EGFR en de long

Annelies Janssens
Advanced NSCLC: one disease, one treatment

Doublet chemotherapy is gold standard since years...

« one size fits all » therapy is not effective enough

Using biomarkers to customize treatment

Patients with the same diagnosis (NSCLC), but with different molecular profiles and biomarkers

They deserve customized treatment
Signal Transduction Pathways Controlled by the Activation of EGFR

Ciardiello and Tortora. NEJM. 2008; 358:1160-74.
Signal transduction mechanism

- The kinase domain activates a substrate protein, e.g., PI3 kinase, by phosphorylation.
- This activated substrate initiates a signaling cascade culminating in cell proliferation and survival.

Mechanism of action of EGFR-TKIs

The EGFR-TKI:
• Occupies the ATP binding pocket of the kinase domain
• This prevents substrate phosphorylation and signaling
• A lack of signaling inhibits proliferation and survival

Effect of Deletions and Mutations in EGFR on Disease Development and Drug Targeting

- >80% of EGFR mutations result in constitutive EGFR activation.
- Constitutively active TK (ligand independent).
- Associated with acquired resistance to EGFR-TKI.

NSCLC: driver mutations

Genetic alterations responsible for initiating and maintaining lung cancer:

- Squam.Ca
  - EGFR mutations (10-40%)
- AdenoCA
  - KRAS mutations (10-30%)
  - EML4-ALK fusion (~10%)
- Large cell CA
  - other
Using biomarkers to customize treatment

Patients with the same diagnosis (NSCLC), but with different molecular profiles and biomarkers

EML4 ALK : PF-02341066

Squamous cell carcinoma
  Gemcitabine
  IGFR inhibitor ?

Adenocarcinoma, Low TS :
  ALIMTA

RRM1(-) : gemcitabine

ERCC1(-) : Cisplatin

XRCC3(Met/Met) : Cis-Gem

EGFR mutation : EGFR-TKI
  10-15% of NSCLC advanced population
IPASS: 1st line EGFR-TKI vs chemotherapy in selected patients

**Inclusion criteria:**
- Chemonaive Asian pts
- PS 0-2
- Adenocarcinoma
- Never or light ex-smokers *

**Gefitinib arm:**
Gefitinib 250 mg/d until PD

**Chemotherapy arm:**
- Carboplatin (AUC 5 or 6)
- Paclitaxel 200 mg/m² (Q3wks for 6 cycles)

* Never smoker: <100 cigarettes in lifetime; light ex-smoker: stopped ≥15y ago and <10PY total

**Statistics:** Progression-free survival as primary endpoint

Mok et al. NEJM 2009; 361:947-57.
IPASS: Overall survival

All patients

At progression ~40% of patients in each arm crossed over to other treatment modality

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<thead>
<tr>
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<th>Gefitinib</th>
<th>CarboPacli</th>
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<tbody>
<tr>
<td>Median OS</td>
<td>18.6 m</td>
<td>17.3 m</td>
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HR (95% CI) = 0.91 (0.76 to 1.10)
IPASS: Progression Free Survival by mutation status

Primary Cox analysis with covariates; ITT population; HR <1 implies a lower risk of progression on gefitinib
IPASS: Progression Free Survival by mutation status

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

Probability of PFS

Time from randomisation (months)

Primary Cox analysis with covariates; ITT population; HR <1 implies a lower risk of progression on gefitinib

Treatment by subgroup interaction test, p<0.0001

EGFR M+ HR (95% CI) 0.48 (0.36, 0.64), p<0.0001
EGFR M- HR (95% CI) 2.85 (2.05, 3.98), p<0.0001
IPASS: Progression-free survival

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<thead>
<tr>
<th>EGFR-mutation positive</th>
<th>EGFR-mutation negative</th>
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<tr>
<td><strong>Hazard ratio</strong>, 0.48 (95% CI, 0.36–0.64)</td>
<td><strong>Hazard ratio</strong>, 2.85 (95% CI, 2.05–3.98)</td>
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<tr>
<td><em>P</em> &lt; 0.001</td>
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<tr>
<td>Events: gefitinib, 97 (73.5%); carboplatin plus paclitaxel, 111 (86.0%)</td>
<td>Events: gefitinib, 88 (96.7%); carboplatin plus paclitaxel, 70 (82.4%)</td>
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<tr>
<td><strong>Response rate</strong></td>
<td>71% *</td>
<td>47%</td>
</tr>
<tr>
<td><strong>Median PFS</strong></td>
<td>9.6 m *</td>
<td>6.3 m</td>
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<th>Carbo/Pacli</th>
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<tbody>
<tr>
<td><strong>Response rate</strong></td>
<td>1%</td>
<td>23% *</td>
</tr>
<tr>
<td><strong>Median PFS</strong></td>
<td>1.5 m</td>
<td>5.5 m</td>
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</table>

* *P* < 0.05

Mok et al. NEJM 2009; 361:947-57.
The presence of an EGFR mutation:
- is a strong predictive biomarker for response rate (both to chemotherapy and EGFR-TKI)
- is a strong predictive biomarker for PFS with EGFR-TKI versus chemotherapy
- is a favourable prognostic factor

At progression ~40% of patients in each arm crossed over to other treatment modality
Iressa®: Significant Greater Objective Response Rate

- 7/10 EGFR+ patients will respond* to Iressa® in 1st line. Less than 5/10 will respond to chemotherapy.

* Defined by ORR in EGFR M+ subgroup,

Iressa®: Better Symptom Control*

- Iressa® in 1st line significantly improves lung cancer symptoms in EGFR M+ patients compared to chemotherapy

*Defined by FACT-L, TOI and LCS scores in EGFR M+ subgroup.

Adapted from Mok T et al. N Engl J Med 2009; 361, supplementary appendix - fig. 3.
Progression-free survival by biomarkers

**Known mutation status**
- EGFR mutation positive
- EGFR mutation negative

**Known EGFR-gene-copy number status**
- High EGFR-gene-copy number
- Low EGFR-gene-copy number

**Known expression status**
- EGFR expression positive
- EGFR expression negative

**Treatment-by-subgroup interaction test p-value**
- p<0.001 for EGFR mutation
- p=0.0437 for EGFR-gene-copy number
- p=0.2135 for EGFR expression

HR (gefitinib vs carboplatin/paclitaxel) and 95% CI

Favors gefitinib
Favors carboplatin/paclitaxel

ITT population
Cox analysis with covariates
HR <1 implies a lower risk of progression/death on gefitinib

Mok et al 2009
Progression-free survival by biomarkers

- **Known mutation status**
  - EGFR mutation positive
  - EGFR mutation negative

- Treatment-by-subgroup interaction test p-value
  - p<0.001 for EGFR mutation

- **Known EGFR-gene-copy number status**
  - High EGFR-gene-copy number
  - Low EGFR-gene-copy number

- Treatment p-value
  - p=0.0437 for EGFR-gene-copy number

- **Known expression status**
  - EGFR expression positive
  - EGFR expression negative

- Treatment p-value
  - p=0.2135 for EGFR expression

- Cox analysis with covariates
  - HR <1 implies a lower risk of progression/death on gefitinib

Mok et al 2009
Gefitinib or Chemotherapy for Non–Small-Cell Lung Cancer with Mutated EGFR

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Figure 1. Randomization and Follow-up of the Study Patients, According to Treatment Group.
230 Patients were randomly assigned to a treatment group

115 Were assigned to receive gefitinib

1 Was ineligible

114 Met criteria and were included in intention-to-treat population

114 Were included in safety population

114 Were included in the progression-free–survival population

115 Were assigned to receive carboplatin–paclitaxel

1 Was ineligible

114 Met criteria and were included in intention-to-treat population

113 Were included in safety population

3 Were not evaluated
1 Had severe allergic reaction to paclitaxel
2 Withdrew consent

110 Were included in the progression-free–survival population

Figure 1. Randomization and Follow-up of the Study Patients, According to Treatment Group.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Gefitinib (N = 114)</th>
<th>Carboplatin–Paclitaxel (N = 114)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>42 (36.8)</td>
<td>41 (36.0)</td>
</tr>
<tr>
<td>Female</td>
<td>72 (63.2)</td>
<td>73 (64.0)</td>
</tr>
<tr>
<td>Age — yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>63.9±7.7</td>
<td>62.6±8.9</td>
</tr>
<tr>
<td>Range</td>
<td>43–75</td>
<td>35–75</td>
</tr>
<tr>
<td>Smoking status — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoked</td>
<td>75 (65.8)</td>
<td>66 (57.9)</td>
</tr>
<tr>
<td>Previous or current smoker</td>
<td>39 (34.2)</td>
<td>48 (42.1)</td>
</tr>
<tr>
<td>ECOG performance status score — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>54 (47.4)</td>
<td>57 (50.0)</td>
</tr>
<tr>
<td>1</td>
<td>59 (51.8)</td>
<td>55 (48.2)</td>
</tr>
<tr>
<td>2</td>
<td>1 (0.9)</td>
<td>2 (1.8)</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD. ECOG denotes Eastern Cooperative Oncology Group.
Table 1. Baseline Characteristics of the Intention-to-Treat Population, According to Treatment Group.*

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<th>Gefitinib (N = 114)</th>
<th>Carboplatin–Paclitaxel (N = 114)</th>
</tr>
</thead>
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<tr>
<td>Histologic diagnosis — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>103 (90.4)</td>
<td>110 (96.5)</td>
</tr>
<tr>
<td>Large-cell carcinoma</td>
<td>1 (0.9)</td>
<td>0</td>
</tr>
<tr>
<td>Adenosquamous carcinoma</td>
<td>2 (1.8)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Squamous-cell carcinoma</td>
<td>3 (2.6)</td>
<td>2 (1.8)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (4.4)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Clinical stage — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III B</td>
<td>15 (13.2)</td>
<td>21 (18.4)</td>
</tr>
<tr>
<td>IV</td>
<td>88 (77.2)</td>
<td>84 (73.7)</td>
</tr>
<tr>
<td>Postoperative relapse</td>
<td>11 (9.6)</td>
<td>9 (7.9)</td>
</tr>
<tr>
<td>Type of EGFR mutation — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exon 19 deletion</td>
<td>58 (50.9)</td>
<td>59 (51.8)</td>
</tr>
<tr>
<td>L858R</td>
<td>49 (43.0)</td>
<td>48 (42.1)</td>
</tr>
<tr>
<td>Other</td>
<td>7 (6.1)</td>
<td>7 (6.1)</td>
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* Plus–minus values are means ±SD. ECOG denotes Eastern Cooperative Oncology Group.
A Progression-free–Survival Population

- Gefitinib (n=114)
  - Median PFS: 10.8 m
  - HR (95%CI): 0.30 (0.22-0.41)
  - P value: <0.001

- Carbo/Pacl (n=110)
  - Median PFS: 5.4 m

Neither in the chemotherapy arm, no significant difference in response rate and PFS was observed between the two types of EGFR mutation.
C Intention-to-Treat Population

- Gefitinib (n=114)
  - Median survival time: 30.5 m
  - 2-year survival rate: 61.4%
  - P value: 0.31

- Carbo/Pacl (n=114)
  - Median survival time: 23.6 m
  - 2-year survival rate: 46.7%

Table 1. Summary of presented gefitinib first-line efficacy data in patients with *EGFR* mutation-positive advanced non-small-cell lung cancer.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patient origin and selection</th>
<th>Treatment and number of patients</th>
<th>Primary end point</th>
<th>Response rate (%)</th>
<th>PFS (HR or median [months])</th>
<th>Overall survival (HR or median [months])</th>
<th>Ref.</th>
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<td>Phase III studies</td>
<td></td>
<td></td>
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<td>IPASS</td>
<td>Asia Never- or light ex-smoker, adenocarcinoma</td>
<td>Gefitinib (n = 609 total; n = 132 <em>EGFR</em> M+); Carboplatin/paclitaxel (n = 608 total; n = 129 <em>EGFR</em> M+)</td>
<td>PFS (overall population)</td>
<td>71.2</td>
<td>HR: 0.48; 95% CI: 0.36–0.64; p &lt; 0.001</td>
<td>HR: 0.78*; 95% CI: 0.50–1.20</td>
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<td>First-SIGNAL</td>
<td>Asia Never-smoker, adenocarcinoma</td>
<td>Gefitinib (n = 159 total; n = 26 <em>EGFR</em> M+); Gemcitabine (n = 150 total; n = 16 <em>EGFR</em> M+)</td>
<td>Overall survival (overall population)</td>
<td>84.6</td>
<td>HR: 0.61; 95% CI: 0.31–1.22; p = 0.08</td>
<td>HR: 0.82; 95% CI: 0.35–1.92; p = 0.65</td>
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</tr>
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<td>Asia <em>EGFR</em> mutation</td>
<td>Gefitinib (n = 98 <em>EGFR</em> M+); Carboplatin/paclitaxel (n = 100 <em>EGFR</em> M+)</td>
<td>PFS</td>
<td>74.5</td>
<td>HR: 0.36; 95% CI: 0.25–0.51; p &lt; 0.001</td>
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<td>WJTOG 3405</td>
<td>Asia <em>EGFR</em> mutation</td>
<td>Gefitinib (n = 86 <em>EGFR</em> M+); Cisplatin/docetaxel (n = 86 <em>EGFR</em> M+)</td>
<td>PFS</td>
<td>62.1</td>
<td>HR: 0.49; 95% CI: 0.34–0.71; p &lt; 0.001</td>
<td>HR: 1.64*; 95% CI: 0.75–3.58</td>
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*Post-hoc analysis (overall survival follow-up ongoing).*

*Overall survival follow-up ongoing.*

*Projected median overall survival.*

*Time to treatment failure.*

*EGFR: EGF receptor; First-SIGNAL: First-Line Single Agent IRESSA Versus Gemcitabine and Cisplatin Trial in Never-Smokers with Adenocarcinoma of the Lung; HR: Hazard ratio; I-CAMP: IRESSA Combined Analysis of Mutation Positives; IPASS: IRESSA Pan-Asia Study; M+: Mutation-positive; NEJ: North East Japan; OR: Odds ratio; ORR: Objective response rate; PFS: Progression-free survival; PS: Performance status; WJTOG: West Japan Thoracic Oncology Group.*
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In the INTEREST Subgroup analysis, in non-Asian patients only, has also shown that PFS was significantly longer with gefitinib compared with docetaxel in the non-Asian EGFR mutation-positive patients (HR: 0.12; 95% CI: 0.03–0.51; p = 0.005), although the patient numbers were low (Figure 3).

The ORR and PFS achieved with gefitinib in patients with EGFR mutations from western populations in these studies are comparable to those observed in the Phase III studies already described and in other prospective Phase II studies of first-line gefitinib in Asian patients with EGFR mutation-positive tumors, in which ORRs of 51–78% have been reported (Table 1).
EGFR mutation & treatment with an EGFR-TKI in non-Asian patients

**Figure 3.** Kaplan–Meier curves for progression-free survival for non-Asian patients with *EGFR* mutation-positive status in INTEREST.

EGFR: EGF receptor; HR: Hazard ratio; INTEREST: IRESSA NSCLC Trial Evaluating Response and Survival Versus Taxotere; PFS: Progression-free survival.

HR (95% CI): 0.12 (0.03–0.51), p = 0.005
Survival of patients with activating EGFR-mutations who received erlotinib therapy
Survival of patients with activating EGFR-mutations who received erlotinib therapy
These results indicate that the presence of an EGFR mutation is the driving factor that determines outcome rather than the ethnicity and that the efficacy of the EGFR-TKI in EGFR mutation-positive patients is independent from the line of therapy.
SATURN: erlotinib as maintenance in 1\textsuperscript{st}-line treatment of advanced NSCLC

**Inclusion criteria:**
- Stage IIIB/IV NSCLC
- PS 0-1
- Non-PD following 4 cycles of platinum-based chemotherapy*

**Statistics:** PFS as primary endpoint

- **Maintenance arm (n=438):** Erlotinib 150 mg/d until PD
- **Control arm (n=451):** Placebo 1x/d until PD

* 1\textsuperscript{st} line chemotherapy: Cisplatin/Carboplatin + Docetaxel/Paclitaxel/Gemcitabine/Vinorelbine

Cappuzzo et al. ASCO 2009: abstract 8001.
SATURN: PFS subgroup analysis

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>HR (95% CI)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>0.71 (0.62–0.82)</td>
<td>884</td>
</tr>
<tr>
<td>Male</td>
<td>0.78 (0.66–0.92)</td>
<td>654</td>
</tr>
<tr>
<td>Female</td>
<td>0.56 (0.42–0.76)</td>
<td>230</td>
</tr>
<tr>
<td>Caucasian</td>
<td>0.75 (0.64–0.88)</td>
<td>744</td>
</tr>
<tr>
<td>Asian</td>
<td>0.58 (0.38–0.87)</td>
<td>128</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>0.60 (0.48–0.75)</td>
<td>401</td>
</tr>
<tr>
<td>Squamous-cell</td>
<td>0.76 (0.60–0.95)</td>
<td>359</td>
</tr>
<tr>
<td>Never smoker</td>
<td>0.56 (0.38–0.81)</td>
<td>152</td>
</tr>
<tr>
<td>Former smoker</td>
<td>0.66 (0.50–0.88)</td>
<td>242</td>
</tr>
<tr>
<td>Current smoker</td>
<td>0.80 (0.67–0.97)</td>
<td>490</td>
</tr>
</tbody>
</table>

Cappuzzo et al. ASCO 2009: abstract 8001.
EGFR mutations identify patients who derive a greater PFS-benefit from erlotinib maintenance (median PFS 11m vs 3 m).
SATURN: overall survival

**EGFR-wild type**

HR = 0.77 (0.61–0.97)
Log-rank p = 0.0243

**EGFR-mutation positive * **

HR = 0.83 (0.34–2.02)
Log-rank p = 0.6810

*67% of patients with EGFR mutation+ disease in the placebo arm received a second-line EGFR TKI.

Brugger, et al. WCLC 2009
**Erlotinib maintenance in NSCLC: SATURN trial**

<table>
<thead>
<tr>
<th></th>
<th>EGFR wild type</th>
<th>EGFR mutation +</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PFS</strong></td>
<td>HR 0.78 (0.63-0.96)</td>
<td>HR 0.10 (0.04-0.25)</td>
</tr>
<tr>
<td><strong>OS</strong> *</td>
<td>HR 0.77 (0.61-0.97)</td>
<td>HR 0.83 (0.34-2.02)</td>
</tr>
<tr>
<td><strong>OS</strong></td>
<td>MST ~11 m</td>
<td>MST ~24 m</td>
</tr>
</tbody>
</table>

- **EGFR mutations** identify patients who derive a **greater** PFS-benefit from erlotinib maintenance (median PFS 11m vs. 3 m).
- The **EGFR mutation** is a **favourable prognostic factor**

*67% of patients with *EGFR* mutation+ disease in the placebo arm received a second-line *EGFR* TKI*
Phase II study of 1st-line gefitinib for poor PS pts with NSCLC harboring activating EGFR-mutations

- Chemo-naïve NSCLC
- Poor PS:
  - 20-74 yrs: PS 3-4
  - 75-79 yr: PS 2-4
  - ≥80 yr: PS 1-4

EGFR-mutation

Activating EGFR-mutation:
Gefitinib (n 30)

Wildtype EGFR:
No Gefitinib (n 31)

<table>
<thead>
<tr>
<th>EGFR mutation +</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response rate</td>
</tr>
<tr>
<td>Disease control rate</td>
</tr>
<tr>
<td>PS improvement rate</td>
</tr>
<tr>
<td>median PFS</td>
</tr>
<tr>
<td>median OS</td>
</tr>
<tr>
<td>1-yr OS rate</td>
</tr>
</tbody>
</table>

Topical trial: erlotinib in pts unfit for chemo

- Advanced NSCLC
- Chemo-naïve
- Unfit for platinum chemo

**Experimental arm:**
- Erlotinib 150 mg/d

**Control arm:**
- Best Supportive Care

**N = 670**

<table>
<thead>
<tr>
<th>Trial demographics</th>
<th>Erlotinib</th>
<th>BSC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age</td>
<td>77y</td>
<td></td>
</tr>
<tr>
<td>PS 2-3</td>
<td>84%</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>39%</td>
<td></td>
</tr>
<tr>
<td>AdenoCA</td>
<td>38%</td>
<td></td>
</tr>
<tr>
<td>Never smokers</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>median PFS</td>
<td>2.8 m</td>
<td>2.7 m</td>
</tr>
<tr>
<td>median OS</td>
<td>3.8 m</td>
<td>3.6 m</td>
</tr>
<tr>
<td>female</td>
<td>5.3 m *</td>
<td>4.3 m</td>
</tr>
<tr>
<td>EGFR m+</td>
<td>11 m</td>
<td>2.8 m</td>
</tr>
</tbody>
</table>

* p=0.025

§ PS 2-3 or GFR <60ml/min

Lee et al. ASCO 2010: abstract 7504.
Erlotinib ± CarboPacli in 1ˢᵗ line

- Chemo-naïve NSCLC
- Never or former light § smoker
- AdenoCA

Erlotinib
N = 82

Erlotinib + CarboPacli (6x)
N = 100

§ ≤10PY and ≥1y stop smoking

EGFR genotyping in 95% of pts → EGFR mutation in 39% of pts

<table>
<thead>
<tr>
<th></th>
<th>RR</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>34%</td>
<td>6.7m</td>
<td>24.0m</td>
</tr>
<tr>
<td>EFGR mutant</td>
<td>66%</td>
<td>16.4m</td>
<td>27.6m</td>
</tr>
<tr>
<td>EGFR WT</td>
<td>8%</td>
<td>2.8m</td>
<td>15.4m</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>RR</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>47%</td>
<td>6.0m</td>
<td>19.6m</td>
</tr>
<tr>
<td>EFGR mutant</td>
<td>69%</td>
<td>17.2m</td>
<td>39.0m</td>
</tr>
<tr>
<td>EGFR WT</td>
<td>31%</td>
<td>4.8m</td>
<td>13.7m</td>
</tr>
</tbody>
</table>

Janne et al. ASCO 2010: abstract 7503.
American Society of Clinical Oncology Clinical Practice Guideline Update on Chemotherapy for Stage IV Non–Small-Cell Lung Cancer


The first-line use of gefitinib may be recommended for patients with known EGFR mutation; for negative or unknown EGFR mutation status, cytotoxic chemotherapy is preferred.
2009 recommendation A7

- In unselected patients with stage IV NSCLC, erlotinib or gefitinib should not be used in combination with cytotoxic chemotherapy as first-line therapy.
- In unselected patients, evidence is insufficient to recommend single-agent erlotinib or gefitinib as first-line therapy.
- The first-line use of gefitinib may be recommended for patients with activating EGFR mutations.
- If EGFR mutation status is negative or unknown, then cytotoxic chemotherapy is preferred.
EGF receptor mutation testing is likely to become used more routinely to select patients for treatment with an EGFR-TKI; therefore, limitations of the current techniques need to be addressed.

Another limitation of EGFR mutation analysis is the availability of tissue for testing.

In the lung cancer setting, diagnoses are often based on small biopsies or cytologic specimens; tumors are often inaccessible and the collection of sufficient good-quality tissue samples is difficult.

The use of surrogate (non tumor) samples, including serum, plasma and cytology samples, has been explored; however, current methods have been found to lack sufficient sensitivity with a false-negative rate of approximately 50%.
The detection of EGFR mutations is fundamental in identifying those patients who will benefit most from treatment with gefitinib.

Results from the IPASS indicate that if patients with EGFR mutation-positive tumors are treated with gefitinib, they will have superior PFS and ORR than if they receive chemotherapy.

The detection of EGFR mutations in patients with NSCLC is the first molecular predictive factor that offers patients a more effective and convenient targeted therapy than conventional chemotherapy regimens.

This is the first step leading to individualized treatment for patients with advanced NSCLC that will improve both disease outcomes and QoL.
Recommendation A7 supports the first-line use of gefitinib over carboplatin and paclitaxel in patients whose NSCLC tumors harbor EGFR mutation based on a clinically significant improvement in PFS, favorable toxicity profile, and improved quality of life.

These data justify attempts to test NSCLC tumors for the presence of EGFR mutation.
Survival of patients with activating EGFR-mutations who received gefitinib therapy

A

Proportion of progression-free survivors

- chemo naive (n = 91)
- chemotherapy-treated (n = 61)

log rank = 0.804

B

Proportion of survivors

- chemo naive (n = 91)
- chemotherapy-treated (n = 61)

log rank = 0.207

Progression-free survival after gefitinib (months)

Overall survival after first-line anti-tumor therapy (months)
WJTOG3405: 1st line gefitinib vs chemotherapy

**Inclusion criteria:**
- Chemonaive Asian pts
- EGFR activating mutation

**Statistics:** PFS as primary endpoint

**Gefitinib arm:** Gefitinib 250 mg/d until PD

**Chemotherapy arm:** Cisplatin + Docetaxel (6 cycles)

Effect of Deletions and Mutations in EGFR on Disease Development and Drug Targeting

>80% of EGFR mutations; results in constitutive EGFR activation

Oncogene-addiction to activated EGFR-pathway

Antitumorale activiteit van EGFR-TKI en EGFR-biomarkers