MANAGEMENT OF SMALL CELL LUNG CANCER

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Primary carcinoma of the lung was an uncommon cancer until the 1930s. At that time a dramatic increase in the incidence of lung cancer began that has not yet abated.

Although the overall incidence of lung cancer has dramatically increased over the past 30 years, the relative incidence of squamous cell carcinoma has decreased, and adenocarcinoma has become the dominant cell type—a phenomenon that has been temporally associated with the changes in tobacco blends and the use of filters in cigarettes.

Lung cancer is now the most common cause of cancer mortality in both males and females.
WHO pathological classification

A. Squamous Cell Ca  30%
B. Small Cell Ca      20%
C. Adenocarcinoma    40%:
    - Acinar
    - Papillary
    - Bronchoalveolar
    - Mucinous
D. Large Cell Ca
E. Mixed
Small cell lung cancer (SCLC)

- It is one of the most aggressive, fast growing tumors
- Without treatment the median survival is 6-9 weeks
Staging

Limited or Extensive stage

1. Limited- tumour confined to ipsilateral thorax and nodes and able to fit in one radiation field.

2. Extensive- disease which can not fit in one radiation field
Staging

Points of uncertainty in current staging
- contralateral supraclavicular lymphnodes
- pleural effusion
- pericardial effusion
- value of TNM
PROGNOSTIC FACTORS

- **Stage**: limited vs extensive
- **Histologic subclassification**: poor if large cells are involved
- **Metastasis**
  - Tumors with c-myc: more aggressive course
  - N-myc: poor response to chemo
  - p-53 Ab: no correlation? survival! (cf NSCLC)
- **Serum NSE**: inversely related to survival algorithm:
  \[ PI = z\text{NSE} + z\text{(stage)} + 2z\text{PS}, \]
  where PI represents the prognostic index, and \( z \) represents the regression coefficient. This algorithm segregated the patients into four groups with clearly different prognoses.
  - **Cyfra 21-1** level over 3.6 ng/mL or a tissue polypeptide-specific antigen level over 140 U/L significantly indicated a poor survival rate.
  - **Serum chromogranin level**: poor prognosis
Principals of Management
Surgery

Surgery in Limited stage SCLC

- Fewer than 3% of patients with small-cell lung cancer (SCLC) present with super-limited, resectable disease
- If possible surgery should be offered.
- Adjuvant chemotherapy still to be administered with PCI in CR on post chemo assessment
- May have possible role in isolated thoracic relapse
Principals of Management
Chemotherapy

- Mainstay of treatment, because of the chemo-responsiveness of the SCLC and frequent dissemination at the time of diagnosis
Principals of Management Chemotherapy

Response rates:
- 75-90% for limited stage
- 75% for extensive stage
- 50% of limited stage have complete response (CR)
- 25% CR for the extensive stage
Cytotoxic agents for SCLC

- Alkylating agents: Cyclophosphamide 1500 mg/m² IV q 3wk
  Ifosfamide 5000 mg/m² IV day 1 q 3wk
  Hexamethylmelamine
  Lomustine
- Vinca alkaloids: Vincristine 2 mg IV q 3 wk
  Vindesine
- Epipodophyllotoxin: Etoposide 80 mg/m² IV d1-3 q 3wk
  Teniposide
- Platinum analogues: Cisplatin 80 mg/m² IV q 3wk, day 1
  Carboplatin 300 mg/m² day 1 q 3 wk
- Miscellaneous: Doxorubicin 40 mg/m² IV q 3 wk
  Methotrexate
- 3rd generation drugs: irinotecan, topotecan, paclitaxel
Platinum-based chemotherapy:

- TTP – 4-6 mths.
- Median Survival – 9-11 mths.
- 2 yr Survival - 5%
Platinum-based chemotherapy:

**Carboplatin can be Substituted for Cisplatin**

- 220 elderly or poor risk patients
- randomized to etoposide with either:
  - Carbo AUC 5 d1
  - Cisplatin 25 mg/m2 iv d1-3

**Results**

- Similar toxicity profiles and efficacy
- (MST ~10 mos; 1 yr 35-40%)

*Okamoto et al, Abstract 7010, ASCO ‘05*
EP BASED CHEMOTHERAPY - STANDARD OF CARE


- CAV x 6 (18 weeks)
- CAV/EP (6) (18 weeks)
- EP (4) (12 weeks)
Better Prognosis
Platinum Regimens

Meta-analysis Cisplatin –
4.4% survival benefit at 1 year

Pujol; et al. Br J Cancer 2000

CbE equivalent to PE

Principals of Management
Chemotherapy

Cisplatin-based:
Cisplatin 80 mg/m day 1 and etoposide 80 mg/m days 1, 2, 3
Cisplatin 25 mg/m days 1, 2, 3 and etoposide 100 mg/m days 1, 2, 3

Doxorubicin-based
Cyclophosphamide 1000 mg/m day 1 and doxorubicin 45 mg/m day 1
and vincristine 1.4 mg/m day 1

Ifosfamide-based
Ifosfamide 1200 mg/m days 1, 2, 3, 4 and etoposide 75 mg/m days 1, 2, 3, 4
and cisplatin 20 mg/m days 1, 2, 3, 4

Mesna given along with ifosfamide.
Strategies to improve survival

- More drug combinations
- Alternate Chemotherapy
- Better drug combinations
- Addition of biologicals
More Drug Combinations

Randomised Phase III Trial
Etoposide and Cisplatin with or without Paclitaxel in ED-SCLC
N = 587, no prior treatment, P.S 0-1

Cisplatin 80mg/m² D1-D3
Etoposide 80 mg/m² D1-D3
6 cycles q3wkly

Cisplatin 80mg/m² D1-D3
Etoposide 80 mg/m² D1-D3
Paclitaxel 175mg/m² D1
G-CSF d4-d18
6 cycles q3wkly

MST 10.6 Vs 9.9 Mths.
More treatment related deaths in Paclitaxel arm

Neill at al. J Clin Oncol 2005
Consolidation with Topotecan after EP in ED SCLC

PE (N=402):
Cisplatin 60 mg/m² (d1)
Etoposide 120 mg/m² (d1-3)
Q 21D x 4 CYCLES

PR/SD

RANDOMISE

Topotecan
N=112

Observation
N=111

PD

Off study

Topotecan after EP

Better Combinations

- Irinotecan plus cisplatin
- Irinotecan plus carboplatin
- Topotecan plus carboplatin
- Pemetrexed plus carboplatin
Cisplatin + Irinotecan Randomized Trials in Patients with ED-SCLC

**JCOG 9511**
Noda et al. NEJM 346:85, 2002

- **P** - 60 mg/m² iv d 1
- L - 60 mg/m² iv d 1, 8, 15 q4 wks X 6

- **N** = 154

**North American /Australian**
Hanna et al. JCO 24:2038 2006,

- **P**: 30 mg/m², d 1 & 8, q3wk +
- L: 65 mg/m², d 1 & 8, q3wk
- Q 4 cycles

- **N** = 331

- **P** - 80 mg/m² iv d 1
- E - 100 mg/m² iv d1,2,3 q3 wks X 6

- **P** - 60 mg/m² iv d 1
- E - 120 mg/m² iv d1,2,3 q3 wks X 4
Cisplatin + Irinotecan Randomized Trials in Patients with ED-SCLC

JCOG 9511

N AMER/AUS

<table>
<thead>
<tr>
<th>Survival</th>
<th>Irino + P</th>
<th>EP</th>
<th>Irino + P</th>
<th>EP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (95% c.i.)</td>
<td>12.8 m</td>
<td>9.4 m</td>
<td>9.3 m</td>
<td>10.2 m</td>
</tr>
<tr>
<td>% 1 yr</td>
<td>58.4%</td>
<td>37.7%</td>
<td>35%</td>
<td>35.2%</td>
</tr>
<tr>
<td>% 2 yr</td>
<td>19.5%</td>
<td>5.2%</td>
<td>8.0%</td>
<td>7.9%</td>
</tr>
</tbody>
</table>
S0124: IP vs EP
Natale et al, ASCO 2008, Abst 7512

671 Patients
ED-SCLC

Randomized

Stratified:
PS 0 vs 1/2, # met sites, LDH, wt loss

N = 336
N = 335

1° endpoint:
MS with IP

Arm 1
Irinotecan 60 mg/m2 d 1,8,15
CDDP 60 mg/m2 d 1
Q 4 weeks x 4 cycles

Arm 2
Etoposide 100 mg/m2 d 1,2,3
CDDP 80 mg/m2 d 1
Q 3 weeks x 4 cycles
S0124: Survival Natale et al, ASCO 2008,
A randomised phase III trial
IV Topotecan/cisplatin versus cisplatin/etoposide
ED-SCLC

- Chemo-naïve with confirmed ED-SCLC
- Male or female
- Age 18-75 yrs
- ECOG PS (0/1 vs 2)
- LDH

Cisplatin/etoposide (n=346)
- Cisplatin: 75 mg/m2 IV d5
- Etoposide: 100 mg/m2/day IV d1-3

Topotecan/cisplatin (n=357)
- Topotecan: 1 mg/m2/day IV d1-5
- Cisplatin: 75 mg/m2 IV d1

Topotecan/etoposide (TE) (n=92)
- Topotecan: 1 mg/m2/day IV d1-5
- Etoposide: 80–100 mg/m2 IV d3-5

Cycles (maximum of 6) repeated q21d

Heigener; ASCO 2008
Survival and Time to Progression (ITT)

<table>
<thead>
<tr>
<th></th>
<th>Cis + Eto (PE) (n=334)</th>
<th>Topo + Cis (TP) (n=346)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of deaths n (%)</td>
<td>282 (84.4%)</td>
<td>283 (81.8%)</td>
<td></td>
</tr>
<tr>
<td>Median survival (months) (95% CI)</td>
<td>9.4 (8.1 – 10.8)</td>
<td>10.3 (9.3 – 11.3)</td>
<td>(unadjusted) 0.30</td>
</tr>
<tr>
<td>1-year survival (95% CI)</td>
<td>36.1% (30.9 – 41.4)</td>
<td>39.7% (34.5 – 44.9)</td>
<td>0.27</td>
</tr>
<tr>
<td>Median TTP (months) (95% CI)</td>
<td>6.0 (5.6 – 6.7)</td>
<td>7.0 (6.5 – 7.5)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Heigener; ASCO 2008
Phase III Study
Pemetrexed/Carboplatin Versus etoposide/ Carboplatin
ED-SCLC

Eligibility
• ES-SCLC
• PS 0-2
• No prior chemo

Randomize

Pem -500 mg/m2, d1
Cb – AUC 5 d1
Q 21 d X 6 cycles
Prophylactic Folic acid, B12, dexamethasone

E 100 mg/m2, d1, 2, 3
Cb – AUC 5 d1
Q 21 d X 6 cycles

Socinski et al., ASCO 2008
Interim results of the Gales/ JMHO TRIAL
GALES / JMHO: Interim PFS Analysis

Socinski et al., ASCO 2008
Interim results of the Gales/JMHO TRIAL
Newer agents - Amrubicin

Promising for 2nd line: Amrubicin

- Synthetic anthracycline
- Undergoing trials in 1st line
- There is concern about increased toxicity and especially in combination
Newer agents - Amrubicin

### Phase II Studies of Amrubicin for the Treatment of Extensive-stage Small Cell Lung Cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Type of Study</th>
<th>Drugs (doses)</th>
<th>Patient Population</th>
<th>Overall Response</th>
<th>Progression-free Survival</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-line Treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yana T et al⁶</td>
<td>Single arm</td>
<td>Amrubicin† (45 mg/m²/d, days 1 to 3)</td>
<td>35 (33)</td>
<td>76%</td>
<td>Not reported</td>
<td>11.7 months</td>
</tr>
<tr>
<td>Ohe Y et al⁵²</td>
<td>Single arm</td>
<td>Amrubicin (40 to 45 mg/m²/d, days 1 to 3) AND cisplatin (60 mg/m² day 1)</td>
<td>44 (44)</td>
<td>89%</td>
<td>Not reported</td>
<td>13.6 months</td>
</tr>
<tr>
<td><strong>Second-line Treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Onoda S et al⁷</td>
<td>Single arm</td>
<td>Amrubicin (40 mg/m²/d, days 1 to 3)</td>
<td>Total 60</td>
<td>52%</td>
<td>11.2 months</td>
<td>11.6 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sensitive 44</td>
<td>52%</td>
<td>4.2 months</td>
<td>11.6 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Refractory 16</td>
<td>50%</td>
<td>2.6 months</td>
<td>10.3 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Refractory 75 (66)</td>
<td>17%</td>
<td>3.2 months</td>
<td>—</td>
</tr>
<tr>
<td>Ettinger DS et al⁹</td>
<td>Single arm</td>
<td>Amrubicin (40 mg/m²/d, days 1 to 3)</td>
<td>Total 60 (59)</td>
<td>53%</td>
<td>3.9 months</td>
<td>9.9 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sensitive Amrubicin 17</td>
<td>53%</td>
<td>3.0 months</td>
<td>11.7 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Topotecan 19</td>
<td>21%</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Refractory Amrubicin 12</td>
<td>17%</td>
<td>2.6 months</td>
<td>5.3 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Topotecan 11</td>
<td>0%</td>
<td>1.5 months</td>
<td>5.4 months</td>
</tr>
<tr>
<td>Inoue A et al⁸</td>
<td>Randomized</td>
<td>Amrubicin (40 mg/m²/d, days 1 to 3) OR topotecan (1.0 mg/m²/d, days 1 to 5)</td>
<td>Total 60 (59)</td>
<td>35%</td>
<td>4.6 months</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sensitive Amrubicin 50</td>
<td>35%</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Topotecan 26</td>
<td>4.3%</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

ASCO 2009
Principals of Management Radiotherapy

60% of the relapses after chemotherapy are in the thorax. TI reduces the risk of relapse by 50%
- Has role in SVCS and spinal cord compression
- High risk of brain metastases in SCLC (20% have brain involvement at diagnosis, 80% have brain involvement at death)
  prophylactic cranial RT increases 3 year survival by 5% and is usually given if the patient is in CR post chemotherapy

Palliative RT – short course of irradiation to either the primary tumor or site of metastases can provide useful symptom control.
Despite the excellent response rates, cure is very unusual.

Median survival for Limited stage is 14 months and for extensive stage 7 months.
SCLC: More than 1 disease

• Extremely chemotherapy sensitive
• Extremely chemotherapy resistant
• What are the biological differences?
• Many drugs are effective on chemotherapy sensitive cells
• No drugs are highly effective against the resistant clones
• Improved outcomes will come ONLY when we defeat the highly resistant clones
Thoracic Irradiation for LS SCLC

2 meta-analysis of thoracic XRT in LS SCLC:
1. Pignon et al. – NEJM ’92: 3-year survival and prognostic factors
2. Warde and Payne – JCO ’92: 2-year survival, local control and toxicity
Timing of Thoracic XRT in LD SCLC

Murray et al, JCO 1993;11:336-44
Multivariate Analysis for Survival for Patients with LD SCLC

### Table 5. Multivariate Analysis for Survival

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td>.0066</td>
</tr>
<tr>
<td>Male</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>0.72</td>
<td>0.57 to 0.91</td>
<td></td>
</tr>
<tr>
<td>Chest radiotherapy</td>
<td></td>
<td></td>
<td>.0051</td>
</tr>
<tr>
<td>Sequential</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomittant</td>
<td>0.72</td>
<td>0.57 to 0.91</td>
<td></td>
</tr>
<tr>
<td>PCI</td>
<td></td>
<td>&lt; .0001</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.52</td>
<td>0.41 to 0.65</td>
<td></td>
</tr>
<tr>
<td>Lactate dehydrogenase</td>
<td></td>
<td></td>
<td>.0002</td>
</tr>
<tr>
<td>Grade 0</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade &gt; 0</td>
<td>1.71</td>
<td>1.30 to 2.26</td>
<td></td>
</tr>
<tr>
<td>Platelets</td>
<td></td>
<td></td>
<td>.0019</td>
</tr>
<tr>
<td>&lt; 221 $10^9$/L</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\geq 221 \times 10^9$/L</td>
<td>1.44</td>
<td>1.14 to 1.81</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: PCI, prophylactic cranial irradiation.

Giaccone et al, JCO 2005;23:6854-64
Timing of Thoracic XRT in LD SCLC

![Diagram](image)

**Fig 2.** Three-year overall survival risk ratio forest plot for early vs late thoracic radiation therapy (RT).

Fried et al, JCO 2004;22:4837-45
Turrisi et al: BID vs QD XRT in LS SCLC with Concurrent EP
*(NEJM 1999; 340(4):265-271)*
N = 417 patients with LS SCLC

RANDOMIZE

4 Cycles of EP +
Daily 1.8 Gy/25F over 5 weeks starting day 1 of chemotx
Total dose 45 Gy

4 Cycles of EP +
BID 1.5 Gy/30F over 3 weeks starting day 1 of chemotx
Total dose 45 Gy

PCI for both if in CR
Hyperfractionated Radiotherapy Improves Survival

Reduction in local failure:
36% vs 52%

Increased toxicity:
Grade 3 esophagitis
27% vs 11%

But no increase in mortality

Turrisi et al. NEJM 1999; 340(4):265-271
QD vs BID XRT in LD SCLC

Bonner et al, JCO 1999;17:2681-91
Role of PCI

- It was frequently practiced in complete response (CR) and occasionally in good partial response (PR) patients, it was not unequivocally proved to produce superior survival
- Fear of toxicity: decline in neurocognitive function
- The issue was taken by meta-analysis by Perez et al (1981):
  - ↓ relative risk of death
  - absolute \( \bar{se} \) in 3yr survival by 5.4%
  - absolute \( \bar{se} \) in ds free survival by 8.8%
  - ↓ cumulative risk for CNS metastasis
  - issue of toxicity was clearly discarded
- The current approach is to administer PCI at the time of achieving CR, but its timing becomes important to avoid administration concurrently with CHT, and thus more CNS toxicity
PCI in Small cell lung cancer
Local treatment in a systemic disease

• Meta Analysis:
  – 7 trials, 987 pts 1977 - 1991:
  – Only one trial (32 pts) used Plat Etop
  3 yr intracranial relapse 25% \( \uparrow \) in dfs and OS by 5%

PCI OI-EULINT1
High VS. Standard Dose PCI
In LS SCLC Complete Responders

Primary endpoint: incidence of brain metastases at 2 years
Secondary endpoints: survival, QoL
Brain metastasis incidence

Primary endpoint: incidence of brain metastases at 2 years
HR of brain metastasis in 36 Gy versus 25 Gy: 0.77 (0.55-1.08), p=0.13
PCI with a total dose of 25 Gy remains the standard of care in LD SCLC
PCI in ED SCLC

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

ED SCLC, PS 0-2

- Response following 4-6 cycles chemo
- Randomized to PCI vs Observation
  - PCI: 20-30 Gy in 5-12 fractions
- Baseline brain imaging NOT mandated unless symptoms warranted imaging

Slotman et al, ASCO 2007, abst 4
## PCI in ED SCLC: Patient Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>PCI</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>143</td>
<td>143</td>
</tr>
<tr>
<td>PS 0-1</td>
<td>92.3%</td>
<td>89.5%</td>
</tr>
<tr>
<td>Persistent 1° disease</td>
<td>75.5%</td>
<td>76.9%</td>
</tr>
<tr>
<td>Bone mets</td>
<td>22%</td>
<td>26%</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>50%</td>
<td>47%</td>
</tr>
<tr>
<td>“Other sites of mets”</td>
<td>64%</td>
<td>82%</td>
</tr>
<tr>
<td>No mets present</td>
<td>30.8%</td>
<td>27.3%</td>
</tr>
<tr>
<td>Received 20 Gy in 5 fx</td>
<td>~67%</td>
<td>-----</td>
</tr>
</tbody>
</table>

Slotman et al, ASCO 2007, abst 4
Symptomatic Brain Metastases incidence

1 year: 14.6% vs. 40.4%

HR: 0.27 (0.16-0.44); p<0.001

Slotman et al, ASCO 2007, abst 4
Survival from Randomization

1 year: 27.1% vs. 13.3%

HR: 0.68 (0.52-0.88); p=0.003

Slotman et al, ASCO 2007, abst 4
Thoracic RT in ED

Next step....
Wait and see ? no
• PCI ? Yes/ 25 Gy

• Thoracic control is a problem:
  –75% persisting thoracic disease after initial chemotherapy
  –90% thoracic disease progression after at 1 year after initial chemotherapy

Is there a role of thoracic radiotherapy in ES SCLC?
SCLC – ED
ROLE OF THORACIC RADIOTHERAPY

- 3 cycles of EP and CR at distant sites / any response intrathoracically
  - Thoracic radiotherapy at 54 Gy/18#s and low dose chemotherapy and 2 cycles of PE
  - An additional 4 cycles of PE
    - MS 17 mths Vs 11 mths
    - 5yr 9.1% Vs 2.7% p=0.041
    - First relapse 13 mths Vs 9 mths

Jeremic et al; JCO 1999
Proposed randomized phase II trial
Dutch Lung Cancer Study Group

ED-SCLC without brain mets or pleural mets
Any response to 4-6 cycles chemotherapy

Randomize

PCI + Thoracic RTH

PCI only
Treatment of Recurrent Small Cell Lung Cancer

- Possible Chemotherapy Agents:
  - topotecan (Hycamtin): only FDA-approved drug for recurrent disease
  - oral etoposide (VP-16)
  - paclitaxel (Taxol)
  - irinotecan/CPT-11 (Camptosar)
  - CAV
  - others in clinical trials

- Palliative radiation to relieve symptoms
Complexity of Lung Cancer defined by chromosomal painting

Complex disease
- Not a single agent responsible for disease as in polio or small pox.
- Not a single gene responsible like cystic fibrosis or sickle cell anemia
SCLC and Anti-angiogenic Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Target</th>
<th>Agent</th>
<th>Schema</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCI-C/EORTC Bayer</td>
<td>MMP</td>
<td>Marimastat</td>
<td>+/- Maintenance</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BAY 12-9566</td>
<td>+/- Maintenance</td>
<td>Negative</td>
</tr>
<tr>
<td>ECOG CALGB HOG</td>
<td>VEGF</td>
<td>BEV (B)</td>
<td>Chemo + B</td>
<td>Positive</td>
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<td></td>
<td>Chemo + B</td>
<td>Negative</td>
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<tr>
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<td></td>
<td></td>
<td>Chemo + B</td>
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</tr>
<tr>
<td>United Kingdom</td>
<td>Vascular stabilizer</td>
<td>Thalidomide</td>
<td>Chemo +/- T</td>
<td>Negative</td>
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<tr>
<td>NCI-C</td>
<td>VEGFR TKi</td>
<td>ZD 6474</td>
<td>+/- Maintenance</td>
<td>Negative</td>
</tr>
<tr>
<td>SWOG</td>
<td>VEGFR TKi</td>
<td>Sorafenib</td>
<td>Monotherapy</td>
<td>Negative</td>
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# SCLC and Targeted Agents

<table>
<thead>
<tr>
<th>Study</th>
<th>Target</th>
<th>Agent</th>
<th>Schema</th>
<th>Result</th>
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<tbody>
<tr>
<td>Rudin</td>
<td>Bcl-2</td>
<td>Oblimersen</td>
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<td>Negative</td>
</tr>
<tr>
<td>ECOG</td>
<td>MTOR</td>
<td>CCI-779</td>
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<tr>
<td>HOG</td>
<td>EGFR</td>
<td>Gefitinib</td>
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<td>Johnson</td>
<td>C-Kit</td>
<td>Imatinib</td>
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<td>Negative</td>
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<tr>
<td>Krug Dy</td>
<td></td>
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<td>Monotherapy</td>
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</tr>
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<td>Monotherapy</td>
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</tr>
<tr>
<td>EORTC</td>
<td>GD-3</td>
<td>BEC2/BCG</td>
<td>+/- Maintenance</td>
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<td>SWOG</td>
<td>Proteosome</td>
<td>Bortezomib</td>
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<tr>
<td>SWOG</td>
<td>RAF/VEGF</td>
<td>Sorafenib</td>
<td>Monotherapy</td>
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Conclusion
first line therapy

- SCLC is an aggressive but highly sensitive disease.
- Etoposide/Cisplatin (carboplatin) standard of care in SCLC
- The results of Newer combinations i.e. with Irinotecan and topotecan are promising.
- PCI is accepted and improves survival
- Thoracic radiation in LS to be initiated as early as possible
  - Improved outcomes will come ONLY when we defeat the highly resistant clones
- Role of Thoracic RT in ED appears promising in maintenance.