LUNG CANCER: 2006 update

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Leader, Lung Cancer Program,
Georgia Cancer Specialists;
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Georgia Cancer Foundation;
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Cancer Death Rates in the U.S. 1930-2000

Lung Cancer in the U.S. in 2005: Incidence and Mortality

- New cases: 172,570
  93,010 males #2
  79,560 females #2

- Annual deaths: 163,510
  90,490 males #1
  73,020 females #1

- Risk for developing lung cancer
  1:13 males
  1:18 females

- 5-year survival rate (all stages): 15%

Frequent Symptoms of Lung Cancer

- Fatigue
- Cough ± hemoptysis
- Dyspnea
- Decreased appetite
- Weight loss
- Pain

Lung Cancer Histology

- Non-small cell (NSCLC)
  Squamous-cell (1)
  Adenocarcinoma (1)
  BAC (1)
  Large-cell
  Other (NOS)

- Small-cell (SCLC)
  Decreasing incidence
  Now <15% of all lung cancers

LUNG CANCER: risk factors

- Tobacco……….85%
- Second hand smoking
- Radon gas
- Asbestos……….3-4%
- Inflammation/scarring
- Family history
- Other carcinogens (ether, polycyclic aromatic hydrocarbons, chromium, nickel, organic arsenics
TNM* Staging of NSCLC

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IB</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIA</td>
<td>T1</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>IIB</td>
<td>T2</td>
<td>N1</td>
<td>M0</td>
</tr>
</tbody>
</table>

*T = primary tumor; N = nodal involvement; M = distant metastasis

IASLC staging system project:

1997 Lung Cancer Staging System:
1. T3 N0 M0 belongs to Stage IIIB (instead of IIIA)
2. Malignant pericardial effusion added to T4
3. Satellite tumors within same lobe added to T4
4. Ipsilateral distant metastasis classified as M1

5-year Survival by clinical stage:

<table>
<thead>
<tr>
<th>Stage</th>
<th>Survival Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>72.1%</td>
</tr>
<tr>
<td>IB</td>
<td>49.9%</td>
</tr>
<tr>
<td>IIA</td>
<td>48.7%</td>
</tr>
<tr>
<td>IIIA</td>
<td>40.6%</td>
</tr>
<tr>
<td>IIIB</td>
<td>35.8%</td>
</tr>
<tr>
<td>IV</td>
<td>28.0%</td>
</tr>
</tbody>
</table>

Based on these, the new staging system most likely will merge current TNM stages and will create new sub-stages based on a large worldwide database.

LUNG CANCER:

**prognostic factors**

**Good prognostic factors:**
- Early stage
- Good PS
- No weight loss (<5%)
- Female gender

**Poor biologic prognostic factors:**
- p53 mutation
- K-ras oncogene activation

**Neutral prognostic factors:**
- Age
- Pathology
- Histology (BAC TTF-1+/CK20+/CK7+) (TTF-1+/*CK7+/CK20+)

EGFR:
**EGFR MUTATION:**
*NEJM, 2004; 350:2129* *Lynch T et al.*

- Of 275 pts treated with gefitinib, 25 reached PR.
- 9:25 PR pts. (all AdenoCa & BAC), with a MS > 18m, were evaluated for EGFR gene mutations in the entire gene coding region.

<table>
<thead>
<tr>
<th>Responders</th>
<th>Non-Responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer Tissue</td>
<td>Normal Tissue</td>
</tr>
<tr>
<td>Mutation</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>8:9 (88.9%)</td>
<td>0:7</td>
</tr>
</tbody>
</table>

Best response: women, non-smokers, BAC histology: 50%!!

Mutations were, heterozygous, somatic, either small, in frame deletions or amino acid substitution clustered around the ATP-binding pocket of the TK domain, and located in exons 19 and 21.

**EGFR MUTATION-I (cont’d):**
*NEJM, 2004; 350:2129* *Lynch T et al.*

**Conclusions:**
- Screening for specific EGFR mutations may identify sensitive patients to gefitinib.
- Structural analysis of the mutant receptors may help understand the mechanism of EGFR activation and help the design of more specific inhibitors of the mutant receptors.

**DNA repair genes:**

**PROGNOSTIC FACTORS IN LUNG CANCER: ERCC1 & RRM1**

ASCO ’03, Abs # 2590. *R Rosell et al.*

ERCC1 (DNA repair) & RRM1 expression predicts response to platinum and OS in advanced disease.

81 pts, Stage-IIIB “wet” or –IV, Rx’d with Cis/Gem

<table>
<thead>
<tr>
<th>TTP</th>
<th>MS</th>
<th>Ideal Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low ERCC1</td>
<td>8.3mo</td>
<td>13.7mo</td>
</tr>
<tr>
<td>High ERCC1</td>
<td>5.1</td>
<td>3.6</td>
</tr>
<tr>
<td>Low RRM1</td>
<td>8.3</td>
<td>N/R</td>
</tr>
<tr>
<td>High RRM1</td>
<td>2.7</td>
<td>6.8</td>
</tr>
</tbody>
</table>

192 pts. available for analysis

Design:

- A – Control-Cis/Docetaxel
- B1 – low ERCC1 Cis/Docetaxel
- B2 – high ERCC1 Gem/Docetaxel
- Resistance to cisplatin

**ERCC1 mRNA-based, Ph-III-r trial in Stage-IV NSCLC:**

*ASCO 2005, Abstract #7002; Rosell R et al.*
ERCC1 mRNA-based, Ph-III-r trial in Stage-IV NSCLC:

<table>
<thead>
<tr>
<th>ERCC1</th>
<th>Low</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1-Low</td>
<td>47.3%</td>
<td>56.6%</td>
</tr>
<tr>
<td>A1-Low</td>
<td>40.4%</td>
<td>37.7%</td>
</tr>
<tr>
<td>B2-High</td>
<td>21.2%</td>
<td>26.1%</td>
</tr>
</tbody>
</table>

ERCC1 mRNA-based, Ph-III-r trial in Stage-IV NSCLC:

Conclusions:
1. **Low ERCC1 expressers**: better than average response to Platinum-based therapy (doc/cis) \([56.6\%]\).
2. **High ERCC1 expressers**: trend to better response to a non-Platinum regimen (doc/gem).
   \([\text{ORR } 37.7\% \text{ vs. } 26.1\%; \text{MS } 9.5\text{ mo. vs. } 8.0\text{ mo.}]\)

SMOKING CESSATION:

Chantix® (*varenicline tartrate*) daily for 12 weeks + 12 extra weeks for pts who quit smoking to increase likelihood of long-term smoking cessation.

**COMMENT**: Chantix® (*Pfizer*) was approved by the FDA in 6/06 to help smokers stop smoking (eases withdrawal symptoms and blocks nicotine effects if pts resume smoking) based on six clinical trials (3,659 pts, average 21 cigarettes/day x 25 years). Chantix was superior to placebo in all trials, and superior to Zyban (bupropion) in 2 placebo-controlled studies. Major adverse effects: N/V, HA, flatulence, insomnia, abnormal dreams, and dysgeusia (change in taste perception).

SCREENING:

Low dose spiral CT-scan in early diagnosis of LuCa:

**Conclusions**:
1. Effective in early diagnosis
2. Potential increase in cure rate
3. Very low rate of procedures for benign dz.

**National Lung Screening Trial (NLST)**

American College of Radiology Imaging Network [ACRIN]
Spiral CT-scan vs. CXR
http://www.cancer.gov/nlst
CHEMOPREVENTION:
SWOG E5597 (NCCN 2006)

Design: double blind, placebo controlled study of selenium yeast, 1 tablet/day x 4 years vs. placebo, 1 tablet in AM x 4 years.

Eligibility:
1. Totally resected Staged IA (pT1N0)
2. Free of disease.
3. 6 - 36 months from date of surgical resection
4. No prior or current chemo or radiation therapy
5. ECOG PS 0-1

Journal of the National Comprehensive Cancer Network, July 2006

NSCLC: Therapeutic Options by Stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>Treatment Options</th>
<th>5-Year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>Surgery</td>
<td>&gt;70%</td>
</tr>
<tr>
<td>IB</td>
<td>Surgery + Adjuvant CT</td>
<td>60%</td>
</tr>
<tr>
<td>IIA</td>
<td>Surgery + Adjuvant CT</td>
<td>50%</td>
</tr>
<tr>
<td>IIIB</td>
<td>Surgery + Adjuvant CT</td>
<td>40-60%</td>
</tr>
<tr>
<td>IIIA (N2-) IIIA (N2-)</td>
<td>Surgery + Adjuvant CT</td>
<td>25-40%</td>
</tr>
<tr>
<td></td>
<td>CT + XRT + Surgery</td>
<td>10-30%</td>
</tr>
</tbody>
</table>

NSCLC: Therapeutic Options by Stage

Case #1:
MW- initial visit: 11/10/05

62 y/o WF, with recurrent RUL pneumonias between July and October, 2005. Repeat CXR after ATBx therapy showed R hilar mass. Chest CT-scan showed a 4.58 x 4.23 cm RUL pulmonary mass with possible direct extension to the medial pleura, possible R paratracheal and pre-carinal LN's, a 2.5 x 1.6 cm L adrenal lesion, and a L1 lytic lesion. Transbronchial Bx of the RUL mass showed large cell undifferentiated carcinoma of the lung. Bx of the L1 lesion was reported as benign.

Case #1:

A whole body PET-scan showed the adrenal mass and the possible bony lesions NOT to be hypermetabolic. Clinical (c)stage IIIA (T2N2M0).

Therapeutic recommendation upon consultation to the Multidisciplinary Lung Cancer Clinic: *neo-adjuvant combined modality concurrent chemo-radiation therapy f/b re-evaluation with intent to resection*.

Patient was treated with two cycles of cisplatin (60 mg/m2) and etoposide (120 mg/m2/day x 3), every 3 weeks with concurrent XRT (50 Gy over 25 treatment fractions) to the tumor and adjacent positive adenopathies and areas of likely sub-clinical involvement.

Case #1:

On 4/4/06 the patient underwent a VATS RULobectomy with chest wall resection.

Interval re-evaluation was planned for after completion of chemoradiation. If the patient was not found a candidate for surgery, she was to continue XRT to a definitive dose up to 65 Gy and consolidation chemotherapy with two cycles of docetaxel 100 mg/m2 every 3 weeks.

Upon completion of chemoradiation, a chest CT-scan was done showing objective response as per table:

<table>
<thead>
<tr>
<th></th>
<th>10/31/05</th>
<th>2/14/06</th>
</tr>
</thead>
<tbody>
<tr>
<td>RUL mass</td>
<td>4.58 x 4.23 cm</td>
<td>3.0 x 2.3 cm</td>
</tr>
<tr>
<td>L adrenal mass</td>
<td>2.5 x 1.6 cm</td>
<td>2.45 x 1.58 cm</td>
</tr>
</tbody>
</table>

Upon completion of chemoradiation, a chest CT-scan was done showing objective response as per table:

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>N1 nodes (station 10-14)</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>N2 nodes (station 1-9)</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>N3 nodes</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>Distant metastasis</td>
<td>Not examined</td>
<td></td>
</tr>
</tbody>
</table>
The second week in May the patient developed persistent HA’s and weakness. Brain MRI with contrast showed a **single R occipital mass c/w metastasis.** Upon consult with NS the mass was debulked and she received **30 Gy** in 12 treatment fractions to the whole brain, from 5/24 through 6/12/06, plus temozolomide (75mg/m2/day).

**Case #1:**

On 5/23/06 she was sent for a whole body CT/PET scan for restaging of the LuCa and due to progressive pain in the R paraspinal area, at T8-9 level.

A new, abnormal focal area of hypermetabolism was found along the paramedial aspect of the posterior R pleura at T9 level with SUV of 9.1. Bx proved this to be NSCLC, metastatic.

**Case #1:**

She received **35 Gy** delivered in 7 treatment fractions, using IMRT, from 6/21 through 6/29/06. On 7/25/06 a thoracic and lumbar spinal MRI was done due to progressive back pain. It showed metastatic disease to T10 with tumor extension into the neural foramina and chronic compression of L1.

**Case #1:**

On 7/27/06 the patient was seen last in the office with significant deterioration of her condition, confused and with 7-8:10 pain in the mid/low back, even on combined narcotic analgesia. At this point she and her family requested terminal care with Hospice at home.

**NSCLC: Therapeutic Options by Stage (cont)**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Treatment Options</th>
<th>5-Year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIIB (N2-3)</td>
<td>CT/TRT ≥ CT</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>IIIB T4N0</td>
<td>CT/TRT ≥ Surgery</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>IIIB (with pleural effusion)</td>
<td>CT, MTT</td>
<td>&lt;2%</td>
</tr>
<tr>
<td>IV</td>
<td>CT, MTT Palliative Radiation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Symptom Management</td>
<td></td>
</tr>
</tbody>
</table>


**EARLY STAGE**

*adjuvant therapy*
**TNM* Staging of NSCLC**

<table>
<thead>
<tr>
<th>Stage IA</th>
<th>T1</th>
<th>N0</th>
<th>M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IB</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>T1</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>T2</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
</tbody>
</table>

*T = primary tumor; N = nodal involvement; M = distant metastasis

**TNM* Staging of NSCLC (cont)**

<table>
<thead>
<tr>
<th>Stage IIA</th>
<th>T1-3</th>
<th>N2</th>
<th>M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IIIA</td>
<td></td>
<td>N1</td>
<td>M0</td>
</tr>
</tbody>
</table>

*A. On clinical trial, if available
B. High-risk patients (angiolymphatic invasion, high histologic grade, high nuclear grade)

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**Adjuvant chemotherapy for Stg IB NSCLC:**

**CALGB 9633:**

Design: 13% OS impr./50% 5-y S.
Median F/U: 34mo

<table>
<thead>
<tr>
<th>344 pts</th>
<th>150 deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IB</td>
<td>T2N0</td>
</tr>
<tr>
<td>Lobectomy 89%</td>
<td></td>
</tr>
<tr>
<td>Cb-6/Pacl-200 q 21 days x 4 cycles</td>
<td>71% 61%</td>
</tr>
<tr>
<td>Observation</td>
<td>59% 50%</td>
</tr>
<tr>
<td>pValue</td>
<td>0.028 0.035</td>
</tr>
</tbody>
</table>

GM Strauss et al., PASCO 2004

<table>
<thead>
<tr>
<th>2004</th>
<th>2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>54 mo F/U</td>
<td>4-yS 5-yDFS OS 5-yS</td>
</tr>
<tr>
<td>4-yS</td>
<td>71% HR: 0.74 HR: 0.80 60%</td>
</tr>
<tr>
<td>5-yDFS</td>
<td>0.80</td>
</tr>
<tr>
<td>OS</td>
<td>0.10</td>
</tr>
</tbody>
</table>

GM Strauss et al., PASCO 2006, Abstr 7036
TNM* Staging of NSCLC

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIA</td>
<td>T1</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>IIB</td>
<td>T2</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
</tbody>
</table>

*T = primary tumor; N = nodal involvement; M = distant metastasis

ANITA:
JY Douillard et al., ASCO '05, Abstr #7013

- 840 pts.
- Stage IB/II/IIIA
- 7-yS
- Cis-50/Vin-25 q 28 days x 4 cycles, 45%
- Observation, 37%

<table>
<thead>
<tr>
<th>5-y S.</th>
<th>Stg-IB</th>
<th>Stg-II</th>
<th>Stg-III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>62%</td>
<td>52%</td>
<td>42%</td>
</tr>
<tr>
<td>Observation</td>
<td>63%</td>
<td>39%</td>
<td>26%</td>
</tr>
</tbody>
</table>

Adjuvant chemotherapy in early stage NSCLC:
Consensus:
1. Chemotherapy of choice: cis-based (Vinorelbine, VP-16, Vinca alkaloids)
2. Patient eligibility: Stage II & III
3. Stage IB:
   a. On clinical trial, if available
   b. High-risk patients (angiolymphatic invasion, high histologic grade, high nuclear grade)
4. Age NOT a limiting factor

Adjuvant chemo in elderly patients:
JBR.10 (Cis/VNR)

<table>
<thead>
<tr>
<th>213 pts.</th>
<th>&lt;65</th>
<th>≥65</th>
<th>&gt;75</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS HR</td>
<td>0.77 p=0.004</td>
<td>0.61 p=0.04</td>
<td>1.95 p=0.02</td>
</tr>
<tr>
<td>SqCellCa</td>
<td>32% p=0.01</td>
<td>49% p=0.001</td>
<td>--</td>
</tr>
<tr>
<td>PS 0-1</td>
<td>53% p=0.01</td>
<td>41% p=0.001</td>
<td>--</td>
</tr>
<tr>
<td>Dose Int.</td>
<td>13.2 p=0.004</td>
<td>9.9 p=0.004</td>
<td>--</td>
</tr>
<tr>
<td>2. Cis</td>
<td>18.0 p=0.001</td>
<td>14.1 p=0.001</td>
<td>--</td>
</tr>
<tr>
<td>Toxicity</td>
<td>SAME</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

Genomics and prognosis of early NSCLC:
Lung Metagene Model

Method: 89 pts. initial retrospective DNA microarray (genes that predict recurrence in early NSCLC) on long term survivors. Blinded validation in previously treated pts on trials.

Results: Accuracy: 79% PPV: 79% NPV: 80%

<table>
<thead>
<tr>
<th>Stg-I</th>
<th>RISK</th>
</tr>
</thead>
<tbody>
<tr>
<td>low</td>
<td>93%</td>
</tr>
<tr>
<td>intern</td>
<td>70%</td>
</tr>
<tr>
<td>high</td>
<td>&lt;10%</td>
</tr>
</tbody>
</table>

SH Harpole et al., PASCO 2006, Abstr 7028
Genomics and prognosis of early NSCLC: 
*Lung Metagene Model*

**CALGB 30506:**
(ongoing)
Prospective evaluation of risk factors in early stage NSCLC, and adjuvant chemotherapy.

DH Harpole et al., PASCO 2006, Abstr 7026

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### TNM* Staging of NSCLC (cont)³

<table>
<thead>
<tr>
<th>Stage IIIA</th>
<th>T1-3</th>
<th>N2</th>
<th>M0</th>
<th>M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>T3</td>
<td>N1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*T = primary tumor; N = nodal involvement; M = distant metastasis.


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### INTERMEDIATE STAGE

**NEO-ADJUVANT CHEMOTHERAPY**

**resectable** disease

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### Surgery alone vs. pre-Op. Carbo/paclit. in Stage-IB & **non-N2** -IIIA NSCLC: S9900

**RESECTABLE**

Population:
- Stage-IB (63%)
- Stage-IIA/B (33%)
- Stage-III A (4%)

Primary endpoint: 30% improvement in MS (3.6 yrs) over surgery alone (2.7 yrs).

Surgery: at least lobectomy with mediastinal LN sampling.

ASCO 2005 LBA # 7012. C Pisters et al.

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### Surgery alone vs. pre-Op. Carbo/paclit. in Stage-IB & **non-N2** -IIIA NSCLC: S9900

³ 700 pts., randomized 1:1.

<table>
<thead>
<tr>
<th>Treatments</th>
<th>OS</th>
<th>1-yS</th>
<th>2-yS</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pacl-225</td>
<td>42m</td>
<td>82%</td>
<td>68%</td>
<td>0.88</td>
</tr>
<tr>
<td>Carb AUC6</td>
<td>q 3w x 3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

37m 79% 64% 1.0

ASCO 2005 LBA # 7012. C Pisters et al.
Resectable non-N2 NSCLC:

**Consensus:**
1. Resectable non-N2 disease, should be offered **definite R0 intervention**, with at least 4 regional LN's sampling.
2. Borderline resectable non-N2 disease, can be treated with **induction therapy** (Carbo or Cis-based doublet for 2-3 cycles) /b. re-evaluation for resection.

**NEO-ADJUVANT CHEMO/RADIATION THERAPY**

**Resectable disease**

**ROLE OF SURGERY?!**

---

**Phase-III CHRT vs. CHRT f/b Surgery in Stage-IIIA (pN2) NSCLC: RTOG 9309**

<table>
<thead>
<tr>
<th>RESECTABLE</th>
<th>Primary endpoint: PFS, OS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>396 pts.</td>
</tr>
<tr>
<td>PEx2+TRT-45Gy</td>
<td>12.8 22.4 23.6</td>
</tr>
<tr>
<td>Surg &gt;&gt; PEx2</td>
<td>m % m</td>
</tr>
<tr>
<td>PEx4+TRT-61Gy</td>
<td>10.5 11.1 22.2</td>
</tr>
<tr>
<td>pValue</td>
<td>0.017 0.008 0.24</td>
</tr>
</tbody>
</table>

**ASCO 2005, Abstract #7014; Albain K et al.**

Conclusions:
1. Significant improvement in **PFS** but **not OS** when surgery follows CHRT in Stage-IIIA (pN2)
2. Trend for better 5-y Survival with **trimodality** therapy.

**ROLE OF SURGERY??**

---

** MANAGEMENT OF LOCALLY ADVANCED LUNG CANCER:**

**unresectable disease**

---

**TNM* Staging of NSCLC**

(cont)³

<table>
<thead>
<tr>
<th>Stage IIIB</th>
<th>T4 Any T</th>
<th>Any N N3</th>
<th>M0 M0</th>
</tr>
</thead>
</table>

³ = primary tumor; N = nodal involvement; M = distant metastasis

SWOG 9504
Stage-IIIB

UNRESECTABLE

83 Prs. Stage-IIIB T4 & N3

INDUCTION
Cis 50mg/m² d1,8,29,36
VP-16 50mg/m² d1-5; 29-33
XRT 61 GY, from d1

CONSOLIDATION
TXT 75-100mg/m²
q 21days x 3 cycles

Results: MS-Mo 1-Y 2-Y 3-Y
27 76% 54% 40%

D Gandara et al, ASCO 2001; Abs.#1255

SWOG 9504

2005

Stage IIIB T4N3

5-y MS 26mo
1-Y S 76%
2-Y S 54%
3-Y S 40%
5-Y S 29%

Gandara D et al, ASCO ‘05, Abs #7659

ADVANCED DISEASE

TNM* Staging of NSCLC (cont)³

Stage IV | Any T | Any N | M1

* T = primary tumor; N = nodal involvement; M = distant metastasis

Goals in Advanced NSCLC ⁴

• Extend Survival
  1st-, 2nd-, and 3rd-line options

• Improve Quality of Life
  Palliate disease-related symptoms
  Manage treatment-related side effects
  Support patient and family turmoil

Provide the Longest Duration of Quality of Life!!!

Agents with “Activity” in Advanced NSCLC⁵,⁶

<table>
<thead>
<tr>
<th>Older</th>
<th>Newer</th>
<th>Newest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>Carboplatin</td>
<td>Pemetrexed**</td>
</tr>
<tr>
<td>Etoposide</td>
<td>Docetaxel</td>
<td>Erlotinib</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>Irinotecan</td>
<td>Gefitinib</td>
</tr>
<tr>
<td>Mitomycin-C</td>
<td>Gemcitabine*</td>
<td>Bevacizumab</td>
</tr>
<tr>
<td>Vinblastine</td>
<td>Paclitaxel</td>
<td></td>
</tr>
<tr>
<td>Vinorelbin</td>
<td>Topotecan</td>
<td></td>
</tr>
</tbody>
</table>

Note: Not all these agents are approved by the FDA for the treatment of NSCLC.
*Gemcitabine/cisplatin is approved for 1st-line NSCLC
**Pemetrexed is approved for 2nd-line treatment of NSCLC

⁶ Seminars in Oncology. 2006
PFIZER A8501001
1st line induction chemotherapy +/- dendritic cell vaccine in advanced NSCLC.

**Eligibility:** Stage IIIb (with pleural effusion) and Stage IV NSCLC.

**Design:**
Arm-A: Carboplatin AUC-6/Paclitaxel 200 mg/m² on d1, every 21 days, x 6cycles, plus DNA recombinant dendritic cell vaccine.
Arm-B: Carboplatin AUC-6/Paclitaxel 200 mg/m² on d1, every 21 days, x 6cycles.

---

**Comparative table:**

<table>
<thead>
<tr>
<th>Author</th>
<th>RR %</th>
<th>TTP mo</th>
<th>MS mo</th>
<th>1-yS %</th>
<th>2-yS %</th>
<th>Carbo/Pacl</th>
<th>Carbi/Pacl/Be vacizumab</th>
<th>Carbo/Gem</th>
<th>Cis/Taxotere</th>
<th>Gem/Paclit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belani</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sandler</td>
<td>27</td>
<td>6.4</td>
<td>12.5</td>
<td>--</td>
<td>--</td>
<td>34</td>
<td>5.2</td>
<td>7.6</td>
<td>31.0</td>
<td>8.0</td>
</tr>
<tr>
<td>Tritt</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>32</td>
<td>--</td>
<td>11.3</td>
<td>--</td>
<td>21</td>
</tr>
<tr>
<td>Fossella</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>44</td>
<td>4.79</td>
<td>8.4</td>
<td>33.0</td>
<td>8.0</td>
</tr>
</tbody>
</table>

---

**Advanced NSCLC:**

Significant improvement in MS of @ 8 weeks, with NO negative financial impact or on QOL.

**Stephens RJ: The Big Lung Trial** Cisplatin-based chemo vs. BSC only in NSCLC. PASCO 21: 291, 2002. Abs. #1161

---

**Cisplatin-based chemo in the elderly:**

**MILES-2P**

<table>
<thead>
<tr>
<th>169 pts ≥ 70 y/o ECOG 0-1</th>
<th>Toxicity</th>
<th>ORR</th>
<th>DFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>anemia 5%</td>
<td>thromb 10%</td>
<td>cardiac 10%</td>
<td>renal 7%</td>
</tr>
<tr>
<td>Cispl-60 d1 Gem-1000 d1.8  q21d x 6 cycles</td>
<td>43%</td>
<td>25 wks.</td>
<td>44 wks.</td>
<td></td>
</tr>
<tr>
<td>Cispl-40 d1 Vinor-25 d1.8  q21d x 6 cycles</td>
<td>36%</td>
<td>21 wks.</td>
<td>33 wks.</td>
<td></td>
</tr>
</tbody>
</table>

**Conclusions:** Cis-60/Gem is safe and active in fit elderly patients.

**TARGETED THERAPY**
**Angiogenesis**

**Tumor Growth**

**Anti-apoptosis**

**Gene Activation**

**MAPK**

**ERK**

**jnk**

**ras**

**Rho-B MEK**

**sek**

**PI3-K Akt**

**mTOR**

**G2**

**S**

**M**

**G1**

**Ininsensitivity to anti-growth signals**

**Self sufficiency in growth signals**

**Tissue invasion**

**and metastasis**

**Insensitivity to anti-growth signals**

**Angiogenesis**

**EGFR-Targeted Approaches**

- **cetuximab (C225)**
- **erlotinib (Tarciva®)**
- **gefitinib (Iressa®)**

Adapted from Noonberg and Benz. Drugs. 2000;59:753.

**Prospective erlotinib trial in advanced NSCLC with EGFR-mut.:**

**SLCG**

Bock, EGFR-mut predicts response (60-90%) and long TTP (12-21 mo) to the tk-inhibitors erlotinib & gefitinib.

**Population:** 127 (15.1%);1047 pts. EGFR-mut (+) (exon 19 & 21)

- **M-age:** 68
- **Stg-IV:** 90%
- **Female/male:** 65%
- **AdenoCa:** 75%

**Eligibility & treatment:**

- **Eligibility:** Stg IIIb/IV, EGFR-mut (+), PS 0-2, Prior Rx: 60
- **Treatment:** Rx naïve: 67, Erlotinib 150 mg/day PO

L. Paz-Ares et al., PASCO 2006 Abstr7020

**Results:**

**Prospective erlotinib trial in advanced NSCLC with EGFR-mut.:**

**SLCG**

<table>
<thead>
<tr>
<th></th>
<th>MS (mo)</th>
<th>1-y S (%)</th>
<th>CR (%)</th>
<th>RR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exon-19-mut</td>
<td>33</td>
<td>82</td>
<td>20</td>
<td>95</td>
</tr>
<tr>
<td>Exon-21-mut</td>
<td></td>
<td></td>
<td>5.5</td>
<td>68</td>
</tr>
</tbody>
</table>

**Response by site:**

<table>
<thead>
<tr>
<th>POOR:</th>
<th>GOOD:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>CNS</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>Liver</td>
</tr>
<tr>
<td>Bone</td>
<td></td>
</tr>
</tbody>
</table>

**Conclusions:**

Prospective predictors of response to tk-inhibitors:

a. EGFR-mut (exon-19 > 21)…p=0.038
b. Non-smoking history……… p=0.043
c. Female gender…………….. p=0.203

L. Paz-Ares et al., PASCO 2006 Abstr7020;
CHEMO-TARGETED THERAPY IN ADVANCED NSCLC

Targeting VEGF

Bevacizumab
rHu-MoAb to VEGF-A

Bevacizumab plus chemotherapy has provided a survival advantage to patients with metastatic colorectal carcinoma.

VEGF as a target for the treatment of Cancer:
- Tumors require new blood vessel growth
- A number of pro-(PAF) and anti-angiogenic factors (AAF) discovered over the past years.
- VEGF is critical angiogenic factor for new blood vessel growth
- VEGF overexpression is associated with disease progression and death

VEGF as a target for the treatment of Cancer:
- Bevacizumab (Avastin\textsuperscript{R}; Anti-VEGF Ab)
  - precludes VEGF from binding to VEGFR
  - Activity as single agent and in combination with cytotoxic agents
  - Initial clinical trials disappointing.
  - Recent successful trials:
    - ASCO '03: CRC.
    - ECOG 4599 '05: NSCLC

VEGF as a target for the treatment of Cancer:

Endothelial Cell

Anti-VEGF MoAb (Avastin\textsuperscript{R})

VEGF

ATP

VEGFR-1

VEGFR-2

Small Molecules (tki)

Anti-VEGF

BLOOD CLOT

Blood vessel obstruction

APOPTOSIS

? BLOCKS CHEMO DELIVERY
VEGF as a target for the treatment of Cancer:

![Diagram showing Vasculature and Pressure](image)

Jain et al, Nature Medicine, 2004

**Objective**
- 30% improved MS (8.0>10.4 mo.)

**Eligibility**
- Stage-IIIB/IV
- Non-surgical
- ECOG ≤1

**Randomize**
- 1:1

**Carbo/Paclit +/- Bevacizumab**
- (Adenocarcinomas)

- **Carbo-6/Taxol-200, q21 days, x 6 cycles**
- **Carbo-6/Taxol-200 + Bevaciz 15 mg/kg, q 21 d, x 6 cycles f/b**
- Bevacizumab until DP


**Survival by Treatment**

![Graph showing Survival by Treatment](image)

**Carbo/paclitaxel +/- bevacizumab: unplanned subset survival analysis by gender**

<table>
<thead>
<tr>
<th></th>
<th>PC</th>
<th>PCB</th>
<th>pValue</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS</td>
<td>10.3 mo</td>
<td><strong>12.3 mo</strong></td>
<td>0.003</td>
</tr>
<tr>
<td>Males</td>
<td>8.7 mo</td>
<td><strong>11.7 mo</strong></td>
<td><strong>0.001</strong></td>
</tr>
<tr>
<td>Females</td>
<td>13.1 mo</td>
<td>13.3 mo</td>
<td>0.87</td>
</tr>
</tbody>
</table>

**ORR**
- **23.6%**
- **38.5%**

**TTP**
- 6.8 mo

JR Brahmer et al., PASCO 2006, Abstr 7036.
Carbo/paclitaxel +/- bevacizumab: unplanned subset survival analysis by gender
ECOG 4599

<table>
<thead>
<tr>
<th></th>
<th>HTN %</th>
<th>Constip %</th>
<th>Abd Pain %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>4.2</td>
<td>1.4</td>
<td>0.9</td>
</tr>
<tr>
<td>Female</td>
<td>9.9</td>
<td>4.7</td>
<td>5.2</td>
</tr>
<tr>
<td><em>p</em> Value</td>
<td>0.02</td>
<td>0.05</td>
<td>0.01</td>
</tr>
</tbody>
</table>

JR Brahmer et al., PASCO 2006, Abstr 7836;

**Consensus:**
1. Female patients **should be offered** bevacizumab-based Carbo/Paclitaxel combinations, until further gender data is available

Carbo/paclitaxel/bevacizumab
female patients

Retinoids:
*mechanism of action*

**Retinoids:**
*mechanism of action*

Retinoids:
*RxR-β tumor expression and survival in resected NSCLC*

<table>
<thead>
<tr>
<th></th>
<th>Pts #</th>
<th>5-y S</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (&gt;12.9)</td>
<td>27</td>
<td>74.1%</td>
</tr>
<tr>
<td>Low (&lt;12.9)</td>
<td>61</td>
<td>34.4%</td>
</tr>
</tbody>
</table>


Bexarotene:
*clinical experience*
**Concurrent** bexarotene and chemotherapy in advanced NSCLC:

*Design:* Plat- Based CH + bexarotene.

<table>
<thead>
<tr>
<th>Phase-I/II</th>
<th>OR (%)</th>
<th>MS (mo)</th>
<th>1-y S (%)</th>
<th>2-y S (%)</th>
<th>3-y S (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1069-18</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cis/Vin+Bexarotene (100/30-15 400mg/m2/d)</td>
<td>25</td>
<td>14</td>
<td>61</td>
<td>32</td>
<td>19</td>
</tr>
<tr>
<td>All dose groups</td>
<td>--</td>
<td>11.7</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>TAX326 (Cis/Vin)</td>
<td>--</td>
<td>10.1</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>


---

**ECOG 1594:** survival curve

Survival by Treatment Group

![Survival Graph]

---

**Concurrent & sequential** bexarotene and chemo. in advanced NSCLC:

*Design:* Plat- Based CH + vs. f/b. bexarotene.

<table>
<thead>
<tr>
<th>Phase-II</th>
<th>OR (%)</th>
<th>TTP (days)</th>
<th>1-y S (%)</th>
<th>MS (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carb-6/Tax-100/bexarotene-400 (PR)</td>
<td>58</td>
<td>166.2</td>
<td>45</td>
<td>(11.7)</td>
</tr>
<tr>
<td>C S</td>
<td>162</td>
<td>171</td>
<td>50</td>
<td>43</td>
</tr>
<tr>
<td>C S</td>
<td>12.6</td>
<td>10.8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

11 pts are still alive 407 to 1036 days from registration on the trial.


---

**LOOKING INTO THE CRISTAL BALL:**

EMERGING OF A NEW PARADIGM IN THE TREATMENT OF LUNG CANCER.

**OLD THERAPEUTIC PARADIGM:**
- Tumor Anti-proliferative drugs
- Maximal cytoreduction > CR(PR)/SD/PD (CT-scan)*
- Eradication of malignant cell clone/Cure
- Severe nonspecific toxicity

**NEW THERAPEUTIC PARADIGM:**
- Modulators of tumor cell growth (“cytostasis”)
- Maximal functionality > TTP/MS/QOL (PET)*
- Delay disease progression/tumor proliferation
- Less nonspecific toxicity

CANCER AS A CHRONIC DISEASE
PROTRACTED USE OF THERAPY
CHRONIC TOXICITY

---

**RODOLFO TO START INFECTION ON FEB 29TH, 11:40 AM AFTER NOTICING THE DISCHARGE SUMMARY**

DISCHARGE SUMMARY
DISCHARGE SUM.....
2006 TREATMENT OF CANCER:
CONCLUSIONS:

HOPE