Systemic therapy for Non-Small Cell Lung Cancer in 2013 (What you should know)

Inter-hospital Conference, 16th March 2013
Systemic therapy for NSCLC in 2013
(What you should know)

- Evolution of chemotherapy and targeted agents in advanced lung cancer
- Adjuvant chemotherapy in resectable stage I – III
- Chemotherapy in unresectable stage III
## Cancer Incidence in Thailand

### 2008 Population (Millions)

<table>
<thead>
<tr>
<th>Total</th>
<th>65</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>32</td>
</tr>
<tr>
<td>Females</td>
<td>33</td>
</tr>
</tbody>
</table>


### Incidence, Prevalence, Mortality, and Mortality-to-Incidence Ratios for Common Cancers in Males and Females

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Incidence</th>
<th>5-Year Prevalence</th>
<th>Mortality</th>
<th>Mortality-to-Incidence Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age-Standardized Rate per 100,000</td>
<td>Number of New Cases of Cancer</td>
<td>Rate per 100,000 (not age-standardized)</td>
<td>Number of Persons Living with Cancer</td>
</tr>
<tr>
<td>Liver</td>
<td>38.6</td>
<td>10,195</td>
<td>16.0</td>
<td>4,984</td>
</tr>
<tr>
<td>Long and Bronchus</td>
<td>25.5</td>
<td>6,429</td>
<td>15.7</td>
<td>4,875</td>
</tr>
<tr>
<td>Colon and Rectum</td>
<td>10.7</td>
<td>2,744</td>
<td>20.9</td>
<td>6,488</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>4.8</td>
<td>1,195</td>
<td>10.6</td>
<td>3,283</td>
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<tr>
<td>Non-Hodgkin Lymphoma</td>
<td>4.7</td>
<td>1,336</td>
<td>8.6</td>
<td>2,681</td>
</tr>
<tr>
<td>Uterine Cervix</td>
<td>19.8</td>
<td>6,243</td>
<td>62.6</td>
<td>19,846</td>
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<tr>
<td>Liver</td>
<td>17.2</td>
<td>4,995</td>
<td>7.5</td>
<td>2,390</td>
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<tr>
<td>Breast</td>
<td>16.6</td>
<td>5,282</td>
<td>60.2</td>
<td>19,096</td>
</tr>
<tr>
<td>Lung and Bronchus</td>
<td>10.4</td>
<td>3,026</td>
<td>7.6</td>
<td>2,412</td>
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<tr>
<td>Colon and Rectum</td>
<td>7.1</td>
<td>2,108</td>
<td>16.2</td>
<td>5,147</td>
</tr>
</tbody>
</table>

Age-standardized to the World Standard Population.

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Advanced NSCLC: what are our treatment goals for patients?

- ‘Longer life’
  - increased overall survival

- ‘Better life’
  - symptom improvement
  - prolonged time to progression
  - improved disease control rate
  - reduced toxicity
  - improved quality of life (QoL)
Significant milestones in lung cancer therapy

Meta-analyses confirm survival benefit with chemotherapy in advanced NSCLC

1990s

Results shown for cisplatin-based regimens only (11 trials)

NSCLC Collaborative Group.
BMJ 1995;311:899–909
Significant milestones in lung cancer therapy

1970s: BSC 2–4 months
1980s: Cisplatin-based regimens: 6–8 months
1990–2005: Platinum-based doublets (3G): 8–10 months
2008: Bevacizumab/Cetuximab + platinum-based doublet: >12 months
First-Line Therapy
Platinum-Based Regimens in stage IV NSCLC
Summary of conventional doublets

Column A:
Cisplatin
Carboplatin

Column B:
Paclitaxel
Docetaxel
Gemcitabine
Pemetrexed*
Irinotecan
Vinorelbine
Etoposide

Column C:
Bevacizumab
Cetuximab

Doublets Regimen: Choose 1 from each column
* Non-squamous histology
# Pros and Cons of the Various Regimens

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Convenience</th>
<th>Cost</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>N,V</td>
</tr>
<tr>
<td>Cb/Pac</td>
<td>+++</td>
<td>$$</td>
<td>-</td>
</tr>
<tr>
<td>Cb/G</td>
<td>+++</td>
<td>$$$</td>
<td>-</td>
</tr>
<tr>
<td>Cis/G</td>
<td>++</td>
<td>$$</td>
<td>-</td>
</tr>
<tr>
<td>Cis/Vin</td>
<td>+</td>
<td>$</td>
<td>-</td>
</tr>
<tr>
<td>Cis/Doc</td>
<td>+++</td>
<td>$$</td>
<td>-</td>
</tr>
<tr>
<td>Cb/Doc</td>
<td>++++</td>
<td>$$$</td>
<td>-</td>
</tr>
</tbody>
</table>

Pac Paclitxel; G gemcitabine; Vin vinorelbine; Doc docetaxel
Treatment Options for Advanced NSCLC
(The Evolution)

1st line
Standard platinum based regimens
- Platinum + paclitaxel
- Platinum + gemcitabine
- Platinum + docetaxel
- Platinum + vinorelbine
- Platinum + pemetrexed

2nd line
Docetaxel /Pemetrexed

3+ line
Erlotinib/ Gefitinib

EGFR TKI: inhibitors of Tyrosine kinase domain epidermal growth factor receptor
Gefetinib, Erlotinib
Treatment Options for Advanced NSCLC (The recent Paradigm)

1st line
- Standard platinum based regimens
  - Platinum + paclitaxel
  - Platinum + gemcitabine
  - Platinum + docetaxel
  - Platinum + vinorelbine
  - Platinum + pemetrexed

2nd line
- Docetaxel /Pemetrexed
  - Erlotinib/ Gefitinib

3+ line
- Erlotinib/ Gefitinib

EGFR TKI: inhibitors of Tyrosine kinase domain epidermal growth factor receptor
- Gefitinib, Erlotinib

Cetuximab – monoclonal antibody to extracellular domain of EFGR

Bevacizumab – monoclonal antibody to vascular endothelial growth factor (VEGF)
Treatment Options for Advanced NSCLC (The recent Paradigm)

1st line
Standard platinum based regimens
- Platinum + paclitaxel
- Platinum + gemcitabine
- Platinum + docetaxel
- Platinum + vinorelbine
- Platinum + pemetrexed

Maintenance

2nd line
Docetaxel /Pemetrexed

3+ line
Erlotinib/ Gefitinib

Required authorization

Not reimburse in Thailand !!
Treatment Options for Advanced NSCLC
(The Real world)

1\textsuperscript{st} line
Standard platinum based regimens
- Platinum + paclitaxel
- Platinum + gemcitabine
- Platinum + docetaxel
- Platinum + vinorelbine
- Platinum + pemetrexed

2\textsuperscript{nd} line
Docetaxel /Pemetrexed

3+ line

Required authorization

Erlotinib/ Gefitinib
Treatment Options for Advanced NSCLC (The Very Real world)

1st line

- Platinum + paclitaxel
- Standard platinum based regimens

2nd line

Docetaxel

Required authorization
<table>
<thead>
<tr>
<th>Performance status</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active; no performance restrictions</td>
</tr>
<tr>
<td>1</td>
<td>Strenuous physical activity restricted; fully ambulatory and able to carry out light work</td>
</tr>
<tr>
<td>2</td>
<td>Capable of all selfcare but unable to carry out any work activities. Up and about &gt;50 percent of waking hours.</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited selfcare; confined to bed or chair &gt;50 percent of waking hours</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled; cannot carry out any selfcare; totally confined to bed or chair</td>
</tr>
</tbody>
</table>

Important considerations for optimising outcomes when selecting therapy for NSCLC

<table>
<thead>
<tr>
<th>Molecular markers (EGFR, ALK)</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHC</td>
<td>Squamous (1/3 patients)</td>
</tr>
<tr>
<td>FISH</td>
<td>Squamous-cell carcinoma</td>
</tr>
<tr>
<td>PCR</td>
<td>Non-squamous (2/3 patients)</td>
</tr>
<tr>
<td>EGFR epidermal growth factor receptor</td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>ALK anaplastic lymphoma kinase</td>
<td>Large-cell carcinoma</td>
</tr>
</tbody>
</table>

- EGFR: Epidermal growth factor receptor
- ALK: Anaplastic lymphoma kinase
- IHC: Immunohistochemistry
- FISH: Fluorescence in situ hybridization
- PCR: Polymerase chain reaction
The EGFR/HER Family

Ligand binding domain

Transmembrane domain

Tyrosine kinase domain

erb-b1 EGFR HER1

neu Erb-b2 HER2

Erb-b3 HER3

Erb-b4 HER4

Cetuximab (Erbitux)

Trastuzumab (Herceptin)

Gefitinib (Iressa)

Erlotinib (Tarceva)

Lapatinib (Tykerb)
Common clinical characteristics of NSCLC patients with \textit{EGFR} mutations

- **Ethnicity:** Asian
- **Gender:** female
- **Smoking history:** never smoker
- **Histology:** adenocarcinoma

60\% of all \textit{EGFR} mutation-positive patients

Mok, et al. NEJM 2009

Retrospective review of 2,880 cases
Histology is increasingly important when making treatment decisions for advanced NSCLC

- Pemetrexed is more effective in non-squamous histology
- Bevacizumab is more toxic in squamous histology

Molecular marker now guides treatment decisions in specific groups of patients

- patients with EGFR mutation-positive disease gain more benefit from EGFR TKIs (Gefetinib, erlotinib) than chemotherapy in both first and second line
- patients with rearrangements of the anaplastic lymphoma kinase (ALK) gene gain more benefit from ALK TKI (crizotinib) than chemotherapy in second line therapy
EGFR TKI as first-line treatment for patients with EGFR mutation positive advanced NSCLC

<table>
<thead>
<tr>
<th>Study (n)</th>
<th>Comparison</th>
<th>Eligible Mutations</th>
<th>ORR (%)</th>
<th>PFS (M)</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>LUX-lung 3 (n=345)</td>
<td>Afatinib v. Cis/Pem EGFR 29</td>
<td>19del/L858R</td>
<td>61 v 22% 56 v 23%</td>
<td>13.6 v 6.9 11.1 v 6.9</td>
<td>0.47 [0.34,0.65] 0.58 [0.34,0.65]</td>
</tr>
<tr>
<td>EURTAC (n=174)</td>
<td>Erlotinib v. Chemotherapy*</td>
<td>19del/L858R</td>
<td>58 v 15%</td>
<td>10.4 v 5.4</td>
<td>0.47 [0.28,0.78]</td>
</tr>
<tr>
<td>OPTIMAL (n=165)</td>
<td>Erlotinib v. Carbo/Gem</td>
<td>19del/L858R</td>
<td>83 v 36%</td>
<td>13.1 v 4.6</td>
<td>0.16 [0.10,0.26]</td>
</tr>
<tr>
<td>WJOTG (n=172)</td>
<td>Gefitinib v. Cis/Docet</td>
<td>19del/L858R</td>
<td>62 v 32%</td>
<td>9.2 v 6.3</td>
<td>0.49 [0.34,0.71]</td>
</tr>
<tr>
<td>NEJ002 (n=230)</td>
<td>Gefitinib v. Carbo/Pac</td>
<td>19del/L858R + other (6.1%)</td>
<td>74 v 31%</td>
<td>10.8 v 5.4</td>
<td>0.30 [0.22,0.41]</td>
</tr>
<tr>
<td>IPASS** (n=261)</td>
<td>Gefitinib v. Carbo/Pac EGFR 29</td>
<td>19del/L858R</td>
<td>71 v 47%</td>
<td>9.5 v 6.3</td>
<td>0.48 [0.36,0.64]</td>
</tr>
</tbody>
</table>

* Cisplatin or carboplatin plus Docetaxel or Gemcitabine
**Post-hoc analysis of EGFR mutant patients
Why EGFR TKI in first-line treatment?

**Gridelli, et al. Lung Cancer 2011**

**EGFR Act MUT+ NSCLC**

<table>
<thead>
<tr>
<th></th>
<th>First-line EGFR TKI</th>
<th>Second-line chemotherapy (3rd line)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong></td>
<td>PD</td>
<td>PD</td>
</tr>
<tr>
<td><strong>B</strong></td>
<td>First-line chemotherapy</td>
<td>PD</td>
</tr>
<tr>
<td></td>
<td><strong>C</strong> First-line EGFR TKI</td>
<td>Rapid worsening</td>
</tr>
<tr>
<td></td>
<td>PD</td>
<td>Death</td>
</tr>
<tr>
<td></td>
<td><strong>D</strong> First-line chemotherapy</td>
<td>Rapid worsening</td>
</tr>
</tbody>
</table>

Patients who receive only one line of therapy

Theoretical survival
Important considerations for optimising outcomes when selecting therapy for NSCLC

Molecular markers (EGFR, ALK)

| Issue of testing in Thailand | Availability of test | Availability of drugs | Turn around time | Reimbursement |

Histology

- Squamous (1/3 patients)
  - Squamous-cell carcinoma

- Non-squamous (2/3 patients)
  - Adenocarcinoma
  - Large-cell carcinoma
EGFR TKI (erlotinib, gefitinib)

\[
\text{NSHR} = 0.16 (0.10–0.26) \quad \text{Log-rank} \ p < 0.0001
\]

Carboplatin/Gemcitabine X 4 cycles VS Erlotinib

\[
\text{NRHR} = 0.37 (0.25–0.54) \quad ; \ p < 0.0001
\]

Chemotherapy VS Erlotinib

EUROC 0.30 (0.22–0.41), \ p < 0.001

Carboplatin/Paclitaxel > 3 cycles Vs Gefetinib

NEJSG 0.489 (0.336–0.710), \ p < 0.0001

Cisplatin/Docetaxel X 3-6 cycles VS Gefetinib

WJTOG3405 0.48 (0.36–0.64), \ p < 0.0001

Carboplatin/Paclitaxel X 6 cycles VS Gefetinib

IPASS

OS (hazard Ratio) PFS (Hazard Ratio) Chemo. Study

Treatment Options for Advanced NSCLC

1st line
- Standard platinum based regimens
  - carbo + paclitaxel (+ BV or Ctux)
  - cisplatin + gemcitabine (+ BV or Ctux)
  - carboplatin + docetaxel (+ Ctux)
  - cisplatin + vinorelbine (+ Ctux)

2nd line
- Docetaxel /Pemetrexed

3+ line
- Erlotinib/ Gefitinib

Maintenance therapy
- Not reimburse in Thailand !!

Required authorization
- Not reimburse in Thailand !!

(+ BV or Ctux)
(+ BV or Ctux)
(+ Ctux)
(+ Ctux)
Initial approach to patients with newly diagnosed non-small cell lung cancer

1. Newly diagnosed stage IV non-small cell lung cancer
   - Genotyping ordered (EGFR mutation, ALK translocation)
   - Systemic treatment required before genotype results known
     - Initiate systemic chemotherapy pending genotype testing results
       - EGFR mutation or ALK translocation positive: continue chemotherapy x 4 cycles; use targeted therapy as maintenance after chemotherapy. Alternatively, discontinue chemotherapy and initiate targeted therapy.
   - Immediate treatment not required: wait to treat until results of genotype testing known
     - EGFR/ALK negative: chemotherapy
     - EGFR positive: EGFR TKI
     - ALK positive: crizotinib
     - EGFR/ALK negative: continue chemotherapy
Chemotherapy Today and the Need for Targeted Therapies

- The choice of treatment depends upon the histologic subtype, molecular abnormalities, general medical condition.

- Doublet chemotherapy for 4-6 cycles is standard (good PS)

- Targeted drugs can add to doublet chemotherapy
  - Bevacizumab and cetuximab with survival benefit

- Targeted agents where target is known can replace first-line chemotherapy (EGFR-TKI in EGFR mutants)

- Most patients eventually progress and require additional therapy.
  - Maintenance therapy improves survival
  - Second-line therapy improves survival
Lung Cancer Molecular Consortium Analysis in Lung Adenocarcinomas

- Mutations found in 54\% (280/516) of tumors completely tested (95\% CI: 50\% to 59\%)
NSCLC Meta-analysis of Cisplatin Containing Regimens in Adjuvant Lung Cancer

- 8 cisplatin-based trials examined (n = 1394)
  - Patients randomized to surgery alone or surgery + adjuvant chemotherapy
- 13% reduction in risk of death with surgery + adjuvant chemotherapy vs surgery alone ($P = .08$)
## Major Changes in New Staging Classification

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T1 (≤ 3 cm)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1a (≤ 2 cm)</td>
<td>T1a (≤ 2 cm)</td>
<td>IA</td>
<td>IIA</td>
<td>IIA</td>
<td>IIIA</td>
<td>IIIB</td>
</tr>
<tr>
<td>T1b (&gt; 2-3 cm)</td>
<td>T1b (&gt; 2-3 cm)</td>
<td>IA</td>
<td>IIA</td>
<td>IIA</td>
<td>IIIA</td>
<td>IIIB</td>
</tr>
<tr>
<td><strong>T2 (&gt; 3 cm)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2a (&gt; 3-5 cm)</td>
<td>T2a (&gt; 3-5 cm)</td>
<td>IB</td>
<td>IIA (IIB)</td>
<td>IIIA</td>
<td>IIIB</td>
<td></td>
</tr>
<tr>
<td>T2b (&gt; 5-7 cm)</td>
<td>T2b (&gt; 5-7 cm)</td>
<td>IIA (IB)</td>
<td>IIB</td>
<td>IIIA</td>
<td>IIIB</td>
<td></td>
</tr>
<tr>
<td>T3 (&gt; 7 cm)</td>
<td>T3 (&gt; 7 cm)</td>
<td>IIB (IB)</td>
<td>IIIA (IIB)</td>
<td>IIIA</td>
<td>IIIB</td>
<td></td>
</tr>
<tr>
<td><strong>T3 invasion</strong></td>
<td>T3</td>
<td>IIB</td>
<td>IIIA</td>
<td>IIIA</td>
<td>IIIB</td>
<td></td>
</tr>
<tr>
<td><strong>T4 (same lobe nodules)</strong></td>
<td>T3</td>
<td>IIB (IIB)</td>
<td>IIIA (IIB)</td>
<td>IIIA (IIB)</td>
<td>IIIB</td>
<td></td>
</tr>
<tr>
<td><strong>T4 (extension)</strong></td>
<td>T4</td>
<td>IIIA (IIB)</td>
<td>IIIA (IIB)</td>
<td>IIIB</td>
<td>IIIB</td>
<td></td>
</tr>
<tr>
<td><strong>M1 (ipsilateral lung)</strong></td>
<td>T4</td>
<td>IIIA (IV)</td>
<td>IIIA (IV)</td>
<td>IIIB (IV)</td>
<td>IIIB (IV)</td>
<td></td>
</tr>
<tr>
<td><strong>T4 (pleural effusion)</strong></td>
<td>M1a</td>
<td>IV (IIB)</td>
<td>IV (IIB)</td>
<td>IV (IIB)</td>
<td>IV (IIB)</td>
<td></td>
</tr>
<tr>
<td><strong>M1 (contralateral lung)</strong></td>
<td>M1a</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
<td></td>
</tr>
<tr>
<td><strong>M1 (distant)</strong></td>
<td>M1b</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Rx</th>
<th>n</th>
<th>5-Yr OS, %</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>IALT[1]</td>
<td>Surgery Cis + VP16/vinca</td>
<td>935</td>
<td>40.4</td>
<td>0.86</td>
</tr>
<tr>
<td>IB-IIIA</td>
<td></td>
<td>932</td>
<td>44.5</td>
<td></td>
</tr>
<tr>
<td>CALGB[2]</td>
<td>Surgery Carbo/paclitaxel</td>
<td>171</td>
<td>58.0</td>
<td>0.83</td>
</tr>
<tr>
<td>IB</td>
<td></td>
<td>173</td>
<td>60.0</td>
<td></td>
</tr>
<tr>
<td>JBR.10[3]</td>
<td>Surgery Cis/vinorelbine</td>
<td>240</td>
<td>54.0</td>
<td>0.69</td>
</tr>
<tr>
<td>IB-II</td>
<td></td>
<td>242</td>
<td>69.0</td>
<td></td>
</tr>
<tr>
<td>ANITA[4,5]</td>
<td>Surgery Cis/vinorelbine</td>
<td>433</td>
<td>43.0</td>
<td>0.80</td>
</tr>
<tr>
<td>IB, II, IIIA</td>
<td></td>
<td>407</td>
<td>51.0</td>
<td></td>
</tr>
</tbody>
</table>

LACE Meta-analysis of Adjuvant Chemotherapy: Is It for Everyone?

Chemotherapy 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 vs 43% for other stages)


<table>
<thead>
<tr>
<th>Category</th>
<th>No. Deaths/No. Patients</th>
<th>HR for OS (Chemo vs Control)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IA</td>
<td>104/347</td>
<td>1.40 (0.95-2.06)</td>
<td></td>
</tr>
<tr>
<td>Stage IB</td>
<td>515/1371</td>
<td>0.93 (0.78-1.10)</td>
<td></td>
</tr>
<tr>
<td>Stage II</td>
<td>893/1616</td>
<td>0.83 (0.73-0.95)</td>
<td>Test for trend: $P = .04$</td>
</tr>
<tr>
<td>Stage III</td>
<td>878/1247</td>
<td>0.83 (0.72-0.94)</td>
<td></td>
</tr>
</tbody>
</table>
Adjuvant Chemotherapy: What Lessons Have We Learned

- **For whom:** Stage
  - II-IIIa
  - IB?
  - Not for IA

- **Which Agents**
  - Platinum agents important: cisplatin
  - Not enough data available on carboplatin
  - Vinorelbine effective
  - Not enough data on other drugs with appropriate dose of cisplatin
Phase III NATCH Study: Post-op chemo vs Pre-op chemo vs Surgery Alone

Untreated patients with resectable stage IA (T > 2 cm), IB, II and T3N1 NSCLC (N = 624)

Stratified by tumor size (< 3 vs 3-5 vs > 5 cm) and age (≤ 60 vs > 60 yrs)

- Primary endpoint: 5-yr DFS
- Secondary endpoints: toxicity, OS, biomarker analysis

Adjuvant vs Preop Chemotherapy vs Surgery Alone: NATCH Phase III Results

More patients in preoperative chemotherapy arm received treatment
Similar resectability rates, surgical procedures, postoperative mortality across arms


<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Outcome</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5-Yr DFS, %</td>
<td>5-Yr OS, %</td>
<td>Median OS,Mos</td>
</tr>
<tr>
<td>Surgery alone</td>
<td>34.1</td>
<td>44</td>
<td>48.8</td>
</tr>
<tr>
<td>Chemo → surgery</td>
<td>38.3</td>
<td>46.6</td>
<td>55.2</td>
</tr>
<tr>
<td>Surgery → chemo</td>
<td>36.6</td>
<td>45.5</td>
<td>50.3</td>
</tr>
</tbody>
</table>
### NATCH: Clinical Stages of Patients on Enrollment

<table>
<thead>
<tr>
<th>Clinical Stage, %</th>
<th>Preop Chemotherapy (n = 199)</th>
<th>Surgery Alone (n = 210)</th>
<th>Adjuvant Chemotherapy (n = 210)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1N0</td>
<td>8.0</td>
<td>9.5</td>
<td>14.3</td>
</tr>
<tr>
<td>T2N0</td>
<td>66.3</td>
<td>63.8</td>
<td>63.3</td>
</tr>
<tr>
<td>T1N1</td>
<td>2.0</td>
<td>0.5</td>
<td>1.4</td>
</tr>
<tr>
<td>T2N1</td>
<td>12.1</td>
<td>11.9</td>
<td>11.9</td>
</tr>
<tr>
<td>T3N0</td>
<td>9.1</td>
<td>12.4</td>
<td>8.6</td>
</tr>
<tr>
<td>T3N1</td>
<td>2.0</td>
<td>1.9</td>
<td>0.5</td>
</tr>
<tr>
<td>T4N0*</td>
<td>0.5</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

*Patient not eligible.

## Phase III “Targeted” Therapy Adjuvant Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Stage</th>
<th>Therapy</th>
<th>Target</th>
<th>N</th>
<th>Primary Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>JBR.19[1]</td>
<td>IB-IIIA</td>
<td>Gefitinib x 2 yrs</td>
<td></td>
<td>503</td>
<td>OS</td>
</tr>
<tr>
<td>RADIANT[2]</td>
<td>I-IIIA</td>
<td>Erlotinib x 2 yrs</td>
<td>EGFR-IHC+</td>
<td>945</td>
<td>DFS</td>
</tr>
<tr>
<td>MAGRIT[3]</td>
<td>IB-IIIA</td>
<td>Vaccine x 27 mos</td>
<td>MAGE-A3</td>
<td>2270</td>
<td>DFS</td>
</tr>
<tr>
<td>E1505[4]</td>
<td>IB (≥ 4 cm)-IIIA</td>
<td>Chemo ± bevacizumab</td>
<td></td>
<td>1500</td>
<td>OS</td>
</tr>
</tbody>
</table>

Management of stage III non-small cell lung cancer

- Resected stage IIIA disease
  - Adjuvant chemotherapy with a cisplatin-based doublet
  - Post-op RT: N2, margin+/uncertain, ? LN sampling

- Unresected stage III disease: +N2 or N3 documented prior to definitive treatment
  - (Induction chemo) Concurrent chemoradiotherapy with a platinum-based doublet (consolidation chemo)
  - Sequential chemotherapy followed by definitive RT
  - RT alone
  - ? Surgery after induction Chemo or Chemo-RT.