Disclaimers

- The information provided here includes views of the presenter that do not necessarily represent those of the Global Resource for Advancing Cancer Education (GRACE) in general, nor those of Swedish Cancer Institute.

- The contents of this program do not constitute medical advice and is intended to supplement but not replace input from an individual patient’s medical team.
Early Stage (Resectable) Non-Small Cell Lung Cancer

Clinical/Pathologic Staging of NSCLC

(Mountain, Chest 111:1710, 1997)

<table>
<thead>
<tr>
<th></th>
<th>T1 N0</th>
<th>T2 N0</th>
<th>T1 N1</th>
<th>T2 N1</th>
<th>T3 N0</th>
<th>T3 N1</th>
<th>T1-3 N2</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-year Survival,</td>
<td>61%</td>
<td>38%</td>
<td>34%</td>
<td>24%</td>
<td>22%</td>
<td>9%</td>
<td>13%</td>
</tr>
<tr>
<td>Clinical Staging</td>
<td></td>
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<tr>
<td>5-year Survival,</td>
<td>67%</td>
<td>57%</td>
<td>55%</td>
<td>39%</td>
<td>38%</td>
<td>25%</td>
<td>23%</td>
</tr>
<tr>
<td>Path/Surg Staging</td>
<td></td>
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</tbody>
</table>

- Distant failures in 50-70% in most studies, representing micrometastatic disease
- Even early stage NSCLC is a systemic (“whole body”) disease
**BR.10 - Study Design**

- T1-2, N0-1 NSCLC
- N2 nodes sampled
- N = 482

**Stratified by:**
- N0 vs N1
- Ras pos, neg, or unknown

- Cisplatin 50 mg/m² d1, 8
- Vinorelbine 30→25 mg/m²/wk x 4

**No chemotherapy**

Winton, NEJM 352:2582, 2005

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**BR.10: Efficacy Results**

<table>
<thead>
<tr>
<th>N = 482 pts 41 Ineligible</th>
<th>Chemotherapy N = 243</th>
<th>Observation N = 239</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Survival</td>
<td>94 months (P = 0.012) HR 0.7</td>
<td>73 months</td>
</tr>
<tr>
<td>5-Year Survival</td>
<td>69% (P = 0.012) HR 0.7</td>
<td>54%</td>
</tr>
<tr>
<td>PFS</td>
<td>Not reached (P = 0.0004)</td>
<td>46.7 months</td>
</tr>
</tbody>
</table>
**BR.10 – Survival Curves**

*Image 1: A. Recurrence-free Survival, All Patients*

- **A. Recurrence-free Survival, All Patients**
  - **Years vs. Probability (%)**
  - **No. at Risk**
    - Observation: 249, 131, 78, 37, 10, 0
    - Vinorelbine plus cisplatin: 242, 174, 101, 41, 9, 0
  - **P=0.001**

*Image 2: B. Overall Survival, All Patients*

- **B. Overall Survival, All Patients**
  - **Years vs. Probability (%)**
  - **No. at Risk**
    - Observation: 240, 182, 94, 47, 13, 0
    - Vinorelbine plus cisplatin: 242, 139, 121, 51, 10, 0
  - **P=0.009**

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**Winton, NEJM 352:2582, 2005**

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**BR.10 – Survival Curves by Stage**

*Image 3: C. Overall Survival, Patients with Stage IB Non-Small-Cell Lung Cancer*

- **C. Overall Survival, Patients with Stage IB Non-Small-Cell Lung Cancer**
  - **Years vs. Probability (%)**
  - **No. at Risk**
    - Observation: 108, 91, 57, 29, 8, 0
    - Vinorelbine plus cisplatin: 111, 95, 65, 27, 6, 0
  - **P=0.79**

*Image 4: D. Overall Survival, Patients with Stage II Non-Small-Cell Lung Cancer*

- **D. Overall Survival, Patients with Stage II Non-Small-Cell Lung Cancer**
  - **Years vs. Probability (%)**
  - **No. at Risk**
    - Observation: 132, 91, 37, 18, 3, 0
    - Vinorelbine plus cisplatin: 131, 100, 56, 24, 4, 0
  - **P=0.004**

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**Winton, NEJM 352:2582, 2005**
Chemo may be detrimental for stage IA, but stage IA patients were generally not given the potentially best combination cisplatin/vinorelbine (13% of stage IA patients versus ~43% for other stages).

Pignon, Proc ASCO 2007

- 761 pts. (28 centers, 14 countries) evaluable for ERCC1 expression
- ERCC1 repairs cisplatin-DNA adducts, so expression indicates platinum resistance
- ERCC1 a “double-edged sword”; worse prognosis of NSCLC if low expression, but more responsive to platinum
Overall Survival by ERCC-1 Expression

ERCC1-Negative Tumors

- Adjusted HR = 0.65, 95% PI [0.50-0.86], p = 0.002

ERCC1-Positive Tumors

- Adjusted HR = 1.14, 95% CI [0.84-1.55], p = 0.40

Olaussen, NEJM 2006

15-gene Signature is Prognostic in Stage I and Stage II Patients

Stage IB (n=34)

- HR 13.32 (95% CI 2.86-62.11) p<0.0001

Stage II (n=28)

- HR 13.47 (95% CI 3.00-60.43) p<0.0001

Tsao, Proc ASCO 2008, A#7510
Chemotherapy Benefits JBR.10 High Risk but *Not* Low Risk Patients

**JBR.10, high risk (n=67)**

- HR 0.33 (95% CI 0.17-0.63)
- p=0.0005

**JBR.10, low risk (n=66)**

- HR 3.67 (95% CI 1.22-11.06)
- p=0.0133

**Interaction p = 0.0001**

Tsao, Proc ASCO 2008, A#7510

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15-Gene Signature for Prognosis of Adjuvant Chemo Candidates: Conclusions

- 15 gene signature may refine prognosis with implications on choice of adjuvant chemotherapy
- Need further validation by prospectively before incorporation into standard of care
- Requirement of snap frozen tissue limits generalizability

Tsao, Proc ASCO 2008, A#7510
**ECOG 1505/Intergroup Adjuvant Trial**

**PI** – Heather Wakelee

NSCLC s/p surgery

Stage IB (>4 cm only)
Stage II
Stage III (Non-N2)

Primary endpoint: Overall Survival

Cisplatin-based chemo
- cisplatin-vinorelbine
- cisplatin-gemcitabine
- cisplatin-docetaxel
- cisplatin-pemetrexed (non-squamous)

+ bevacizumab 15 mg/kg q3wk

**Randomized Double-blind trial In Adjuvant NSCLC with Erlotinib (RADIANT)**

**N** = 945 patients
- St IB – IIIA NSCLC
- EGFR positive (IHC and/or FISH)
- No Chemo or up to 4 cycles of std platinum-based, adjuvant chemo

2yrs or until one of the following:
- Relapse
- Death
- Pt request
- Investigator decision
- Intolerable toxicity

Follow up visit Q 6 months X 5 years, then yearly

PI – Dr. Karen Kelly
Resectable MAGE-A3+ NSCLC

Surgery

Pathological stage IB, II, IIIA

No chemotherapy

R

MAGE-A3 ASCI

Placebo

Powered for efficacy

Up to 4 cycles platinum based chemotherapy

R

MAGE-A3 ASCI

Placebo

Powered for efficacy

Randomized Phase III Study Design - MAGRIT

(My) Current Conclusions on Systemic Therapy for Early Stage NSCLC

- Clinically, statistically significant OS benefit w/platinum doublet in stage II-IIIA
  - Would now generally recommend cisplatin-based doublet when feasible
- Stage IB treatment may still be individualized
  - Some evidence for giving chemo for larger but not smaller IB tumors
- However, recent work suggests small but real long-term mortality risk: patients with less to gain from chemo (by stage or molecular criteria) may be harmed
- Molecular selection based on ERCC1, gene signature, etc. may help us refine predicted benefits much better; requires much more corroborative work
- Current questions: role of Avastin? EGFR inhibitors? Vaccine-based therapy?
- These data apply to a disproportionately young, good PS population, not to everyone