Recent Advances in Chemo and Targeted therapy of NSCLC

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Disclosure

- Medical Advisor Oncology - Eli Lilly

- Opinion expressed in this presentation is of the speaker and not reflective of recommendations of “Eli Lilly and company”
Worldwide incidence for lung cancer

- Lung cancer is the most common cancer in the world

<table>
<thead>
<tr>
<th>Lung Cancer</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>World</td>
<td>&gt;1.3 million</td>
</tr>
<tr>
<td>Continent</td>
<td>% of World</td>
</tr>
<tr>
<td>Asia</td>
<td>49</td>
</tr>
<tr>
<td>Europe</td>
<td>28</td>
</tr>
<tr>
<td>North America</td>
<td>17</td>
</tr>
<tr>
<td>Central/South America</td>
<td>4</td>
</tr>
<tr>
<td>Africa</td>
<td>1</td>
</tr>
</tbody>
</table>

- Lung cancer is the most common cause of cancer deaths in the world

NSCLC: Survival by stage at diagnosis*

*Historical data; recent developments and increases in survival not reflected

- Early ~25%
- LAD ~35%
- AD ~40%
Why Are The Survival Rates So Low?

- Majority present with late-stage disease
  - Effective and efficient screening tools needed
- Older patients with significant co-morbidities
  - 80% are current or former smokers
- Chemotherapy (and radiation) only somewhat effective
  - Why? How are cells resistant?
  - Who should we target? What drugs should we use?
Standard Therapy for NSCLC

- “Early stage” – surgical resection
  - Benefit of adjuvant chemotherapy for appropriate patients
- “Locally advanced” – combined radiation and chemotherapy
  - Sometimes surgery
- “Advanced” or metastatic – palliative chemotherapy and/or radiation
  - Combinations of chemotherapy agents
  - Newer targeted drugs
Systemic Treatments for advanced NSCLC patients

- Chemotherapy
  Cisplatin, carboplatin, gemcitabine, paclitaxel, docetaxel, vinorelbine, pemetrexed, irinotecan, etoposide etc.

- Targeted therapy
  Gefitinib, erlotinib, bevacizumab, cetuximab etc.
Selecting treatments for patients

- **Clinical selection**
  
  Stage, Performance Status, Age, Pathology, Gender, Smoking status, Ethnicity

- **Molecular selection**
  
  EGFR mutation / FISH, k-ras mutation, Thymidylate synthase etc.
Individualized treatment for NSCLC

All patients With the same diagnosis

- No Benefit + Toxicity
- + Benefit + Toxicity
- + Benefit No Toxicity
- No Benefit No Toxicity

Definition of a “Biomarker”

“Indicator signaling an event or condition in a biological system or sample and giving a measure of exposure, effect, or susceptibility*.”


- Blood, bodily fluids and/or tissue
- Reproducible
- Affordable
- Technically feasible
- Results in something clinically meaningful

* Note: Such an indicator may be a measurable chemical, biochemical, physiological, behavioral or other alteration within an organism.
Biomarkers

Predictive marker:

- Characteristic of a patient or a tumor that identifies a subgroup within which the effect of a treatment will be different from those who do not have this feature

Prognostic marker:

- Characteristic that identifies a subgroup who will have a different outcome regardless of treatment effects
Biomarkers in NSCLC: Simple histology

- Within NSCLC are subcategories of squamous, adeno, BAC, and large cell:
  - Squamous (Sq) histology is associated with:
    - High level of thymidylate synthase (TS)
    - EGFR expression but not mutations
    - Rare K-ras mutations
  - Adenocarcinoma histology is associated with:
    - EGFR mutations
    - K-ras mutations

- Histology now plays an important role in treatment selection:
  - “not otherwise specified” is no longer an acceptable distinction
Biomarkers in NSCLC: EGFR pathway

Figure reproduced with permission from Huang SM, Harari PM. *Investig New Drugs* 2000;17:259-69.
Biomarkers in NSCLC: EGFR pathway

● **Quantification of EGFR**
  - IHC intensity of staining
  - FISH overexpression

● **Function of EGFR**
  - Activating mutations
  - Resistance mutations
Biomarkers in NSCLC: Downstream in the EGFR pathway

- 3 genes H-ras, K-ras, N-ras
- Ras mutations are detectable in ~20% of lung cancers, usually in smokers
  - 90% of mutations are due to K-ras
- K-ras mutations appear to be important for:
  - EGFR TKI therapy as a negative predictor of response
  - Lack of responses to adjuvant cisplatin-vinorelbine chemotherapy

Biological Correlates: What goes in…

Quality of any biomarker study will depend on what goes into it:

- Characteristics of the disease
- Characteristics of the individual patient
- Characteristics of the actual sample:
  - How many patients participate?
  - Quality of the samples?
    - blocks vs. slides
  - Consistency and reproducibility of testing?
ADVANCED-NSCLC TREATMENT

“Old” CT Cis-based > BSC

CT ADVANTAGE

MST= + 1.5 months
1-YS= + 10 %

Meta-Analysis, BMJ 1995
Should chemotherapy combinations for advanced non-small cell lung cancer be platinum-based? A meta-analysis of phase III randomized trials

Fig. 3 Overall response rate with platinum-based vs. non-platinum chemotherapy regimens. The summary odds ratio for the risk of being non responder to chemotherapy was 0.87 (95% CI, 0.73–0.99, p = 0.049) indicating a 2.5% benefit for response for patients treated with a platinum-based chemotherapy doublet (*, data non available).

JL Pujol et al, Lung Cancer 2006
**ECOG 1594: Treatment Schema**

**Stage IIIB or IV NSCLC patients**

Stratified by:
- Extent of disease
- PS
- Weight loss
- Brain metastases

**RANDOMIZE**

<table>
<thead>
<tr>
<th>Arm</th>
<th>Protocol Details</th>
</tr>
</thead>
</table>
| **A** | Paclitaxel: 135 mg/m², day 1  
               Cisplatin: 75 mg/m², day 2 |
| **B** | Cisplatin: 100 mg/m², day 1  
               Gemcitabine: 1000 mg/m², days 1, 8, 15 |
| **C** | Docetaxel: 75 mg/m², day 1  
               Cisplatin: 75 mg/m², day 1 |
| **D** | Paclitaxel: 225 mg/m², day 1  
               Carboplatin: AUC=6, day 1 |

*Control arm.*

ECOG 1594: Kaplan-Meier Estimates of Overall Survival

Survival (%) over months for different treatment regimens:
- Cisplatin and paclitaxel
- Cisplatin and gemcitabine
- Cisplatin and docetaxel
- Carboplatin and paclitaxel

Challenge in 2000: Which drug to choose?

- Cisplatin / Carboplatin
- Gemcitabine
- Docetaxel
- Vinorelbine
- Paclitaxel
Treatment selection based on clinical parameters

- Pathology
- Gender
- Smoking status
- **Performance status**
- Age
- Response/reaction to therapy
Treatment of advanced non-small-cell lung cancer patients with ECOG performance status 2: results of an European Experts Panel

C. Gridelli¹*, A. Ardizzoni², T. Le Chevalier³, C. Manegold⁴, F. Perrone⁵, N. Thatcher⁶, N. van Zandwijk⁷, M. Di Maio⁵, O. Martelli⁸ & F. De Marinis⁸

¹Division of Medical Oncology, ‘S.G.Moscati’ Hospital, Avellino; ²Department of Medical Oncology, National Institute for Cancer Research, Genoa, Italy; ³Department of Medicine, Institute Gustave Roussy, Villejuif, France; ⁴Department of Medical Oncology, Thoraxklinik, Heidelberg, Germany; ⁵Clinical Trials Unit, National Cancer Institute, Naples, Italy; ⁶Department of Medical Oncology, Christie Hospital, Manchester, UK; ⁷Department of Thoracic Oncology, Netherlands Cancer Institute, Amsterdam, The Netherlands; ⁸Fifth Pulmonary-Oncology Unit, Lung Disease Department, Forlanini Hospital, Rome, Italy

Received 1 July 2003; revised 7 October 2003; accepted 27 October 2003
Treatment of advanced non-small-cell lung cancer patients with ECOG performance status 2: results of an European Experts Panel

### Table 4. Consensus on treatment of patients with advanced NSCLC and ECOG PS2 in clinical practice

<table>
<thead>
<tr>
<th>Preferred option</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single-agent chemotherapy with a third generation drug</td>
</tr>
<tr>
<td>(e.g. gemcitabine, vinorelbine, taxanes)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Alternative options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboplatin-based doublets</td>
</tr>
<tr>
<td>Cisplatin-based doublets with attenuated doses of cisplatin</td>
</tr>
</tbody>
</table>

Cesare Gridelli, Matti Aapro, Andrea Ardizzoni, Lodovico Balducci, Filippo De Marinis, Karen Kelly, Thierry Le Chevalier, Christian Manegold, Francesco Perrone, Rafael Rosell, Frances Shepherd, Luigi De Petris, Massimo Di Maio, and Corey Langer
Table 5. Treatment Options for Elderly Patients With Advanced NSCLC in Clinical Practice

<table>
<thead>
<tr>
<th>Treatment Option</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single-agent chemotherapy</td>
<td>with a third-generation drug (eg, vinorelbine, gemcitabine, taxanes) in PS 0-2 patients</td>
</tr>
<tr>
<td>Platinum-based (cisplatin or carboplatin) doublets</td>
<td>in fit patients (PS 0-1) selected for adequate organ function</td>
</tr>
<tr>
<td>Best supportive care</td>
<td>(in addition to chemotherapy or as exclusive therapeutic option for those patients unsuitable for active treatment)</td>
</tr>
</tbody>
</table>

C Gridelli et al, JCO 2005
Chemotherapy prolongs survival and is most appropriate for individuals with good performance status (PS 0 or 1, and possibly 2)

Chemotherapy should be a platinum-based two-drug combination regimen

Non-platinum containing regimens may be used as alternatives to platinum-based regimens. For elderly patients, or patients with PS 2, available data support the use of single-agent chemotherapy

Chemotherapy should be stopped at 4 cycles in patients who are not responding to treatment, and should be administered for no more than six cycles

If chemotherapy is to be given it should be initiated while the patient still has good PS

Treatment selection based on clinical parameters

Pathology
  Gender
  Smoking status
  Performance status
  Age
  Response/reaction to therapy
Lung Cancer - Histology

Adenocarcinoma

Squamous cell Carcinoma

Large cell Carcinoma
Adenocarcinoma

- Cancer arising out of glandular tissues
- Most frequent type diagnosed in lung cancer (30 – 40%)
- Common in smokers and non-smokers
- More common in women than in men
- Usually arise in the peripheral areas of lung and metastasize quickly
- Bronchoalveolar carcinoma (BAC) is a subtype of adenocarcinoma and is found more in women and is associated with scars of tuberculosis
- Early diagnosis is rare and prognosis is poor
Squamous cell carcinoma

- Accounts for 30% of lung cancers
- Strongly associated with smoking
- Tend to be more centrally located
- Forms necrotic cavities, that can be seen on X-rays
- Cell doubling rate is slow and surgical resection leads to a 30% 5 year survival rate
- 5 year survival rate of all SCC is 5 – 7%
Trends in squamous cell carcinoma and adenocarcinoma incidence rates in Europe

Histology may be used to determine treatment approach and may also be prognostic

European incidence rates
- AC: 34%
- SC: 44%
- LCC: 13%
- Other**: 8%
  (LCC=large-cell carcinoma)

* Generally similar trends were observed in other European countries (Eindhoven Netherlands, Varese Italy, Slovenia, France, Spain, and Switzerland)
**Other includes histology types that are not clearly AC, SCC, or LCC, and may include mixed histology types

• Previously Untreated
• Stage IIIB or IV
• ECOG PS 0-1
  n=1,725

Pemetrexed/Cisplatin (P 500 mg/m² d1; C 75 mg/m² d1) every three weeks, up to 6 cycles,
  n=862

Gemcitabine/Cisplatin (G 1250 mg/m² d1,8; C 75 mg/m² d1) every three weeks, up to 6 cycles
  n=863

• The primary endpoint: **non-inferiority, overall survival.**
• The Largest trial ever reported in this setting with **1,725** patients from 177 sites in 26 countries*

Scaglioni GV et al, J Clin Oncol 2008 20;3543-51
Pem/cisplatin is similar to Gem/cisplatin: Overall survival (overall population)

<table>
<thead>
<tr>
<th></th>
<th>PEM + Cisplatin</th>
<th>Gemc + Cisplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N=862)</td>
<td>(N=863)</td>
</tr>
<tr>
<td>Median OS</td>
<td>10.3 mos</td>
<td>10.3 mos</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(9.8, 11.2)</td>
<td>(9.6, 10.9)</td>
</tr>
<tr>
<td>Adjusted HR</td>
<td>0.94 (0.84, 1.05)</td>
<td></td>
</tr>
<tr>
<td>(95% CI)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Scaglioni GV et al, J Clin Oncol 2008 20;3543-51
Pem/Cis vs. Gem/Cis

Scagliotti GV et al, J Clin Oncol 2008 20;3543-51
Is the toxicity profile different among the histology groups examined in this study?

Grade 3 or 4 Toxicity: Pemetrexed + Cisplatin

<table>
<thead>
<tr>
<th>G 3/4 Toxicity</th>
<th>Adenocarcinoma (n=425)</th>
<th>Large Cell Carcinoma (n=76)</th>
<th>Other Histology (n=103)</th>
<th>Squamous Carcinoma (n=235)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>15.5%</td>
<td>14.5%</td>
<td>12.6%</td>
<td>15.7%</td>
</tr>
<tr>
<td>Anemia</td>
<td>4.0%</td>
<td>3.9%</td>
<td>9.7%</td>
<td>7.2%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>3.1%</td>
<td>2.6%</td>
<td>6.8%</td>
<td>5.1%</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>4.0%</td>
<td>3.9%</td>
<td>4.9%</td>
<td>6.4%</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>1.4%</td>
<td>0.0%</td>
<td>1.9%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Alopecia (all grades)</td>
<td>14.1%</td>
<td>11.8%</td>
<td>4.9%</td>
<td>11.1%</td>
</tr>
<tr>
<td>Nausea</td>
<td>7.3%</td>
<td>11.8%</td>
<td>7.8%</td>
<td>5.1%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5.4%</td>
<td>6.6%</td>
<td>9.7%</td>
<td>5.5%</td>
</tr>
<tr>
<td>Dehydration (all grades)</td>
<td>4.0%</td>
<td>3.9%</td>
<td>4.9%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6.4%</td>
<td>7.9%</td>
<td>6.8%</td>
<td>6.8%</td>
</tr>
</tbody>
</table>

• No clinically relevant differences were observed for the safety profile of pemetrexed + cisplatin within the histology subgroups

1. Data on file. Eli Lilly and Company
2. ALIMTA [Summary of Product Characteristics]. Eli Lilly and Co; Approved 08 April 2008.
Significant treatment-related differences observed by histology type

Scagliotti GV et al, J Clin Oncol 2008 20;3543-51
## Gender, Smoking, PS, ethnics are prognostic factors

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of Patients</th>
<th>Cisplatin/Pemetrexed</th>
<th>Cisplatin/Gemcitabine</th>
<th>Adjusted Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Median</td>
<td>95% CI</td>
<td>Median</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 65 years</td>
<td>1,118</td>
<td>10.3</td>
<td>9.6 to 11.3</td>
<td>10.3</td>
</tr>
<tr>
<td>≥ 65 years</td>
<td>607</td>
<td>10.1</td>
<td>9.2 to 12.0</td>
<td>10.2</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>1,210</td>
<td>9.6</td>
<td>8.8 to 10.2</td>
<td>9.9</td>
</tr>
<tr>
<td>Females</td>
<td>515</td>
<td>13.3</td>
<td>12.3 to 15.0</td>
<td>11.4</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1,349</td>
<td>10.0</td>
<td>9.3 to 10.8</td>
<td>10.1</td>
</tr>
<tr>
<td>East/South East Asian</td>
<td>220</td>
<td>13.8</td>
<td>10.2 to 17.1</td>
<td>11.9</td>
</tr>
<tr>
<td>All other</td>
<td>156</td>
<td>9.9</td>
<td>8.6 to 12.8</td>
<td>11.5</td>
</tr>
<tr>
<td><strong>Smoking status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Former/current smoker</td>
<td>1,266</td>
<td>10.0</td>
<td>9.4 to 11.1</td>
<td>10.3</td>
</tr>
<tr>
<td>Never-smoker</td>
<td>250</td>
<td>15.9</td>
<td>13.8 to 20.2</td>
<td>15.3</td>
</tr>
<tr>
<td><strong>Disease stage</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIIB</td>
<td>415</td>
<td>11.9</td>
<td>10.0 to 14.2</td>
<td>11.3</td>
</tr>
<tr>
<td>IV</td>
<td>1,310</td>
<td>10.0</td>
<td>9.3 to 10.8</td>
<td>10.1</td>
</tr>
<tr>
<td><strong>Performance status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>612</td>
<td>13.4</td>
<td>11.9 to 14.9</td>
<td>12.2</td>
</tr>
<tr>
<td>1</td>
<td>1,110</td>
<td>9.1</td>
<td>8.1 to 9.9</td>
<td>9.0</td>
</tr>
</tbody>
</table>

Scagliotti GV et al, J Clin Oncol 2008 20;3543-51
Stage IIIB/IV NSCLC
PS 0-1
4 prior cycles of gem, doc, or tax + cis or carb, with CR, PR, or SD

Randomization factors:
- gender
- PS
- stage
- best tumor response to induction
- non-platinum induction drug
- brain mets

2:1 Randomization

Primary Endpoint = PFS

Pemetrexed 500 mg/m² (d1, q21d) + BSC (N=441)*

Placebo (d1, q21d) + BSC (N=222)*

*B₁₂, folate, and dexamethasone given in both arms

Ciuleanu. ASCO. 2008 (abstr 8011)
Progression-free Survival

HR = 0.60 (95% CI: 0.49–0.73)

\( p < 0.00001 \)
Overall Survival (Intent-to-treat Population)

HR=0.79 (95% CI: 0.65–0.95)
\( p =0.012 \)

Pemetrexed 13.4 mos
Placebo 10.6 mos
Efficacy by Histologic Groups

<table>
<thead>
<tr>
<th>Histology Groups</th>
<th>Median OS, mos</th>
<th>$P$-value (HR)</th>
<th>Median PFS, mos</th>
<th>$P$-value (HR)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pem</td>
<td>Plac</td>
<td>Pem</td>
<td>Plac</td>
</tr>
<tr>
<td>Non-squamous (n=481)</td>
<td>15.5</td>
<td>10.3</td>
<td>0.002</td>
<td>4.4</td>
</tr>
<tr>
<td>Adeno (n=329)</td>
<td>16.8</td>
<td>11.5</td>
<td>0.026</td>
<td>4.6</td>
</tr>
<tr>
<td>Large cell (n=20)</td>
<td>8.4</td>
<td>7.9</td>
<td>0.964</td>
<td>4.5</td>
</tr>
<tr>
<td>Other (n=133)</td>
<td>11.3</td>
<td>7.7</td>
<td>0.025</td>
<td>4.1</td>
</tr>
<tr>
<td>Squamous (n=182)</td>
<td>9.9</td>
<td>10.8</td>
<td>0.678</td>
<td>2.4</td>
</tr>
</tbody>
</table>

There was a statistically significant treatment-by-histology interaction with both PFS ($P=0.036$) and OS ($P=0.033$).
Survival with ALIMTA is comparable to docetaxel for second-line treatment of advanced NSCLC

<table>
<thead>
<tr>
<th></th>
<th>ALIMTA (N=265)</th>
<th>Docetaxel (N=276)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median survival</td>
<td>8.3</td>
<td>7.9</td>
</tr>
<tr>
<td>(months)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.99 (0.8-1.20)</td>
<td></td>
</tr>
<tr>
<td>(95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-year survival</td>
<td>29.7</td>
<td>29.7</td>
</tr>
<tr>
<td>OS (%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

JMEI: Retrospective Analysis of Histology and Survival

Nonsquamous* (n=399)

Survival Probability (%)

HR=0.778
(95% CI: 0.607–0.997)

p=0.048

Pemetrexed
Median OS: 9.3 mos

Docetaxel
Median OS: 8.0 mos

Squamous (n=172)

Survival Probability (%)

HR=1.563
(95% CI: 1.079–2.264)

p=0.018

Pemetrexed
Median OS: 6.2 mos

Docetaxel
Median OS: 7.4 mos

Peterson et al., JTO 2, 8 (suppl4), 851 (Abstr. P2-328), 2007
NSCLC: Pemetrexed is more effective in patients with non-squamous tumors

Peterson et al., JTO 2, 8 (suppl4), 851 (Abstr. P2-328), 2007
TS gene expression level is higher in Squamous NSCLC

Comparative results were documented through immunohistochemistry (IHC) analysis where patients with squamous cell carcinoma had higher TS expression compared with patients with adenocarcinoma ($p=0.0269$).

* $\frac{\text{TS mRNA}}{\beta\text{-actin mRNA}} = \text{Unitless ratio}$

TS: Thymidylate Synthase

Treatment selection based on clinical parameters

Pathology
  Gender
  Smoking status
  Performance status
  Age
Response/reaction to therapy
**NSCLC: Bevacizumab following Standard Triplet CT**

ECOG 4599: Carbo/Paclitaxel

- Previously untreated stage IIIB/IV non-squamous NSCLC

Bevacizumab

- Bevacizumab (15mg/kg) every 3 weeks + CP
  - Bevacizumab every 3 weeks until progression

**RANDOMISE**

- Previously untreated, stage IIIB, IV or recurrent non-squamous NSCLC

AVAiL: Cis/Gem

- Bevacizumab
  - 7.5mg/kg + CG (2)
  - Placebo + CG (1)
- Placebo + CG (1)
- Bevacizumab
  - 15mg/kg + CG (2)

PD
Histology as a predictive factor – VEGF

- Histology may also be useful in defining patient population based on safety.

- Phase-2 trial of an anti-VEGF agent in 67 patients
  - Similar efficacy in squamous and adeno groups
  - Life threatening pulmonary haemorrhages in 6 patients
    - 4/13 patients (31%) had squamous carcinoma
    - 2/54 patients (4%) had adenocarcinomas

- Squamous cell tumours
  - more frequently centrally located
  - have a greater tendency to cavitate as compared to adenocarcinoma

Present Standard at USA: ECOG 4599 for Non-Squamous Cell Carcinoma

Bevacizumab + PacCar (%)
Paclitaxel Carboplatin (%)

HR = hazard ratio Sandler NEJM 2006

HR=0.80 (0.69, 0.93); p=0.003
Treatment selection based on clinical parameters

Pathology
Gender
Smoking status
Performance status
Age
Response/reaction to therapy
Lung Cancer in Never Smokers

At a glance

- About 25% of lung cancer cases worldwide are not attributable to tobacco smoking. Thus, lung cancer in never smokers is the seventh leading cause of cancer deaths in the world, killing more people every year than pancreatic or prostate cancers.
- Globally, lung cancer in never smokers demonstrates a marked gender bias, occurring more frequently among women. In particular, there is a high proportion of never smokers in Asian women diagnosed with lung cancer.
- Although smoking-related carcinogens act on both proximal and distal airways inducing all the major forms of lung cancer, cancers arising in never smokers target the distal airways and favour adenocarcinoma histology.
- Environmental tobacco smoke (ETS) is a relatively weak carcinogen and can only account for a minority of lung cancers arising in never smokers.
- Although multiple risk factors, including environmental, hormonal, genetic and viral factors, have been implicated in the pathogenesis of lung cancer in never smokers, no clear-cut dominant factor has emerged that can explain the relatively high incidence of lung cancer in never smokers and the marked geographic differences in gender proportions.
- Molecular epidemiology studies, in particular of the TP53, KRAS and epidermal growth factor receptor (EGFR) genes, demonstrate strikingly different mutation patterns and frequencies between lung cancers in never smokers and smokers.
- There are major clinical differences between lung cancers arising in never smokers and smokers and their response to targeted therapies. Indeed, non-smoking status is the strongest clinical predictor of benefit from the EGFR tyrosine kinase inhibitors.
- The above-mentioned facts strongly suggest that lung cancer arising in never smokers is a disease distinct from the more common tobacco-associated forms of lung cancer.
- Further efforts are needed to identify the major cause or causes of lung cancers arising in never smokers before successful strategies for prevention, early diagnosis and novel therapies can be implemented.

Lung Cancer in Never Smokers

iPASS - Study design

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

Gefitinib (250 mg / day)
1:1 randomization

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

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

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

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

*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

IPASS: Demography (ITT population)

<table>
<thead>
<tr>
<th></th>
<th>Gefitinib, % (N=609)</th>
<th>Carboplatin / paclitaxel, % (N=608)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;65 years</td>
<td>73</td>
<td>74</td>
</tr>
<tr>
<td>Median age (range), years</td>
<td>57 (24-84)</td>
<td>57 (25-84)</td>
</tr>
<tr>
<td>Femalea</td>
<td>79</td>
<td>79</td>
</tr>
<tr>
<td>WHO PS 0 / 1 / 2a</td>
<td>26 / 64 / 10</td>
<td>26 / 63 / 11</td>
</tr>
<tr>
<td>Never smokera</td>
<td>94</td>
<td>94</td>
</tr>
<tr>
<td>Light ex-smokera</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Mean smoking duration, years</td>
<td>11.5 (N=38)</td>
<td>14.5 (N=39)</td>
</tr>
<tr>
<td>Mean time since cessation, years</td>
<td>24.6 (N=38)</td>
<td>23.4 (N=39)</td>
</tr>
<tr>
<td>Metastatic disease</td>
<td>75</td>
<td>76</td>
</tr>
<tr>
<td>Time since diagnosis: &lt;6 months</td>
<td>96</td>
<td>94</td>
</tr>
<tr>
<td>Chinese ethnicityb</td>
<td>52</td>
<td>50</td>
</tr>
<tr>
<td>Japanese ethnicityb</td>
<td>19</td>
<td>20</td>
</tr>
</tbody>
</table>

WHO, World Health Organization
a1 of the 3 stratification factors
bnot the same as country of residence

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

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

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

Progression-free survival in EGFR mutation positive and negative patients

EGFR mutation positive

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

HR (95% CI) = 0.48 (0.36, 0.64)
p<0.0001
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)
p<0.0001
No. events gefitinib, 88 (96.7%)
No. events C / P, 70 (82.4%)

Treatment by subgroup interaction test, p<0.0001

ITT population
Cox analysis with covariates

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 (%)

71.2% 47.3% 1.1% 23.5%
(n=132) (n=129) (n=91) (n=85)

Mutation positive patients

Mutation negative patients

Odds ratio >1 implies greater chance of response on gefitinib

**PFS: Gefitinib vs. Paclitaxel/carbo in iPASS**

- **Treatment-by-subgroup interaction test p-value**
  - **p > 0.05 for gender**
  - **p = 0.0256 for age**
  - **p > 0.05 for WHO PS, smoking status, disease stage**

**Cox analysis with covariates**

Green band is the 95% CI for the HR for “all patients”

- **HR (gefitinib vs carboplatin / paclitaxel) and 95% CI**
  - **Favours gefitinib**
  - **Favours carboplatin / paclitaxel**
Treatment selection based on clinical parameters

Pathology
Gender
Smoking status
Performance status
Age
Response/reaction to therapy
FLEX
Study design

NSCLC wet IIIB/IV EGFR-expressing

Chemotherapy + Cetuximab

Maintenance
Cetuximab until PD or intolerable toxicity

Chemotherapy

Chemotherapy (CT)
Cisplatin 80 mg/m² day 1
Vinorelbine 25 (30) mg/m² days 1, 8
Every 3 weeks, up to 6 cycles

Cetuximab
initial dose 400 mg/m²
then 250 mg/m² weekly

Pirker et al, J Clin Oncol 2008, 18S (Abstract 3)
FLEX Overall survival

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median OS</th>
<th>1-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT + Cetuximab</td>
<td>11.3 months</td>
<td>47%</td>
</tr>
<tr>
<td>(n=557)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT</td>
<td>10.1 months</td>
<td>42%</td>
</tr>
<tr>
<td>(n=568)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HR=0.871 (95% CI 0.762-0.996), p=0.044

Patients at risk
CT + Cetuximab: 557, 383, 251, 155, 53, 3
CT: 568, 383, 225, 134, 48, 0

p-value = stratified log-rank test (2-sided)
Pirker et al, J Clin Oncol 2008, 18S (Abstract 3)
FLEX: Overall survival and early acne-like rash

FLEX: Overall survival
Early acne-like rash
CT + Cetuximab

HR=0.631 (95% CI: 0.515–0.774)*
p<0.001

8.8 months
15.0 months

Gatzemeier et al. JTO 3, 11, 4, (Abstr. 8), 2008
Conclusions

- Need to individualize treatment for patients based on clinical characteristics and biomarkers
- Clinical parameters may be surrogate markers for target biomarkers
- Clinical parameters are still useful in most part of the world when biomarker analysis are not available
- The clinical applications of biomarkers need to be proven in well-designed trials