Is more better?
Consolidation and maintenance therapy in Lung cancer

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Goals

• Explore whether or not further therapy following initial treatment for lung ca leads to improvements:
  – PCI for SCLC
  – Adjuvant therapy for resectable NSCLC
  – Chemo consolidation after RT Chemo induction
  – Early vs late docetaxel chemo in advanced disease
  – Maintenance chemo for advanced disease
• Small cell lung cancer
PCI in Small cell lung cancer
Local treatment in a systemic disease

• **Meta Analysis:**
  – 7 trials, 987 pts 1977 -1991:
  – Only one trial (32 pts) used Plat Etop
  ➢ 3 yr intracranial relapse 25%↓
    OS by 5% ↑

Role of PCI in ED-SCLC EORTC trial
Plenary session
LBA #4

Primary end point: Cumulative incidence of symptomatic brain metastases

Slotman et al. NEJM 2007; 357
EORTC PCI schemes

Residual disease pre-PCI:
76% in thorax
71% in distant sites
LBA #4
Overall survival

1 year: 27.1% vs. 13.3%
MS    6.7 vs 5.4 mo
HR: 0.68 (0.52-0.88);  p=0.003
LBA # 4
Symptomatic brain metastases

1 year: 14.6% vs. 40.4%

HR: 0.27 (0.16-0.44);  p<0.001
Investigator’s conclusions

- PCI reduces incidence of symptomatic brain metastases
- Well tolerated
- Does not adversely affect QOL
- Should be routinely offered in patients with ED-SCLC who respond to systemic therapy
Management of NSCLC-Early Stage

• Stage I/II:
  – Survival with surgery alone:
    • Stage IA 61-67%
    • Stage IB 38-57%
    • Stage IIA 34-55%
    • Stage IIB 24-39%

• Pattern of failure: 75% of relapses are as metastases

LUNG CANCER is a systemic disease

META-ANALYSIS OF SURVIVAL IN RANDOMIZED TRIALS OF SURGERY ALONE OR SURGERY WITH POSTOPERATIVE CHEMOTHERAPY

Hazard ratio = 0.87
P = 0.08
Study design

**RESECTED NSCLC**

Chemotherapy  

± Thoracic Radiotherapy ≤ 60 Gy*

*optional, but predefined by N stage at each center

Control
Adjuvant Chemotherapy: JBR10 Trial

Stratification:
- N₀ vs N₁
- Ras mutation ±

Stage IB, II (T₃ N₀ excluded)

Surgery

Cisplatin 50 mg/m² Days 1, 8
Vinorelbine 25 mg/m²/wk × 4 Cycles

Observation

CALGB 9633
Randomized Controlled Clinical Trial (RCT) of Adjuvant Chemotherapy in Stage IB NSCLC

T2N0M0 Stage IB NSCLC → Complete Surgical Resection → Randomization within 4–8 weeks of resection

Adjuvant Chemotherapy
- paclitaxel 200 mg/m²
- carboplatin AUC = 6
- 4 cycles for 12 weeks

Observation

STRATIFICATION
- squamous vs other
- poorly differentiated vs other
- mediastinoscopy: yes vs no

ANITA - Study Design

- Open, multicenter, randomized study (1:1).
- Stratified after surgery by center, stage and histology.

800 patients to be included.

Arm A
Observation

Arm B
NVB: 30 mg/m² I.V. Weekly x 16/20
CDDP: 100 mg/m² I.V. D1, D29, D57, D85

* Radiation therapy was upon center choice
## Subset Analysis by Stage of Adjuvant NSCLC Studies - 2006

<table>
<thead>
<tr>
<th>Study</th>
<th>Overall</th>
<th>IB</th>
<th>II</th>
<th>IIIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>IALT IB-III A</td>
<td>0.86</td>
<td>0.95</td>
<td>0.93</td>
<td>0.79</td>
</tr>
<tr>
<td>(ASCO 03)</td>
<td>P&lt;0.03</td>
<td>(0.74- 1.23)</td>
<td>(0.72- 1.20)</td>
<td>(0.66-0.95)</td>
</tr>
<tr>
<td>CALGB IB</td>
<td>0.80</td>
<td>0.80</td>
<td>Not tested</td>
<td>Not tested</td>
</tr>
<tr>
<td>(ASCO 03)</td>
<td>P= 0.10</td>
<td>(0.6- 1.07)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCI-C IB-II</td>
<td>0.69</td>
<td>0.94</td>
<td>0.59</td>
<td>Not tested</td>
</tr>
<tr>
<td>(ASCO 04)</td>
<td>P = 0.04</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANITA IB, II, IIIA</td>
<td>0.79</td>
<td>1.10</td>
<td>0.71</td>
<td>0.69</td>
</tr>
<tr>
<td>(ASCO 05)</td>
<td>P= 0.0.13</td>
<td>(0.76- 1.57)</td>
<td>(0.49- 0.94)</td>
<td>(0.53-0.90)</td>
</tr>
</tbody>
</table>
Adjuvant chemotherapy for:
- NSCLC stage > IB
- NSCLC stage ≤ IIIA works!
- World-wide, should save over 7000 lives/year

Magnitude of benefit similar or better to that observed in other malignancies

Given the number of questions yet to be answered, participation in clinical trials is key
• Non-small cell lung cancer – Locally advanced
Concurrent Chemoradiotherapy in unresectable IIIB NSCLC: SWOG 9019

Unresectable stage IIIB NSCLC

N=83

Concurrent Chemoradiotherapy:
Cisplatin (50 mg/m² on days 1, 8, 29, 36) +
Etoposide (50 mg/m² on days 1-5, 29-33) +
Radiotherapy (61 Gy chest [1.8-2.0 Gy/d])
starting on day 1

Cisplatin (50 mg/m² on days 1, 8, 29, 36)
Etoposide (50 mg/m² on days 1-5, 29-33)

66% completed all planned treatment

Albain, JCO 2002; 20: 3454-3460
Unresectable stage IIIB NSCLC: N=83

Concurrent Chemoradiotherapy → Consolidation Docetaxel in Unresectable Stage IIIB NSCLC: SWOG 9504

- **Cisplatin** (50 mg/m² on days 1, 8, 29, 36) + **Etoposide** (50 mg/m² on days 1-5, 29-33) + **Radiotherapy** (61 Gy chest [1.8-2.0 Gy/d]) starting on day 1

- **Docetaxel** (75-100 mg/m²) q3w for 3 cycles

Primary end point: Survival
Secondary end points: Toxicities, survival rates, site of first failure

**SWOG S9504 vs S9019 Outcomes**

<table>
<thead>
<tr>
<th></th>
<th>SWOG S9504 Cis/Etop/RT → Docetaxel (n=83)</th>
<th>SWOG S9019 Cis/Etop/RT → Etoposide/Cisplatin (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median survival (mo)</td>
<td>26</td>
<td>15</td>
</tr>
<tr>
<td>3-year survival rate</td>
<td>37%</td>
<td>17%</td>
</tr>
<tr>
<td>4-year survival rate</td>
<td>29%</td>
<td>17%</td>
</tr>
<tr>
<td>5-year survival rate</td>
<td>29%</td>
<td>17%</td>
</tr>
</tbody>
</table>
• Is consolidation docetaxel required?
Unresectable stage IIIA/B NSCLC

**Concurrent chemo/RT with or without consolidation docetaxel**

Abstract # 7512

- **Docetaxel** (75-100 mg/m²) q3w for 3 cycles

- **Cisplatin** (50 mg/m² on days 1, 8, 29, 36)
- **Etoposide** (50 mg/m² on days 1-5, 29-33)
- **Radiotherapy** (59.4 Gy chest) starting on day 1

- **Observation**

N=73

N=74

1° Endpoint: Overall Survival

Hanna et al for the Hoosier Oncology Group (HOG), ASCO 2007
Abstract # 7512
Overall Survival

Observation: 3yr S 27.6%
Docetaxel: 3yr S 27.2%
P-value: 0.940
Abstract # 7512

Results

<table>
<thead>
<tr>
<th></th>
<th>Doc</th>
<th>Obs</th>
<th>P value</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS (mo)</td>
<td>12.3</td>
<td>12.9</td>
<td>0.9412</td>
<td>0.61</td>
</tr>
<tr>
<td>OS (mo)</td>
<td>21.5</td>
<td>24.1</td>
<td>0.9402</td>
<td>0.71</td>
</tr>
</tbody>
</table>

Gr 3/4 Toxicity with Docetaxel: 11% FN, 8% pneumonitis,
29% hospitalized, 5% death
Unresectable stage III NSCLC

- **Consolidation or maintenance therapy**
- Does not improve OS
- Associated with increased toxicity
- Should not be routinely used
• Can targeted agents improve survival after consolidation docetaxel?
Gefitinib maintenance in inoperable IIIA/ IIIB NSCLC
Updated results of SWOG 0023
Abstract # 7513

Cisplatin
50 mg/2 d 1,8,29,36
Etoposide
50 mg/m2 d1-5, 29-33
XRT
1.8- 2 Gy/d 61 Gy

DOCETAXEL
75 mg/m2 x 3 cycles

1° Endpoint: Overall Survival; 2° Endpoint: PFS, toxicity and correlative

Abstract # 7513
Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>Gefitinib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>118</td>
<td>125</td>
</tr>
<tr>
<td>Events</td>
<td>71</td>
<td>54</td>
</tr>
<tr>
<td>Median in Months</td>
<td>23</td>
<td>35</td>
</tr>
<tr>
<td>1 YR OS</td>
<td>73%</td>
<td>81%</td>
</tr>
<tr>
<td>2 YR OS</td>
<td>46%</td>
<td>59%</td>
</tr>
</tbody>
</table>

P = .01

Median FU time: 27 months
### Causes of Death by Treatment Arm

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Gefitinib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dead</td>
<td>71%</td>
<td>54%</td>
</tr>
<tr>
<td>Alive</td>
<td>47%</td>
<td>71%</td>
</tr>
<tr>
<td>Cancer</td>
<td>61%</td>
<td>43%</td>
</tr>
<tr>
<td>Toxicity</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Other Causes</td>
<td>1%</td>
<td>3%</td>
</tr>
<tr>
<td>Unknown</td>
<td>7%</td>
<td>8%</td>
</tr>
</tbody>
</table>
• First line chemotherapy should be 4-6 cycles.

» ASCO and NCCN guidelines
## Maintenance Chemotherapy for Advanced NSCLC

<table>
<thead>
<tr>
<th>Author</th>
<th>Chemotherapy</th>
<th>MS</th>
<th>1yrS</th>
<th>p</th>
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<tbody>
<tr>
<td>Westeel</td>
<td>MIP x4 → Obs</td>
<td>12.5 mo</td>
<td>50%</td>
<td>0.48</td>
</tr>
<tr>
<td>JNCI 2005;97</td>
<td>MIP x4 → Vin</td>
<td>10.2 mo</td>
<td>42%</td>
<td></td>
</tr>
<tr>
<td>Socinski,</td>
<td>carbo/Taxol x 4</td>
<td>6.6 mo</td>
<td>28%</td>
<td>0.63</td>
</tr>
<tr>
<td>JCO,2002;20</td>
<td>carbo/Taxol → PD</td>
<td>8.5 mo</td>
<td>34%</td>
<td></td>
</tr>
<tr>
<td>Smith,</td>
<td>3 cycles MVP vs 6 mo</td>
<td>6 mo</td>
<td>22%</td>
<td>0.2</td>
</tr>
<tr>
<td>JCO,2001;19</td>
<td>6 cycles MVP</td>
<td>7 mo</td>
<td>25%</td>
<td></td>
</tr>
</tbody>
</table>

↑ Toxicity seen in all studies with ↑ in chemotherapy cycles
• Maintenance therapy with second line drug may be of benefit
Docetaxel maintenance

- NSCLC Stage IIIb/IV
- Chemonaïve
- PS 0-2

GC Phase
- Gemcitabine, 1000 mg/m², Days 1, 8
- Carboplatin AUC 5, Day 1
- Every 21 days: 4 cycles

Immediate Docetaxel
- 75mg/m² day 1, every 21 days until progression or maximum of 6 cycles

Delayed Docetaxel
- at PD
- 75mg/m² on day 1, every 21 days, until PD or 6 cycles

1°: OS

Fidias, ASCO 2007 #7516
Immediate vs. Delayed Second-Line Docetaxel: PFS

Please note: the PFS curves only showed up to 24 months since very few patients left without PD/survival 24 months after randomization.

<table>
<thead>
<tr>
<th></th>
<th>Immediate D (n=153)</th>
<th>Delayed D (n=154)</th>
<th>Log-Rank p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS months</td>
<td>6.5</td>
<td>2.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>12-month PFS, %</td>
<td>20%</td>
<td>9%</td>
<td></td>
</tr>
</tbody>
</table>

I: 153
D: 154

Patients at Risk: 2
Immediate vs. Delayed Second-Line Docetaxel: Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>Immediate D (n=153)</th>
<th>Delayed D (n=154)</th>
<th>Log-Rank p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, months</td>
<td>11.9</td>
<td>9.1</td>
<td>0.071</td>
</tr>
<tr>
<td>12-month survival, %</td>
<td>48.5%</td>
<td>38.3%</td>
<td></td>
</tr>
</tbody>
</table>

Survival Probability vs. Overall Survival Time (in Months)

Patients at Risk:

I: 153 111 56 27 12 5 2
D: 154 98 45 22 9 3 2

Log-Rank p-Value 0.071
Maintenance therapy

• Maintenance docetaxel produced ↑ PFS without impact on OS
• Results are intriguing
• Further results from randomized trials are needed
• In the meantime, maintenance chemotherapy should still be considered experimental
Mark your calendars

13th World conference on lung cancer.
September 2009,
San Francisco