Lung Cancer: Personalized Approaches to Non-Small Cell and Small Cell Lung Cancer

Speaker:

Bruce E. Johnson, MD
Chief Clinical Research Officer, Dana-Farber Cancer Institute
Professor of Medicine, Harvard Medical School

2017 Master Class Course
The following relationships exist related to this presentation:

Bruce E. Johnson, MD
- Serves as an advisor for Novartis, Merck, AstraZeneca, Clovis Oncology, Chugai Pharmaceuticals, Genentech, and Eli Lilly,
- Post-marketing Royalties for EGFR mutation testing

Off-label/Investigational Discussion
In accordance with Annenberg Health Sciences policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.
Lung Cancer: Personalized Approaches to Non-Small Cell and Small Cell Lung Cancer

- Screening for Lung Cancer
- Current Standards and Studies for Metastatic NSCLC
- Adjuvant Therapy
- Chemotherapy With Surgery and Radiation in Locally Advanced Disease
- Relapsed Non-Small Cell Lung Cancer
- Small Cell Lung Cancer
Smoked >1 pack per day of cigarettes for 30 years
Age 55-74

Primary Endpoint:
Mortality Due to Lung Cancer

August, 2002 – September, 2004
53,454 participants at Risk for Lung Cancer

August 2002 – September 2004
Low-dose spiral CT
Chest X-Ray

Randomize
Year 1  Year 2  Year 3

NLST Research Team, Radiology 2011 258(1)
Screening for Lung Cancer

- Lung Cancer
- Deaths from Lung Cancer


National Lung Screening Trial Research Team *NEJM* 368:1980, 2013
Screening for Lung Cancer

- The incidence of lung cancer was 645 cases and 247 lung cancer deaths per 100,000 person-years (1060 cancers) in the low-dose CT group.
- The incidence of lung cancer was 572 cases and 309 lung cancer deaths per 100,000 person-years (941 cancers) in the radiography group.
- This represents a 20% reduction in lung cancer deaths in the CT screened group.
- 2015- The Centers for Medicare & Medicaid Services issued a national coverage determination.

Aberle et al. NEJM. 365:395, 2011
National Lung Screening Trial Research Team NEJM. 368:1980, 2013
Lung Cancer: Personalized Approaches to Non-Small Cell and Small Cell Lung Cancer

• Screening for Lung Cancer
• **Current Standards and Studies for Metastatic NSCLC**
• Adjuvant Therapy
• Chemotherapy With Surgery and Radiation in Locally Advanced Disease
• Relapsed Non-Small Cell Lung Cancer
• Small Cell Lung Cancer
• Mesothelioma
Current Standards and Studies for Metastatic NSCLC

**ECOG 4599 – Carbo/Pacl vs. Carbo/Pacl/Bev**

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>ORR</th>
<th>Median PFS</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>P+Cb</td>
<td>444</td>
<td>15%</td>
<td>4.5 mo</td>
<td>10.3 mo</td>
</tr>
<tr>
<td>P+Cb+Bev</td>
<td>434</td>
<td>*35%</td>
<td>*6.2 mo</td>
<td>*12.3 mo</td>
</tr>
</tbody>
</table>

*P < .05

# Current Standards and Studies for Metastatic NSCLC

## Bevacizumab Use in Specific Clinical Populations

<table>
<thead>
<tr>
<th>Squamous cell cancers</th>
<th>Toxic – hemoptysis: some fatal(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated brain metastases</td>
<td>Similar CNS bleed incidence as general population(^2)</td>
</tr>
<tr>
<td>Elderly patients (&gt; 70)</td>
<td>More toxic; No survival benefit(^3)</td>
</tr>
<tr>
<td>Patients on anticoagulation</td>
<td>Safe; no increased bleeding risk(^4)</td>
</tr>
<tr>
<td>Predictors of hemoptysis</td>
<td>Baseline tumor cavitation(^5)</td>
</tr>
</tbody>
</table>

**PointBreak - Phase III Trial in Nonsquamous NSCLC**

**Eligibility**
- Stage III/IV NSCLC
- Nonsquamous
- No prior chemo
- Treated brain metastases
- PS 0-1
- Measurable disease
- Prior radiation allowed

**Randomize**

**Induction Phase**
- q21d, 4 cycles
  - Bevacizumab 15 mg/kg q3w + Pemetrexed/Carboplatin

**Maintenance Phase**
- q21d until PD
  - Bevacizumab + Pemetrexed

**Current Standards and Studies for Metastatic NSCLC**

**Primary end point:** OS
**Secondary end point:** PFS
Superiority trial; N = 900

Current Standards and Studies for Metastatic NSCLC

Randomization Factors

- Stage
- Performance status
- Gender
- Histologic vs. cytologic diagnosis
- History of brain metastases

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

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Pemetrexed + Cisplatin</th>
<th>Gemcitabine + Cisplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>1725</td>
<td>10 months CI 0.84 to 1.05</td>
<td>10 months</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>847</td>
<td>13 months CI 0.71 to 0.98</td>
<td>11 months</td>
</tr>
<tr>
<td>Squamous cell</td>
<td>473</td>
<td>9 months</td>
<td>11 months CI 0.99 to 1.5</td>
</tr>
<tr>
<td>Large cell</td>
<td>153</td>
<td>10 months CI 0.48 to 0.97</td>
<td>7 months</td>
</tr>
</tbody>
</table>

Quinazoline type EGFR inhibitors

Located in TK domain
Exon 19 and 21 most common

Gefitinib
Erlotinib
Afatinib
Current Standards and Studies for Metastatic NSCLC; EGFR+

**Graphical Representation**

- **Erlotinib (N=82)**
- **Gemcitabine plus carboplatin (N=72)**

HR 0.16 (95% CI 0.10–0.26)
Log-rank p<0.0001

**Number at risk**
- Erlotinib: 82, 70, 51, 20, 2
- Gemcitabine plus carboplatin: 72, 26, 4, 0, 0

---

## Current Standards and Studies for Metastatic NSCLC; EGFR+

<table>
<thead>
<tr>
<th>Study</th>
<th>Drugs</th>
<th>N (EGFR mutation)</th>
<th>RR</th>
<th>Median PFS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPASS</td>
<td>Gefitinib vs carboplatin/paclitaxel</td>
<td>261</td>
<td>71.2% vs 47.3%</td>
<td>9.5 vs 6.3</td>
</tr>
<tr>
<td>WJTOG 3405</td>
<td>Gefitinib vs cisplatin/docetaxel</td>
<td>172</td>
<td>62.1% vs 32.2%</td>
<td>9.2 vs 6.3</td>
</tr>
<tr>
<td>NEJGSG002</td>
<td>Gefitinib vs carboplatin/paclitaxel</td>
<td>224</td>
<td>73.7% vs 30.7%</td>
<td>10.8 vs 5.4</td>
</tr>
<tr>
<td>EURTAC</td>
<td>Erlotinib vs cisplatin/docetaxel</td>
<td>173</td>
<td>58.1% vs 14.9%</td>
<td>9.7 vs 5.2</td>
</tr>
<tr>
<td>OPTIMAL</td>
<td>Erlotinib vs gemcitabine/carboplatin</td>
<td>154</td>
<td>83.0% vs 36.0%</td>
<td>13.7 vs 4.6</td>
</tr>
<tr>
<td>LUX-Lung 3</td>
<td>Afatinib vs cisplatin/pemetrexed</td>
<td>345</td>
<td>56.0% vs 23.0%</td>
<td>11.1 vs 6.9</td>
</tr>
<tr>
<td>LUX-Lung 6</td>
<td>Afatinib vs gemcitabine/cisplatin</td>
<td>364</td>
<td>66.9% vs 23.0%</td>
<td>11.0 vs 5.6</td>
</tr>
</tbody>
</table>

Exon 19 Deletion

- Median, months: Afatinib (n=236) - 31.7 (28.1-35.1), Chemotherapy (n=119) - 20.7 (16.3-25.6)
- HR (95% CI): Afatinib - 0.59 (0.45-0.77), Chemotherapy - 1.25 (0.92-1.71)
- p value: Afatinib - 0.0001, Chemotherapy - 0.16

L858R Mutation

- Median, months: Afatinib (n=183) - 22.1 (19.6-25.4), Chemotherapy (n=93) - 26.9 (23.2-31.7)
- HR (95% CI): Afatinib - 0.59 (0.45-0.77), Chemotherapy - 1.25 (0.92-1.71)
- p value: Afatinib - 0.0001, Chemotherapy - 0.16

**Number at risk**
- Afatinib: 236 230 223 217 202 192 173 160 145 131 117 90 50 38 22 6 1 0
- Chemotherapy: 119 113 103 95 87 72 63 55 51 43 38 27 14 9 1 1 0 0


Current Standards and Studies for Metastatic NSCLC; Crizotinib for First Line NSCLC

Randomized phase III trial of Crizotinib vs. chemotherapy in chemotherapy naïve EML4-ALK NSCLC

Key entry criteria
- Diagnosis of locally advanced/metastatic non-squamous NSCLC; ECOG 0-2
- Positive for ALK
- No prior treatment for advanced disease
- Brain metastases allowed

Arm A: Crizotinib 250 mg BID administered on a continuous dosing schedule
N=160

Arm B: Pemetrexed/ cisplatin or pemetrexed/ carboplatin
Day 1 of a 21-day cycle
N=160

N=320

Patients in Arm B who have RECIST-defined PD as determined by the independent radiology review will be allowed to cross over to Arm A

Primary end point: PFS
Secondary end point: ORR

www.clinicaltrials.gov(NCT0115414)
Current Standards and Studies for Metastatic NSCLC; Crizotinib for First Line NSCLC

**A** Progression-free Survival

Hazard ratio for progression or death in the crizotinib group, 0.45 (95% CI, 0.35–0.60)
P<0.001 (two-sided stratified log-rank test)

**B** Overall Survival

Hazard ratio for death in the crizotinib group, 0.82 (95% CI, 0.54–1.26)
P=0.36 (two-sided stratified log-rank test)

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Crizotinib</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months</td>
<td>0  5  10  15  20  25  30  35</td>
<td></td>
</tr>
<tr>
<td>Crizotinib</td>
<td>172  120  65  38  19  7  1  0</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>171  105  36  12  2  1  0  0</td>
<td></td>
</tr>
</tbody>
</table>

Solomon et al. *NEJM* 2014; 371:2167
Ceritinib vs. Pemetrexed Platinum in ALK Positive Non-Squamous NSCLC

- Non-Squamous NSCLC
- Previously UnRx ALK+ NSCLC
- Central confirmation of ALK rearrangement
- WHO 0 - 2

Ceritinib
750 mg Day

Pemetrexed 500 mg/m2
Cis/Carbo q 3 Wks

Soria et al. *Lancet* 2017; 389:917
Ceritinib vs. Pemetrexed Platinum in ALK Positive Non-Squamous NSCLC

Kaplan-Meier median progression-free survival
Ceritinib 16.6 months (95% CI 12.6-27.2)
Chemotherapy 8.1 months (95% CI 5.8-11.1)
HR 0.55 (95% CI 0.42-0.73)
p<0.00001 by stratified log-rank test

Kaplan-Meier median overall survival
Ceritinib not estimable (95% CI 29.3 to not estimable)
Chemotherapy 26.2 months (95% CI 22.8 to not estimable)
HR 0.73 (95% CI 0.50-1.08)
p=0.056 by stratified log-rank test

Soria et al. Lancet 2017; 389:917
J-ALEX Phase III Study Design

Key Entry Criteria
- Stage IIIIB/IV or recurrent ALK-positive NSCLC
- ALK centralized testing (IHC and FISH or RT-PCR)
- ECOG PS 0-2
- ≥1 measurable lesion assessed by investigator
- Treated/asymptomatic brain metastases allowed
- ≤1 prior chemotherapy

Stratification factors:
Clinical stage (IIIB/IV vs. Recurrent)
Prior chemotherapy (0 vs. 1)
ECOG PS (0/1 vs. 2)

Endpoints
- Primary
  - PFS assessed by IRF*
- Secondary
  - OS
  - ORR
  - PK
  - QOL
  - CNS PFS
  - Safety

Alectinib 300 mg BID PO, 28-day cycle (N=100)
Crizotinib 250 mg BID PO, 28-day cycle (N=100)

*IRF Independent Review Facility
JapicCTI-132316

Presented by: Hiroshi Nokihara ASCO 2016
ALK+ Non-Small Cell Lung Cancer; Alectinib

December 2015-FDA Approved Alectinib
With ALK Rearrangements in NSCLC

<table>
<thead>
<tr>
<th></th>
<th>Alectinib (N=103)</th>
<th>Crizotinib (N=104)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>25 (24.3%)</td>
<td>58 (55.8%)</td>
</tr>
<tr>
<td>Median, mo [95% CI]</td>
<td>NR [20.3 - NR]</td>
<td>10.2 [8.2 - 12.0]</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.0001</td>
<td>0.34 [0.17 - 0.71]</td>
</tr>
</tbody>
</table>

Progression-free survival rate (%)

No. of patients at risk

Alectinib | Crizotinib
---|---
103 | 104
103 | 102
93  | 86
76  | 65
49  | 40
36  | 21
27  | 14
9   | 4
1   | 1

Time (months)
Current Standards and Studies for Metastatic NSCLC; Crizotinib to Delay Brain Recurrence

![Graph showing survival outcomes with Crizotinib vs chemotherapy.](image-url)

<table>
<thead>
<tr>
<th>Events, no. (%)</th>
<th>Crizotinib (n = 39)</th>
<th>Chemotherapy (n = 40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 (23)</td>
<td>12 (30)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Median, months</th>
<th>Crizotinib</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>15.7</td>
<td>12.5</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HR (95% CI)</th>
<th>Crizotinib</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.45 (0.19 to 1.07)</td>
<td>0.60 (0.34 to 1.05)</td>
<td></td>
</tr>
</tbody>
</table>

*P* = .063

No. at risk

<table>
<thead>
<tr>
<th>Crizotinib</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>172</td>
<td>171</td>
</tr>
<tr>
<td>119</td>
<td>107</td>
</tr>
<tr>
<td>65</td>
<td>39</td>
</tr>
<tr>
<td>40</td>
<td>14</td>
</tr>
<tr>
<td>21</td>
<td>3</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Crizotinib</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>39</td>
<td>40</td>
</tr>
<tr>
<td>26</td>
<td>15</td>
</tr>
<tr>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Solomon et al. JCO 2016; 34:2858
ROS1+ Non-Small Cell Lung Cancer Rx with Crizotinib

- Advanced NSCLC
- ROS1 Rearrangement
- PS 0-2
- Measureable Disease

Shaw et al. *NEJM* 2014 371:1963
ROS1+ Non-Small Cell Lung Cancer Rx with Crizotinib

- Advanced NSCLC
- ROS1 Rearrangement
- PS 0-2
- Measureable Disease

March 2016- FDA Approved Crizotinib with ROS1 Rearrangements in NSCLC

<table>
<thead>
<tr>
<th>Months</th>
<th>No. at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crizotinib</td>
</tr>
<tr>
<td>0-1</td>
<td>50</td>
</tr>
<tr>
<td>1-2</td>
<td>41</td>
</tr>
<tr>
<td>2-3</td>
<td>30</td>
</tr>
<tr>
<td>3-4</td>
<td>21</td>
</tr>
<tr>
<td>4-5</td>
<td>8</td>
</tr>
<tr>
<td>5-6</td>
<td>7</td>
</tr>
</tbody>
</table>

Shaw et al. *NEJM* 2014 371:1963
Pembrolizumab vs. Chemotherapy in Advanced Previously Untreated NSCLC

- NSCLC
- >50% PD-L1 Positive
- No Prior Therapy
- ECOG 0 or 1
- No Immune Disorders

Pembrolizumab
200 mg q 3 weeks

Investigators Choice
Platinum-Based Chemotherapy

Reck M et al. *NEJM* 2016. October epub
Pembrolizumab vs. Chemotherapy in Advanced Previously Untreated NSCLC

Hazard ratio for death, 0.60 (95% CI, 0.41–0.89)
P = 0.005

<table>
<thead>
<tr>
<th>Month</th>
<th>No. at Risk Pembrolizumab</th>
<th>No. at Risk Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>154</td>
<td>151</td>
</tr>
<tr>
<td>3</td>
<td>136</td>
<td>123</td>
</tr>
<tr>
<td>6</td>
<td>121</td>
<td>106</td>
</tr>
<tr>
<td>9</td>
<td>82</td>
<td>64</td>
</tr>
<tr>
<td>12</td>
<td>39</td>
<td>34</td>
</tr>
<tr>
<td>15</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td>18</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>21</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Reck M et al. *NEJM* 2016. October epub
The major recommendations are to use testing for EGFR mutations and ALK fusions to guide patient selection for therapy with an epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) inhibitor, respectively, in all patients with advanced-stage adenocarcinoma, regardless of sex, race, smoking history, or other clinical risk factors, and to prioritize EGFR and ALK testing over other molecular predictive tests.
Current Standards and Studies for Metastatic NSCLC; Pemetrexed Maintenance

PARAMOUNT – Continuation Maintenance Therapy

- Induction Therapy: 4 cycles, q21d
- Continuation Maintenance Therapy: q21d until PD

- Pemetrexed + Cisplatin
- Placebo + BSC
- CR/PR/SD per RECIST
- R 2:1

Stratified for:
- PS (0 vs. 1)
- Disease stage (IIIB vs IV) prior to induction
- Response to induction (CR/PR vs SD)

Current Standards and Studies for Metastatic NSCLC; Pemetexed Maintenance

Pemtrexed: median = 13.9 mos (12.8 to 16.0 mos)
Placebo: median = 11.0 mos (10.0 to 12.5 mos)
Log-rank P = .0195
Unadjusted HR: 0.78 (0.64 to 0.96)

## Current Standards and Studies for Metastatic NSCLC; Maintenance

### “Switch Maintenance”

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Agent</th>
<th>Median Survival “Control”</th>
<th>Median Survival “Agent Added”</th>
<th>Survival Benefit With “Agent Added”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciuleanu - All</td>
<td>633</td>
<td>pemetrexed</td>
<td>10.6 mo</td>
<td>13.4 mo</td>
<td>+2.8 mo</td>
</tr>
<tr>
<td>Ciuleanu - AdenoCa</td>
<td>328</td>
<td>pemetrexed</td>
<td>11.5 mo</td>
<td>16.8 mo</td>
<td>+5.3 mo</td>
</tr>
<tr>
<td>Fidias</td>
<td>566</td>
<td>docetaxel</td>
<td>9.7 mo</td>
<td>12.3 mo</td>
<td>+2.6 mo</td>
</tr>
<tr>
<td>Cappuzzo</td>
<td>889</td>
<td>erlotinib*</td>
<td>11 mo</td>
<td>12 mo</td>
<td>+1 mo</td>
</tr>
<tr>
<td>Johnson</td>
<td>768</td>
<td>erlotinib*</td>
<td>13.3</td>
<td>14.4</td>
<td>+1.1 mo</td>
</tr>
</tbody>
</table>
# Current Standards and Studies for Metastatic NSCLC; Maintenance

## “Continuation Maintenance”

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Agent</th>
<th>Median Survival “Control”</th>
<th>Median Survival “Agent Added”</th>
<th>Survival Benefit With “Agent Cont’d”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brodowicz</td>
<td>206</td>
<td>gemcitabine</td>
<td>11 mo</td>
<td>13 mo</td>
<td>+2.0 mo</td>
</tr>
<tr>
<td>Perol</td>
<td>310</td>
<td>gemcitabine</td>
<td>10.8 mo</td>
<td>12.1 mo</td>
<td>+1.3 mo</td>
</tr>
<tr>
<td>Paz-Ares</td>
<td>539</td>
<td>pemetrexed</td>
<td>11.0 mo</td>
<td>13.9 mo</td>
<td>+ 2.9 mo</td>
</tr>
</tbody>
</table>

*On October 18, 2016, the U.S. Food and Drug Administration modified the indication for erlotinib for treatment of NSCLC to limit use to patients whose tumors have specific EGFR mutations

[https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm525739.htm](https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm525739.htm)
Management of Untreated NSCLC

- Patients with non-squamous histology should be treated with pemetrexed cisplatin or paclitaxel carboplatin with bevacizumab (pemetrexed cisplatin if they have any of the exclusion criteria for bev)
- NSCLC Pts with an EGFR mutation and those with an ALK or ROS1 rearrangement should be treated with gefitinib, erlotinib or afatinib (EGFR) or crizotinib
- Patients with >50% PD-L1 staining in their tumor should be treated with pembrolizumab
- Patients with squamous cell histology should be treated with gemcitabine cisplatin or docetaxel cisplatin
- Patients with good performance status should be treated with maintenance therapy using pemetrexed if non-squamous histology and potentially with docetaxel if they have squamous histology
Lung Cancer: Personalized Approaches to Non-Small Cell and Small Cell Lung Cancer

• Screening for Lung Cancer
• Current Standards and Studies for Metastatic NSCLC
• Adjuvant Therapy
• Chemotherapy With Surgery and Radiation in Locally Advanced Disease
• Relapsed Non-Small Cell Lung Cancer
• Small Cell Lung Cancer
## Benefits of Adjuvant Chemotherapy for Surgically Resected NSCLC

<table>
<thead>
<tr>
<th></th>
<th># Pts</th>
<th>↑ 5 yr (%)</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1209</td>
<td>3</td>
<td>0.96</td>
<td>0.81-1.13</td>
<td>.59</td>
</tr>
<tr>
<td>2</td>
<td>1867</td>
<td>4</td>
<td>0.86</td>
<td>0.76-0.98</td>
<td>.03</td>
</tr>
<tr>
<td>3</td>
<td>482</td>
<td>15</td>
<td>0.70</td>
<td>0.52-0.92</td>
<td>.01</td>
</tr>
<tr>
<td>4</td>
<td>344</td>
<td>2</td>
<td>0.80</td>
<td>0.60-1.07</td>
<td>.10</td>
</tr>
<tr>
<td>5</td>
<td>840</td>
<td>8</td>
<td>0.79</td>
<td>0.66-0.95</td>
<td>.01</td>
</tr>
<tr>
<td>Meta06</td>
<td>4584</td>
<td>4</td>
<td>0.89</td>
<td>0.82-0.96</td>
<td>.005</td>
</tr>
</tbody>
</table>

*JNCI 03; NEJM 04; NEJM 05; J Clin Oncol 08; Lancet Oncol 06*
Adjuvant Therapy: CALGB 9633

CALGB 9633: Carboplatin/paclitaxel vs. Obs in Stage IB NSCLC

_A_ Survival Probability vs. Time (Months)

- **All Patients**
  - HR = 0.83
  - 90% CI: 0.64 to 1.08
  - *P* = 0.125

- **Tumors ≥ 4 cm**
  - HR = 0.69
  - 90% CI: 0.48 to 0.99
  - *P* = 0.043

Adjuvant Therapy: JBR.10

JBR.10: Adjuvant Cisplatin/Vinorelbine vs. Placebo in Stages IB-II NSCLC

A

All Patients

Observation
Chemotherapy

Percentage

No. at risk
Observation 240 155 117
Chemotherapy 242 182 135

Stratified log rank: \( P = .04 \)
HR 0.78 (95% CI, 0.61 to 0.99)

B

Stage II Patients

Observation
Chemotherapy

Percentage

No. at risk
Observation 108 83 69 40 5 0
Chemotherapy 111 87 70 36 6 0

C

Stage 1B Patients

Observation
Chemotherapy

Percentage

Log rank: \( P = .37 \)
HR 1.03 (95% CI, 0.70 to 1.52)
Adjuvant Therapy: JBR.10

JBR.10: Impact of Adjuvant Chemotherapy in Tumors ≥ 4 cm

Adjuvant Therapy

Adjuvant Chemotherapy for Surgically Resected NSCLC

- Four cycles adjuvant cisplatin based therapy is standard of care for resected stage II and III NSCLC (ASCO guidelines)
  - Cisplatin/vinorelbine
  - Cisplatin/docetaxel
  - Cisplatin/gemcitabine
  - Cisplatin/pemetrexed

- Areas of controversy (not routine clinical use)
  - Stage IB—(maybe for larger tumors)
  - Role of carboplatin-based regimens—(OK if not cisplatin candidate)
**ECOG 1505**

*Specified regimens*
- Cisplatin and docetaxel
- Cisplatin and vinorelbine
- Cisplatin and gemcitabine
- Cisplatin and pemetrexed

**Eligibility**
- Resected IB (> 4 cm) - IIIA
- ≥ Lobectomy
- No previous chemotherapy
- No planned XRT
- No CVA/TIA
- No ATE in 12 months

**N = 1500**

**Primary end point:** overall survival

**Secondary end points:** disease-free survival, safety [bleeding and arterial thromboembolic events (ATEs)]

No difference in outcome Wakelee et al. WCLC 2015
Adjuvant Therapy: EGFR or ALK Inhibitors in NSCLC

- **RADIANT**
  - Adjuvant EGFR TKI or placebo in EGFR IHC/FISH patients
  - Improved DFS but not OS in EGFR mutant patients

- **ALCHEMIST**
  - National screening trial in surgically resected NSCLC
  - Screen 8000 patients for EGFR mutations or ALK rearrangements
  - Enroll patients into adjuvant clinical trials of erlotinib (EGFR) or crizotinib (ALK) for 2 years. Primary endpoint OS.
  - Added a Nivolumab Arm

---

1Kelly et al. *J Clin Oncol* 2015; 33:4007
Lung Cancer: Personalized Approaches to Non-Small Cell and Small Cell Lung Cancer

- Screening for Lung Cancer
- Current Standards and Studies for Metastatic NSCLC
- Adjuvant Therapy
- Chemotherapy With Surgery and Radiation in Locally Advanced Disease
- Relapsed Non-Small Cell Lung Cancer
- Small Cell Lung Cancer
- Mesothelioma
Management of Stage III NSCLC: Etoposide Cisplatin vs. Pemetrexed Cisplatin

Eligibility
- Nonsquamous NSCLC
- Stage IIIA/IIIB
- PS 0,1
- Radiation plan <20 Gy to <35% Lung Vol

2 Gy/Fx daily/5 Days per Week to a Target Dose of 60 to 66 Gy in 30 to 33 Fx Started on Day 1 of Chemotherapy.

Pemetrexed 500 mg/m2
Cisplatin 75 mg/m2
Q 3 Weeks

Etoposide 50 mg/m2 D 1-5
Cisplatin 50 mg/2 D1, 8
Q 4 Weeks

Management of Stage III NSCLC: Etoposide Cisplatin vs. Pemetrexed Cisplatin

Median overall survival, mo (95% CI)
- Pem-Cis: 26.8 (20.4 to 30.9)
- Eto-Cis: 25.0 (22.2 to 29.8)
HR (95% CI), 0.98 (0.79 to 1.20)
Log-rank $P = .831$

No. at risk
- Pem-Cis: 301 282 268 239 221 194 178 157 145 126 98 75 67 56 46 42 33 25 19 14 10 3 1 0 0
- Eto-Cis: 297 278 262 232 216 201 179 164 140 113 97 82 69 56 49 46 31 26 22 16 10 6 3 1 0

Senen et al. *J Clin Oncol.* 2016 34:953
Management of Stage III NSCLC

RTOG 0617

- **RT: 60 Gy**
  - Paclitaxel
  - Carboplatin +/- Cetuximab

- **RT: 74 Gy**
  - Paclitaxel
  - Carboplatin +/- Cetuximab

- Paclitaxel Carboplatin X 2 +/- Cetuximab

Bradley JD *Lancet Oncology* 2015; 6: 87
Management of Stage III NSC: 60 vs. 74 Gy in RTOG 0617

Bradley JD *Lancet Oncology* 2015; 6: 87
Management of Stage III NSCLC

Post-operative Radiation Therapy in Resected NSCLC

• N2 involvement documented at surgery
• Incompletely resected Stage II and Stage III NSCLC
  – Gross primary/nodal residual disease
  – Positive margins

Lung Cancer: Personalized Approaches to Non-Small Cell and Small Cell Lung Cancer

- Screening for Lung Cancer
- Current Standards and Studies for Metastatic NSCLC
- Adjuvant Therapy
- Chemotherapy With Surgery and Radiation in Locally Advanced Disease
- **Relapsed Non-Small Cell Lung Cancer**
- Small Cell Lung Cancer

Docetaxel vs. Supportive Care

Patient characteristics

- Relapsed IIIB/IV NSCLC
- PS 0-2
- No prior paclitaxel therapy

BSC 100 pts vs. docetaxel (two doses) 104 pts.

Outcome measures

<table>
<thead>
<tr>
<th></th>
<th>Docetaxel</th>
<th>BSC</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR</td>
<td>5.8%</td>
<td>0%</td>
</tr>
<tr>
<td>TTP (weeks)</td>
<td>10.6*</td>
<td>6.7</td>
</tr>
<tr>
<td>OS (months)</td>
<td>7.0</td>
<td>4.6</td>
</tr>
<tr>
<td>1-year survival</td>
<td>29%</td>
<td>19%</td>
</tr>
</tbody>
</table>

*P = .001

Retrospective analysis of impact of histology in second-line treatment: pemetrexed vs. docetaxel

Retained analysis of impact of histology in second-line treatment: pemetrexed vs. docetaxel

- All patients: 8.3 vs. 7.9, HR = 0.99
- "Non-Squamous": 9.3 vs. 8.0, HR = 0.778
- Squamous: 6.2 vs. 7.4, HR = 1.563


FDA label change for “nonsquamous” histology

“Non-Squamous” includes large cell carcinoma

FDA label change for “nonsquamous” histology

“Non-Squamous” includes large cell carcinoma
Relapsed Non-Small Cell Lung Cancer; Ramucirumab plus Docetaxel

- NSCLC
- Metastatic
- Progressed after 1st line Platinum-Based Chemo.
- PS 0-1

Random 1 to 1 Balanced: Gender Region PS Maintenance

Docetaxel 75 mg/m²
n = 625

Docetaxel 75 mg/m² Ramucirumab 10 mg/kg q 3 weeks = 628

Primary endpoint
- OS
2ndary endpoints
- PFS
- Response
- Side-effects
- QOL

Garon et al. Lancet. 2014; 384:665
Dec 12, 2014—Today, the US FDA expanded the indication of Ramucirumab to include the Rx of Metastatic NSCLC.
Management of Relapsed NSCLC

- No survival benefit demonstrated for any novel agent compared to docetaxel or pemetrexed

- No survival benefit demonstrated for any combination agent compared to docetaxel or pemetrexed (See below)

- Docetaxel and pemetrexed remain the standard chemotherapy for patients with relapsed NSCLC

- Adding Ramucirumab to docetaxel increases median survival by 1.4 months with HR of 0.86
EGFR+ Relapsed Non-Small Cell Lung Cancer; Osimertinib

October 2013

February 2015
Confirmed ORR in patients with centrally tested T790M+ was 61% (78/127; 95% CI 52, 70)

DCR (CR+PR+SD) was 95% (121/127; 95% CI 90, 98)
EGFR+ Relapsed NSCLC; Osimertinib-PFS in T790M+ and T790- patients

December 2015-FDA Approved Osimertinib T790M EGFR Mutant NSCLC

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>T790M-positive</th>
<th>T790M-negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>December</td>
<td>138</td>
<td>62</td>
</tr>
<tr>
<td>November</td>
<td>100</td>
<td>27</td>
</tr>
<tr>
<td>October</td>
<td>70</td>
<td>13</td>
</tr>
<tr>
<td>September</td>
<td>14</td>
<td>3</td>
</tr>
<tr>
<td>August</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Janne et al. NEJM 2015 372:1689
Osimertinib vs. Pemetrexed Platinum in T790M Positive EGFR mutant NSCLC

RANDOMIZE

1. Pemetrexed 500 mg/m2 Cis/Carbo q 3 Wks
2. Osimertinib 80 mg Day

- Non-Squamous NSCLC
- EGFR+ NSCLC with Progression on EGFR-TKI
- Central confirmation of T790M variant
- ECOG 0 or 1

Mok et al. NEJM 2017; 376:629
Osimertinib vs. Pemetrexed Platinum in T790M Positive EGFR mutant NSCLC

A Patients in Intention-to-Treat Population

<table>
<thead>
<tr>
<th>Month</th>
<th>No. at Risk</th>
<th>Osimertinib</th>
<th>Platinum–pemetrexed</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>279</td>
<td>240</td>
<td>162</td>
</tr>
<tr>
<td>3</td>
<td>279</td>
<td>240</td>
<td>162</td>
</tr>
<tr>
<td>6</td>
<td>279</td>
<td>240</td>
<td>162</td>
</tr>
<tr>
<td>9</td>
<td>279</td>
<td>240</td>
<td>162</td>
</tr>
<tr>
<td>12</td>
<td>279</td>
<td>240</td>
<td>162</td>
</tr>
<tr>
<td>15</td>
<td>279</td>
<td>240</td>
<td>162</td>
</tr>
<tr>
<td>18</td>
<td>279</td>
<td>240</td>
<td>162</td>
</tr>
<tr>
<td>279</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>140</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Median Progression-free Survival

- Osimertinib: 279 patients, 10.1 mo (95% CI, 8.3–12.3)
- Platinum–pemetrexed: 140 patients, 4.4 mo (95% CI, 4.2–5.6)

Hazard ratio for disease progression or death: 0.30 (95% CI, 0.23–0.41) P<0.001

Mok et al. NEJM 2017; 376:629
Nivolumab vs. Docetaxel in Advanced Squamous-Cell NSCLC

- Squamous Cell Lung Cancer
- Prior Therapy with Platin-based regimen
- ECOG 0 or 1
- No Immune Disorders

Nivolumab
3 mg/kg q 2 weeks

Docetaxel 75 mg/m2
q 3 weeks

Brahmer et al. *NEJM* 2015; 373:123
Nivolumab vs. Docetaxel in Advanced Squamous-Cell NSCLC

Median Overall Survival

Nivolumab (N=135) 9.2 (7.3–13.3)
Docetaxel (N=137) 6.0 (5.1–7.3)

1-Yr Overall Survival

% of patients (95% CI)

Nivolumab 42 (34–50)
Docetaxel 24 (17–31)

No. of Deaths

86
113

Hazard ratio for death, 0.59 (0.44–0.79)
P<0.001

No. at Risk

Nivolumab 135 113 86 69 52 31 15 7 0
Docetaxel 137 103 68 45 30 14 7 2 0

Brahmer et al. NEJM 2015; 373:123
Nivolumab vs. Docetaxel in Advanced Squamous-Cell NSCLC

- NonSquamous NSCLC
- Prior Therapy with Platin-based regimen
- ECOG 0 or 1
- No Immune Disorders

Nivolumab
3 mg/kg q 2 weeks

Docetaxel 75 mg/m2 q 3 weeks

Borghaei H et al. NEJM 2015;373:1627
Nivolumab vs. Docetaxel in Advanced NonSquamous-Cell NSCLC

Borghaei H et al. *NEJM* 2015;373:1627
Pembrolizumab vs. Docetaxel in Advanced NSCLC

- NSCLC
- <1% PDL Positive
- Prior Therapy with Platin-based regimen
- ECOG 0 or 1
- No Immune Disorders

Pembrolizumab
2 mg/kg or 10 mg/kg
q 3 weeks

Docetaxel 75 mg/m²
q 3 weeks

Herbst et al. Lancet 2016; 387:1540
Pembrolizumab vs. Docetaxel in Advanced NSCLC

PDL-1-50% or Greater

PDL-1-1% or Greater

Nivolumab and Pembrolizumab for Advanced NSCLC

• October 9th, 2015-The FDA expanded the approved use of nivolumab for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy.

• October 2nd, 2015-The FDA granted accelerated approval to pembrolizumab for the treatment of patients with metastatic NSCLC whose tumors express programmed death ligand 1 (PD-L1) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy.

• On October 18, 2016, FDA approved atezolizumab (TECENTRIQ, Genentech Oncology) for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose disease progressed during or following platinum-containing chemotherapy.

• [http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs](http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs)
Lung Cancer: Personalized Approaches to Non-Small Cell and Small Cell Lung Cancer

- Screening for Lung Cancer
- Current Standards and Studies for Metastatic NSCLC
- Adjuvant Therapy
- Chemotherapy With Surgery and Radiation in Locally Advanced Disease
- Relapsed Non-Small Cell Lung Cancer
- Small Cell Lung Cancer
Small Cell Lung Cancer; Genomic Characterization

Small Cell Lung Cancer; Staging

- The staging classification for these patients is a simple two-stage Veterans Administration Lung Study Group System, updated in 1989 by International Association for the Study of Lung Cancer.
  - Limited stage: Disease confined to 1 hemithorax with regional lymph nodes including either ipsilateral or bilateral hilar, mediastinal, and supraclavicular lymph node metastases and without ipsilateral pleural effusion that fit within a tolerable chest radiation field
  - IASLC now recommends staging them using TNM; stage I-III and IV is roughly equivalent to limited or extensive stage disease.¹
  - Extensive stage: Disease beyond these boundaries

1,574 patients had pT1-2N0M0 SCLC from 2003-2011

954 patients (61%) underwent complete R0 resection

566 (59%) were treated with adjuvant therapy

354 were treated with chemotherapy alone

190 were treated with chemotherapy plus irradiation

99 patients who underwent cranial irradiation) and 22 radiation alone.

Small Cell Lung Cancer; Resectable Disease

![Graph showing overall survival comparison between no adjuvant therapy and adjuvant chemotherapy ± radiation therapy. The graph includes the following data:

- **No adjuvant therapy**
  - Median survival: 42.1 (34.0 to 51.8) months
  - 5-year survival: 40.4% (35.2% to 45.5%)
  - No. at risk:
    - 388 at 0 months
    - 320 at 12 months
    - 247 at 24 months
    - 192 at 36 months
    - 151 at 48 months
    - 105 at 60 months

- **Adjuvant chemotherapy ± RT**
  - Median survival: 66.0 (56.8 to 79.3) months
  - 5-year survival: 52.7% (48.2% to 57.0%)
  - No. at risk:
    - 544 at 0 months
    - 489 at 12 months
    - 402 at 24 months
    - 333 at 36 months
    - 272 at 48 months
    - 194 at 60 months

Log-rank $P < .01$}
Small Cell Lung Cancer:
Limited Stage Small Cell Lung Cancer

Platinum - 60; Etoposide - 120 / Cycle Q 21 days PCI: 25 Gy

Small Cell Lung Cancer: Limited Stage Small Cell Lung Cancer


![Graph showing survival probability with twice-daily and once-daily radiotherapy](image)

- **P = 0.04 by log-rank test**

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>0–20 Mo</th>
<th>20–40 Mo</th>
<th>40–60 Mo</th>
<th>60–80 Mo</th>
<th>80–100 Mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Once daily</td>
<td>108/206</td>
<td>48/96</td>
<td>15/47</td>
<td>4/21</td>
<td>0/5</td>
</tr>
<tr>
<td>Twice daily</td>
<td>100/211</td>
<td>47/109</td>
<td>7/62</td>
<td>5/42</td>
<td>1/14</td>
</tr>
</tbody>
</table>

Small Cell Lung Cancer; Extensive Stage

- 140 limited and extensive stage patients treated with transplant doses of ifosfamide, carboplatin and etoposide (Tx) versus standard doses of the same drugs¹
- 651 patients given irinotecan irinotecan 60 mg/m² IV on days 1, 8, and 15 plus cisplatin 60 mg/m² on day 1 on 28 day cycle versus etoposide 100 mg/m² on days 1, 2, and 3 plus cisplatin 80 mg/m² on day 1 every 3 weeks²
- 795 patients given topotecan 1.0 mg/m² IV days 1-5 plus cisplatin 75 mg/m² IV day 1 versus etoposide 100 mg/m² IV days 1-3 plus cisplatin³
- 954 patients given etoposide 100 mg/m² IV days 1-3 plus cisplatin 75 mg/m² or carboplatin AUC 5 plus ipilimumab 10 mg/kg or placebo every 3 weeks⁴

Patients with extensive stage SCLC should be treated with 2 drugs which produce moderate myelosuppression. Etoposide/cisplatin remains the standard treatment.

Maintenance therapy after induction chemotherapy does not prolong survival.

Patients with SCLC treated with intensive chemotherapy (adding paclitaxel or autologous transplant doses) do not live longer than patients treated with standard doses.
• 498 patients with extensive stage SCLC with response to 4 to 6 cycles of chemotherapy

• Thoracic treatment volume considered treatable using acceptable radiation fields; prophylactic cranial RT was used as well

• Patients were followed for time to progression and survival

Thoracic Radiation for Extensive Stage SCLC

Small Cell Lung Cancer; PCI

Survival for Limited and Extensive Stage
N=987

Survival for Extensive Stage
N=286

Auperin et al. NEJM. 1999;341

Slotman B, et al. NEJM. 2007;357:664
• Patients with SCLC have a 60-80% actuarial risk of developing brain metastases within 2 years after the start of treatment

• PCI has been shown to prolong survival for patients with both limited and extensive SCLC with a response to chemotherapy. Further information awaits publication of the Study in Japan

• PCI (2500 cGy) administered at the time of complete remission can reduce the chance of developing brain metastases by 50-67%

Seto et al ASCO 2014
Previously treated patients with sensitive relapse SCLC (48) or refractory SCLC (16)

24 had brain metastases including 13 with target lesions assessable by RECIST

Treated with 21/28 days of 75 mg/m2 of temozolomide

Followed for toxicity, response, time to progression, and survival
4 of 13 Brain Mets had CR and 1 had a PR (38%RR)
Rovalpituzumab Tesirine (Rova-T™, SC16LD6.5)

A delta-like protein 3 (DLL3)-targeted antibody-drug conjugate (ADC)

- Drug-to-antibody ratio = 2

Rudin et al. *Lancet Oncol* 2017; 18:42
Small Cell Lung Cancer: (Rova-T™, SC16LD6.5)

Rudin et al. Lancet Oncol 2017; 18:42
'Lung Cancer: Personalized Approaches to Non-Small Cell and Small Cell Lung Cancer

- Screening for Lung Cancer
- Current Standards and Studies for Metastatic NSCLC
- Adjuvant Therapy
- Chemotherapy With Surgery and Radiation in Locally Advanced Disease
- Relapsed Non-Small Cell Lung Cancer
- Small Cell Lung Cancer
A 59-yo current male smoker presented with a cough. Chest CT scan and PET show FDG avid 3 cm right upper lobe mass and enlarged right sided adenopathy but no distant mets. Endobronchial ultrasound identified enlarged lymph nodes and biopsy of the nodes showed an adenocarcinoma (Stage III). Randomized studies show the patient should be treated with:

1. Paclitaxel/carbo plus 74 Gy chest
2. Paclitaxel/carbo/cetuximab plus 74 Gy chest
3. **Paclitaxel/carbo plus 60 Gy chest**
4. Paclitaxel/carbo/cetuximab plus 60 Gy chest
5. 74 Gy chest alone
A 53 year old smoker presented with adenocarcinoma of the lung with mets to the liver. The characterization of his tumor showed it did not have mutations of EGFR or rearrangements of ALK or ROS1. PD-L1 staining showed more than 50% of his tumor cells stained positive. The patient should be treated with:

1. Pemetrexed cisplatin
2. Pemetrexed carboplatin bevacizumab.
3. Nivolumab
4. Pembrolizumab
5. Atezolizumab