7. Rosell et al, in press 2012
The actual tissue samples pose many obstacles

- Minute specimens derived from small core biopsies

- Heterogeneous tumor samples comprised of normal tissue and cancerous cells which dilute the mutant alleles of interest

- Poor quality fragmented nucleic acid obtained from FFPE tissue.
You may think oncologists are too demanding…..

Why do we ask pulmonologists, radiologist to get more tissue?

Why do we ask pathologists to do more molecular biomarkers with such amount of tissue?
Lung Cancer Molecular Consortium Analysis in Lung Adenocarcinoma

Potential “Druggable” Molecular Targets?

- Mutations found in 54% (280/516) of tumors completely tested (95% CI: 50% to 59%)
- Referral to appropriate biomarker-driven clinical trial based on patient-specific analysis
Emerging “Druggable” Targets in NSCLC-Squamous Subtype

<table>
<thead>
<tr>
<th>Gene</th>
<th>Event Type</th>
<th>Frequency, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>FGFR1</td>
<td>Amplification</td>
<td>20-25</td>
</tr>
<tr>
<td>FGFR2</td>
<td>Mutation</td>
<td>5</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>Mutation</td>
<td>9</td>
</tr>
<tr>
<td>PTEN</td>
<td>Mutation-deletion</td>
<td>18</td>
</tr>
<tr>
<td>CCND1</td>
<td>Amplification</td>
<td>8</td>
</tr>
<tr>
<td>CDKN2A</td>
<td>Deletion/mutation</td>
<td>45</td>
</tr>
<tr>
<td>PDGFRA</td>
<td>Amplification-mutation</td>
<td>9</td>
</tr>
<tr>
<td>EGFR</td>
<td>Amplification</td>
<td>10</td>
</tr>
<tr>
<td>MCL1</td>
<td>Amplification</td>
<td>10</td>
</tr>
<tr>
<td>BRAF</td>
<td>Mutation</td>
<td>3</td>
</tr>
<tr>
<td>DDR2</td>
<td>Mutation</td>
<td>4</td>
</tr>
<tr>
<td>ERBB2</td>
<td>Amplification</td>
<td>2</td>
</tr>
</tbody>
</table>

Emerging “Druggable” Targets in NSCLC-Squamous Subtype

Molecular-targeted agents under investigation in lung cancer

Phase I
- Bortezomib
- Celecoxib
- Bexarotene
- AZD6244
- Tipifarnib
- Talabostat
- PF-3512676
- AS1404
- RAD001
- CP-751871
- ABT-751

Phase II
- Erlotinib
- Gefitinib
- Icotinib
- XL647
- Vandetanib
- Neratinib
- Dacomitinib
- Afatinib
- PF-3512676

Phase III
- Vatalanib
- VEGF TRAP
- Sunitinib
- BIBF1120
- Vandetanib
- Motesanib
- Sorafenib

Approved
- Avastin
- Erlotinib
- Gefitinib

Other molecular-targeted therapies
- Other molecular-targeted therapies

EGFR TKI inhibitors

Angiogenesis inhibitors

Jean-Charles Soria, ESMO 2011
EGFR: Potential Consequences of Dysregulation

- Invasion
- Metastasis
- Survival
- Angiogenesis (new blood vessels)
- Proliferation (cell growth)
- Apoptosis

EGFR

PI3K

MAPK (KRAS)

Signaling cascades

Gene activation
Cell cycle progression

Myc, Fos, Jun

M → G1 → G2 → S
**EGFR in NSCLC: two distinct pathways**

- Greater signalling through the MAPK pathway producing excessive cell proliferation
- Higher affinity for ATP than mutant receptor, so greater competition with EGFR TKIs for binding sites; higher concentrations needed to inhibit
- Successful inhibition of wild-type EGFR reduces proliferation and halts tumour growth
- Higher incidence of stable disease

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Sordella, et al. Science 2004

**EGFR wild-type**

**Survival**

**Proliferation**

- GDP-RAS → GTP-RAS
- RAF
  - MEK
  - MAPK
- Transcription factors
- Nucleus

ATP

"Greater signalling through the MAPK pathway producing excessive cell proliferation"

"Higher affinity for ATP than mutant receptor, so greater competition with EGFR TKIs for binding sites; higher concentrations needed to inhibit"

"Successful inhibition of wild-type EGFR reduces proliferation and halts tumour growth"

"Higher incidence of stable disease"
Activating mutations in EGFR: what are the consequences?

- Preferential signalling through the PI3K-mediated anti-apoptotic pathway – ‘oncogene addiction’
- The EGFR protein is permanently activated, even in the absence of ligands
- Reduced affinity for ATP means EGFR TKIs have less competition for binding sites; lower concentrations sufficient to inhibit
- Successful inhibition of mutated EGFR produces ‘apoptotic shock’
- Higher incidence of complete or partial response

Act Mut+ = activating mutation positive
ATP = adenosine triphosphate

Mutations identified in **EGFR** gene

**EGFR transcript**

- **Exons 1–16**
- **Exon 17**
- **Exons 18–24**
- **Exons 25–28**

**Confer sensitivity/resistance to EGFR TKIs**

- G719A/S
- Deletions
- D761Y
- D770_N771 insNPG
- T790M
- L858R
- L861X

**Unclear effect on sensitivity to EGFR TKIs**

- L688P
- V689M
- P694X
- V700D
- E709X
- I715S
- L718P
- S720X
- G735S
- V738F
- V742A
- T751I
- E746K
- S752Y
- D761N
- A763V
- N765A
- S768I
- T783A
- L792P
- L798F
- G810S
- N826S
- L833V
- H835L
- H850N
- V851X
- I853T
- H850N
- V851X
- A859T
- G863D
- A864T
- E866K

**EGFR and mutations within TK Domain**

Figure: Sequist, LV, et al. *J Clin Oncol* 2007;25:587-95
Screening for Epidermal Growth Factor Receptor Mutations in Lung Cancer

Rafael Rosell, M.D., Teresa Moran, M.D., Cristina Queralt, B.S., Rut Porta, M.D.,
Felipe Cardenal, M.D., Carlos Camps, M.D., Margarita Majem, M.D.,
Guillermo Lopez-Vivanco, M.D., Dolores Isla, M.D., Mariano Provencio, M.D.,
Arnélia Insa, M.D., Bartomeu Massuti, M.D., José Luis Gonzalez-Larribe, M.D.,
Luis Paz-Ares, M.D., Isabel Bover, M.D., Rosario García-Campelo, M.D.,
Miguel Angel Moreno, M.D., Silvia Catot, M.D., Christian Rolfo, M.D.,
Noemí Reguart, M.D., Ramon Palmero, M.D., José Miguel Sánchez, M.D.,
Román Bastús, M.D., Clara Mayo, Ph.D., Jordi Bertran-Alamillo, B.S.,
Miguel Angel Molina, Ph.D., Jose Javier Sanchez, M.D., and Miquel Taron, Ph.D.,
for the Spanish Lung Cancer Group
Clinical characteristics do not reliably predict *EGFR* mutation status

Spanish Lung Cancer Group trial in advanced NSCLC patients with *EGFR* mutations (n=350)

- **Gender**
  - Male: 30%
  - Female: 70%
- **Smoking status**
  - Never smoker: 26%
  - Former smoker: 74%
- **Histology**
  - Adenocarcinoma: 9%
  - Non-adeno/BAC: 91%

Significant proportion of *EGFR* mutation-positive population falls outside typical subgroups.

Rosell, et al. NEJM 2009
Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non-Small-Cell Lung Cancer to Gefitinib

Thomas J. Lynch, M.D., Daphne W. Bell, Ph.D., Raffaella Sordella, Ph.D., Sarada Gurubhagavatula, M.D., Ross A. Okimoto, B.S., Brian W. Brannigan, B.A., Patricia L. Harris, M.S., Sara M. Haserlat, B.A., Jeffrey C. Supko, Ph.D., Frank G. Haluska, M.D., Ph.D., David N. Louis, M.D., David C. Christiani, M.D., Jeff Settleman, Ph.D., and Daniel A. Haber, M.D., Ph.D.
Distinct differences in response rates between \textit{EGFR} mutation +ve and wild-type NSCLC

- Regardless of treatment, lower response rates are seen in patients with \textit{EGFR} wild-type disease.
- Stable disease is a more likely outcome of treatment in wild-type NSCLC.

\begin{itemize}
  \item \textbf{IPASS}
  \begin{itemize}
    \item Gefitinib: 71.2% (n=132)
    \item CP: 47.3% (n=129)
  \end{itemize}
  \begin{itemize}
    \item Gefitinib: 23.5% (n=91)
    \item CP: 1.1% (n=85)
  \end{itemize}

\end{itemize}

\textbf{Yoshioka et al.}
\begin{itemize}
  \item No. of patients: 85
  \item Response rate: 3.3% (1/30)
  \item Stable disease: 60% (18/30)
  \item PFS, months: 2.1
  \item OS, months: 9.2
\end{itemize}

Mok, et al. NEJM 2009; Yoshioka, et al. JTO 2010
Different EGFR TKIs have different PK properties

<table>
<thead>
<tr>
<th></th>
<th>Erlotinib(^1) (150mg/day)</th>
<th>Gefitinib(^2) (225mg/day)</th>
<th>Gefitinib(^2) (525mg/day)</th>
<th>Gefitinib(^2) (700mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(C_{max}) (ng/mL)</td>
<td>2,120</td>
<td>307</td>
<td>903</td>
<td>2,146</td>
</tr>
<tr>
<td>AUC(_{0-24}) (ng•hour/mL)</td>
<td>38,420</td>
<td>5,041</td>
<td>14,727</td>
<td>36,077</td>
</tr>
</tbody>
</table>

- For gefitinib to achieve equivalent drug concentrations to erlotinib, patients would need to take >3 times the recommended 250mg dose.
- This may explain the differences in efficacy seen in EGFR wild-type NSCLC.

PK=pharmacokinetic; \(C_{max}\) = maximum plasma concentration; AUC = area under the curve.

2. Ranson, et al. JCO 2002
## Randomized studies in first line with reversible TKi in EGFR mutated NSCLC

<table>
<thead>
<tr>
<th>TRIAL</th>
<th>Reversible TKi</th>
<th>Nº EGFR(^m) mut</th>
<th>RR (TK vs CT) (%)</th>
<th>Median PFS (TK vs CT) (mo)</th>
<th>OS (TKI vs CT) (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subset analysis of phase III trials selected by clinical backgrounds</strong>*:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First-Signal(^1)</td>
<td>Gefitinib</td>
<td>27</td>
<td>84 vs 37</td>
<td>8.4 vs 6.7</td>
<td>30.6 vs 26.5</td>
</tr>
<tr>
<td>IPASS(^2)</td>
<td>Gefitinib</td>
<td>132</td>
<td>71 vs 47</td>
<td>9.8 vs 6.4</td>
<td>21.6 vs 21.9</td>
</tr>
<tr>
<td>CALGB 30406(^3)</td>
<td>Erlotinib</td>
<td>33</td>
<td>67</td>
<td>15.7</td>
<td>31.3</td>
</tr>
<tr>
<td><strong>Phase III trials selected by EGFR mutation status:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NEJGSG002(^4)</td>
<td>Gefitinib</td>
<td>228</td>
<td>74 vs 29</td>
<td>10.8 vs 5.4</td>
<td>27.7 vs 26.6</td>
</tr>
<tr>
<td>WJTOG3405(^5)</td>
<td>Gefitinib</td>
<td>172</td>
<td>62 vs 32</td>
<td>9.2 vs 6.3</td>
<td>NA</td>
</tr>
<tr>
<td>OPTIMAL(^6)</td>
<td>Erlotinib</td>
<td>154</td>
<td>83 vs 36</td>
<td>13.7 vs 4.6</td>
<td>NA</td>
</tr>
<tr>
<td>EURTACC(^7)</td>
<td>Erlotinib</td>
<td>173</td>
<td>58 vs 15</td>
<td>9.7 vs 5.2</td>
<td>NA</td>
</tr>
</tbody>
</table>

RR = response rate; PFS = progression-free survival; HR = hazard ratio; CT=chemotherapy

EGFR-TKIs vs CT in first line: phase III clinical trials in “Biomarker selected” population

NEJ002
- Chemonaive
- Stage III-IV
- Adenocarcinoma
- EGFR mut
- PS 0-1

1:1 randomisation
- Gefitinib
  (250 mg / day)
- Carboplatin
  (AUC 5 or 6) / paclitaxel
  (200 mg / m²)
  3 weekly

WJTOG 3405
- Chemonaive
- Stage III-IV
- Adenocarcinoma
- EGFR mut
- PS 0-1

1:1 randomisation
- Gefitinib
  (250 mg / day)
- Cisplatin (80mg/m²)
  / docetaxel (60 mg / m²)
  3-weekly

* Primary endpoint PFS
Gefitinib phase III trials in Asiatic EGFR mutated NSCLC

**IPASS**
HR (95% CI) = 0.40
p = 0.001

**NEJ002**
HR (95% CI) = 0.307
p = 0.001

**WJTOG3405**
HR (95% CI) = 0.40
p = 0.001

**Survival**
- Gefitinib: 9.5 m
- Carb/pacl: 6.3 m

**Progression-Free Survival**
- Gefitinib: 74.5%
- Carb/pacl: 47.3%

**Median Interval**
- Gefitinib: 10.4 m
- Carb/pacl: 5.5 m

**Response Rate**
- Gefitinib: 82.1%
- Carb/pacl: 32.2%

References:

Kennis / Ervaring / Zorg
Erlotinib vs CT in first line: phase III clinical trials in “Biomarker selected” population

**OPTIMAL**
- Chemonaïve
- Stage III-IV
- Adenocarcinoma
- EGFR mut
- PS 0-1
- n 165

1:1 randomisation

- Erlotinib (150 mg QD)
- Carboplatin + Gemcitabine 3 weekly

**EURTAC**
- Chemonaïve
- Stage III-IV
- Adenocarcinoma
- EGFR mut
- PS 0-2
- n 146

1:1 randomisation

- Erlotinib (150 mg QD)
- Platinum-based

Primary endpoint PFS
Cross-over at PD allowed

Erlotinib, n=82  
Gem/Carbo, n=72  
HR=0.16 (0.10–0.26)  
Log-rank p<0.0001  

**OPTIMAL PFS: updated analysis (ITT)**

![Graph showing PFS probability vs. time (months) for Erlotinib and Gem/Carbo treatments.](image)

**Patients at risk**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erlotinib</td>
<td>82</td>
<td>82 70 51 20 2</td>
</tr>
<tr>
<td>Gem/Carbo</td>
<td>72</td>
<td>72 26 4 0 0</td>
</tr>
</tbody>
</table>

Zhou C, Lancet 2011
OPTIMAL Trial: Subgroup analysis of PFS

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>HR (95% CI)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>0.16 (0.10–0.26)</td>
<td>154</td>
</tr>
<tr>
<td>Stage IV</td>
<td>0.18 (0.11–0.28)</td>
<td>138</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>0.27 (0.06–1.16)</td>
<td>16</td>
</tr>
<tr>
<td>Female</td>
<td>0.13 (0.07–0.24)</td>
<td>91</td>
</tr>
<tr>
<td>Male</td>
<td>0.26 (0.14–0.50)</td>
<td>63</td>
</tr>
<tr>
<td>Age ≥65</td>
<td>0.17 (0.07–0.43)</td>
<td>38</td>
</tr>
<tr>
<td>Age &lt;65</td>
<td>0.19 (0.11–0.31)</td>
<td>116</td>
</tr>
<tr>
<td>PS 0–1</td>
<td>0.16 (0.10–0.26)</td>
<td>144</td>
</tr>
<tr>
<td>PS 2</td>
<td>0.21 (0.01–1.28)</td>
<td>10</td>
</tr>
<tr>
<td>Never smoker</td>
<td>0.14 (0.08–0.25)</td>
<td>109</td>
</tr>
<tr>
<td>Current/former smoker</td>
<td>0.21 (0.09–0.49)</td>
<td>45</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>0.17 (0.11–0.28)</td>
<td>134</td>
</tr>
<tr>
<td>Non-adenocarcinoma</td>
<td>0.22 (0.06–0.73)</td>
<td>20</td>
</tr>
</tbody>
</table>

Zhou C, Lancet 2011
Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial


THE LANCET Oncology
EURTAC: erlotinib first-line in EGFR mutation+ NSCLC

- Study initiated by the Spanish Lung Cancer Group (GECP)
- Recruitment extended to Italy and France

**Chemonaïve advanced NSCLC**
- *EGFR* mutation+ (exon 19 or L858R)
- PS 0–2
- n~150

**Erlotinib 150mg/day until PD**

**Platinum-doublet chemotherapy**

- Primary endpoint: PFS
- Secondary endpoints: ORR, 1-year survival, OS, safety, QoL, localisation of PD
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Erlotinib (n=77)</th>
<th>Chemotherapy (n=76)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, yrs (range)</td>
<td>64 (24–82)</td>
<td>64 (29–82)</td>
</tr>
<tr>
<td>Age &lt;65 years / ≥65 yrs, %</td>
<td>49 / 51</td>
<td>51 / 49</td>
</tr>
<tr>
<td>Male / female, %</td>
<td>32 / 68</td>
<td>21 / 79</td>
</tr>
<tr>
<td>Stage IIIB / IV, %</td>
<td>9 / 91</td>
<td>7 / 93</td>
</tr>
<tr>
<td>ECOG PS 0 / 1 / 2, %</td>
<td>30 / 57 / 13</td>
<td>34 / 54 / 12</td>
</tr>
<tr>
<td>Current smoker / former smoker / never-smoker, %</td>
<td>4 / 26 / 70</td>
<td>13 / 13 / 74</td>
</tr>
<tr>
<td>Adenocarcinoma / squamous / other, %</td>
<td>95 / 1 / 4</td>
<td>91 / 0 / 9</td>
</tr>
<tr>
<td>Exon 19 deletion / L858R mutation, %</td>
<td>64 / 36</td>
<td>63 / 37</td>
</tr>
</tbody>
</table>

All patients were Caucasian
Data cut-off: 2 Aug 2010

Courtesy Dr. Rosell
EURTAC: Erlotinib significantly improves PFS as first-line treatment for EGFR mutant NSCLC

- Erlotinib provided significant benefit over chemotherapy
  - 63% reduction in risk of progression or death; HR=0.37
  - ORR was improved with erlotinib vs chemotherapy (58% versus 15%; P<0.0001)
  - Median OS for erlotinib vs chemotherapy: 22.9 months vs 18.8 months; P=0.8702
- OS data are immature and confounded by second-line treatment

**PFS probability**

- **Erlotinib (n=86)**
- **Chemotherapy (n=87)**

**Median PFS**
- Erlotinib: 9.7 months
- Chemotherapy: 5.2 months
- HR=0.37 (0.25–0.54); log-rank P<0.0001

ORR= overall response rate; OS= overall survival

Rosell R et al. Lancet Oncology 2012
### Subgroup Analyses of PFS

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>HR (95% CI)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>0.42 (0.27–0.64)</td>
<td>153</td>
</tr>
<tr>
<td>&lt;65 yrs</td>
<td>0.53 (0.29–0.97)</td>
<td>77</td>
</tr>
<tr>
<td>≥65 yrs</td>
<td>0.28 (0.15–0.55)</td>
<td>76</td>
</tr>
<tr>
<td>Male</td>
<td>0.41 (0.17–0.96)</td>
<td>41</td>
</tr>
<tr>
<td>Female</td>
<td>0.39 (0.23–0.66)</td>
<td>112</td>
</tr>
<tr>
<td>PS 0</td>
<td>0.19 (0.07–0.54)</td>
<td>49</td>
</tr>
<tr>
<td>PS 1</td>
<td>0.43 (0.24–0.76)</td>
<td>85</td>
</tr>
<tr>
<td>PS 2</td>
<td>0.53 (0.17–1.70)</td>
<td>19</td>
</tr>
<tr>
<td>Current smoker</td>
<td>0.92 (0.23–3.74)</td>
<td>13</td>
</tr>
<tr>
<td>Former smoker</td>
<td>0.90 (0.32–2.57)</td>
<td>30</td>
</tr>
<tr>
<td>Never smoker</td>
<td>0.23 (0.13–0.40)</td>
<td>110</td>
</tr>
<tr>
<td>Exon 19 del</td>
<td>0.31 (0.18–0.55)</td>
<td>97</td>
</tr>
<tr>
<td>L858R</td>
<td>0.65 (0.33–1.27)</td>
<td>56</td>
</tr>
</tbody>
</table>

Data cut-off: 2 Aug 2010

Courtesy Dr. Rosell
## Summary of safety data

<table>
<thead>
<tr>
<th>Event</th>
<th>Erlotinib (n=75)</th>
<th>Erlotinib (n=75)</th>
<th>Chemotherapy (n=74)</th>
<th>Chemotherapy (n=74)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse events (AEs), all grades</td>
<td>72 (96)</td>
<td>73 (99)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment-related AEs, all grades</td>
<td>69 (92)</td>
<td>70 (95)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3 / 4 AEs</td>
<td>34 (45)</td>
<td>60 (81)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose modification / interruption due to AE</td>
<td>20 (27)</td>
<td>39 (53)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose modification / interruption due to treatment-related AE</td>
<td>17 (23)</td>
<td>35 (47)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discontinuation due to AEs</td>
<td>9 (12)</td>
<td>11 (15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discontinuation due to treatment-related AE</td>
<td>4 (5)</td>
<td>10 (14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any serious AEs</td>
<td>20 (27)</td>
<td>19 (26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment-related serious AEs</td>
<td>5 (7)</td>
<td>12 (16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment-related death</td>
<td>1 (1)</td>
<td>2 (3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data cut-off: 2 Aug 2010

Courtesy Dr. Rosell
Conclusions

- EURTAC is the first prospective study of an EGFR tyrosine-kinase inhibitor (TKI) versus chemotherapy for first-line treatment of EGFR mutation-positive NSCLC in Caucasian patients.

- Interim analysis confirms significant benefit in PFS of erlotinib over standard chemotherapy:
  - 58% reduction in risk of progression / death (HR=0.42)

- OS data are immature, with high level of known crossover.

- No new safety findings, and better than chemotherapy.

- Erlotinib provides significant benefits over first-line chemotherapy in EGFR mutation-positive disease.

Courtesy Dr. Rosell
Erlotinib phase III trials in EGFR mutated NSCLC

**OPTIMAL**

HR (95% CI) = 0.16
p<0.0001

**EURTAC**

HR (95% CI) = 0.37
p<0.001

**Graphs:**
- **Left Graph:**
  - Erlotinib (n=82)
  - Gem/carbo (n=72)
  - Time (months): 0, 5, 10, 15, 20
  - PFS probability: 1.0, 0.8, 0.6, 0.4, 0.2, 0.0
  - ORR %: 100, 83, 36
  - p<0.0001

- **Right Graph:**
  - Erlotinib (n=86)
  - Chemotherapy (n=87)
  - Time (months): 0, 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33
  - PFS probability: 1.0, 0.8, 0.6, 0.4, 0.2, 0.0
  - ORR %: 100, 58, 15
  - p<0.0001

**References:**
TKI Resistance
Mutations identified in *EGFR* gene

**EGFR transcript**
- Exons 1–16
- Exon 17
- Exons 18–24
- Exons 25–28

**Confer sensitivity/resistance to EGFR TKIs**
- **G719A/S**
- **Deletions**
- **D761Y**
- **D770_N771 insNPG**
- **T790M**
- **L858R**
- **L861X**

**Unclear effect on sensitivity to EGFR TKIs**
- L688P
- V689M
- P694X
- V700D
- E709X
- I715S
- L718P
- S720X
- G735S
- V738F
- V742A
- T751I
- E746K
- S752Y
- D761N
- L730F
- P733L
- G736V
- A763V
- N765A
- S768I
- L792F
- T783A
- L798F
- G810S
- N826S
- L833V
- H835L
- L838V
- T847I
- H850N
- I853T
- V851X
- A859T
- G863D
- E866K
- A864T

EGFR TKI resistance: Clinical definition?

- Tumour flare on stopping TKI and response to reinitiation\(^1\)
- Clinical definition of resistance proposed by Jackman et al\(^2\):

<table>
<thead>
<tr>
<th>Criteria for acquired resistance to EGFR TKIs in lung cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Previously received treatment with a single-agent EGFR TKI (e.g. gefitinib or erlotinib)</td>
</tr>
<tr>
<td>2. Either of the following:</td>
</tr>
<tr>
<td>A. A tumour that harbors an EGFR mutation known to be associated with drug sensitivity (ie, G719X, exon 19 deletion, L858R, L861Q)</td>
</tr>
<tr>
<td>B. Objective clinical benefit from treatment with an EGFR TKI as defined by either:</td>
</tr>
<tr>
<td>i. Documented partial or complete response (RECIST or WHO), or</td>
</tr>
<tr>
<td>ii. Significant and durable (6 months) clinical benefit (stable disease as defined by RECIST or WHO) after initiation of gefitinib or erlotinib</td>
</tr>
<tr>
<td>3. Systemic progression of disease (RECIST or WHO) while on continuous treatment with gefitinib or erlotinib within the last 30 days</td>
</tr>
<tr>
<td>4. No intervening systemic therapy between cessation of gefitinib or erlotinib and initiation of new therapy</td>
</tr>
</tbody>
</table>

---

Acquired resistance mechanisms to EGFR-TKIs

- Secondary EGFR mutations: T790M.
- MET amplification.
- HGF high levels.
- Downstream effectors: PTEN loss, PI3K mut.
- Small cell lung cancer (SCLC) transformation.
- Epithelial to Mesenchimal Transition (EMT).
- DRG: BRCA1 mRNA levels.
- FAS and NFKB signalling.
- VEGF/VEGFR.
- IGFR1, IGFBP
- AXL
- BIM
Acquired resistance mechanisms to EGFR-TKIs
## Frequency of acquired resistance mechanisms to EGFR-TKIs

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>T790M</th>
<th>MET amplif</th>
<th>HGF high</th>
<th>PI3KCA mut</th>
<th>SCLC</th>
<th>EMT</th>
<th>Unk</th>
</tr>
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<tbody>
<tr>
<td><strong>Yano, JTO 11</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acquired</td>
<td>23</td>
<td>52%</td>
<td>9%</td>
<td>61%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Intrinsic</td>
<td>45</td>
<td>0%</td>
<td>4%</td>
<td>29%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sensitive</td>
<td>29</td>
<td>0%</td>
<td>0%</td>
<td>13%</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td><strong>Arcila, CCR 11</strong></td>
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<td></td>
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<tr>
<td>Acquired</td>
<td>99</td>
<td>68%</td>
<td>11%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td><strong>Sequist L, STM 11</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Acquired</td>
<td>37</td>
<td>49%</td>
<td>5%</td>
<td>-</td>
<td>5%</td>
<td>14%</td>
<td>3/12</td>
<td>30%</td>
</tr>
</tbody>
</table>
The most common mechanism of resistance to EGFR TKIs (50-68%) Pretreatment T790M found in high frequency (31.5%) with longer survival to TKIs (Su et al. JCO 2012)

Display surprisingly slow rates of growth (Chmielecki J Sci Transl Med 2011).

May have a better prognosis than non-T790M mechanisms.

The irreversible EGFR inhibitors can block the growth of NSCLC cell lines harboring T790M mutations.

Is the T790M an actionable and druggable mutation? – diagnostic, prognostic or therapeutic
Strategies to overcome acquired resistance

- **T790M:**
  - Irreversible inhibition of T790M
  - Downstream inhibition (PI3K, mTOR)
  - Dual inhibition with EGFR mAb

- **MET:**
  - Dual inhibition of EGFR and MET pathways

- **Others (in vitro):**
  - IGF-1R inhibition
  - VEGF inhibition
  - EMT inhibition (E-cadherin): HDACi
  - PIK3CA inhibition
  - Chemotherapy?

30% basal without TKI

Over 20% in literature

Neratinib (HKI272)

- NSCLC patients with ≥12 weeks of prior TKI therapy were placed in:
  - Arm A, if EGFR mutation positive (91p)
  - Arm B, if EGFR wild-type (48p)

- All patients received daily oral neratinib, initially at 320 mg but subsequently reduced to 240 mg because of excessive diarrhea (50% Grade 3)

- Low activity (PR 3%) in EGFR mut patients with prior benefit from TKIs.

- No responses in EGFRwt and T790M.

- Striking activity in exon 18 G719X +:
  - 3/4 patients with PR.
  - Median PFS 52.7 weeks

Sequist L, J Clin Oncol 2010
NSCLC patients with ≥12 weeks of prior TKI therapy and/or T790M +.
- Forty-one patients enrolled, 33 evaluable for efficacy.

XL647 300 mg was administered once daily.

Only 1 PR (3%) was observed.

Better outcome in p without T790M (PD 14% vs 67%).

T790M+ patients had a significantly worse progression-free survival.

- PFS 10 m – OS 22 m (exon 19)
- 7m (exon 21) (Pietanza, JTO 2012)
Waterfall plot of best response with new irreversible EGFR inhibitors in EGFR mut+

Phase II Dacomitinib (Study 1017)  Phase II Afatinib (LUX-Lung 2)

ORR 81%  ORR 88%

Best change from baseline (%)

-100  -80  -60  -40  -20  0  20

PR

Exon 19 deletion
L858R
Exon 18 and/or 20

PF299804 is a potent, irreversible, orally bioavailable small-molecule inhibitor of EGFR (human epidermal growth factor receptor [HER]1), HER2, and HER4 tyrosine kinases. In preclinical NSCLC models, PF299804 has demonstrated antitumor activity against EGFR-activating mutations and T790M, a mutation detected in the tumors of approximately 50% of patients who develop resistance to gefitinib or erlotinib.\(^{1-4}\)
In 53 Patient with EGFR mutant lung cancers
- 74% experienced PR
- 74% remained progression free at 1 year
- Median PFS was 17 month
Phase III Dacomitinib vs Erlotinib in NSCLC: (recruiting) NCT01360554
ARCHER Trial: Study design
Dacomitinib vs Erlotinib

M Boyer,1 PA Jänne,2 T Mok,3 K O’Byrne,4 L Paz-Ares, et al; ASCO 2012, #TPS7615

Recruiting Ongoing
Overview of Dacomitinib Ongoing Clinical Programme

Phase 1

Solid tumors
- **1001**: US; Solid tumors; N=121 (n=57 lung cohort)
- **1005**: Japanese; Solid tumors; N=13 (n=9 lung cohort)

Novel combinations
- **A8081006**: crizotinib; N=70 (recruiting)

Clinical pharmacology
- **1039**: N=14 (healthy volunteers)
- **1020**: N=6 (healthy volunteers)

Phase 2

NSCLC
- **1002**: Adv. NSCLC, KRAS WT, post ≥ 1 chemotherapy, post-TKI failure
- **1003**: Ph1/2, Adv. NSCLC, Korean
- **1028**: Adv. NSCLC vs. Erlotinib, post 1-2 chemotherapies
- **1017**: Adv. NSCLC, EGFRmu/selected, 1st line, Asian (recruiting)

Other tumors
- **1027**: Recurrent or metastatic SCCHN, 1st-line
- Rationale for Pan-HER inhibition in other tumors investigated

Phase 3

NSCLC
- **ARCHER 1009**: Adv. NSCLC vs. Erlotinib, post 1-2 chemotherapies (recruiting)
- **NCIC BR.26/1011**: Adv. NSCLC, prior 1-2 chemotherapies, post-TKI failure (recruiting)
Afatinib: an irreversible ErbB Family Blocker

Afatinib is an orally available, irreversible ErbB Family Blocker, with high efficacy potential. Inhibition of ErbB Family receptor heterodimerization. *In vitro* activity against EGFR-resistant T790M mutation.


Yang JC, et al.
LUX-Lung 3: a randomized, open-label, Phase III study of afatinib vs cisplatin/pemetrexed as 1st-line treatment for patients with advanced adenocarcinoma of the lung harboring EGFR-activating mutations

**LUX-Lung 3: Study design**

**Stage IIIIB (wet)/IV lung adenocarcinoma (AJCC version 6)**

**EGFR mutation in tumor**
(central lab testing; Therascreen EGFR29* RGQ PCR)

Randomization 2:1
Stratified by:
EGFR mutation (Del19/L858R/other)
Race (Asian/non-Asian)

Afatinib 40 mg/day†

Cisplatin + Pemetrexed
75 mg/m² + 500 mg/m²
i.v. q21 days, up to 6 cycles

Primary endpoint: PFS (RECIST 1.1, independent review)‡
Secondary endpoints: ORR, DCR, DoR, tumor shrinkage, OS, PRO§, safety, PK

---

*EGFR29:19 deletions in exon 19, 3 insertions in exon 20, L858R, L861Q, T790M, G719S, G719A and G719C (or G719X), S768I.
†Dose escalated to 50 mg if limited AE observed in cycle 1. Dose reduced by 10 mg decrements in case of related G3 or prolonged G2 AE.
‡Tumor assessments: q6 weeks until Week 48 and q12 weeks thereafter until progression/start of new therapy.
§Patient-reported outcomes: Q-5D, EORTC QLQ-C30 and QLQ-LC13 at randomization and q3 weeks until progression or new anti-cancer therapy.
Patient disposition

- 1269 screened
- 452 EGFR mutation (+)
- 345 randomized
- 107 did not meet eligibility criteria or did not enter

- 230 assigned to afatinib
  - 1 did not receive treatment

  - PFS event at data cut-off
    - 155 by investigator assessment
    - 152 by independent assessment

  - 65 on treatment

- 115 assigned to Cisplatin + Pemetrexed
  - 4 did not receive treatment

  - PFS event at data cut-off
    - 83 by investigator assessment
    - 69 by independent assessment

  - 0 on treatment

Yang JC, et al.
## Patient demographics/characteristics

<table>
<thead>
<tr>
<th></th>
<th>Afatinib (n=230)</th>
<th>Cis/Pem (n=115)</th>
<th>Total (n=345)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>83 (36)</td>
<td>38 (33)</td>
<td>121 (35)</td>
</tr>
<tr>
<td>Female</td>
<td>147 (64)</td>
<td>77 (67)</td>
<td>224 (65)</td>
</tr>
<tr>
<td><strong>Age, years, median (range)</strong></td>
<td>62 (28–86)</td>
<td>61 (31–83)</td>
<td>61 (28–86)</td>
</tr>
<tr>
<td><strong>Race, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>61 (27)</td>
<td>30 (26)</td>
<td>91 (26)</td>
</tr>
<tr>
<td>Eastern Asian</td>
<td>165 (72)</td>
<td>83 (72)</td>
<td>248 (72)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (1)</td>
<td>2 (2)</td>
<td>6 (2)</td>
</tr>
<tr>
<td><strong>Smoking status, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoked</td>
<td>155 (67)</td>
<td>81 (70)</td>
<td>236 (68)</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>70 (30)</td>
<td>32 (28)</td>
<td>102 (30)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>5 (2)</td>
<td>2 (2)</td>
<td>7 (2)</td>
</tr>
<tr>
<td><strong>Stage (AJCC 6.0), n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIIB (wet)</td>
<td>20 (9)</td>
<td>17 (15)</td>
<td>37 (11)</td>
</tr>
<tr>
<td>IV</td>
<td>210 (91)</td>
<td>98 (85)</td>
<td>308 (89)</td>
</tr>
<tr>
<td><strong>ECOG PS, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>92 (40)</td>
<td>41 (36)</td>
<td>133 (39)</td>
</tr>
<tr>
<td>1</td>
<td>138 (60)</td>
<td>73 (64)</td>
<td>211 (61)</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>1 (1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td><strong>EGFR mutation, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Del19</td>
<td>113 (49)</td>
<td>57 (49)</td>
<td>170 (49)</td>
</tr>
<tr>
<td>L858R</td>
<td>91 (40)</td>
<td>47 (41)</td>
<td>138 (40)</td>
</tr>
<tr>
<td>Other</td>
<td>26 (11)</td>
<td>11 (10)</td>
<td>37 (11)</td>
</tr>
</tbody>
</table>
Primary endpoint: PFS
Independent review – all randomized patients

Progression-free survival (probability)

<table>
<thead>
<tr>
<th></th>
<th>Afatinib n=230</th>
<th>Cis/pem n=115</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS event, n (%)</td>
<td>152 (66)</td>
<td>69 (60)</td>
</tr>
<tr>
<td>Median PFS (months)</td>
<td>11.1</td>
<td>6.9</td>
</tr>
<tr>
<td>Hazard ratio (95% confidence interval)</td>
<td>0.58 (0.43–0.78)</td>
<td>p=0.0004</td>
</tr>
</tbody>
</table>

Progression-free survival (months)

Number at risk
Afatinib   Cis/Pem
230        115
180        72
151        41
120        21
77         11
50         7
31         3
10         2
3          0
0          0
Progression-free survival (probability)

<table>
<thead>
<tr>
<th></th>
<th>Afatinib n=204</th>
<th>Cis/pem n=104</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS event, n (%)</td>
<td>130 (64)</td>
<td>61 (59)</td>
</tr>
<tr>
<td>Median PFS (months)</td>
<td>13.6</td>
<td>6.9</td>
</tr>
<tr>
<td>Hazard ratio (95% confidence interval)</td>
<td>0.47 (0.34–0.65)</td>
<td>p&lt;0.0001</td>
</tr>
</tbody>
</table>

PFS: Common mutations (Del19/L858R)
Independent review – patients with Del19/L858R (n=308)

Yang JC, et al.
## PFS subgroup analysis
### Investigator review – all randomized patients

<table>
<thead>
<tr>
<th>Factors</th>
<th>Number of patients</th>
<th>Hazard ratio (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>345</td>
<td>0.49 (0.37–0.65)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>121</td>
<td>0.45 (0.28–0.70)</td>
</tr>
<tr>
<td>Female</td>
<td>224</td>
<td>0.51 (0.36–0.72)</td>
</tr>
<tr>
<td><strong>Age at baseline (&lt;65 v ≥65 years)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>211</td>
<td>0.43 (0.30–0.61)</td>
</tr>
<tr>
<td>≥65 years</td>
<td>134</td>
<td>0.63 (0.40–0.98)</td>
</tr>
<tr>
<td><strong>Race stratification factor</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Asian</td>
<td>96</td>
<td>0.62 (0.36–1.06)</td>
</tr>
<tr>
<td>Asian</td>
<td>249</td>
<td>0.45 (0.33–0.62)</td>
</tr>
<tr>
<td><strong>EGFR mutation category</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Del19/L858R (common)</td>
<td>308</td>
<td>0.41 (0.31–0.55)</td>
</tr>
<tr>
<td>Del19</td>
<td>170</td>
<td>0.27 (0.18–0.41)</td>
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<tr>
<td>L858R</td>
<td>138</td>
<td>0.60 (0.39–0.93)</td>
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<tr>
<td><strong>Baseline ECOG score</strong></td>
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<tr>
<td>0</td>
<td>133</td>
<td>0.47 (0.30–0.75)</td>
</tr>
<tr>
<td>1</td>
<td>211</td>
<td>0.53 (0.38–0.75)</td>
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<tr>
<td><strong>Smoking history</strong></td>
<td></td>
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<tr>
<td>Never smoked</td>
<td>236</td>
<td>0.48 (0.34–0.69)</td>
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<tr>
<td>&lt;15 packet years + stop &gt;1 year</td>
<td>30</td>
<td>0.34 (0.14–0.85)</td>
</tr>
<tr>
<td>Other current/ex-smoker</td>
<td>79</td>
<td>0.54 (0.33–0.91)</td>
</tr>
</tbody>
</table>

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Yang JC, et al.

Kennis / Ervaring / Zorg

Universiteit Antwerpen

UZA
Objective response

All patients

Common mutations (Del19/L858R)

Median duration of response: 11.1 vs. 5.5 months (all patients; independent review)

p<0.001

p<0.001

p<0.0001

p<0.0001
Summary

- LUX-Lung 3 is the largest global prospective trial in EGFR mutation-positive lung cancer and the first using cisplatin and pemetrexed as the comparator.

- LUX-Lung 3 met its primary endpoint of PFS (independent review):
  - **Overall study population:**
    - Median PFS of 11.1 months for afatinib; 6.9 months for chemotherapy (HR=0.58 [95% CI: 0.43–0.78]; p=0.0004)
  - **Patients with common mutations (Del19+L858R):**
    - Median PFS of 13.6 months for afatinib; 6.9 months for chemotherapy (HR=0.47 [95% CI: 0.34–0.65]; p<0.0001)
  - Consistent efficacy in all relevant subgroups.
NSCLC patients with clinically defined AR (Jackman JCO 2010) received oral afatinib 40 mg daily with escalating dose cohorts of biweekly cetuximab at 250 and 500 mg/m2.

47 of 80 patients have been enrolled and received the predefined maximum dose (RP2D):
- afatinib 40 mg +
- cetuximab 500 mg/m2

Confirmed PRs were observed in 18/45 evaluable patients (40%), including 9/26 PRs in patients with documented T790M mutations.
Front-line Afatinib clinical program in EGFR mutated NSCLC

**LUX-LUNG 7**
- Phase IIB
- Gefitinib 250 mg QD vs Afatinib 40 QD
- Adv. NSCLC, first line
- End point: PFS

**LUX-LUNG 3**
- ASCO 2012
- Phase III study of afatinib vs cisplatin/pemetrexed as 1st-line
- Median PFS (months)
  - Afatinib: 11.1 months
  - Cisplatin/pemetrexed: 6.9 months
- Common mutations
  - Median PFS (months)
    - Afatinib: 13.6 months
    - Cisplatin/pemetrexed: 6.9 months

**LUX-LUNG 6**
- Phase III (n 330)
- Afatinib 40 QD vs cisplatin-gemcitabine
- Adv. NSCLC, first line (recruiting in Korea)
- End point: PFS
Overcoming T790M: Irreversible EGFR inhibitors: summary

Neratinib HKI-272 (EGFR + Her2) phase II
- RR 2% in TKI-resistant patients.
- Intriguing responses in G719X patients. (Sequist, JCO 2010)

XL-647 (EGFR, Her2, VEGF)
- RR 3% in TKI-resistant patients. (Pietanza, JTO 2011)
- PFS 10 m – OS 22 m(exon 19) 7m (exon 21) (Pietanza, JTO 2012)

SKLB1206, (T790M, ErbB2, ErbB4, VEGFR2)

Afatinib BIBW-2992 (EGFR + Her2)
- RR 7% in TKI-resistant patients, ~13 weeks PFS (Miller, Lanc Onc ‘12)
- RR 40% in Ph1 combining afatinib and cetuximab. (Janjigian, ASCO 2011)

Dacomitinib PF-299804 (EGFR + Her2)
- RR 7% in TKI-resistant patients. (Janne, ASCO ’09)
MET amplification

- Redundant activation of Her3 permits cells to transmit same downstream signaling in the presence of EGFR-TKI

- Concomitant inhibition of both EGFR and MET is required to kill resistant cells

- Less than 20% of NSCLC with acquired resistance had MET amplification in specimens

- MET inhibitors may be able to overcome MET-mediated resistance to EGFR kinase inhibitors, even in cells harboring T790M mutation (Bean J, PNAS 2007).
MET amplification

EGFR-TKI

Tivantinib (ARQ197)

- Previously treated advanced NSCLC.
- but **EGFR TKI–NAIVE !!!**
- Oral erlotinib (150 mg daily) plus oral tivantinib (360 mg twice daily) or erlotinib plus placebo (EP).
- Trend to superior PFS for the dual inhibition (3.8 vs 2.3 months)
- Superior PFS for E+T in non-squamous and KRASmut subsets.
- A global phase III clinical trial evaluating this combination in second- and third-line patients with NSCLC is now underway.

Schiller J, J Clin Oncol 2011
Overcoming MET amplification

Tivantinib, ARQ-197 (specific MET inhibitor)
- T + erlotinib significantly increases PFS in KRAS mut subset
  (Schiller, ASCO 2010)

Met-mab
- Met-mab + erlotinib significantly increases PFS in MET + (IHC) patients
  (Spigel, ASCO 2011)

Cabozantinib, XL-184 (MET + RET + VEGFR2)
- Some PRs in TKI-resistant patients in the Phase 1 setting (Wakelee, ASCO 2010)
- Phase II in monotherapy pretreated metastatic NSCLC pts with 4.2 months median PFS, 10% RECIST response, and 64% rate of objective tumor regression. (Pts with prior exposure to anti-EGFR therapy 50%) (Hellerstedt ASCO 2012)
- Phase 2 trial erlotinib +/- XL-184 in TKI resistant Patients, active, no recruiting yet.
Overcoming MET amplification: Ornatuzumab (MetMAb)
MetLUNG study 2011: Phase II

Efficacy in Met Diagnostic Positive Patients

**PFS:** HR = 0.53, p = 0.04

- Placebo
- MetMAb + erlotinib
- erlotinib

<table>
<thead>
<tr>
<th>Median (mos)</th>
<th>Placebo</th>
<th>MetMAb + erlotinib</th>
<th>erlotinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5</td>
<td>2.9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**OS:** HR = 0.37, p = 0.002

- Placebo
- MetMAb + erlotinib
- erlotinib

<table>
<thead>
<tr>
<th>Median (mos)</th>
<th>Placebo</th>
<th>MetMAb + erlotinib</th>
<th>erlotinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.8</td>
<td>12.6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

With permission from Spigel DR et al. Proc ASCO 2011; Abstract: 7505.
The MetLUNG study: phase III study of onartuzumab (MetMAb) plus erlotinib in patients with advanced, MET-positive NSCLC
Strategies to overcome acquired resistance

- **T790M:**
  - Irreversible inhibition of T790M
  - Downstream inhibition (PI3K, mTOR)
  - Dual inhibition with EGFR mAb

- **MET:**
  - Dual inhibition of EGFR and MET

- **HGF**

- **Others** (*in vitro*):
  - IGF-1R inhibition
  - VEGF inhibition
  - EMT inhibition (E-cadherin): HDACi
  - PIK3CA inhibition

**ALK??** **Chemotherapy?** Over 20% in literature

30% basal without TKI
Recently, high-level HGF expression was detected both in tumors with intrinsic (29%) and acquired resistance (61%) (Yano JTO 2011).

HGF induces gefitinib-resistance by restoring the PI3K/Akt pathway through Gab1, but not EGFR or ErbB3 (Yano, Cancer Res 2008; Turke, Ca Cell 2010).

Inhibition of EGFR signaling induces HGF-mediated clonal selection of pretreatment MET amplification (Turke, Ca Cell 2010).

A humanized MAb to HGF, TAK-701, combined with gefitinib, overcome gefitinib resistance induced by HGF in a preclinical model (Okamoto, Mol Ca Cell 2010).

PI3K/Akt pathway inhibition could overcome HGF-mediated resistance to EGFR-TKIs (Donev IS, CCR 2011).
Recently, greater induction of apoptosis following EGFR TKI treatment correlated with higher basal BIM expression across a panel of EGFR-mutant lung cancers; BIM was also expressed in the H1975 cell line, where the degree of apoptosis was second only to that in PC9 (Faber et al. Cancer Discovery 2011)

courtesy R.Rosell- EURTAC –ASCO 2012
Resistance To EGFR TKIs can be indolent... ...but not when the drug is stopped


Tumor growth can be rapid once EGFR TKI is stopped
Is there a biologic rational to keep the pressure on TK in EGFR mutated patients after progression?

<table>
<thead>
<tr>
<th>Histology</th>
<th>Adeno</th>
<th>Adeno</th>
<th>Adeno</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype</td>
<td>L858R</td>
<td>TP53</td>
<td>L858R</td>
</tr>
<tr>
<td>EGFR TKI status</td>
<td>Sensitive</td>
<td>Resistant</td>
<td>Sensitive</td>
</tr>
<tr>
<td>Tumor burden</td>
<td></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>
</table>

<table>
<thead>
<tr>
<th>Histology</th>
<th>Adeno</th>
<th>SCLC</th>
<th>Adeno</th>
<th>SCLC</th>
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<tbody>
<tr>
<td>Genotype</td>
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<td>L858R</td>
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<td>Sensitive</td>
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<tr>
<td>Tumor burden</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>Erlotinib</td>
<td></td>
<td>Erlotinib</td>
<td>C+RT</td>
</tr>
<tr>
<td>Timeline</td>
<td>2008</td>
<td>2009</td>
<td>2010</td>
<td></td>
</tr>
</tbody>
</table>

Overall response rate was 25.9% (95% confidence interval, 9.4%–42.4%) the median PFS was 7.0 months (95% CI, 6.2–7.8 months) and the median survival time was 11.4 months (95% CI, 9.4–13.5 months)
What’s nex?
A sample of ongoing upcoming trials

- AUY922 (Hsp90 inhib- Garon, Moran, Sequist; #7543 ASCO 2012; Ueno et al Lung Cancer. 2012 Apr;76(1):26-31)
- Afatinib + Cetuximab Phase II NCT01090011
- Erlotinib + MM121(Her3 Mab) (Phase I NCT00994123) Cancer Res March 15, 2010 70; 2485
- PI3K inhibitors + MEK drugs
- Anti-PD1 drugs + Erlotinib
- PI3K inhibitors + Erlotinib
- Antibodies targeting the MET ligand HGF (AMG102): AMG 102 + Erlotinib NCT01233687
- NOV120101 (Poziotinib) NCT01718847 – (Phase 2 Study in NSCLC Patients With Aquired Resistance to 1st Generation EGFR Tyrosine Kinase Inhibitors ) Korea
- WZ4002, a third-generation EGFR inhibitor (Sakuma, Laboratory Investigation (2012) 92, 371–383)
Challenges

• Important to continue to study preclinical models (and tumors) that have developed resistance to uncover novel resistance mechanisms

• Several challenges in translating preclinical studies into effective clinical therapies

• Multiple mechanisms of resistance can occur concurrently in same patient

• Both EGFR T790M and MET have been detected in same specimens (occur independently in different metastatic sites in the same patient)

• Therapeutic strategy aimed solely at one mechanism may not be effective or lead only to partial regressions

• Combination strategies may be more comprehensive and potentially more effective
Rebiopsy in Acquired Resistance

The re-biopsy of patients with acquired resistance is feasible and provides sufficient material for mutation analysis in most patients. Using higher sensitivity methods, the T790M may be detected in up to 68% of patients with EGFR-mutant lung cancer and acquired resistance.
It is clear that RECIST progression is not the single determining factor for terminating TKI in EGFR-mutant NSCLC patients. Although retrospective, the results of this study indicate the need for additional criteria beyond RECIST, which is specifically designed for EGFR-mutant NSCLC patients treated with EGFR-TKI to better guide therapeutic decision making.
Patient Follow up

PRE-TREATMENT  POST-TREATMENT  PROGRESSION

COUGH

RADIOLOGICAL PROGRESSION

DEL EXON 19

T790M
Final comments

- Reversible EGFR TKIs gefitinib & erlotinib have an established role in NSCLC (\textit{EGFR} mutation)

- Treatment strategy after resistance to upfront reversible TKI remains to be defined

- New irreversible kinase inhibitors are highly effective in EGFR mutated population BUT are those the answer?:
  - are they superior to reversible ones (first line)?
  - are they effective in refractory tumours (beyond reversible TKI PD)?

- Even pts with EGFR mut will eventually relapse and die and 20\% will not respond to TKIs
ALK traslocation
Identification of the transforming EML4–ALK fusion gene in non-small-cell lung cancer

EML4-ALK fusion gene detected in subset of NSCLC pts, promising candidate for therapeutic target (Soda Nature 2007)
EML4–ALK is a Potent “Oncogenic” Driver

Inhibition of ALK leads to dramatic *in vivo* tumor regression

- EML4-ALK-positive tumors more frequent in never/light smokers and ADC pts (Koivunen CCR 2008)

- EML4-ALK positivity associated to resistance to EGFR TKIs (Shaw JCO 2009)

- EML4-ALK mutually exclusive of EGFR, KRAS and ERBB2 muts (Sun JCO 2010)
Potential detection methods for ALK-positivity in solid tumors include:
- Fluorescent _in-situ_ hybridization (FISH) using break-apart probes to detect chromosomal rearrangements\(^1,2\)
- Immunohistochemistry for the aberrant expression of the ALK protein\(^3,4\)
- RT-PCR using primers directed against specific fusion pairings\(^5\)

All ALK positive patients within the crizotinib trial were identified using FISH as the screening technique

\(^1\)Shaw et al. J Clin Oncol 2009;27:4247–4253
\(^5\)Danenberg et al. J Clin Oncol 2010;28:15S abstract 10535
FISH assay for detection of ALK rearrangement

*Assay is positive if rearrangements can be detected in ≥15% of cells

Source: Bang et al. ASCO Annual Meeting 2010 Presentation


2p23 region

Telomere 3′

Centromere 5′

~250 kb

~300 kb

EML4 42.3

ALK 29.3

t(2;5) ALK gene breakpoint region

Break-apart FISH assay for ALK-fusion genes
Patients with *ALK*-positive NSCLC Do not Appear to Respond to EGFR TKIs

<table>
<thead>
<tr>
<th></th>
<th>ALK (N=12)</th>
<th>EGFR (N=8)</th>
<th>WT/WT* (N=34)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Response rate, %</strong></td>
<td>25</td>
<td>50</td>
<td>35</td>
</tr>
<tr>
<td><strong>TTP, months</strong></td>
<td>9</td>
<td>10</td>
<td>8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>ALK (N=10)</th>
<th>EGFR (N=23)</th>
<th>WT/WT* (N=23)</th>
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</thead>
<tbody>
<tr>
<td><strong>Response rate, %</strong></td>
<td>0</td>
<td>70</td>
<td>13</td>
</tr>
<tr>
<td><strong>TTP, months</strong></td>
<td>5</td>
<td>16</td>
<td>6</td>
</tr>
</tbody>
</table>

**TTP for chemotherapy**

**TTP for EGFR TKI**
## Studies Evaluating EML4-ALK NSCLC in the Western Population

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>% EML4-ALK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perner et al</td>
<td>603</td>
<td>3%</td>
</tr>
<tr>
<td>Koivunen et al</td>
<td>138</td>
<td>1%</td>
</tr>
<tr>
<td>Shaw et al</td>
<td>141</td>
<td>13%</td>
</tr>
<tr>
<td>Rodig et al</td>
<td>227</td>
<td>0.5%</td>
</tr>
</tbody>
</table>
Clinical characteristics of NSCLC patients with EML4-ALK + (Shaw AT, JCO 09)

- Exclusive with mutations of EGFR / KRAS
- Younger patients and men often
- Often no smoking
- EGFR TKIs  Resistance-related
Clinical Selection???

Be careful with the topics...
# Clinical characteristics ALK

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Alk + (%)</th>
<th>Median Age (Years)</th>
<th>Male/ Female</th>
<th>Method</th>
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<tbody>
<tr>
<td>Takahashi, Ann Surg Oncol 2010</td>
<td>313</td>
<td>5 (1.6%)</td>
<td>65.3</td>
<td>1/4</td>
<td>RT-PCR</td>
</tr>
<tr>
<td></td>
<td>211</td>
<td>5 ADC (2.4%)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>75</td>
<td>0</td>
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<td>27</td>
<td>0</td>
<td></td>
<td></td>
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<tr>
<td>Shaw, JCO 2009</td>
<td>141</td>
<td>19 (13%)</td>
<td>52</td>
<td>11/8</td>
<td>FISH</td>
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<tr>
<td></td>
<td>89</td>
<td>16 ADC</td>
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<td>41</td>
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<tr>
<td></td>
<td>11</td>
<td>0</td>
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<td>Wong, Cancer 2009</td>
<td>266</td>
<td>11 ADC</td>
<td></td>
<td></td>
<td>RT-PCR</td>
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<td></td>
<td>209</td>
<td>7 ADC</td>
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<td>34</td>
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<tr>
<td></td>
<td>23</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inamura, JTO 2008</td>
<td>200</td>
<td>5 ADC</td>
<td></td>
<td></td>
<td>RT-PCR</td>
</tr>
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<td></td>
<td>149</td>
<td>0</td>
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<td></td>
<td>48</td>
<td>0</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>3</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kwak, NEJM 2010</td>
<td>1500</td>
<td>82 (5.4%)</td>
<td>51</td>
<td>43/39</td>
<td>FISH</td>
</tr>
<tr>
<td></td>
<td>79</td>
<td>1 SCC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>2 other</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

124 ALK +

117 ADC / 7 Other

94.3% vs 5.6%
Smoking history

Table 1 - Frequency of EML4-ALK translocations broken down based on smoking history.

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of smokers</th>
<th>No. of never smokers</th>
<th>EML4-ALK+ (smokers) (%)</th>
<th>EML4-ALK+ (never smokers) (%)</th>
<th>p-Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soda et al.</td>
<td>24</td>
<td>9</td>
<td>8.3</td>
<td>11.1</td>
<td>1.0</td>
<td>4</td>
</tr>
<tr>
<td>Inamura et al.</td>
<td>84</td>
<td>65</td>
<td>2.4</td>
<td>4.6</td>
<td>0.65</td>
<td>5</td>
</tr>
<tr>
<td>Inamura et al.</td>
<td>147</td>
<td>105</td>
<td>3.4</td>
<td>5.7</td>
<td>0.53</td>
<td>6</td>
</tr>
<tr>
<td>Koivunen et al.</td>
<td>184</td>
<td>69</td>
<td>1.1</td>
<td>8.5</td>
<td>&lt;.01</td>
<td>7</td>
</tr>
<tr>
<td>Shinmura et al.</td>
<td>41</td>
<td>22</td>
<td>4.9</td>
<td>0</td>
<td>0.54</td>
<td>8</td>
</tr>
<tr>
<td>Martelli et al.</td>
<td>101</td>
<td>16</td>
<td>7.9</td>
<td>6.3</td>
<td>1.0</td>
<td>9</td>
</tr>
<tr>
<td>Wong et al.</td>
<td>125</td>
<td>141</td>
<td>0.8</td>
<td>8.5</td>
<td>&lt;.01</td>
<td>11</td>
</tr>
<tr>
<td>Shaw et al.</td>
<td>56</td>
<td>85</td>
<td>0</td>
<td>22.4</td>
<td>&lt;.0001</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>762</td>
<td>514</td>
<td>2.9</td>
<td>9.4</td>
<td>&lt;.0001</td>
<td></td>
</tr>
</tbody>
</table>
ALK considerations ...

- Prognostic significance of ALK translocation (conflicting data)

- Need to select people for screening: There is no group that has not been detected translocation (smokers, squamous, mutated EGFR)

- Comparison with standard therapy: phase III

- Resistance, how to prevent or fight?
ALK considerations ...

- FISH sometimes gives false negative results and these patients are identified by IHC and RT-PCR.
- FISH may not be the best predictive marker of response

Response according to FISH was 48% in contrast with 81% (P=0.007) in those patients in which ALK was identified by RT-PCR.

These findings suggest that a substantial number of patients who were identified as having ALK rearrangements by means of FISH analysis had false positive results. Since immunohistochemical staining and RT-PCR had not been performed before treatment, selection bias should be considered in that additional assays tended to be examined for patients with a good response. However, the limitation of diagnosis with the use of FISH is evident. A reconsideration of the diagnostic method, such as immunohistochemical staining, is needed for further studies of ALK inhibitors.
EML4-ALK Translocations in NSCLC

Detection of ALK Gene Rearrangement in Non-small Cell Lung Cancer

A Comparison of Fluorescence In Situ Hybridization and Chromogenic In Situ Hybridization with Correlation of ALK Protein Expression

Hyojin Kim, MD,* Sceol-Bong Yoo, MD,* Ji-Young Choe, MD,* Jin Ho Paik, MD, PhD,† Xianhua Xu, MD,† Hiroaki Nitta,‡ Wenjun Zhang,§ Thomas M. Grogan,¶ Choon-Taek Lee, MD, PhD,¶ Sanghoon Jheon, MD, PhD,∥ and Jin-Haeng Chung, MD, PhD*†

Journal of Thoracic Oncology • Volume 6, Number 8, August 2011

TABLE 3. Comparison of ALK Rearrangement Pattern between FISH and CISH

<table>
<thead>
<tr>
<th>CISH Positive</th>
<th>FISH Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>BA</td>
<td>IRS</td>
</tr>
<tr>
<td>BA</td>
<td>12 (100%)</td>
</tr>
<tr>
<td>IRS</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>12</td>
</tr>
</tbody>
</table>

k = 1.00 (>0.75, excellent; 0.4–0.7, good; <0.4, poor agreement).

CISH: chromogenic in situ hybridization; FISH, fluorescence in situ hybridization; BA, break-apart; IRS, isolated red signal.

TABLE 4. Comparison of ALK Status Between IHC and CISH

<table>
<thead>
<tr>
<th>CISH</th>
<th>IHC</th>
</tr>
</thead>
<tbody>
<tr>
<td>3+</td>
<td></td>
</tr>
<tr>
<td>2+</td>
<td></td>
</tr>
<tr>
<td>0/1+</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
</tr>
</tbody>
</table>

k = 0.82 (>0.75, excellent; 0.4–0.7, good; <0.4, poor agreement).

CISH: chromogenic in situ hybridization; IHC, immunohistochemistry; NA, not applicable.

FIGURE 3. Chung’s SNUBH ALK protocol presents schematic diagram to predict ALK gene rearrangement by IHC. IHC, immunohistochemistry; CISH, chromogenic in situ hybridization; FISH, fluorescence in situ hybridization.
Why is it important to detect ALK + patients?
Overview of crizotinib clinical trials in NSCLC

PROFILE 1001

A8081001 (NCT00858195): Adv. NSCLC, phase I, ALK+ enriched population

PROFILE 1005

A8081005 (NCT00932451): Adv. NSCLC, phase II, > 1 chemotherapies, progressive disease arm B profile 1007 (recruiting)

PROFILE 1007

A8081007 (NCT00932893): Adv. NSCLC, phase III (1 prior chemotherapy) Versus Standard Of Care Chemotherapy (Pemetrexed Or Docetaxel) (ongoing not yet recruiting)

PROFILE 1004

A8081004 (NCT01154140) : Adv. NSCLC, phase III, first line Versus Standard Chemotherapy Pemetrexed Plus Cisplatin Or Carboplatin (recruiting)
Progression-Free Survival (PFS) from a Phase 1 Study of Crizotinib (PF-02341066) in Patients with ALK-Positive Non-Small Cell Lung Cancer (NSCLC)

DR Camidge\(^\text{1}\), Y Bang\(^\text{2}\), EL Kwak\(^\text{3}\), A Shaw\(^\text{3}\), AJ Iafrete\(^\text{3}\), RG Maki\(^\text{4}\), B Solomon\(^\text{5}\), I Ou\(^\text{6}\), R Salgia\(^\text{7}\), K Wilner\(^\text{8}\), DB Costa\(^\text{9}\), G Shapiro\(^\text{10}\), P LoRusso\(^\text{11}\), P Stephenson\(^\text{12}\), Y Tang\(^\text{8}\), K Ruffner\(^\text{8}\), J Clark\(^\text{3}\)

\(^\text{1}\)University of Colorado Denver, Aurora, CO; \(^\text{2}\)Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea; \(^\text{3}\)Massachusetts General Hospital, Boston, MA; \(^\text{4}\)Memorial Sloan-Kettering Cancer Center, New York, NY; \(^\text{5}\)Peter MacCallum Cancer Centre and Cancer Trials Australia, Melbourne, Australia; \(^\text{6}\)University of California at Irvine, Irvine, CA; \(^\text{7}\)University of Chicago, Chicago, IL; \(^\text{8}\)Pfizer, Oncology; \(^\text{9}\)Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA; \(^\text{10}\)Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; \(^\text{11}\)Karmanos Cancer Institute, Detroit, MI; \(^\text{12}\)Rho, Inc. Chapel Hill, NC

Presented at the ASCO Annual Meeting 2011, June 3–7, Chicago, IL
Best Percent Change from Baseline in Target Lesions*

Objective response details (all evaluable patients)  
N=116**

<table>
<thead>
<tr>
<th>Metric</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (95% CI)</td>
<td>61% (52, 70)</td>
</tr>
<tr>
<td>Median response duration</td>
<td>48 weeks</td>
</tr>
<tr>
<td>Median time to response</td>
<td>8 weeks</td>
</tr>
<tr>
<td>Disease control rate at 8, 16 weeks</td>
<td>79%, 67%</td>
</tr>
</tbody>
</table>

*excludes patients with early death and indeterminate response (n=106)
**includes patients with early death and indeterminate response (n=116)
Rapid Responses Seen In Some Patients

Day -7

Day +14

Ou et al. J Thoracic Oncol 2010;5:2044-2046
10 months.\textsuperscript{18} By comparison, standard single-agent chemotherapies for previously treated, unselected metastatic NSCLC are associated with an objective response rate of less than 10% and a median PFS of less than 3 months.\textsuperscript{19,20} In the phase 1 trial, crizotinib also
# Patients who Continued Crizotinib >2 Weeks Beyond Documented Disease Progression

<table>
<thead>
<tr>
<th>Patient</th>
<th>Best response</th>
<th>Response duration (days)</th>
<th>Site of PD</th>
<th>Duration of post-PD crizotinib treatment (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PR</td>
<td>56</td>
<td>TL, liver, and lymph node</td>
<td>447+</td>
</tr>
<tr>
<td>2</td>
<td>PR</td>
<td>112</td>
<td>TL and brain</td>
<td>335+</td>
</tr>
<tr>
<td>3</td>
<td>PR</td>
<td>131</td>
<td>Brain</td>
<td>277+</td>
</tr>
<tr>
<td>4</td>
<td>PR</td>
<td>336</td>
<td>TL and lung</td>
<td>204</td>
</tr>
<tr>
<td>5</td>
<td>PR</td>
<td>224</td>
<td>TL</td>
<td>184+</td>
</tr>
<tr>
<td>6</td>
<td>SD</td>
<td>NA</td>
<td>TL</td>
<td>170+</td>
</tr>
<tr>
<td>7</td>
<td>PD</td>
<td>NA</td>
<td>Brain</td>
<td>168</td>
</tr>
<tr>
<td>8</td>
<td>PR</td>
<td>203</td>
<td>Kidney</td>
<td>167+</td>
</tr>
<tr>
<td>9</td>
<td>PR</td>
<td>84</td>
<td>TL</td>
<td>75</td>
</tr>
<tr>
<td>10</td>
<td>PR</td>
<td>282</td>
<td>TL</td>
<td>60</td>
</tr>
<tr>
<td>11</td>
<td>PR</td>
<td>98</td>
<td>TL and lymph node</td>
<td>53</td>
</tr>
<tr>
<td>12</td>
<td>SD</td>
<td>NA</td>
<td>Brain</td>
<td>52</td>
</tr>
<tr>
<td>13</td>
<td>PR</td>
<td>168</td>
<td>TL</td>
<td>35</td>
</tr>
<tr>
<td>14</td>
<td>PR</td>
<td>58</td>
<td>TL and liver</td>
<td>30</td>
</tr>
<tr>
<td>15</td>
<td>SD</td>
<td>NA</td>
<td>TL</td>
<td>29</td>
</tr>
<tr>
<td>16</td>
<td>PR</td>
<td>112</td>
<td>TL, lung and liver</td>
<td>22</td>
</tr>
</tbody>
</table>

+ Continuing crizotinib at the time of data cut-off; NA = not applicable; TL = target lesion; PD based on change in sum of target lesions.
**Treatment-Related Adverse Events**

- Overall, 114 patients (96%) reported a treatment-related AE
- The majority (n=95; 80%) of these patients experienced Grade 1/2 AEs; 19 patients (16%) experienced Grade 3/4 events
- Common treatment-related AEs (>20%):

<table>
<thead>
<tr>
<th>Event</th>
<th>All grades, n (%)</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N=119)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual effects*</td>
<td>74 (62)</td>
<td>–</td>
</tr>
<tr>
<td>Nausea</td>
<td>58 (49)</td>
<td>–</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>51 (43)</td>
<td>–</td>
</tr>
<tr>
<td>Vomiting</td>
<td>42 (35)</td>
<td>–</td>
</tr>
<tr>
<td>Edema**</td>
<td>33 (28)</td>
<td>–</td>
</tr>
<tr>
<td>Constipation</td>
<td>32 (27)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

*Cluster term including visual impairment, photopsia, vision blurred, vitreous floaters and diplopia. No patients required dosing interruption, dose reduction, or permanent discontinuation of crizotinib treatment due to visual effects.

**Cluster term including localized edema, edema and edema peripheral.
Characteristic Visual Effects With Crizotinib

- ‘Trails’ from lights in peripheral vision in low light conditions (e.g. dawn and dusk)

- At edges of vision in low light conditions:
  - Image persistence
  - Flashes of light, which do not appear to be connected to a real light source
  - Flipped registration from high contrast images (e.g. stripes)
**PROFILE 1007 & 1005 Trials**

### Phase III PROFILE 1007

- **Key entry criteria:**
  - Advanced NSCLC
  - ALK+ by central laboratory
  - 1 prior chemotherapy (platinum-based)

- **Primary end point:** PFS 50% improvement (2.9 → 4.4 mo)

Crizotinib 250 mg BID p.o. administered on a continuous dosing schedule

**PROFILE 1005**

- **Key entry criteria:**
  - Advanced NSCLC
  - ALK+ by central laboratory
  - Progressive disease in Arm B of Profile 1007
  - >1 prior chemotherapy

- **Randomise**: N=250

Pemetrexed 500 mg/m² or docetaxel 75 mg/m² (n=159) on day 1 of a 21-day cycle

**R 1:1**

- **disease progression**

- **Crizotinib 250 mg BID p.o. administered on a continuous dosing schedule**
Phase 2 Data for Crizotinib (PF-02341066) in ALK-Positive Advanced Non-Small Cell Lung Cancer (NSCLC): PROFILE 1005

GJ Riely¹, D-W Kim², L Crinò³, PA Janne⁴, F Blackhall⁵, DR Camidge⁶, V Hirsh⁷, TSK Mok⁸, B Solomon⁹, J-C Soria¹⁰, K Park¹¹, S Gadgeel¹², RG Martins¹³, J-Y Han¹⁴, T De Pas¹⁵, A Bottomley¹⁶, A Polli¹⁷, J Petersen¹⁸, V Tassell¹⁹, AT Shaw²⁰

¹Memorial Sloan-Kettering Cancer Center, New York, USA, ²Seoul National University Hospital Seoul, Korea, ³Azienda Ospedaliera di Perugia Perugia, Italy, ⁴Dana Farber Cancer Institute Boston, USA, ⁵Christie NHS Foundation Trust Manchester, UK, ⁶University of Colorado Denver Aurora, USA, ⁷McGill University Health Centre Montreal, Canada, ⁸The Chinese University of Hong Kong, Hong Kong, ⁹Peter MacCallum Cancer Centre East Melbourne, Australia, ¹⁰Institut Gustave-Roussy Villejuif, France, ¹¹Sungkyunkwan University School of Medicine Seoul, Korea, ¹²Kefanow Cancer Institute/Wayne State University Detroit, USA, ¹³University of Washington Seattle, USA, ¹⁴National Cancer Centre Goyang, Korea, ¹⁵European Institute of Oncology Milan, Italy, ¹⁶Quality of Life Department, EORTC, Brussels, Belgium, ¹⁷Pfizer Oncology, Milan, Italy, ¹⁸Pfizer Oncology, New York, USA, ¹⁹Pfizer Oncology, La Jolla, USA, ²⁰Massachusetts General Hospital, Boston, USA
Open-label, Multicenter, Phase II Study of Crizotinib in Advanced ALK-positive Non-Small Cell Lung Cancer

- ALK+ NSCLC by central review
- ECOG PS: 0–3
- ≥1 prior line of chemotherapy
- Brain metastases that were stable/control were allowed
- Not eligible for Phase 3 study

Crizotinib 250 mg BID administered continuously (21-day cycle)

Primary endpoints:
Response rate, safety, and tolerability

Secondary endpoints:
OS, TTR, duration of response, disease control rate, PK, biomarkers, PRO/HRQoL (EORTC QLQ-C30 and LC-13)

N=400 (planned)
Initial Efficacy Results PROFILE 1001-1005

Study 1001 - ORR 61%, n=116

Current Study - ORR 51%, n=133

Camidge DR et al. ASCO 2011, Riely G et al. WLCC 2011
## Safety and tolerability PROFILE 1001-1005

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Treatment-related</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N= 255</strong></td>
<td><strong>All grades N (%)</strong></td>
</tr>
<tr>
<td><strong>Eyes</strong>*</td>
<td>159 (62%)</td>
</tr>
<tr>
<td><strong>GI</strong></td>
<td></td>
</tr>
<tr>
<td>nausea</td>
<td>136 (53%)</td>
</tr>
<tr>
<td>diarrhea</td>
<td>109 (43%)</td>
</tr>
<tr>
<td>vomiting</td>
<td>101 (40%)</td>
</tr>
<tr>
<td>constipation</td>
<td>69 (27%)</td>
</tr>
<tr>
<td>Esophageal</td>
<td>29 (11%)</td>
</tr>
<tr>
<td><strong>General</strong></td>
<td></td>
</tr>
<tr>
<td>edema</td>
<td>72 (28%)</td>
</tr>
<tr>
<td>fatigue</td>
<td>51 (20%)</td>
</tr>
<tr>
<td>anorexia</td>
<td>49 (19%)</td>
</tr>
<tr>
<td><strong>Nervous system</strong></td>
<td></td>
</tr>
<tr>
<td>dizziness</td>
<td>42 (16%)</td>
</tr>
<tr>
<td>neuropathy</td>
<td>34 (13%)</td>
</tr>
<tr>
<td>dysgeusia</td>
<td>30 (12%)</td>
</tr>
<tr>
<td><strong>Liver</strong></td>
<td></td>
</tr>
<tr>
<td>ALT increase</td>
<td>34 (13%)</td>
</tr>
<tr>
<td><strong>Skin</strong></td>
<td></td>
</tr>
<tr>
<td>rash</td>
<td>25 (10%)</td>
</tr>
</tbody>
</table>
PROFILE 1005: Preliminary Patient-Reported Outcomes
Mean Baseline Scores of Select Items of the EORTC QLQ-C30 and QLQ LC13

Mean baseline score (+SD)

Pain
Cough
Dyspnea (QLQ C30)
Fatigue
Nausea/vomiting
Diarrhea
Constipation
QoL

Courtesy F. Blackhall

F. Blackhall, IASLC July 2011, Abstract 1510
Crizotinib history: 2007-2011

For drugs aimed at disease with limited effective treatments, delaying access during phase 2 and 3 trials, creates difficult ethical issues for regulatory agencies and pharmaceutical sponsors and agonizing decisions for physicians and patients.

Chabner et al. NEJM 2011

Aug. 26, 2011

“approved Xalkori (crizotinib) to treat certain patients with late-stage (locally advanced or metastatic), non-small cell lung cancers (NSCLC) who express the abnormal anaplastic lymphoma kinase (ALK) gene.”
PROFILE 1004 First Line Trial

Key entry criteria
- ALK+
- Advanced NSCLC
- No prior treatment for advanced disease

Study Started: Dec 2010

Trial design
<table>
<thead>
<tr>
<th>World-wide</th>
<th>Multicentre</th>
<th>Randomized</th>
<th>Open-label</th>
<th>Focused screening</th>
</tr>
</thead>
</table>

Endpoints
- Primary: PFS*
- Secondary: OS, ORR*, DR, safety, QoL, Lung cancer-specific symptoms

Stratification
- ECOG PS (0/1 vs. 2)
- Ethnicity (Asian vs. non-Asian)
- Brain metastases

**N=320**

**N=160**

Crizotinib 250 mg BID p.o. continuous dosing schedule

Crossover on PD

**N=160**

Pemetrexed/cisplatin or pemetrexed/carboplatin (Day 1/21)
ALK considerations...

**Crizotinib : Latest Champion in the Cancer Wars?**

Bengt Hallberg, Ph.D., and Ruth H. Palmer, Ph.D.


Role of second line treatment at time of progression to crizotinib, including second generation ALK TKI or HSP90 inhibitors (Whether hsp90 inhibitors will show activity in crizotinib-resistant patients is unknown, but there is the theoretical possibility of cross-resistance which may limit the utility of these agents in ALK rearranged NSCLC (Shaw, Solomon: Clin Cancer Res February 2, 2011).
EGFR mut and ALK traslocation

Proof of principle: 63 year old man with an EGFR mutant lung cancer

erlotinib → Developed Resistance

1/30/08 → 3/31/08

Pre-Rx ’08 → Resistant ’09

Rx on clinical trial
**Crizotinib:**

Hits not only ALK, but MET too (and ROS1!)

- know it works in MET amp patients, but we don’t know about EGFR mut TKI resistant pts with MET amp.

**AP26113**

is a novel, synthetic, orally-active tyrosine kinase inhibitor (TKI) that potently inhibits mutant activated forms of anaplastic lymphoma kinase (ALK+) and epidermal growth factor receptor (EGFRm), as well as TKI-resistant forms including L1196M (ALK) and T790M (EGFR). AP26113 does not inhibit native EGFR.

A Phase 1/2 Study of the Oral ALK/EGFR Inhibitor AP26113 is currently recruiting
EGFR Mutation as a resistance mechanism of Crizotinib

Evidence for a separate oncogenic driver

Mutation-driven EGFR activation: Separate Driver

ALK +, EGFR WT  ALK negative, EGFR mutant (L858R)

Camidge ASCO 2012
ALK considerations ...

*LUNGSCAPE: the importance of screening*

- To assay a minimum of 1000 stage I & II resected NSCLC tumours for a panel of markers to include EGFR, K-RAS, B-RAF, PIK3CA, HER2, AKT1, MET, **ALK**, BRCA1 (others ?)

- To determine the prevalence of each marker
  - associations (between markers, with clinical characteristics, histopathology)
  - prognostic significance using standard statistical approaches
Lung Cancer Therapy: 2013 Looking Forward to 2015

- We are making progress
- Progress requires continuing change
  - “Culture change”
  - Requirement for more tumor tissue (molecular profiling)
  - “Ungroup” NSCLC into individual patients (personalized therapy)
  - Change how we develop new cancer drugs (new paradigms)
    - Account for complexity of underlying biologic systems
    - Account for inter- and intrapatient heterogeneity
- Reality: the transition from empiric to rationally selected and personalized therapy is challenging
  - In every challenge, there are opportunities
  - We must take advantage of each of these opportunities if we are to advance the cure of patients with lung cancer
Are you ready to select drugs for Patients in a More Personalized Way?

"You ready?"

Courtesy WK Hong