Clinical research and experience with targeted therapy in advanced NSCLC: Focus on gefitinib

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Tyrosine kinase inhibitor in BAC

26/11/2003
commenced gefitinib

24/12/2003

25/02/2004
Erlotinib v. placebo in previously treated NSCLC: BR21 schema

Entry criteria:
- PS 0-3
- 1-2 prior regimens
- ‘Ineligible for more chemo’
- 18+

Double-blind 2:1 Randomisation

Erlotinib
- 150 mg daily

Placebo
- 1 daily

## BR21 Objective response to therapy

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Response rate %</th>
<th><em>P</em> value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>14.4</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>6.0</td>
<td>.006</td>
</tr>
<tr>
<td>Adenocarcinomas</td>
<td>13.9</td>
<td></td>
</tr>
<tr>
<td>Other histologies</td>
<td>4.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Never-smokers</td>
<td>24.7</td>
<td></td>
</tr>
<tr>
<td>Current/ex-smokers</td>
<td>3.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Unknown</td>
<td>13.0</td>
<td></td>
</tr>
</tbody>
</table>
BR21: overall survival

Median survival: 42.5% increase (6.7 months vs 4.7 months)

Hazard ratio 0.70
(95% CI=0.58–0.85; p<0.001)

- Tarceva (n=488)
- Placebo (n=243)

1-Year survival: 41% increase (31% vs 22%)

BR21 - Clinical and molecular predictors for erlotinib

- **Response – univariate**
  - Female sex
  - Asian origin
  - Never smoker
  - Adenocarcinoma
  - Polysomy or amplification of EGFR

- **Response – multivariate**
  - Never smoker
  - Adenocarcinoma
  - EGFR+, polysomy or amplification of EGFR

- **Survival – multivariate**
  - Erlotinib
  - Adenocarcinoma
  - Never smoker
  - Asian

ISEL (IRESSA Survival Evaluation in Lung Cancer): Clinical Trial Design

A double-blind Phase III survival study comparing gefitinib (250mg) plus BSC vs placebo plus BSC in patients with advanced NSCLC who have received 1–2 prior chemotherapy regimens and are refractory or intolerant to their most recent regimen.

- Randomisation
- 2:1 ratio
- Gefitinib (250mg) + BSC
- Placebo + BSC

Primary endpoint: Survival
Secondary endpoint: TTF, OR, QoL, safety

- 1692 patients in 210 centres across 28 countries
- 342 patients of Asian origin – no Japanese / US sites
Survival in the overall population

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Gefitinib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>At risk</td>
<td>1692 1347</td>
<td>877 485</td>
</tr>
<tr>
<td>Median, months</td>
<td>5.6</td>
<td>5.1</td>
</tr>
<tr>
<td>1-year survival, %</td>
<td>27</td>
<td>21</td>
</tr>
</tbody>
</table>

Log-rank HR 0.89; 95% CI 0.77, 1.02; p=0.087
Cox analysis, p=0.030
HR, hazard ratio

Survival in the adenocarcinoma population

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Gefitinib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>At risk</td>
<td>812 669 446 262 145 66 18</td>
<td></td>
</tr>
<tr>
<td>Median, months</td>
<td>6.3</td>
<td>5.4</td>
</tr>
<tr>
<td>1-year survival, %</td>
<td>30</td>
<td>18</td>
</tr>
</tbody>
</table>

Log-rank HR 0.84; 95% CI 0.68, 1.03; p=0.089
Cox analysis, p=0.033

Thatcher et al, 2005
ISEL survival by smoking history and racial origin (pre-planned analysis)

Cox regression analysis

Thatcher et al, 2005
Survival by EGFR gene copy number (FISH) status

**FISH +**
- N=114, E=68
- Cox HR=0.61 (0.36, 1.04)
- p=0.07

**FISH -**
- N=256, E=157
- Cox HR=1.16 (0.81, 1.64)
- p=0.42

Interaction test: p=0.04

Hirsch et al. 2006
EGFR associated TK mutations

- 2004 - DNA sequencing from TKI sensitive tumours
  - Deletions or amino acid substitutions found in exons 18, 19 or 21 EGFR gene
  - 13/14 in gefitinib sensitive tumours
  - 0/11 gefitinib resistant tumours

Lynch et al. NEJM 2004
Paez et al. Science 2004
A clinical link

- 2004 - In frame deletions exon 19; point mutations exon 21
  - Present in 12/17 gefitinib sensitive tumours
  - Absent in 0/18 gefitinib resistant tumours
  - M+ tumours were from life-long non-smokers with adenocarcinoma

- Screened
  - 15 adenos from untreated never-smokers
    - 7/15 TKI domain mutations
  - 81 resected NSCLC from untreated former or current smokers
    - 4/81 TKI domain mutations (p=0.0001)

Pao et al Proc Nat Acad Sci 2004
Epidermal growth factor receptor

- Extracellular ligand binding domain
- Transmembrane domain
- C-terminal regulatory domain
- Cell membrane
- Nucleus

- EGFR
- EGF
- TK
- C-terminal regulatory domain
EGFR normal functioning
EGFR normal functioning

- Cell membrane
- Dimerisation
- TK
- Nucleus
**EGFR normal functioning**

- **Cell membrane**
- **Dimerisation**
- **ATP**
- **Survival**
- **Phosphorylation of tyrosine residues**
- **Downstream signalling**
  - PI3K-AKT
  - survival
  - Ras-Raf-MAPK
  - proliferation
- **Nucleus**
- **Survival**
- **Proliferation**
- **Differentiation**
Activating mutation in **EGFR TK**

- **EGF**
- **Ligand independent Dimerisation**
- **TK m+**
- **Cell membrane**
- **Nucleus**
Activating mutation in EGFR TK

- EGFR
- EGF
- Cell membrane
- Downstream signalling
- Phosphorylation of tyrosine residues
- ATP
- TK
- TK
- Nucleus

Survival
Proliferation
Differentiation

Anti-apoptosis
Invasiveness
Malignant phenotype
Activating mutation in EGFR TK

- Activating mutation in EGFR TK
- Phosphorylation of tyrosine residues
- Downstream signalling
- Cell membrane
- Nucleus
- Survival
- Proliferation
- Differentiation
- Anti-apoptosis
- Invasiveness
- Malignant phenotype
IPASS: Phase III, randomised, open-label, first-line study of gefitinib vs carboplatin / paclitaxel in clinically selected patients with advanced NSCLC
Mok et al NEJM 2009

- Adenocarcinoma
- Never smokers
  - <100 cigarettes in lifetime;
- Light ex-smokers
  - stopped ≥15 years ago and smoked ≤10 pack years
- 1217 cases randomised
- Median age 57, 79% females
IPASS: Study design

**Patients**
- Chemonaïve
- Age ≥18 years
- Adenocarcinoma histology
- Never or light ex-smokers
- Life expectancy ≥12 weeks
- PS 0-2
- Measurable stage IIIIB/IV disease

**Endpoints**

**Primary**
- Progression-free survival (non-inferiority)

**Secondary**
- Objective response rate
- Overall survival
- Quality of life
- Disease-related symptoms
- Safety and tolerability

**Exploratory**
- Biomarkers
  - EGFR mutation
  - EGFR-gene-copy number
  - EGFR protein expression

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Gefitinib (250 mg/day)

Carboplatin (AUC 5 or 6)/paclitaxel (200 mg/m²) 3 weekly#

1:1 randomisation

#limited to a maximum of 6 cycles.

Carboplatin/paclitaxel was offered to gefitinib patients upon progression.
Objective tumour response

Odds ratio (95% CI) = 1.59 (1.25, 2.01) p=0.0001

Odds ratio >1 implies a greater chance of response on gefitinib
Odds ratio and p-value from logistic regression with covariates
RECIST, Response Evaluation Criteria In Solid Tumours

Mok et al. NEJM 2009.
Objective response rate in EGFR mutation positive and negative patients

Gefitinib
Carboplatin / paclitaxel

EGFR M+ odds ratio (95% CI) = 2.75 (1.65, 4.60), p=0.0001

EGFR M– odds ratio (95% CI) = 0.04 (0.01, 0.27), p=0.0013

Odds ratio >1 implies greater chance of response on gefitinib

Mok et al. NEJM 2009.
IPASS: Progression-free survival in ITT population

Gefitinib demonstrated superiority relative to carboplatin/paclitaxel in terms of PFS.

<table>
<thead>
<tr>
<th></th>
<th>Gefitinib</th>
<th>Carboplatin / paclitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>609</td>
<td>608</td>
</tr>
<tr>
<td>Events</td>
<td>453 (74.4%)</td>
<td>497 (81.7%)</td>
</tr>
</tbody>
</table>

HR (95% CI) = 0.741 (0.651, 0.845) p<0.0001

Median PFS (months) - Gefitinib: 5.7, Carboplatin/paclitaxel: 5.8
4 months progression-free - Gefitinib: 61%, Carboplatin/paclitaxel: 74%
6 months progression-free - Gefitinib: 48%, Carboplatin/paclitaxel: 48%
12 months progression-free - Gefitinib: 25%, Carboplatin/paclitaxel: 7%
IPASS: Progression-free survival by treatment and EGFR mutation status (M+/M-)

- **Gefitinib EGFR M+** (n=132)
- **Gefitinib EGFR M-** (n=91)
- **Carboplatin / paclitaxel EGFR M+** (n=129)
- **Carboplatin / paclitaxel EGFR M-** (n=85)

**Treatment effect M+**
HR (95% CI) = 0.48 (0.36, 0.64)
p<0.0001

**Treatment effect M-**
HR (95% CI) = 2.85 (2.05, 3.98)
p<0.0001

Treatment by subgroup interaction test, p<0.0001
Cox analysis with covariates
IPASS Objective tumor response (RECIST):

Exon 19 deletion
Odds ratio (95% CI) = 7.231 (3.194, 16.370)

Exon 21 L858R missense mut’n
Odds ratio (95% CI) = 1.413 (0.654, 3.049)

Post-hoc analysis
Odds ratio >1 implies a greater chance of response on gefitinib
Odds ratio and CI from logistic regression with covariates
Progression-free survival by EGFR mutation type (ITT population)

Exon 19 deletion

- Gefitinib (n=66)
- Carboplatin/paclitaxel (n=74)

HR (95% CI) = 0.377 (0.255, 0.560)
No. events gefitinib, 46 (69.7%)
No. events C/P, 65 (87.8%)

L858R

- Gefitinib (n=64)
- Carboplatin/paclitaxel (n=47)

HR (95% CI) = 0.553 (0.352, 0.868)
No. events gefitinib, 48 (75.0%)
No. events C/P, 40 (85.1%)

Time from randomisation (months)
Post-hoc Cox analysis with covariates
p-values not calculated due to small patient numbers

Mok et al. WCLC 2009.
IPASS: Superior quality of life and symptom improvement rates for gefitinib in EGFR mutation positive patients

% patients with sustained clinically relevant improvement

<table>
<thead>
<tr>
<th></th>
<th>Gefitinib (n=131)</th>
<th>C/P (n=128)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total FACT-L</td>
<td>70.2</td>
<td>70.2</td>
</tr>
<tr>
<td>TOI</td>
<td></td>
<td>70.2</td>
</tr>
<tr>
<td>LCS</td>
<td>75.6</td>
<td>53.9</td>
</tr>
</tbody>
</table>

p-values from logistic regression with covariates. Post-hoc analysis, EFQ population
Clinically relevant improvement pre-defined as 6-point improvement for FACT-L and TOI; 2-point improvement for LCS, maintained for at least 21 days.

EFQ, evaluable for quality of life; FACT-L, Functional Assessment of Cancer Therapy-Lung; TOI, Trial Outcome Index; LCS, Lung Cancer Subscale
Gefitinib versus doublet chemotherapy in EGFRm+ patients: 3 Phase III studies

**IPASS**
- Gef (n=132)
- Carb / pac (n=129)
- ORR %
- HR 0.48 95% CI 0.36, 0.64
- p<0.0001

**Lee**
- Gef (n=26)
- G / P (n=16)
- ORR %
- HR 0.613 95% CI 0.308, 1.221
- p=0.084 (by log rank test)

**Kobayashi**
- Gef (n=98)
- Carb / pac (n=100)
- ORR %
- HR 0.36 95% CI 0.25, 0.51
- p<0.001

Mok et al 2008, Lee et al 2009, Kobayashi et al 2009
Algorithm for EGFR mutation testing

Approximate % in UHBFT

Advanced NSCLC

Adequate material?
Biopsy – Usually YES
EBUS - Often YES
Washings - Sometimes YES
Brushings – NO

Smoking history
Never smokers
(<100 cigarettes in lifetime)?
Light ex-smokers
(stopped ≥15 years ago and smoked ≤10 pack years)?

Yes
(Never or light Ex-smoker)

No
(Current or Ex-smoker)

Adeno, BAC or NSCLC (NOS)
Not expressing CK5/7

No
ie. Squamous
CK5/7+

No EGFR mut testing

EGFR mut testing

With microdissection to enrich specimen

85

57

28

67

100

95

10
Algorithm for management of advanced NSCLC

UHBFT

Advanced NSCLC

Histological or cytological confirmation

EGFR mutation +?

Yes

No

Squamous CK5/7+

1st line

Cis/Carbo-gemcitabine

2nd line

Non-squamous

Cis-pemetrexed

Docetaxel (+/-Cis)

?Erlotinib

Gefitinib

Cis-pemetrexed
Routine EGFR mutation testing
UHBFT since May 2009

1/ Histology description
   - 185 cases submitted
   - 175 patients testable
   - 6 SCC
   - 119 ADC/BAC
   - 46 NSCLC NOS
   - 2 adenosquamous carcinomas
   - 2 others

2/ Molecular results
   - Activating mutations in EGFR gene exons 19, 21 in 21 cases (12%)
   - 13 cases both histol and cytol, 100% concordance inc 2 with mut’n.

3/ Overall mutation freq’y
   - ~66% of our cases of NSCLC are non-squamous, so activating EGFR mut’n freq’y approx. 8%

4/ KRAS mutations
   - 44/175: 25.1%
TKI in EGFRm+ cases in Birmingham since Feb 2009

- 8 mut’n pos cases treated
  - 2 2\textsuperscript{nd} line erlotinib
  - 6 1\textsuperscript{st} line gefitinib

<table>
<thead>
<tr>
<th>Patient</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>KW</td>
<td>&gt;PR</td>
</tr>
<tr>
<td>ZI</td>
<td>CR</td>
</tr>
<tr>
<td>JB</td>
<td>PR</td>
</tr>
<tr>
<td>BC</td>
<td>PR</td>
</tr>
<tr>
<td>KY</td>
<td>MR</td>
</tr>
<tr>
<td>JH</td>
<td>&gt;PR</td>
</tr>
<tr>
<td>HMB</td>
<td>&gt;PR</td>
</tr>
<tr>
<td>MC</td>
<td>Too early</td>
</tr>
</tbody>
</table>

(months) 0 3 6 9 12
KW  SE Asian 48, life long non-smoker, TTF1+ adenocarcinoma, Gem/carbo, d/c after cycle 1, exon 19 deletion, erlotinib
ZI 54, life-long non-smoker, T2 N0 M1 adenocarcinoma, TTF1+, MR to Gem/carbo, PD 10-09: exon 19 del’n, erlotinib

2 Nov 2009  2 Mar 2010
JB
Caucasian
Age 75
Quit smoking age 30
Cough and SOBOE
TTF1+ adenocarcinoma
Date of diag 15-6-2009
Exon 19 deletion, Gefitinib July 2009
BC
Caucasian
Age 80
Life-long non-smoker (husband heavy smoker)
Cough and SOBOE
TTF1+ adenocarcinoma
Date of diag 7-8-09
Missense mutation L858R exon 21
HM-B Recurrent (lung and bone) TTF1+ adenocarcinoma post R pneumonectomy missense mut’n codon 861 exon 21
Conclusions

- A new type of NSCLC identified
  - Defined by presence of specific activating EGFR mutations
  - EGFR mutation testing is recommended for most advanced NSCLC cases
- ~8% of all NSCLC in Western populations
- ~70% respond to EGFR TKI therapy
- Gefitinib licensed for all lines EGFR M+ patients in EU and in many other countries.