Early Stage Lung Cancer, Targeted Therapies, and Small Cell Lung Cancer

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Disclosures

Financial Relationships with Relevant Commercial Interests

- Post Marketing Royalties for *EGFR* mutation testing from DFCI
- Paid Consultant to Novartis
- Unpaid Consultant to Array BioPharma
- Research Support from Novartis
- Research Support from Cannon Medical Imaging

Resolution
- Reviewed and found to be unbiased.
Early Stage Lung Cancer, Targeted Therapies, and Small Cell Lung Cancer

- **Early Stage Lung Cancer: Surgery, Radiation, Chemotherapy**

- Targeted Therapies: *EGFR, ALK, ROS1, BRAF, and NTRK*

- Small Cell Lung Cancer
Lung Cancer Epidemiology

• Incidence in United States
  – 228,000 new cases/143,000 deaths
  – 13% of all cancers, 24% of all cancer deaths
  – 3.5% decrease/year last 10 years

• Most common cause of cancer death in both men and women
  – 1:1 Male/Female Ratio
  – Smoking, second hand smoking, and industrial exposures are risk factors
  – Smoking contributes to 80 percent and 90 percent of lung cancer deaths in women and men respectively

• Median age at diagnosis: 70 years

Stage I and II NSCLC

Percent of Cases & 5-Year Relative Survival by Stage at Diagnosis: Lung and Bronchus Cancer

- Localized: 55.6%
- Regional: 28.9%
- Distant: 4.5%
- Unknown: 7.5%
Management of Untreated Stage I & II NSCLC

October 2014
Management of Untreated Stage I & II NSCLC

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

All Patients

Stratified log rank: $P = 0.04$
HR 0.78 (95% CI, 0.61 to 0.99)

Stage II Patients

Log rank: $P = 0.01$
HR 0.68 (95% CI, 0.50 to 0.92)

Management of Untreated Stage I & II NCSLC

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

Stage 1B and Tumor Diameter < 4 cm

- Observation
- Chemotherapy

Log rank: $P = 0.056$
HR 1.73 (95% CI, 0.98 to 3.04)

Stage 1B and Tumor Diameter ≥ 4 cm

- Observation
- Chemotherapy

Log rank: $P = 0.133$
HR 0.66 (95% CI, 0.39 to 1.14)

### Benefits of Adjuvant Chemotherapy for Surgically Resected NSCLC

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

References:
- JNCI 03; NEJM 04; NEJM 05; J Clin Oncol 08; Lancet Oncol 06
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 greater than 4 centimeters)
  – Role of carboplatin-based regimens—(OK if not cisplatin candidate)
American Joint Committee on Cancer Stage II or III NSCLC within the National Cancer Data Base

Stage II or III N0-2 NSCLC

Stage III N2 NSCLC Patient

Management of Stage III NSCLC: 60 Versus 74 Gy in RTOG 0617

Bradley, JD. *Lancet Oncology.* 2015; 6: 87
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

R A N D O M I Z E *

Pemetrexed 500 mg/m\textsuperscript{2}
Cisplatin 75 mg/m\textsuperscript{2}
Q 3 Weeks

Etoposide 50 mg/m\textsuperscript{2} 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
Management of Stage III NSCLC

RTOG 0617

Randomeize

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 NSCLC

Post-operative Radiation Therapy in Resected NSCLC

- N2 involvement at surgery
- Incompletely resected Stage II and Stage III NSCLC
- Recommended for:
  - N2 involvement documented at surgery
  - Gross primary/nodal residual disease
  - Positive margins

Rodrigues G et al. Pract Radiat Oncol. 2015;14 June 22, epub
Management of Stage III NSCLC: 60 Versus 74 Gy in RTOG 0617
Management of Stage III NSCLC: Durvalumab vs. Observation in Maintenance

Two Cycles of Platinum-Based Chemotherapy (Etoposide, Vinblastine, Vinorelbine, a Taxane, or Pemetrexed) Plus 5400-6600 Gy Chest RT Concurrently

**Eligibility**
- Nonsquamous NSCLC
- Stage IIIA/IIIB
- PS 0,1
- Radiation plan ≤20 Gy to <35% Lung Vol
- Randomized up to 6 Weeks after Chest RT

**Randomize**
1. Observation
2. Durvalumab 10 mg/kg IV every 2 weeks for 1 Yr

Management of Stage III NSCLC: Durvalumab vs. Observation in Maintenance

Management of Stage III NSCLC: Durvalumab vs. Observation in Maintenance - Survival

**Probability of Overall Survival**

- **No. of events/No. of patients (%)**
  - Durvalumab: 183/476 (38.4)
  - Placebo: 116/237 (48.9)

- **Median OS (95% CI) months**
  - Durvalumab: NR (34.7–NR)
  - Placebo: 28.7 (22.9–NR)

**OS HR = 0.68**
- 99.73% CI, 0.469–0.997†
- P=0.00251

**Graph Details**
- **Time from Randomization (months)**: 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 45
- **No. at Risk**
  - Durvalumab: 476, 464, 431, 415, 385, 364, 343, 319, 274, 210, 115, 57, 23, 2, 0, 0
  - Placebo: 237, 220, 198, 170, 155, 141, 130, 117, 78, 42, 21, 9, 3, 1, 0

Management of Stage III NSCLC

Management of Patients With N2 Disease

• Patients should be treated with concurrent chest irradiation and platin-based chemotherapy (etoposide or pemetrexed are appropriate). Chest radiotherapy given to 60 Gy is an appropriate dose.

• Durvalumab should be administered to fit patients within two months of when the combined modality is completed

• Pemetrexed cisplatin may be considered in addition to etoposide cisplatin for non-squamous NSCLC

• Paclitaxel/carboplatin is also a reasonable combination
Early Stage Lung Cancer, Targeted Therapies, and Small Cell Lung Cancer

• Early Stage Lung Cancer: Surgery, Radiation, Chemotherapy

• **Targeted Therapies:** *EGFR, ALK, ROS1, BRAF, and NTRK*

• Small Cell Lung Cancer
EGFR Mutant NSCLC

EGFR Exon Deletion Mutation

January 2002

October 2004
13 of 14 Patients with Response to Gefitinib Had EGFR Mutation
Management of EGFR Mutant NSCLC

- NSCLC with sensitive EGFR mutations
- Stage IIIb/IV
- No prior chemo.
- PS 0-1
- Age 20-75 y.o

Gefitinib
\( n = 160 \)

CBDCA + TXL
\( n = 160 \)

Primary endpoint
- PFS

Secondary endpoints
- OS
- Response
- Side-effects
- QOL

- The sample size was calculated to be 320 in total (alpha = 5%, power = 80%) to confirm the superiority of Arm A (hazard ratio = 0.69).
- An interim analysis to investigate PFS was planned 4 months after 200 pts were entered.
Hazard Ratio 0.30; P<0.001
Median 10.8 months for gefitinib
Median 5.4 months for chemo

Maemondo M. *NEJM*. 362:2380, 2010
<table>
<thead>
<tr>
<th>Study</th>
<th>Drugs</th>
<th>N</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></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></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></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></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></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></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></td>
<td>66.9% vs 23.0%</td>
<td>11.0 vs 5.6</td>
</tr>
</tbody>
</table>

Third Generation EGFR-TKI
Osimertinib vs. Gefitinib or Erlotinib

Patients with locally advanced or metastatic NSCLC

Key inclusion criteria
• ≥18 years*
• WHO performance status 0 / 1
• Exon 19 deletion / L858R (enrolment by local# or central‡ EGFR testing)
• No prior systemic therapy

Endpoints
• **Primary endpoint:** PFS based on investigator assessment
• **Secondary endpoints:** objective response rate and survival, patient reported outcomes, safety

April 2018: FDA grants approval for use of osimertinib as a first-line treatment for patients with EGFR+ NSCLC

A Progression-free Survival in Full Analysis Set

<table>
<thead>
<tr>
<th></th>
<th>No. of Patients</th>
<th>Median Progression-free Survival (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Osimertinib</td>
<td>279</td>
<td>18.9 (15.2–21.4) mo</td>
</tr>
<tr>
<td>Standard EGFR-TKI</td>
<td>277</td>
<td>10.2 (9.6–11.1) mo</td>
</tr>
</tbody>
</table>

Hazard ratio for disease progression or death, 0.46 (95% CI, 0.37–0.57)

P<0.001

D Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>No. of Patients</th>
<th>Median Overall Survival (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osimertinib</td>
<td>279</td>
<td>NC (NC–NC) mo</td>
</tr>
<tr>
<td>Standard EGFR-TKI</td>
<td>277</td>
<td>NC (NC–NC)</td>
</tr>
</tbody>
</table>

Hazard ratio for death, 0.63 (95% CI, 0.45–0.88)
P=0.007

Ramalingham et al. NEJM. 2018; 378:113
52 Year Old Woman with ALK+ NSCLC Treated with Crizotinib

September 2011

December 2017

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

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 (NCT01154140)
Management of ALK Rearranged NSCLC

2011: Crizotinib Receives Accelerated Approval for ALK+ NSCLC
2013: Crizotinib Receives Full Approval

**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)

**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)

**No. at Risk**

<table>
<thead>
<tr>
<th></th>
<th>Crizotinib</th>
<th>Chemotherapy</th>
</tr>
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<tbody>
<tr>
<td>Months</td>
<td></td>
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</tr>
<tr>
<td>0</td>
<td>172</td>
<td>171</td>
</tr>
<tr>
<td>5</td>
<td>120</td>
<td>105</td>
</tr>
<tr>
<td>10</td>
<td>65</td>
<td>36</td>
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<td>15</td>
<td>38</td>
<td>12</td>
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<tr>
<td>20</td>
<td>19</td>
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<td>25</td>
<td>7</td>
<td>1</td>
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<tr>
<td>30</td>
<td>1</td>
<td>0</td>
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<tr>
<td>35</td>
<td>0</td>
<td>0</td>
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</tbody>
</table>

Management of ALK Rearranged NSCLC

No. at risk:

<table>
<thead>
<tr>
<th></th>
<th>Crizotinib (n = 172)</th>
<th>Chemotherapy (n = 171)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths, No. (%)</td>
<td>71 (41.3)</td>
<td>81 (47.4)</td>
</tr>
<tr>
<td>Median OS (95% CI), months</td>
<td>NR (45.8 to NR)</td>
<td>47.5 (32.2 to NR)</td>
</tr>
</tbody>
</table>

No. at risk:

- Crizotinib: 172 157 144 128 111 98 89 79 65 51 36 20 8 1 0
- Chemotherapy: 171 150 131 118 100 89 82 73 63 46 31 21 11 1 0

(HR, 0.760; 95% CI, 0.548 to 1.053; P = .0978)
KEY ELIGIBILITY
- Advanced or metastatic ALK+ NSCLC
- ALK+ by central IHC testing
- Treatment-naïve
- ECOG PS 0–2
- Measurable disease
- Asymptomatic brain metastases allowed

ENDPOINTS
- Primary
  - PFS (RECIST 1.1), by investigator review
- Secondary
  - PFS by IRC
  - Time to CNS progression
  - ORR, DOR
  - OS
  - Safety and tolerability
  - Patient-reported outcomes

Stratification factors:
- ECOG PS (0/1 vs 2)
- Race (Asian vs non-Asian)
- Brain metastases (present vs absent)

ALK, anaplastic lymphoma kinase; IHC, immunohistochemistry; NSCLC, non-small-cell lung cancer; ECOG PS, Eastern Cooperative Oncology Group Performance Status; PO, by mouth; PFS, progression-free survival; IRC, independent review committee; CNS, central nervous system; ORR, objective response rate; DOR, duration of response; OS, overall survival
Management of ALK Rearranged NSCLC

2015: Accelerated Approval of Alectinib for Previously Rx ALK+ NSCLC
2017: Approval of Alectinib for UnRx ALK+ NSCLC

### Progression-free Survival

- **Hazard ratio for disease progression or death,**
  - 0.47 (95% CI, 0.34–0.65)
  - *P* < 0.001 by log-rank test

### Overall Survival

- **Hazard ratio for death,**
  - 0.76 (95% CI, 0.48–1.20)
  - *P* = 0.24 by log-rank test

---

**No. at Risk**

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Day 1</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
<th>15</th>
<th>18</th>
<th>21</th>
<th>24</th>
<th>27</th>
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<tr>
<td>Alectinib</td>
<td>152</td>
<td>135</td>
<td>113</td>
<td>109</td>
<td>97</td>
<td>81</td>
<td>67</td>
<td>35</td>
<td>15</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Crizotinib</td>
<td>151</td>
<td>132</td>
<td>104</td>
<td>84</td>
<td>65</td>
<td>46</td>
<td>35</td>
<td>16</td>
<td>5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Peters et al. *NEJM*. 2017; epub June 6
Management of ALK Rearranged NSCLC

No. of patients at risk

Alectinib 152
Crizotinib 151

PFS estimate (%)

Time (months)

Day 1 6 12 18 24 30 36

Alectinib (N=152)
Crizotinib (N=151)
Censored

10.9 months
(9.1–12.9)

34.8 months
(17.7–NE)
Management of ROS1 Rearranged NSCLC with Crizotinib

Best Response


Management of ROS1 Rearranged NSCLC with Crizotinib

2016: Crizotinib approved for ROS1 Positive NSCLC in US


Wu et al. *J Clin Oncol*. 2018; 36:1405
Management of BRAF Mutant NSCLC with Dabrabenib plus Trametinib

67 Year Old Man with V600E BRAF Mutation

October 2014

June 2019
**Cohort A (monotherapy) n = 60**

- Stage IV NSCLC
- BRAF V600E
- ECOG 0-2
- At least 1 platinum-based chemotherapy

Dabrafenib 150mg BID → Stage 1 N = 20 → Stage 2 N = 20 → Expansion N = 20

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**Cohort B (combination D+T) n = 40**

- Stage IV NSCLC
- BRAF V600E
- ECOG 0-2
- 1-3 tx lines only (at least 1 platinum-based chemotherapy)

Dabrafenib 150mg BID → Trametinib 2mg once daily → Stage 1 N = 20 → Stage 2 N = 20

Interim futility analyses

Recruitment stopped if fewer than 6 out of the first 20 subjects responded

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Planchard et al. *Lancet Oncol.* 2016 Jul; 17(7):984-93

Management of *BRAF* Mutant NSCLC with Dabrabenib plus Trametinib

**Second Line**
36/57 (64%) Patients had a CR (2) or PR (34)

**First Line**
23/36 (64%) Patients had a CR (2) or PR (21)

Progression-Free Survival of Approximately 10 months; FDA Approval in 2017

Planchard et al. *Lancet Oncol.* 2016 Jul; 17(7):984-93

Management of BRAF Mutant NSCLC with Dabrafenib plus Trametinib

June 2017: FDA approves dabrafenib and trametinib for Pts with metastatic NSCLC with BRAF V600E mutation

<table>
<thead>
<tr>
<th></th>
<th>Investigator Assessed (n = 36)</th>
<th>IRC Assessed (n = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>24 (67)</td>
<td>22 (61)</td>
</tr>
<tr>
<td><strong>Median (95% CI), mo</strong></td>
<td><strong>10.9 (7.0-16.6)</strong></td>
<td><strong>14.6 (7.0-22.1)</strong></td>
</tr>
<tr>
<td>6-mo rate (95% CI), %</td>
<td>72 (53-84)</td>
<td>69 (51-82)</td>
</tr>
</tbody>
</table>
Management of NTRK Rearranged Cancers including NSCLC

Best Response to Larotrectinib with NTRK Rearrangements
US FDA Approval in 2018

A  Maximum Change in Tumor Size, According to Tumor Type

B  Progression-free Survival among All Patients

Drilon et al. *NEJM.* 2018; 378:731
Early Stage Lung Cancer, Targeted Therapies, and Small Cell Lung Cancer

• Early Stage Lung Cancer: Surgery, Radiation, Chemotherapy

• Targeted Therapies: EGFR, ALK, ROS1, BRAF, and NTRK

• Small Cell Lung Cancer
Small Cell Lung Cancer
Markers of neuroendocrine differentiation

- Chromogranin A
- Synaptophysin
- CD56 or Neural Cell Adhesion Molecule (NCAM)
Small Cell Lung Cancer: Genomic Characterization

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Protein</th>
<th>Pts with SCLC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyponatremia of Malignancy</td>
<td>Arginine Vasopressin and Atrial Natriuretic Peptide</td>
<td>15%</td>
</tr>
<tr>
<td>Hypercalcemia of Malignancy</td>
<td>Parathyroid Hormone Related Peptide</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Ectopic ACTH Syndrome</td>
<td>Adrenocorticotrophic Hormone</td>
<td>3%</td>
</tr>
<tr>
<td>Acromegaly</td>
<td>Growth Hormone Releasing Hormone</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>
Small Cell Lung Cancer: Resectable Disease

- 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 probability over time for two groups: No adjuvant therapy and Adjuvant chemo ± RT.](Image)

No. at risk

<table>
<thead>
<tr>
<th>Group</th>
<th>0</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>No adjuvant therapy</td>
<td>388</td>
<td>320</td>
<td>247</td>
<td>192</td>
<td>151</td>
<td>105</td>
</tr>
<tr>
<td>Adjuvant chemo ± RT</td>
<td>544</td>
<td>489</td>
<td>402</td>
<td>333</td>
<td>272</td>
<td>194</td>
</tr>
</tbody>
</table>

Log-rank $P < .01$

Median survival (95% CI) 5-year survival (95% CI)

- No adjuvant therapy: 42.1 (34.0 to 51.8) months 40.4% (35.2% to 45.5%)
- Adjuvant chemo ± RT: 66.0 (56.8 to 79.3) months 52.7% (48.2% to 57.0%)

Patients with a solitary pulmonary nodule and a diagnosis of SCLC should undergo evaluation for resection (2-3%).

Patients should have mediastinoscopy because 20% will have positive lymph nodes.

Patients should be treated with adjuvant chemotherapy following resection.

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.**

- **Extensive stage**: Disease beyond these boundaries.

Small Cell Lung Cancer: Limited Stage Small Cell Lung Cancer

Pre-treatment

2 Years after Treatment
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

P = 0.04 by log-rank test

TREATMENT GROUP | 0–20 Mo | 20–40 Mo | 40–60 Mo | 60–80 Mo | 80–100 Mo
--- | --- | --- | --- | --- | ---
Once daily | 108/206 | 48/96 | 15/47 | 4/21 | 0/5
Twice daily | 100/211 | 47/109 | 7/62 | 5/42 | 1/14

Small Cell Lung Cancer: Limited Stage Small Cell Lung Cancer

Cisplatin – 75 (or 25X3); Etoposide - 100 / Cycle Q 21 days PCI: 25 Gy

4-6 cycles

Faivre-Finn. Lancet Oncol. 2017; Aug;18(8):1116-1125
Small Cell Lung Cancer: Limited Stage Small Cell Lung Cancer

HR 1.18 (95% CI 0.95–1.45); p=0.14

Faivre-Finn. *Lancet Oncol.* 2017; Aug;18(8):1116-1125
Patients with limited stage SCLC should be treated with concurrent chest radiotherapy with etoposide plus cisplatin. These patients lived longer than patients treated with chemotherapy alone.

The chest radiotherapy should start with cycle 1 or 2.

The chest radiotherapy should be given twice daily over 3 weeks. A higher dose (6600 cGY) given once daily for 33 doses gives similar results.

An ongoing trial in the US comparing etoposide cisplatin plus 45 Gy given twice daily over 3 weeks versus 70 Gy once daily in 2 Gy fractions (NCT00632853-Opened in 2008; Still Recruiting 702 of planned 730).
IMpower133: Global Phase 1/3, double-blind, randomized, placebo-controlled trial evaluated atezolizumab + carboplatin + etoposide in 1L ES-SCLC

Patients with (N = 403):
• Measurable ES-SCLC (RECIST v1.1)
• ECOG PS 0 or 1
• No prior systemic treatment for ES-SCLC
• Patients with treated asymptomatic brain metastases were eligible

Stratification:
• Sex (male vs. female)
• ECOG PS (0 vs. 1)
• Brain metastases (yes vs. no)

Induction (4 x 21-day cycles)
Atezolizumab (1200 mg IV, Day 1)
+ carboplatin + etoposide

Placebo
+ carboplatin + etoposide

Carboplatin: AUC 5 mg/mL/min IV, Day 1
Etoposide: 100 mg/m² IV, Days 1–3

Maintenance
Atezolizumab
Treat until PD or loss of clinical benefit

Placebo
PCI per local standard of care

Co-primary end points:
• Overall survival
• Investigator-assessed PFS

Key secondary end points:
• Objective response rate
• Duration of response
• Safety

PCI per local standard of care
Carboplatin: AUC 5 mg/mL/min IV, Day 1
Etoposide: 100 mg/m² IV, Days 1–3


Extensive Stage SCLC Treated with Etoposide + Carboplatin with or without Atezolizumab
Extensive Stage SCLC Treated with Etoposide + Carboplatin with or without Atezolizumab

Overall Survival

Rate of Overall Survival at 12 Mo

Atezolizumab
51.7% (95% CI, 44.4–59.0)

Placebo
38.2% (95% CI, 31.2–45.3)

Stratified hazard ratio for death, 0.70 (95% CI, 0.54–0.91)
P=0.007

No. at Risk
Atezolizumab
Placebo

Months

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24

201 191 187 182 180 174 159 142 130 121 108 92 74 58 46 33 21 11 5 3 2 1

202 194 189 186 183 171 160 146 131 114 96 81 59 36 27 21 13 8 3 3 2 2

Median in the placebo group, 12.3 mo (95% CI, 10.8–15.9)
Median in the atezolizumab group, 10.3 mo (95% CI, 9.3–11.3)
Thoracic Radiation for Extensive Stage SCLC

• 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

Slotman BJ et al. Lancet. 2015;385:36
Thoracic Radiation for Extensive Stage SCLC

Slotman BJ et al. Lancet. 2015;385:36
Small Cell Lung Cancer: Extensive Stage Small Cell Lung Cancer

- Fit Patients with extensive stage SCLC should be treated with etoposide carboplatin with atezolizumab

- Patients with residual chest masses after chemotherapy should be referred to radiation oncologists for consideration of chest RT

- Patients with SCLC treated with alternative chemotherapy combinations including intensive chemotherapy regimens and other agents (adding paclitaxel, autologous transplant doses of chemotherapy, or bevacizumab) do not live longer than patients treated with standard doses of chemotherapy
Small Cell Lung Cancer

Prophylactic Cranial Irradiation for Limited and Extensive Stage

Survival for Limited and Extensive Stage

\( N = 987 \)

Auperin et al. *NEJM.* 1999;341:476

Survival for Extensive Stage

\( N = 286 \)

Small Cell Lung Cancer: PCI

224 out of planned 330 pts randomized
March 2009 – July 2013

Arm A: PCI 113 pts for Efficacy

111 pts for Safety

7 not received PCI

106 pts for Safety

Arm B: no PCI

111 pts for Safety

Small Cell Lung Cancer: Survival by PCI Arm


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**Overall survival (%)**

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<th>Observation</th>
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**Number at risk (censored)**

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HR 1.27 (95% CI 0.96–1.68); log-rank p=0.094

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Small Cell Lung Cancer: Prophylactic Cranial Irradiation

- 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 stage SCLC with a response to chemotherapy

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

- The data recently published does not support administering PCI to patients with extensive stage disease

Slotman B, et al. NEJM. 2007;357(7):664-672
Takahasi T et al. Lancet Oncol. 2017;18:663
Temozolomide for Relapsed SCLC

• 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)
Rovalpitzumab Tesirine (Rova-T™, SC16LD6.5)

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

Cathepsin B - cleavable linker

Drug-to-antibody ratio = 2

Pyrrolobenzodiazepine (PBD) dimer toxin (D6.5 / SC-DR002)

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

Rudin et al. *Lancet Oncol.* 2017; 18:42
• Patients treated with one cycle of platinum-based chemotherapy SCLC

• Progressive SCLC

• High Staining of DLL3 (at least 75% cells)

• Randomized to either Topotecan or Rova-T

• The phase III has been put on hold in late 2018 based on a recommendation from an Independent Data Monitoring Committee due to a shorter overall survival (OS) reported in the Rova-T arm compared with the control arm of topotecan therapy
Early Stage Lung Cancer, Targeted Therapies, and Small Cell Lung Cancer

• Early Stage Lung Cancer: Surgery, Radiation, Chemotherapy

• Targeted Therapies: \textit{EGFR, ALK, ROS1, BRAF, and NTRK}

• Small Cell Lung Cancer