First Line Treatment of EGFR Mutation Positive Lung Cancer: Benefit from First Generation TKI Versus Chemotherapy

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This is a HISTORY lesson
Diagnosis of Advanced NSCLC

Etoposide/Cisplatin
Or
Taxol/Carboplatin

Supportive care
Followed by death
EGFR inhibition was a concept

EGFR signalling mediates important tumourigenic processes

Gefitinib competes with ATP to prevent activation of the EGFR and initiation of downstream signalling

Ligand → EGFR → EGFR TK

Gefitinib

EGFR TK

PI3-K

PTEN

STAT3

pY

GRB2

SOS

RAS

Raf

MEK

MAPK

DNA

Myc

Cyclin D1

JunFos

Gene transcription

Cell-cycle progression

Proliferation

Invasion

Angiogenesis

Inhibition of apoptosis

EGFR over-expression as an target

- 62% NSCLC
  - 82% squamous cell carcinoma
  - 44% adenocarcinoma
  - 80% adenocarcinoma with BAC features

Hirsch et al 2003
## Gefitinib Phase II efficacy in NSCLC

<table>
<thead>
<tr>
<th>Efficacy parameter (95% CI)</th>
<th>IDEAL 1 (RoW)</th>
<th>IDEAL 1 (RoW)</th>
<th>IDEAL 2 (US)</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>250 mg n=103</td>
<td>500 mg n=105</td>
<td>250 mg n=102</td>
<td>500 mg n=114</td>
</tr>
<tr>
<td><strong>ORR (%)</strong></td>
<td>18.4 (11.5-27.3)</td>
<td>19.0 (12.1-27.9)</td>
<td>11.8 (6.2-19.7)</td>
<td>8.8 (4.3-15.5)</td>
</tr>
<tr>
<td><strong>Disease control rate (%)</strong></td>
<td>54.4 (44.3-64.2)</td>
<td>51.4 (41.5-61.3)</td>
<td>42.2 (32.4-52.3)</td>
<td>36.0 (27.2-45.5)</td>
</tr>
<tr>
<td><strong>PFS (months)</strong></td>
<td>2.7 (2.0-2.8)</td>
<td>2.8 (1.9-3.8)</td>
<td>1.9 (1.8-2.8)</td>
<td>2.0 (1.6-2.2)</td>
</tr>
<tr>
<td><strong>Median OS (months)</strong></td>
<td>7.6 (5.3-10.1)</td>
<td>8.0 (6.7-9.9)</td>
<td>6.5 (4.8-8.0)</td>
<td>5.9 (4.6-7.2)</td>
</tr>
<tr>
<td><strong>1-year survival (%)</strong></td>
<td>35 (25-44)</td>
<td>29 (20-38)</td>
<td>29 (19-38)</td>
<td>24 (14-34)</td>
</tr>
</tbody>
</table>

CI, confidence interval; RoW, rest of world; PFS, progression-free survival; ORR, objective response rate; OS, overall survival

*Fukuoka et al 2003; Kris et al 2003*
1st IRESSA approval: July 2002, Japan
IRESSA approved* in US — May 2003

November 2002
The Three Promises

- Randomized second/third line study against placebo
- Randomized second/third line study against chemotherapy
- Randomized first line study against chemotherapy
The Three Promises

• Randomized second/third line study against placebo: ISEL
• Randomized second/third line study against chemotherapy: INTEREST
• Randomized first line study against chemotherapy: IPASS

Unselected population
Phase III placebo-controlled ISEL trial design

- 1692 patients in 210 centres across 28 countries
- Stratified for histology, sex, intolerant / refractory to CT, WHO PS and smoking history

**Patients**
- Locally advanced or metastatic NSCLC
- 1 or 2 prior CT regimens
- Patients intolerant/ refractory to most recent CT regimen or progression ≤90 days of last CT cycle

**Randomisation** (2:1 ratio)

- **Gefitinib (250 mg/day)** + BSC
- **Placebo + BSC**

**Primary endpoint**
- Survival
  - overall population
  - adenocarcinoma (co-primary endpoint)

**Secondary endpoints**
- TTF
- ORR
- QoL, symptoms
- Safety

**Exploratory endpoint**
- Tumour biomarker analysis (eg EGFR)

BSC, best supportive care; CT, chemotherapy; ISEL, IRESSA Survival Evaluation in Lung cancer; WHO PS, World Health Organisation performance status; QoL, quality of life; TTF, time to treatment failure

*Thatcher et al 2005*
ISEL: OS

Median follow-up: 7 months (range 3-15); 58% deaths

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<th>Gefitinib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<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, \( p=0.030 \)

Thatcher et al 2005

HR, hazard ratio
Erlotinib in Previously Treated Non–Small-Cell Lung Cancer

A  Overall Survival

P < 0.001 by stratified log-rank test
Hazard ratio, 0.70 (95% CI, 0.58–0.85)

B  Progression-free Survival

P < 0.001 by stratified log-rank test
Hazard ratio, 0.61 (95% CI, 0.51–0.74)
FISH Predicts Benefit of EGFR-TKIs

Log-rank: p=0.008
HR=0.44 (0.23, 0.82)

Log-rank: p=0.59
HR=0.85 (0.48, 1.51)

ISEL FISH +

Cox: p=0.07
HR=0.61 (0.36, 1.04)

ISEL FISH -

Cox: p=0.42
HR=1.16 (0.81, 1.64)

BR21 FISH +

Log-rank: p=0.00
HR=0.44 (0.23, 0.82)

BR21 FISH -

Log-rank: p=0.59
HR=0.85 (0.48, 1.51)

Interaction Test p value = 0.04

Interaction Test p value = 0.12
Molecular Predictors of Outcome With Gefitinib in a Phase III Placebo-Controlled Study in Advanced Non–Small-Cell Lung Cancer

Fred R. Hirsch, Marileila Varella-Garcia, Paul A. Bunn Jr, Wilbur A. Franklin, Rafał Dzidziońszko, Nick Thatcher, Alex Chang, Purvish Parikh, José Rodrigues Pereira, Tudor Ciuleanu, Joachim von Pawel, Claire Watkins, Angela Flannery, Gillian Ellison, Emma Donald, Lucy Knight, Dinah Parums, Nicholas Botwood, and Brian Holloway
Dramatic changes in USA

Erlotinib was approved as 2nd/3rd line treatment in unselected advanced stage NSCLC

Gefitinib was withdrawn from the US market
Personalized Therapy

- Identifying an oncogenic target
- Finding a biomarker
- Establishing efficacy

EGFR Mutations

• Activating mutation
  – Deletion at exon 19
  – Point mutation at exon 21 L858R

• Concept of oncogenic addiction
  – Tumor with EGFR mutation thrives on EGFR signaling

Lynch et al NEJM 2004
Paez et al Science 2004
**IPASS Study**

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

**Gefitinib**
(250 mg / day)

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

1:1 randomisation

*Never smokers, <100 cigarettes in lifetime; light ex-smokers, stopped ≥15 years ago and smoked ≤10 pack years; *limited to a maximum of 6 cycles
Carboplatin / paclitaxel was offered to gefitinib patients upon progression
PS, performance status; EGFR, epidermal growth factor receptor

Mok et al NEJM 361:947 2009
IPASS: The First Pan-Asian Collaboration: 1217 patients by 87 centers in 18 months

Protocol Deviation: Gefitinib arm 2% Chemotherapy arm 4.6%
IPASS: The First Pan-Asian Collaboration: 1217 patients by 87 centers in 18 months

Protocol Deviation: Gefitinib arm 2% Chemotherapy arm 4.6%
EGFR mutation positive status and clinical characteristics

Overall EGFR mutation positive rate = 59.7% (261 / 437)

% of samples EGFR mutation positive

- Male: 49.0%
- Female: 63.0%
- PS 0/1: 60.0%
- PS 0/2: 57.1%
- Never smoked: 60.7%
- Light ex-smoker: 46.9%
- Locally advanced: 57.8%
- Metastatic: 60.2%
- Age <65 yrs: 56.7%
- Age ≥65 yrs: 68.5%

Mok et al ESMO LBA 2, 2008
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

Overall response rate (%) (n=132) (n=129) (n=91) (n=85)

71.2% 47.3% 1.1% 23.5%

Odds ratio >1 implies greater chance of response on gefitinib

Mok et al NEJM 361:947 2009
IPASS: EGFR Mutation and Progression-free survival

EGFR mutation positive

Gefitinib (n=132)
Carboplatin / paclitaxel (n=129)

HR (95% CI) = 0.48 (0.36, 0.64)

No. events gefitinib, 97 (73.5%)
No. events C / P, 111 (86.0%)

EGFR mutation negative

Gefitinib (n=91)
Carboplatin / paclitaxel (n=85)

HR (95% CI) = 2.85 (2.05, 3.98)

No. events gefitinib, 88 (96.7%)
No. events C / P, 70 (82.4%)

Treatment by subgroup interaction test, p<0.0001

Mok et al NEJM 361:947 2009
EGFR mutation as predictive biomarker
IPASS: FISH vs EGFR mutation

<table>
<thead>
<tr>
<th>High EGFR-gene-copy number</th>
<th>N=198</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR expression positive</td>
<td>N=242</td>
</tr>
<tr>
<td>EGFR mutation positive</td>
<td>N=209</td>
</tr>
<tr>
<td>Positive for all 3 biomarkers</td>
<td>N=132</td>
</tr>
<tr>
<td>Negative for all 3 biomarkers</td>
<td>N=31</td>
</tr>
</tbody>
</table>

*Fukuoka et al. JCO 2010*
Progression-free survival in high and low EGFR-gene-copy number patients

High EGFR-gene-copy number

Gefitinib (n=124)
Carboplatin/paclitaxel (n=125)

HR (95% CI) = 0.66 (0.50, 0.88)
p=0.0050
No. events gefitinib, 98 (79.0%)
No. events C/P, 104 (83.2%)

Low EGFR-gene-copy number

Gefitinib (n=81)
Carboplatin/paclitaxel (n=76)

HR (95% CI) = 1.24 (0.87, 1.76)
p=0.2368
No. events gefitinib, 69 (85.2%)
No. events C/P, 68 (89.5%)

Treatment by EGFR-gene-copy number interaction test, p=0.0437

Cox analysis with covariates; HR <1 implies a lower risk of progression on gefitinib; ITT population
Progression-free survival by mutation status for high EGFR-gene-copy number patients

Cox analysis with covariates; HR <1 implies a lower risk of progression on gefitinib;
Post-hoc analysis in ITT population

High EGFR-gene-copy number, mutation positive

Gefitinib (n=96)
Carboplatin/paclitaxel (n=94)
HR (95% CI) = 0.48 (0.34, 0.67)
No. events gefitinib, 70 (72.9%)
No. events C/P, 79 (84.0%)

High EGFR-gene-copy number, mutation negative

Gefitinib (n=26)
Carboplatin/paclitaxel (n=29)
HR (95% CI) = 3.85 (2.09, 7.09)
No. events gefitinib, 26 (100%)
No. events C/P, 24 (82.8%)
## PFS Outcomes according to FISH and Mutation Status

<table>
<thead>
<tr>
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<th>High gene copy number</th>
<th>Low gene copy number</th>
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<tr>
<td><strong>HR (95% CI)</strong></td>
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<tr>
<td>EGFR mutation positive</td>
<td>0.48 (0.34, 0.67)</td>
<td>0.51 (0.25, 1.04)</td>
</tr>
<tr>
<td>EGFR mutation negative</td>
<td>3.85 (2.09, 7.09)</td>
<td>2.43 (1.58, 3.73)</td>
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HR<1 is in favour of gefitinib
IPASS killed the FISH

he lived a full life

he left an empty tank
Total of 8 first line randomized studies on EGFR mutations

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<th>Author</th>
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<th>N (EGFR mut +)</th>
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What is FIRST-SIGNAL?

First-SIGNAL: First-Line Single-Agent Iressa Versus Gemcitabine and Cisplatin Trial in Never-Smokers With Adenocarcinoma of the Lung

Ji-Youn Han, Keunchil Park, Sang-We Kim, Dae Ho Lee, Hyae Young Kim, Heung Tae Kim, Myung Ju Ahn, Tak Yun, Jin Seok Ahn, Cheolwon Suh, Jung-Shin Lee, Sung Jin Yoon, Jong Hee Han, Jae Won Lee, Sook Jung Jo, and Jin Soo Lee

See accompanying articles on pages 1030 and 1114; listen to the podcast by Dr. Rann at...
Results of FIRST-SIGNAL

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median (months)</th>
<th>1-Year PFS (%)</th>
<th>2-Year PFS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gefitinib</td>
<td>5.8</td>
<td>16.7</td>
<td>3.2</td>
</tr>
<tr>
<td>GP</td>
<td>6.4</td>
<td>2.8</td>
<td>1.4</td>
</tr>
</tbody>
</table>

HR = 1.198 (95% CI, 0.944 to 1.520), P = .138

Fig 2. (A) Overall survival and (B) progression-free survival (PFS). GP, gemcitabine/paclitaxel.
Primary endpoint: OS

<table>
<thead>
<tr>
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<th>Median (months)</th>
<th>1-Year Survival Rate (%)</th>
<th>2-Year Survival Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gefitinib</td>
<td>22.3</td>
<td>74.2</td>
<td>47.7</td>
</tr>
<tr>
<td>GP</td>
<td>22.9</td>
<td>76.2</td>
<td>47.4</td>
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</tbody>
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HR = 0.932 (95% CI, 0.716 to 1.213), \( P = .604 \)
Subgroup analysis for EGFR mutation (n=27)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>EGFR Mutation (n)</th>
<th>Median (months)</th>
<th>HR</th>
<th>95% CI</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gefitinib</td>
<td>Positive (26)</td>
<td>8.0</td>
<td>0.377</td>
<td>0.210 to 0.674</td>
<td>0.544</td>
<td>0.269 to 1.106</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>Negative (27)</td>
<td>2.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GP</td>
<td>Positive (18)</td>
<td>6.3</td>
<td>0.679</td>
<td>0.343 to 1.345</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GP</td>
<td>Negative (27)</td>
<td>6.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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</table>

Overall P = .001

Progression-Free Survival (probability) vs Time from randomisation (months)
Lesson learnt

- FIRST-SIGNAL and IPASS share similar study design and treatment outcomes
- Select of primary endpoint determine the success of a randomized study
- Prevalence of biomarker must be considered in calculation of sample size
### Total of 8 first line randomized studies on EGFR mutations

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Phase III study design

Registered patients

Centralized lab

Positive

Negative

Drug A

Control

Drug A

Control

Marker-by-treatment-interaction Design

Marker-based Strategy Design

Confirmation of improvement of PFS with first line EGFR TKI

PFS

Confirmation of improvement of PFS with first line EGFR TKI

Confirmation of improvement of PFS with first line EGFR TKI
### WJTOG3405: exon 19 vs 21

<table>
<thead>
<tr>
<th>Hazard ratios and 95% CI</th>
<th>Female (n=119)</th>
<th>Male (n=53)</th>
<th>Never smoker (n=118)</th>
<th>Former or current smoker (n=54)</th>
<th>Postoperative recurrence (n=71)</th>
<th>Stage III/IV (n=101)</th>
<th>Exon 19 del (n=87)</th>
<th>L858R (n=85)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.418 (0.267-0.654)</td>
<td>0.671 (0.337-1.334)</td>
<td>0.466 (0.297-0.732)</td>
<td>0.575 (0.294-1.123)</td>
<td>0.574 (0.313-1.052)</td>
<td>0.333 (0.203-0.544)</td>
<td>0.453 (0.268-0.768)</td>
<td>0.514 (0.294-0.899)</td>
</tr>
</tbody>
</table>

- Exon 19 del: 0.453 (0.268-0.768)
- L858R: 0.514 (0.294-0.899)

Favours gefitinib

Favours cisplatin and docetaxel

Mitsudomi et al Lancet Oncology 2010
<table>
<thead>
<tr>
<th></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</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>0.18 (0.11–0.28)</td>
<td>138</td>
</tr>
<tr>
<td>IIIB</td>
<td>0.27 (0.06–1.16)</td>
<td>16</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></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</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥65 years</td>
<td>0.17 (0.07–0.43)</td>
<td>38</td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>0.19 (0.11–0.31)</td>
<td>116</td>
</tr>
<tr>
<td>ECOG PS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>0.16 (0.10–0.26)</td>
<td>144</td>
</tr>
<tr>
<td>2</td>
<td>0.21 (0.04–1.28)</td>
<td>10</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never-smoker</td>
<td>0.14 (0.08–0.25)</td>
<td>109</td>
</tr>
<tr>
<td>Present or former smoker</td>
<td>0.21 (0.09–0.49)</td>
<td>45</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></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>
<tr>
<td>EGFR mutation type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exon 19 mutation</td>
<td>0.13 (0.07–0.25)</td>
<td>82</td>
</tr>
<tr>
<td>Exon 21 mutation</td>
<td>0.26 (0.14–0.49)</td>
<td>72</td>
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</tbody>
</table>
Meta-analysis: exon 19 vs 21

<table>
<thead>
<tr>
<th>Trial</th>
<th>HR</th>
<th>95% CI</th>
<th>Exon 19 deletions</th>
<th>Exon 21 L858R substitution</th>
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</thead>
<tbody>
<tr>
<td>ENSURE</td>
<td>0.20</td>
<td>0.12 to 0.33</td>
<td></td>
<td>0.64</td>
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<tr>
<td>EURTAC</td>
<td>0.27</td>
<td>0.17 to 0.43</td>
<td></td>
<td>0.53</td>
</tr>
<tr>
<td>LUX-Lung 3</td>
<td>0.28</td>
<td>0.18 to 0.44</td>
<td></td>
<td>0.73</td>
</tr>
<tr>
<td>LUX-Lung 8</td>
<td>0.20</td>
<td>0.13 to 0.32</td>
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<td>0.32</td>
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<tr>
<td>NEJ002</td>
<td>0.24</td>
<td>0.15 to 0.38</td>
<td></td>
<td>0.33</td>
</tr>
<tr>
<td>OPTIMAL</td>
<td>0.13</td>
<td>0.07 to 0.24</td>
<td></td>
<td>0.26</td>
</tr>
<tr>
<td>WJTOG 3405</td>
<td>0.42</td>
<td>0.26 to 0.66</td>
<td></td>
<td>0.69</td>
</tr>
<tr>
<td>All</td>
<td>0.24</td>
<td>0.20 to 0.29</td>
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<td>0.48</td>
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</tbody>
</table>

PFS
- HR 0.24 for exon 19
- HR 0.48 for exon 21

Lee et al JCO 2015
## Contribution to understanding on OS

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Name</th>
<th>Treatment</th>
<th>No of Patients</th>
<th>Response Rate</th>
<th>PFS</th>
<th>OS</th>
<th>Months</th>
<th>OS</th>
<th>Months</th>
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</thead>
<tbody>
<tr>
<td>Mok et al²</td>
<td>IPASS (Iressa Pan-Asia Study)</td>
<td>Gefitinib</td>
<td>132</td>
<td>71.2</td>
<td>&lt; .001</td>
<td>9.5</td>
<td>&lt; .001</td>
<td>21.6</td>
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<td>Chemotherapy</td>
<td>129</td>
<td>47.3</td>
<td>6.3</td>
<td>21.9</td>
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<td></td>
<td></td>
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<tr>
<td>Lee et al⁵</td>
<td>First-SIGNAL (First-Line Single-Agent Iressa Versus Gemcitabine and Cisplatin Trial in Never-Smokers With Adenocarcinoma of the Lung)</td>
<td>Gefitinib</td>
<td>22</td>
<td>84.6</td>
<td>.002</td>
<td>8.4</td>
<td>.001</td>
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<tr>
<td>Chemotherapy</td>
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<td>37.5</td>
<td>6.7</td>
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<tr>
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<td>110</td>
<td>30.7</td>
<td>5.4</td>
<td>23.6</td>
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<tr>
<td>Mitsudomi et al⁶</td>
<td>WJTOG 3405 (West Japan Thoracic Oncology Group 3405, Randomized Phase III Trial Comparing Gefitinib With Cisplatin Plus Docetaxel as the First-Line Treatment for Patients With Non-Small-Cell Lung Cancer harboring Mutations of the Epidermal Growth Factor Receptor)</td>
<td>Gefitinib</td>
<td>86</td>
<td>62.1</td>
<td>&lt; .001</td>
<td>9.2</td>
<td>&lt; .001</td>
<td>35.5</td>
<td>.4</td>
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<tr>
<td>Chemotherapy</td>
<td>86</td>
<td>32.2</td>
<td>6.3</td>
<td>38.8</td>
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<tr>
<td>Zhou et al⁸</td>
<td>OPTIMAL (CTONG-0802)</td>
<td>Erlotinib</td>
<td>82</td>
<td>82.9</td>
<td>&lt; .001</td>
<td>13.1</td>
<td>&lt; .001</td>
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<td>N/R</td>
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<tr>
<td>Chemotherapy</td>
<td>72</td>
<td>36.1</td>
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<tr>
<td>Rosell et al⁹</td>
<td>EURTAC (European Tarceva [erlotinib] versus Chemotherapy)</td>
<td>Erlotinib</td>
<td>86</td>
<td>55</td>
<td>&lt; .001</td>
<td>9.7</td>
<td>&lt; .001</td>
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<tr>
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<tr>
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<td>N/R</td>
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</tbody>
</table>

Note: FAS = Full Analysis Set, OS = Overall Survival, PFS = Progression-Free Survival, N/R = Not Reasured.
## Meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Hazard ratio (95% CI)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFRmut^* (first-line therapy)</td>
<td>1.77 (0.50 to 6.25)</td>
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</tr>
<tr>
<td>INTACT 1-2</td>
<td>1.04 (0.50 to 2.18)</td>
<td></td>
</tr>
<tr>
<td>TRIBUTE</td>
<td>0.88 (0.20 to 3.90)</td>
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<tr>
<td>TALENT</td>
<td>0.95 (0.19 to 4.72)</td>
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<tr>
<td>First-SIGNAL</td>
<td>1.00 (0.76 to 1.32)</td>
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</tr>
<tr>
<td>IPASS</td>
<td>1.04 (0.69 to 1.57)</td>
<td></td>
</tr>
<tr>
<td>OPTIMAL</td>
<td>1.19 (0.77 to 1.83)</td>
<td></td>
</tr>
<tr>
<td>WJTOG3405</td>
<td>0.73 (0.14 to 3.82)</td>
<td></td>
</tr>
<tr>
<td>NEJ002</td>
<td>0.89 (0.63 to 1.24)</td>
<td></td>
</tr>
<tr>
<td>TOPICAL</td>
<td>1.07 (0.43 to 2.67)</td>
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</tr>
<tr>
<td>EURTAC</td>
<td>1.04 (0.65 to 1.67)</td>
<td></td>
</tr>
</tbody>
</table>

Subtotal (95% CI): 1.01 (0.87 to 1.18)

Lee et al JNCI 2015
Summary

• Lesson learnt from IPASS and FIRST SIGNAL
  – First demonstrate superiority of first line EGFR TKI over chemotherapy
  – Confirmation of EGFR TKI as predictive biomarker by interaction test
  – IPASS killed the FISH

• Lesson learnt from NEJ002, WJTOG3405, OPTIMAL and EURTAC
  – Confirmation of improvement in PFS
  – Provide sufficient data to demonstrate the difference between exon 19 and 21
  – Confirmation on the lack of OS related to cross-over
Fast Moving Paradigm