ARE ALL LUNG & BREAST CANCERS SAME ??

Dr. DIPTI RANI SAMANTA
ASST PROF,
DEPT OF MEDICAL ONCOLOGY,
A.H. REGIONAL CANCER CENTRE
TREATMENT OF NSCLC BASED ON

PATIENT FACTOR

TUMOR FACTORS
Changes to the T descriptors are:

- **Sub classify:**
  - T1 as
    - T1a (≤ 2 cm) or
    - T1b (> 2 cm to ≤ 3 cm); and
  - T2 as
    - T2a (> 3 to ≤ 5 cm or T2 by other factor and ≤ 5 cm) or
    - T2b (> 5 to ≤ 7 cm).

- **Reclassify:**
  - T2 tumors > 7 cm as T3.
  - T4 tumors by additional nodule/s in the lung (primary lobe) as T3.
  - M1 by additional nodule/s in the ipsilateral lung (different lobe) as T4.
  - Pleural dissemination (malignant pleural or pericardial effusions, pleural nodules) as M1.

Changes to the M descriptors are:

- **Reclassify** pleural dissemination (malignant pleural effusions, pleural nodules) from T4 to M1a.
- Sub classify M1 by additional nodules in the contra lateral lung as M1a.
- Sub classify M1 by distant metastases outside the lung/pleura as M1b.
Current International Staging System with treatment implications for advanced NSCLC

<table>
<thead>
<tr>
<th></th>
<th>M0</th>
<th>M1a</th>
<th>M1b</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>IA</td>
<td>IIA</td>
<td></td>
</tr>
<tr>
<td>N1</td>
<td>IB</td>
<td>IIB</td>
<td></td>
</tr>
<tr>
<td>N2</td>
<td>IIB</td>
<td>IIIA</td>
<td>IV</td>
</tr>
<tr>
<td>N3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Indian Incidence of NSCLC by Stage approx.
NSCLC distribution by stage and associated survival rates

<table>
<thead>
<tr>
<th>NSCLC Stage</th>
<th>Distribution(^1)</th>
<th>NSCLC Stage</th>
<th>1-Year Survival(^2)</th>
<th>5-Year Survival(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>13%–24%</td>
<td>IA</td>
<td>91%</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IB</td>
<td>72%</td>
<td>43%</td>
</tr>
<tr>
<td>II</td>
<td>5%–10%</td>
<td>IIA</td>
<td>79%</td>
<td>36%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IIB</td>
<td>59%</td>
<td>25%</td>
</tr>
<tr>
<td>III</td>
<td>31%–44%</td>
<td>IIIA</td>
<td>50%</td>
<td>19%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IIIB</td>
<td>37%(T4/N0-2/M0)</td>
<td>7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>32%(anyT/N3/M0)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>32%–39%</td>
<td>IV</td>
<td>20%</td>
<td>2%</td>
</tr>
</tbody>
</table>

NON-SMALL CELL LUNG CANCER

Survival by stage

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>100</td>
<td>79</td>
<td>54</td>
<td>64</td>
<td>48</td>
<td>42</td>
</tr>
<tr>
<td>II</td>
<td>100</td>
<td>65</td>
<td>42</td>
<td>32</td>
<td>28</td>
<td>22</td>
</tr>
<tr>
<td>III</td>
<td>100</td>
<td>34</td>
<td>15</td>
<td>9</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>IV</td>
<td>100</td>
<td>24</td>
<td>9</td>
<td>6</td>
<td>4</td>
<td>3</td>
</tr>
</tbody>
</table>

Years
Lung Cancer TYPES

- Squamous-cell: 40%
- Adenocarcinoma: 30%
- Large-cell: 15%
- Small-cell: 20%
Therapeutic Classification of NSCLC

**Resectable NSCLC**
Stage I, II, IIIA

**Unresectable NSCLC**
Stage ?III A/III B

**Advanced/metastatic NSCLC**
T4 any N, N3 any M
## NSCLC: Treatment by Stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I a/b</td>
<td>Tumor of any size is found only in the lung</td>
<td>Surgery</td>
</tr>
<tr>
<td>Stage II a/b</td>
<td>Tumor has spread to lymph nodes associated with the lung</td>
<td>Surgery</td>
</tr>
<tr>
<td>Stage III a</td>
<td>Tumor has spread to the lymph nodes in the tracheal area, including chest wall and diaphragm</td>
<td>Chemotherapy followed by radiation or surgery</td>
</tr>
<tr>
<td>Stage III b</td>
<td>Tumor has spread to the lymph nodes on the opposite lung or in the neck</td>
<td>Combination of chemotherapy and radiation</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Tumor has spread beyond the chest</td>
<td>Chemotherapy and/or palliative (maintenance) care</td>
</tr>
</tbody>
</table>
## Survival in advanced NSCLC

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Median Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best Supportive Care</td>
<td>4 months</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>6 months</td>
</tr>
<tr>
<td>Platinum-based doublet</td>
<td>8-10 months</td>
</tr>
<tr>
<td>Chemotherapy + Targeted Therapy</td>
<td>12 months</td>
</tr>
</tbody>
</table>
Overall Strategy

1st Line Treatment
Platinum-based Doublet

2nd Line Treatment
Targeted Therapy
EGFR-TKI
Chemotherapy
Pemetrexed, Docetaxel

3rd Line Treatment

Before ASCO 2004

Where we were with Chemotherapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Drugs</th>
<th>% of ORR</th>
<th>% of PFS</th>
<th>% of MST</th>
<th>% of I &amp; V</th>
<th># of pts</th>
<th>% of 1 Yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclin' 2002</td>
<td>TAX 326</td>
<td>67</td>
<td>67</td>
<td>67</td>
<td>402</td>
<td>1×1/cis</td>
<td>10.1</td>
</tr>
<tr>
<td>Seaglio' 2002</td>
<td>Gem/cis</td>
<td>67</td>
<td>67</td>
<td>67</td>
<td>408</td>
<td>1×1/cis</td>
<td>10.1</td>
</tr>
<tr>
<td>Seaglio' 2002</td>
<td>Gem/cis</td>
<td>67</td>
<td>67</td>
<td>67</td>
<td>404</td>
<td>1×1/cis</td>
<td>10.1</td>
</tr>
<tr>
<td>Seaglio' 2002</td>
<td>Gem/cis</td>
<td>67</td>
<td>67</td>
<td>67</td>
<td>404</td>
<td>1×1/cis</td>
<td>10.1</td>
</tr>
<tr>
<td>Seaglio' 2002</td>
<td>Gem/cis</td>
<td>67</td>
<td>67</td>
<td>67</td>
<td>404</td>
<td>1×1/cis</td>
<td>10.1</td>
</tr>
<tr>
<td>Seaglio' 2002</td>
<td>Gem/cis</td>
<td>67</td>
<td>67</td>
<td>67</td>
<td>404</td>
<td>1×1/cis</td>
<td>10.1</td>
</tr>
<tr>
<td>Seaglio' 2002</td>
<td>Gem/cis</td>
<td>67</td>
<td>67</td>
<td>67</td>
<td>404</td>
<td>1×1/cis</td>
<td>10.1</td>
</tr>
<tr>
<td>Seaglio' 2002</td>
<td>Gem/cis</td>
<td>67</td>
<td>67</td>
<td>67</td>
<td>404</td>
<td>1×1/cis</td>
<td>10.1</td>
</tr>
<tr>
<td>Seaglio' 2002</td>
<td>Gem/cis</td>
<td>67</td>
<td>67</td>
<td>67</td>
<td>404</td>
<td>1×1/cis</td>
<td>10.1</td>
</tr>
<tr>
<td>Seaglio' 2002</td>
<td>Gem/cis</td>
<td>67</td>
<td>67</td>
<td>67</td>
<td>404</td>
<td>1×1/cis</td>
<td>10.1</td>
</tr>
<tr>
<td>Seaglio' 2002</td>
<td>Gem/cis</td>
<td>67</td>
<td>67</td>
<td>67</td>
<td>404</td>
<td>1×1/cis</td>
<td>10.1</td>
</tr>
<tr>
<td>Seaglio' 2002</td>
<td>Gem/cis</td>
<td>67</td>
<td>67</td>
<td>67</td>
<td>404</td>
<td>1×1/cis</td>
<td>10.1</td>
</tr>
<tr>
<td>Seaglio' 2002</td>
<td>Gem/cis</td>
<td>67</td>
<td>67</td>
<td>67</td>
<td>404</td>
<td>1×1/cis</td>
<td>10.1</td>
</tr>
<tr>
<td>Seaglio' 2002</td>
<td>Gem/cis</td>
<td>67</td>
<td>67</td>
<td>67</td>
<td>404</td>
<td>1×1/cis</td>
<td>10.1</td>
</tr>
<tr>
<td>Seaglio' 2002</td>
<td>Gem/cis</td>
<td>67</td>
<td>67</td>
<td>67</td>
<td>404</td>
<td>1×1/cis</td>
<td>10.1</td>
</tr>
<tr>
<td>Seaglio' 2002</td>
<td>Gem/cis</td>
<td>67</td>
<td>67</td>
<td>67</td>
<td>404</td>
<td>1×1/cis</td>
<td>10.1</td>
</tr>
<tr>
<td>Seaglio' 2002</td>
<td>Gem/cis</td>
<td>67</td>
<td>67</td>
<td>67</td>
<td>404</td>
<td>1×1/cis</td>
<td>10.1</td>
</tr>
<tr>
<td>Seaglio' 2002</td>
<td>Gem/cis</td>
<td>67</td>
<td>67</td>
<td>67</td>
<td>404</td>
<td>1×1/cis</td>
<td>10.1</td>
</tr>
<tr>
<td>Seaglio' 2002</td>
<td>Gem/cis</td>
<td>67</td>
<td>67</td>
<td>67</td>
<td>404</td>
<td>1×1/cis</td>
<td>10.1</td>
</tr>
<tr>
<td>Seaglio' 2002</td>
<td>Gem/cis</td>
<td>67</td>
<td>67</td>
<td>67</td>
<td>404</td>
<td>1×1/cis</td>
<td>10.1</td>
</tr>
<tr>
<td>Seaglio' 2002</td>
<td>Gem/cis</td>
<td>67</td>
<td>67</td>
<td>67</td>
<td>404</td>
<td>1×1/cis</td>
<td>10.1</td>
</tr>
<tr>
<td>Seaglio' 2002</td>
<td>Gem/cis</td>
<td>67</td>
<td>67</td>
<td>67</td>
<td>404</td>
<td>1×1/cis</td>
<td>10.1</td>
</tr>
<tr>
<td>Seaglio' 2002</td>
<td>Gem/cis</td>
<td>67</td>
<td>67</td>
<td>67</td>
<td>404</td>
<td>1×1/cis</td>
<td>10.1</td>
</tr>
<tr>
<td>Seaglio' 2002</td>
<td>Gem/cis</td>
<td>67</td>
<td>67</td>
<td>67</td>
<td>404</td>
<td>1×1/cis</td>
<td>10.1</td>
</tr>
<tr>
<td>Seaglio' 2002</td>
<td>Gem/cis</td>
<td>67</td>
<td>67</td>
<td>67</td>
<td>404</td>
<td>1×1/cis</td>
<td>10.1</td>
</tr>
<tr>
<td>Seaglio' 2002</td>
<td>Gem/cis</td>
<td>67</td>
<td>67</td>
<td>67</td>
<td>404</td>
<td>1×1/cis</td>
<td>10.1</td>
</tr>
<tr>
<td>Seaglio' 2002</td>
<td>Gem/cis</td>
<td>67</td>
<td>67</td>
<td>67</td>
<td>404</td>
<td>1×1/cis</td>
<td>10.1</td>
</tr>
<tr>
<td>Seaglio' 2002</td>
<td>Gem/cis</td>
<td>67</td>
<td>67</td>
<td>67</td>
<td>404</td>
<td>1×1/cis</td>
<td>10.1</td>
</tr>
<tr>
<td>Seaglio' 2002</td>
<td>Gem/cis</td>
<td>67</td>
<td>67</td>
<td>67</td>
<td>404</td>
<td>1×1/cis</td>
<td>10.1</td>
</tr>
<tr>
<td>Seaglio' 2002</td>
<td>Gem/cis</td>
<td>67</td>
<td>67</td>
<td>67</td>
<td>404</td>
<td>1×1/cis</td>
<td>10.1</td>
</tr>
<tr>
<td>Seaglio' 2002</td>
<td>Gem/cis</td>
<td>67</td>
<td>67</td>
<td>67</td>
<td>404</td>
<td>1×1/cis</td>
<td>10.1</td>
</tr>
<tr>
<td>Seaglio' 2002</td>
<td>Gem/cis</td>
<td>67</td>
<td>67</td>
<td>67</td>
<td>404</td>
<td>1×1/cis</td>
<td>10.1</td>
</tr>
<tr>
<td>Seaglio' 2002</td>
<td>Gem/cis</td>
<td>67</td>
<td>67</td>
<td>67</td>
<td>404</td>
<td>1×1/cis</td>
<td>10.1</td>
</tr>
<tr>
<td>Seaglio' 2002</td>
<td>Gem/cis</td>
<td>67</td>
<td>67</td>
<td>67</td>
<td>404</td>
<td>1×1/cis</td>
<td>10.1</td>
</tr>
<tr>
<td>Seaglio' 2002</td>
<td>Gem/cis</td>
<td>67</td>
<td>67</td>
<td>67</td>
<td>404</td>
<td>1×1/cis</td>
<td>10.1</td>
</tr>
<tr>
<td>Seaglio' 2002</td>
<td>Gem/cis</td>
<td>67</td>
<td>67</td>
<td>67</td>
<td>404</td>
<td>1×1/cis</td>
<td>10.1</td>
</tr>
<tr>
<td>Seaglio' 2002</td>
<td>Gem/cis</td>
<td>67</td>
<td>67</td>
<td>67</td>
<td>404</td>
<td>1×1/cis</td>
<td>10.1</td>
</tr>
<tr>
<td>Seaglio' 2002</td>
<td>Gem/cis</td>
<td>67</td>
<td>67</td>
<td>67</td>
<td>404</td>
<td>1×1/cis</td>
<td>10.1</td>
</tr>
<tr>
<td>Seaglio' 2002</td>
<td>Gem/cis</td>
<td>67</td>
<td>67</td>
<td>67</td>
<td>404</td>
<td>1×1/cis</td>
<td>10.1</td>
</tr>
<tr>
<td>Seaglio' 2002</td>
<td>Gem/cis</td>
<td>67</td>
<td>67</td>
<td>67</td>
<td>404</td>
<td>1×1/cis</td>
<td>10.1</td>
</tr>
<tr>
<td></td>
<td>NP</td>
<td>GP</td>
<td>TC</td>
<td>IP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MST</td>
<td>11.4</td>
<td>14.8</td>
<td>12.3</td>
<td>14.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 year survival</td>
<td>48</td>
<td>60</td>
<td>51</td>
<td>59</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TTP</td>
<td>4.1</td>
<td>4.0</td>
<td>4.5</td>
<td>4.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response Rate</td>
<td>33</td>
<td>30</td>
<td>32</td>
<td>31</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Summary: Outcome

Kubota K. et al. Proc. ASCO 2004
## Results: Overall Survival

<table>
<thead>
<tr>
<th>Result</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median, mos</strong></td>
<td></td>
</tr>
<tr>
<td>Gem/platinum</td>
<td>9</td>
</tr>
<tr>
<td>Platinum comparators</td>
<td>8.2</td>
</tr>
<tr>
<td><strong>Hazard ratio</strong></td>
<td>0.90 (0.84-0.96)*</td>
</tr>
<tr>
<td></td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td><strong>Absolute benefit</strong></td>
<td>3.9% (year 1)</td>
</tr>
</tbody>
</table>

*Statistically significant reduction in favor of gem-based arms*
Overall Strategy

1st Line Treatment

Platinum-based Doublet

Gemzar + platinum may be the best 1st line treatment.

- It is the most widely and extensively tested regimen in the world. Treatment outcomes have been universally consistent.
- A meta-analysis of 13 randomized clinical trials indicate a statistically significant \( \uparrow \text{PFS} \) and a slightly \( \uparrow \text{OS} \).
- Side effects among the best tolerated of any 1st line regimen.

1st line treatment may affect 2nd line efficacy
Exploiting the Tumor Molecular Profile of Individual Patients for Selection of Therapy

 Patients with the same Diagnosis & Clinical Features (Stage IV Non-Small Cell Lung Cancer)
Main Molecular Markers in Lung Cancer

MARKERS OF CARCINOGENESIS
- Growth-Regulating Proteins (K-ras, EGFR, HER2/neu)
- Cell-Cycle Specific Proteins (p53, bcl2, RB, p16, FHIT)

MARKERS OF TUMOR INVASION
- Angiogenesis
- Invasion/extracellular Matrix Degradation

MARKERS OF METASTASES
- Adhesion Molecules
- Blood Group Antigens & Precursors

MARKERS OF PROLIFERATION
- Mitotic Index/Ploidy, PCNA, KI67
The distribution of activating mutations among EGFR mutation positive patients is similar in Asian and non-Asian studies

### Distribution of mutation types (% of mutations)

<table>
<thead>
<tr>
<th></th>
<th>Literature review</th>
<th>Asian studies</th>
<th>Non-Asian studies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Most prevalent mutation types</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exon 19 deletion</td>
<td>51%</td>
<td>58%</td>
<td></td>
</tr>
<tr>
<td>Exon 21 point mutation L858R</td>
<td>42%</td>
<td>32%</td>
<td></td>
</tr>
<tr>
<td>Exon 20</td>
<td>2%</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>Exon 18 G719A/C</td>
<td>3%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Exon 21 L861Q</td>
<td>1%</td>
<td>1%</td>
<td></td>
</tr>
</tbody>
</table>

Some patients had more than one mutation type

AstraZeneca data on file 2009
EGFR mutation causes conformational change and increased activation

- Ligand
- Extracellular domain
- Trans-membrane domain
- Tyrosine kinase domain
- Tyrosine phosphorylation

Wild Type EGFR:

- Ras-Raf-MAPK
- Proliferation

Mutant EGFR:

- Pi3K-AKT
- Survival

EGFR internalisation
Degradation/recycling

EGFR signals for longer at the cell membrane

Recommendations for tumour samples for EGFR mutation analysis

- Tumour biopsy from primary tumour or metastases is the “gold standard” for mutation analysis
  - It is recommended that DNA samples are extracted from formalin-fixed, paraffin-embedded tumour biopsy diagnostic samples
  - Robust well validated DNA extraction methodologies are recommended to avoid assay failures and false negative results
  - Mutation testing in surrogate tissues such as serum/plasma, bronchoalveolar lavage fluid or cytology specimens is not currently recommended

EGFR mutation positive status and clinical characteristics

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

% of samples
EGFR mutation positive

<table>
<thead>
<tr>
<th>Category</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>49.0</td>
</tr>
<tr>
<td>Female</td>
<td>63.0</td>
</tr>
<tr>
<td>PS 0</td>
<td>60.0</td>
</tr>
<tr>
<td>PS 2</td>
<td>57.1</td>
</tr>
<tr>
<td>Never smoked</td>
<td>60.7</td>
</tr>
<tr>
<td>Light ex-smoker</td>
<td>46.9</td>
</tr>
<tr>
<td>Locally advanced</td>
<td>60.2</td>
</tr>
<tr>
<td>Meta static</td>
<td>56.7</td>
</tr>
<tr>
<td>Age &lt;65 yrs</td>
<td>68.5</td>
</tr>
<tr>
<td>Age &gt;65 yrs</td>
<td></td>
</tr>
</tbody>
</table>
IPASS (Iressa Pan Asia Study)

**Study design**

**Endpoints**
- Primary: Progression free survival (non-inferiority)
- Secondary: Objective response rate, quality of life
- Exploratory: Disease related symptoms, safety and tolerability

**Randomization**
1:1

**Gefitinib 250 mg/day**

**Carboplatin AUC 5 or 6 and Paclitaxel 220mg/m² 3 weekly**

**Patients**
- Age ≥18 years
- Life expectancy >12 months
- Histology
- Never smokers or light ex-smokers
- PS 0-2
- Stage IIIIB
- Measurable disease

**Carboplatin/paclitaxel was offered to gefitinib patients upon progression**

PS, performance status; EGFR, epidermal growth factor receptor

*Never smokers: < 100 cigarettes in lifetime; light ex-smokers: stopped ≥ 15 years ago and smoked ≤ 10 pack yrs*
Objective tumour response (RECIST) (ITT population)

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

Patients (%)

43.0
Gefitinib
(N=609)

32.2
Carboplatin / Paclitaxel
(N=608)

Mok T, ESMO 2008
IPASS trial: EGFR mutation is a prognostic factor for response to CT

- Overall response rate (%)
  - Gefitinib: 71.2%
  - Carboplatin / paclitaxel: 47.3%

- 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 T, ESMO 2008
IPASS Ph III Study: First-Line Gefitinib vs CP in Advanced NSCLC: ORR


**ORR (%)**

- OR: 2.75, P = .0001
- OR: 0.94, P = .0013
- OR: 1.79, P = .0243
- OR: 0.80, P = .5580
- OR: 1.49, P = .1093
- OR: 1.44, P = .4146

**EGFR Mutation**

- Gefitinib: 71.2%
- CP: 47.3%
- Negative: 1.1%

**EGFR Gene Copy Number**

- Gefitinib: 58.9
- CP: 44.8
- Low: 22.2
- High: 26.3

**EGFR Expression**

- Gefitinib: 51.5
- CP: 41.8
- Positive: 34
- Negative: 26.1

**IPASS: Progression-free survival in ITT population**

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

Mok et al ESMO LBA 2, 2008
**IPASS: First-line Gefitinib vs CP in Advanced NSCLC: PFS**

**PFS: Mutated EGFR**
- Median PFS:
  - Gefitinib (n = 132): 9.5 mos
  - CP (n = 129): 6.3 mos

**PFS: Wild-Type EGFR**
- Median PFS:
  - Gefitinib (n = 91): 1.6 mos
  - CP (n = 85): 5.5 mos

- HR: 0.48
  - $P < .0001$

- HR: 2.85
  - $P < .0001$

*Treatment by EGFR mutation status interaction test, $P < .0001*

<table>
<thead>
<tr>
<th>PFS Hazard Ratio*</th>
<th>P-value</th>
<th>Interaction by Subgroup**</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR mutation status</td>
<td>EGFR-gene-copy number</td>
<td>EGFR protein expression</td>
</tr>
<tr>
<td>N</td>
<td>M+</td>
<td>M-</td>
</tr>
<tr>
<td>261</td>
<td>176</td>
<td>780</td>
</tr>
<tr>
<td>0.48</td>
<td>2.85</td>
<td>0.68</td>
</tr>
<tr>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>0.0437</td>
<td>0.2135</td>
<td></td>
</tr>
</tbody>
</table>

*HR < 1.0 favors gefitinib; **HR in biomarker-positive vs HR in biomarker-negative
Source: Fukuoka M et al. ASCO 2009; Abstract 8006.
Summary and Conclusions

- **EGFR mutation status:** a strong predictive biomarker for a differential PFS and ORR benefit with first-line G versus C/P in clinically selected patients (Interaction by subgroup, $p < 0.0001$)
  - PFS: $(M+ \text{ HR} = 0.48, \ p < 0.0001, \ M^- \text{ HR} = 2.85, \ p < 0.0001)$
  - ORR: $(M+ \text{ OR} = 2.75, \ p = 0.0001, \ M^- \text{ OR} = 0.04, \ p = 0.0013)$

- **EGFR-gene-copy number:** trended toward being predictive of a differential PFS (Interaction by subgroup, $p = 0.0437$)
  - Post hoc explorations suggest that the PFS benefit to gefitinib was driven by the overlap of high EGFR-gene-copy number with a positive EGFR mutation status
  - PFS: High EGFR-gene-copy, $M+ \text{ HR} = 0.48$
  - PFS: High EGFR-gene-copy, $M- \text{ HR} = 3.85$

- **EGFR protein expression:** least differentially predictive

Source: Fukuoka M et al. ASCO 2009; Abstract 8006.
SATURN Ph III: Strong PFS Benefit for Erlotinib Maintenance With Mutated EGFR

- **PFS: Wild-Type EGFR**
  - Erlotinib (n = 199)
  - Placebo (n = 189)
  - HR: 0.78
  - HR: 0.10
  - P = .0185
  - P < .0001

- **PFS: Mutated EGFR**
  - Erlotinib (n = 22)
  - Placebo (n = 27)


SATURN Phase III Study: PFS by Biomarker Status

<table>
<thead>
<tr>
<th>Biomarker Status</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>EGFR, overexpressed</td>
<td>0.69 (0.58-0.82)</td>
<td>618</td>
</tr>
<tr>
<td>EGFR, not overexpressed</td>
<td>0.77 (0.51-1.14)</td>
<td>121</td>
</tr>
<tr>
<td>EGFR, high copy #</td>
<td>0.68 (0.51-0.90)</td>
<td>231</td>
</tr>
<tr>
<td>EGFR, low copy #</td>
<td>0.81 (0.62-1.07)</td>
<td>255</td>
</tr>
<tr>
<td>KRAS, mutated</td>
<td>0.77 (0.50-1.19)</td>
<td>90</td>
</tr>
<tr>
<td>KRAS, wild type</td>
<td>0.70 (0.57-0.87)</td>
<td>403</td>
</tr>
</tbody>
</table>
SATURN Study: Biomarker Analysis

Conclusions

• *EGFR* overexpression and *EGFR* gene copy number do not have adequate predictive power to guide selection of NSCLC patients for erlotinib maintenance therapy

• Erlotinib significantly improves PFS in NSCLC patients with mutated *EGFR*
  – Patients with wild-type *EGFR* benefited to a much lesser degree

• *KRAS* mutations not predictive for erlotinib outcomes
  – Strong negative prognostic factor
BR.21: Survival Benefit by Smoking Status

Current/Former Smokers
- HR = 0.87
- ORR = 3.9%
- Erlotinib (N=358)
- Placebo (N=187)

Never Smokers
- HR = 0.42
- ORR = 24.7%
- Erlotinib (N=104)
- Placebo (N=42)
JMDB: Pemetrexed vs Gemcitabine in advanced NSCLC (Phase III, first line)

Randomization Factors
- Stage
- PS
- Gender
- Histo vs cyto
- Brain mets

Cisplatin 75 mg/m² day 1 plus Pemetrexed 500 mg/m² day 1

Each cycle repeated q3 weeks up to 6 cycles

Cisplatin 75 mg/m² day 1 plus Gemcitabine 1250 mg/m² days 1 & 8

Vitamin B₁₂, folate, and dexamethasone given in both arms

Primary endpoint: survival; non-inferiority design

JMDB: Pemetrexed vs Gemcitabine in advanced NSCLC (Phase III, first line)

Overall Survival

Median (95% CI)
- CP 10.3 (9.8, 11.2)
- CG 10.3 (9.6, 10.9)

Adjusted HR (95% CI)
- CP vs CG 0.94 (0.84-1.05)

Patients at Risk
- CP 862
  - 598
  - 341
  - 146
  - 45
  - 0
- CG 863
  - 590
  - 327
  - 139
  - 34
  - 0

Scagliotti et al J Clin Oncol 26, 3543-3551, 2008
JMDB: Pemetrexed vs Gemcitabine in advanced NSCLC (Phase III, first line)

Nonsquamous* (n=1252)

- Pemetrexed+Cisplatin Median OS: 11.0 mos
- HR=0.844 (95% CI: 0.74–0.96)
- p=0.011

- Gemcitabine+Cisplatin Median OS: 10.1 mos

Squamous (n=473)

- Pemetrexed+Cisplatin Median OS: 9.4 mos
- HR=1.229 (95% CI: 1.00–1.51)
- p=0.051

- Gemcitabine+Cisplatin Median OS: 10.8 mos

NSCLC: Pemetrexed is more effective in patients with non-squamous tumors
(retrospective analysis of Pem vs Doc)

*Peterson et al., JTO 2, 8 (suppl4), 851 (Abstr. P2-328), 2007*
Thymidilate Synthase Expression in Normal Lung Tissue & Lung Cancer

Significantly Higher in Squamous Cell Carcinoma of the Lung than in normal lung tissue

Clinically relevant survival advantage favoring PEMETREXED/cisplatin in adenocarcinoma and large cell carcinoma

<table>
<thead>
<tr>
<th>Median overall survival by histologic group (months)</th>
<th>PEMETREXED/D/CIS (N=862)</th>
<th>GEMCITABINE/CIS (N=863)</th>
<th>Adjusted Hazard ratio (95% CI)</th>
<th>p-Valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma (N=847)</td>
<td>12.6</td>
<td>10.9</td>
<td>0.84 (0.71, 0.99)</td>
<td>0.033</td>
</tr>
<tr>
<td>Large cell carcinoma (N=153)</td>
<td>10.4</td>
<td>6.7</td>
<td>0.67 (0.48, 0.96)</td>
<td>0.027</td>
</tr>
<tr>
<td>Otherb (N=252)</td>
<td>8.6</td>
<td>9.2</td>
<td>1.08 (0.81, 1.45)</td>
<td>0.586</td>
</tr>
<tr>
<td>Squamous cell carcinoma (N=473)</td>
<td>9.4</td>
<td>10.8</td>
<td>1.23 (1.00, 1.51)</td>
<td>0.050</td>
</tr>
</tbody>
</table>

aSuperiority p-values.
bPatients whose histologic diagnosis did not clearly qualify as adenocarcinoma, large cell carcinoma, or squamous cell carcinoma.

Abbreviations: CIS=cisplatin; CI=confidence interval

JMDB: in squamous cell carcinoma Cis/Gem had a better overall survival

Scaglioni et al J Clin Oncol 26, 3543-3551, 2008
ERCC1 and RRM1 in DNA damage repair

ERCC1, a nucleotide excision repair (NER) enzyme, plays a central role in DNA repair pathways. Overexpression of the excision repair cross-complementing 1 (ERCC1) gene, which is crucial in the repair of DNA adducts such as those caused by cisplatin (CDDP), is a limiting factor in the repair process. Ribonucleotide reductase, although not an integral part of the repair complex, catalyzes the biosynthesis of deoxyribonucleotides from the corresponding ribonucleotides, providing the building blocks for the reconstitution of the excised oligonucleotide.

Friedberg EC, Nat Rev Cancer 2001
ERCC1-negative tumors appear to benefit from adjuvant cisplatin-based CT.
Low ERCC1 expression correlates with prolonged survival after Cisplatin + Gemcitabine CT in NSCLC.

ERCC1 expression is a predictive factor for survival after CDDP/Gem therapy in advanced NSCLC.

Although there was a trend toward decreased response with high ERCC1 mRNA levels, this difference failed to reach statistical significance.
Survival for ERCC1, RRM1 & for the combination of both in CDDP-treated pts.

- Median survival time in patients with low ERCC1 was significantly longer (17.3 versus 10.9, \( p = 0.0032 \)) as well as in patients with low RRM1 (13.9 versus 10.9, \( p = 0.039 \)).
- Concomitant low expression levels of ERCC1 and RRM1 were predictive of a better outcome (14.9 versus 10.0, \( p = 0.0345 \)).
- Among cisplatin-treated patients, a low ERCC1 level was highly predictive of a longer survival (23.0 versus 12.4, \( p = 0.0001 \)).
Strongly associated with poor survival, overexpression of BRCA1 mRNA was associated with clinician-based CT.

Levels will benefit from adjuvant chemotherapy and should be candidates for significance worse survival.

Patients with high BRCA1 and whose tumors had high BRCA1 expression had
Prognostic significance of Ras in NSCLC

The combined HR was 1.35 (95% CI: 1.16–1.58), showing a worse survival for NSCLC with KRAS2 mutations or p21 overexpression and, particularly, in adenocarcinomas and in studies using PCR but not in studies using IHC.

RAS appears to be a poorer prognostic factor in terms of survival in NSCLC globally, in adenocarcinoma and when it is studied by PCR.
K-RAS mutations were significantly associated with an absence of response to TKIs (sensitivity = 0.21 [95% CI 0.16–0.28], specificity = 0.94 [0.89–0.97]). This analysis provides empirical evidence that K-RAS mutations are highly specific negative predictors of response (de-novo resistance) to single-agent EGFR TKIs in advanced NSCLC.
EGFR, TP53 and KRAS mutation and smoking dose in patients with adenocarcinoma

Kosaka et al., Cancer Res. 64, 8919-8923, 2004

Note: Incidence of K-ras mutations: US (<20%) >> Japan.
TRU-type adenocarcinoma with EGFR mutations and that with K-ras mutations

TRU type adeno with K-ras mutation, WT EGFR

TRU type adeno with EGFR mutation, WT K-ras
Two classes of genetic abnormalities found in human adenocarcinoma of the lung

Class I: Oncogenes/TSG whose mutations never occur in tumors that have EGFR mutations
  KRAS

Class II: Oncogenes/TSG whose mutations may occur in tumors that have EGFR mutations
  TP53
# Mutations of EGFR, HER2 and KRAS gene in 200 adenocarcinomas (ACC)

Onozato et al., JCA, 2007

<table>
<thead>
<tr>
<th>Gene</th>
<th>No w/ mutation (%)</th>
<th>Poorly diff.</th>
<th>Never-Smoker</th>
<th>Female</th>
<th>TP53 mut</th>
<th>TP53 G-T</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR</td>
<td>100 (50%)</td>
<td>17%</td>
<td>68%</td>
<td>64%</td>
<td>35%</td>
<td>1%</td>
</tr>
<tr>
<td>HER2</td>
<td>6 (3%)</td>
<td>17%</td>
<td>67%</td>
<td>83%</td>
<td>33%</td>
<td>0%</td>
</tr>
<tr>
<td>KRAS</td>
<td>28 (14%)</td>
<td>39%</td>
<td>25%</td>
<td>25%</td>
<td>46%</td>
<td>18%</td>
</tr>
<tr>
<td>unknown</td>
<td>66 (33%)</td>
<td>46%</td>
<td>35%</td>
<td>44%</td>
<td>44%</td>
<td>21%</td>
</tr>
</tbody>
</table>

*Mutually exclusive*
Is adenocarcinoma of the lung one disease?

No!

can be classified according to;
morphology
expression profile
altered oncogenes / tumor suppressor genes
Survival and response rates by subgroup analysis in the overall population

- Survival was better in the gefitinib group than in the placebo group among never smokers (median 8.9 vs 6.1 months; HR 0.67 (p=0.012)
- Survival was better in the gefitinib group than in the placebo group among patients of Asian origin (median 9.5 vs 5.5 months; HR 0.66 (p=0.01)

Thatcher N, Lancet 2005
### Adeno Carcinoma

- **K-RAS2 Over EXPN:** Poor Survival
- **Thymidylate Synthetase:** Low, Better Response to Pemetrexate

### Squamous Cell CA

- Increased Expression of Thymidylate Resistance to GEMCITABINE

### Table:

<table>
<thead>
<tr>
<th>EGFR Mutation</th>
<th>Response to Gefitinib, Erlotinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRAS2 Mutation, p21 Over EXPN</td>
<td>Poor Survival</td>
</tr>
<tr>
<td>TS Expression</td>
<td>Low-Adeno CA, Response to Pemetrexate High-SCC, Response to GEMCITABINE</td>
</tr>
<tr>
<td>ERCC1-VE</td>
<td>Response to Cisplatinum Combn</td>
</tr>
<tr>
<td>BRCA1 Overexpn</td>
<td>Poor Survival</td>
</tr>
<tr>
<td>RRM1 Decrease</td>
<td>Response to GEMCITABINE</td>
</tr>
</tbody>
</table>

### Female Pt

- Adeno Carcinoma
- Never Smoker
- Asian Origin
- Candidate for TKI

ERCC1 α 1/CDDP
RRM α1/GEMCITABINE
β TUBLIN α 1/TAXANE
THY.SYNTH. α 1/ PEMETRAXATE,
Take home messages

- Treatment by histology is the first step for tailored chemotherapy.
- A number of trials have suggested that pemetrexed may be particularly effective in first line nonsquamous NSCLC.
- Gefitinib may be indicated in first line only in adenocarcinoma EGFR + patients.
- In adenocarcinoma (mutation – or unknown mutational status) pemetrexed is a preferred regimen.
- EGFR mutations are prognostic and predictive of response to EGFR inhibitors and prognostic for CT.
- ERCC1/RRM1 could be useful as a prognostic factor in early stages and need further evaluations in prospective trials in advanced NSCLC.
ARE ALL BREAST CANCERS SAME

ER
HER
PR

OTHERS
TOP2A
Ki67
PTEN LOSS
PIK3CA
BRCA1
Upa & PAI1
PROGNOSTIC FACTORS

- AGE
- NODAL STATUS
- NUCLEAR GRADE
- RECEPTOR STATUS(ER, PR)
BREAST CANCER
NODE –VE

LOW RISK
ER,PR +VE
T \( \leq 1 \) CM
Gr-1

INT RISK
ER,PR +VE
T = 1-2 CM
Gr- 2-3

HIGH RISK
ER,PR -VE
T \( \geq 2 \) CM
Gr-2-3
HER +Ve

- HER 1 & 2
  - LAPATINIB
- HER 2
  - HERCEPTIN
HER 2 +VE

- HER 2 ECD +VE
  - POOR PROGNOSIS
  - RESISTANCE TO TAMOXIFEN & AROMATASE INHIBITOR
  - BENEFIT FROM HERCEPTIN - CONTROVERSIAL

- HER 2 ECD - Ve
- SENSITIVE TO HERCEPTIN

RESISTANCE TO TAMOXIFEN & AROMATASE INHIBITOR
BENEFIT FROM HERCEPTIN - CONTROVERSIAL

• POOR PROGNOSIS
• RESISTANCE TO TAMOXIFEN & AROMATASE INHIBITOR
• BENEFIT FROM HERCEPTIN - CONTROVERSIAL
HER 2 + Ve

P 95 HER 2+Ve

- NODE +Ve
- POOR PROGNOSIS
- LACKS HERCEPTIN /TRASTUZUMAB BINDING DOMAIN
- RETAINS TYROSIN KINASE ACTIVITY.
- LAPATINIB IS TREATMENT OF CHOICE

P 95 HER 2 -Ve

HERCEPTIN
LAPATINIB

PTEN LOSS, PIK3CA MUTATION
ACQUIRED RESISTANCE TO TRASTUZUMAB
REVERAL BY M-TOR INHIBITOR-EVORLIMUS
### Table 1. Risk classification St. Gallen 2005/2007

<table>
<thead>
<tr>
<th>Low risk</th>
<th>Intermediate risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>pN0 and all of the following criteria:</td>
<td>pN0 and at least 1 further criterion:</td>
<td>pN+ (N1–3) and HER2 overexpression or pN+ (N ≥ 4)</td>
</tr>
<tr>
<td>size of tumor max. 2 cm</td>
<td>size of tumor &gt;2 cm</td>
<td></td>
</tr>
<tr>
<td>G1</td>
<td>G2 / G3</td>
<td></td>
</tr>
<tr>
<td>no vessel invasion</td>
<td>vessel invasion present</td>
<td></td>
</tr>
<tr>
<td>ER-/PR-positive</td>
<td>HER2 overexpression</td>
<td></td>
</tr>
<tr>
<td>HER2-negative</td>
<td>age &lt; 35 years</td>
<td>or pN+ (N 1–3) and HER2-negative</td>
</tr>
<tr>
<td>age ≥ 35 years</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 2. Therapy recommendations, St. Gallen Consensus 2005/2007

<table>
<thead>
<tr>
<th>Low risk</th>
<th>Intermediate risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>endocrine therapy or no therapy</td>
<td>endocrine responsive</td>
<td>endocrine responsive</td>
</tr>
<tr>
<td></td>
<td>endocrine therapy or chemotherapy then endocrine therapy</td>
<td>chemotherapy then endocrine therapy</td>
</tr>
<tr>
<td></td>
<td>trastuzumab where appropriate</td>
<td>trastuzumab where appropriate</td>
</tr>
<tr>
<td></td>
<td>uncertain endocrine responsiveness</td>
<td>endocrine non-responsive</td>
</tr>
<tr>
<td></td>
<td>chemotherapy then endocrine therapy</td>
<td>chemotherapy</td>
</tr>
<tr>
<td></td>
<td>trastuzumab where appropriate</td>
<td>trastuzumab where appropriate</td>
</tr>
<tr>
<td></td>
<td>endocrine non-responsive</td>
<td></td>
</tr>
<tr>
<td></td>
<td>chemotherapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>trastuzumab where appropriate</td>
<td></td>
</tr>
</tbody>
</table>
ROLE OF UROKINASE PLASMINOGEN ACTIVATOR & PLASMINOGEN ACTIVATOR INHIBITOR

• POOR PROGNOSIS
• NODE –VE WITH INCREASED LEVEL
• BENIFITED FROM CMF
Amplification and Overexpression of Topoisomerase II
Predict Response to Anthracycline-based Therapy in Locally Advanced Breast Cancer

IHC

Coon, et al., Clin Cancer Res. 8: 1061-1067, 2002

FTISH:
Topo IIα

Chr 17 centromere

c-erbB2
Responses to doxorubicin preoperative chemotherapy according to HER2/topoisomerase II-α (topoll) amplification status (CISH)

<table>
<thead>
<tr>
<th>Response</th>
<th>n (%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2- / topo II-</td>
<td>17 (47)</td>
<td>36</td>
</tr>
<tr>
<td>HER2+ / topo II-</td>
<td>9 (75)</td>
<td>12</td>
</tr>
<tr>
<td>HER2+ / topo II+</td>
<td>18 (95)</td>
<td>19</td>
</tr>
</tbody>
</table>

P=0.038.

*Park, et al., Eur J Cancer 39: 631-34, 2003*
p53 Mutations Associated With Resistance to Doxorubicin (A)

- A-induced apoptosis is prevented
- p53 mutations could hamper response to A even in tumors carrying topo II α gene amplification

PerezASCO’03

tumor subtype predictions

Stanford data

van't Veer data

p < 0.001

Time to distant metastasis

Relapse free survival (local or distant)

Luminal A
Luminal B
Basal
HER2+
Normal breast-like

No BRCA samples in relapse analysis

Sorlie T et al.
PNAS 2003

TripathyASCO’05
BREAST CANCER MOLECULAR CLASSIFICATION: ≥ 5 DISEASES?

<table>
<thead>
<tr>
<th>Basal-like</th>
<th>HER-2 +++</th>
<th>Luminal A</th>
<th>Luminal B</th>
<th>Luminal C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mostly grade 3</td>
<td>Mostly grade 1</td>
<td>Mostly grade 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal characteristics</td>
<td>Luminal characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Courtesy of M Piccart*
Molecular Portrait of Breast Cancers

Luminal A
Luminal B

Both ER+, but different prognosis

Sorlie T et al, PNAS 2001
Traditional approach

Node negative

Node positive

New Approach

HER-2 +

ER-, HER-2 –
Basal-like cancers

ER++
Luminal A

ER+
Luminal B
Breast Cancer Subtypes based on Gene Expression Analysis

Sorlie et al. PNAS 2003
TRIPLE –VE BREAST CANCER

- YOUNG AGE
- HIGH HISTOLOGICAL GRADE
- BASAL LIKE HISTOPATHOLOGICAL PHENOTYPE
- TRIPLE –VE PHENOTYPE(ER-VE,PR-VE,HER 2 –VE)
- CARRIERS OF BRCA1 MUTATION
- HIGHLY SENSITIVE TO PLATINUM BASED CT
- PARP INHIBITORS(Poly ADP Ribose polymerase)
ONCOTYPE DX

• 21 GENE SIGNATURE
• ER, PR, HER 2, KI-67
• PREDICTOR OF TAMOXIFEN EFFICACY
• PREDICTS BENEFIT OF CMF ADJUVANT IN SAME PTS POPULATION.
• PROGNOSTIC AND PREDICTIVE VALUE IN NODE POSITIVE, ER POSITIVE POST MENOPAUSAL PTS RECEIVING CAF & TAMOXIFEN ADJUVANT.
Oncotype DX 21 Gene Recurrence Score (RS) Assay

16 Cancer and 5 Reference Genes From 3 Studies

**PROLIFERATION**
- Ki-67
- STK15
- Survivin
- Cyclin B1
- MYBL2

**ESTROGEN**
- ER
- PR
- Bcl2
- SCUBE2

**INVASION**
- Stromolysin 3
- Cathepsin L2

**HER2**
- GRB7
- HER2

**REFERENCE**
- Beta-actin
- GAPDH
- RPLPO
- GUS
- TFRC

<table>
<thead>
<tr>
<th>Category</th>
<th>RS (0 - 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>RS &lt; 18</td>
</tr>
<tr>
<td>Int risk</td>
<td>RS ≥ 18 and &lt; 31</td>
</tr>
<tr>
<td>High risk</td>
<td>RS ≥ 31</td>
</tr>
</tbody>
</table>
RS as a Predictor of C/MF Chemotherapy Benefit in Node (-), ER (+) Pts

Low Risk (RS < 18)

- Tam + Chemo
- Tam

p = 0.76

N | Events
---|---
218 | 11
135 | 5

96% 95%

Interm. Risk (RS 18–30)

- Tam + Chemo
- Tam

p = 0.71

N | Events
---|---
89 | 9
45 | 8

89% 90%

High Risk (RS ≥ 31)

- Tam + Chemo
- Tam

p = 0.001

N | Events
---|---
117 | 13
47 | 18

88% 60%

ONCOTYPE DX
ER,PR +VE

LOW RISK 18
ENDOCRINE TREATMENT

INT RISK-18-30
ENDOCRINE+/- CT
TAILORX trial

HIGH RISK-31
ENDOCRINE+CT
MAMMAPRINT

• 70 GENE SIGNATURE
• YOUNG PATIENTS
• NODE –Ve
• EARLY STAGE I & II
• DNA MICRO ARRAY BASED DIAGNOSTIC TOOL REQUIRES FRESH FROZEN TISSUE.
• MINDACT
• LOW RISK MOLECULAR PROGNOSIS AND HIGH RISK CLINICAL PROGNOSIS
MAPQUANT DX

• A genomic grade Index
• RECLASSIFICATION GRADE 2 TUMORS IN TO HIGH RISK & LOW RISK RECURRENCE GROUP.
TAKE HOME MESSAGE

• BREAST CANCER IS HETEROGENEOUS WITH RESPECT TO BIOLOGY AS WELL AS THERAPEUTIC APPROACH

• ONCOTYPE DX AND RECURRENT SCORE IN A SUBSET POPULATION GIVE A NEW INSIGHT FOR DECISION MAKING REGARDING TREATMENT POLICY

• TRIPLE –VE BREAST CANCER IS A SEparate ENTITY CAN BE TREATED WITH PLATINUM BASED CT AND PARP INHIBITORS.
Prognostic vs. Predictive Markers

**Prognostic**
Provides information on outcome, regardless of which treatment is used.

**Predictive**
Provides information on outcome with regards to a specific therapy.

Many biomarkers have both predictive and prognostic value.

Controlled studies or meta-analyses are required to determine the prognostic and predictive contributions made by a particular marker.
Prognostic versus predictive markers

Prognostic factors
who to treat?

Predictive factors
how to treat?
Getting the right drug into the right patient

Pharmacogenomics will help explain why drugs work better in some patients than in others. It also presents numerous commercial opportunities for both startups and established biotechnology companies.

Proportion of patients who respond to drug

Current state of drug development research

Patients learning drug
Cancer Treatment in the Future?

"Here's my sequence"

The New Yorker
THANK YOU