Update on the Treatment of Small Cell Lung Cancer and Neuroendocrine Lung Cancers

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Samuel Oschin Comprehensive Cancer Institute
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Lung Cancer in the U.S. in 2018

234,000 new cases*

- 85% Non-Small Cell Lung Cancer
  - 60% Adenocarcinoma
  - 20% SCCa (Squamous Cell Carcinoma)
  - 10% NOS (Not Otherwise Specified)

- 12% Small Cell Lung Cancer
  - High Grade
    - 1-2+ necrosis
    - >10 mitoses/2 mm²

- 2-3% Carcinoids
  - Intermed Grade ("Atypical carcinoids")
    - 0-1+ necrosis
    - 2-10 mitoses/2 mm²
  - Low Grade ("Typical Carcinoids")
    - 3+ necrosis
    - >10 mitoses/2 mm²
  - High Grade
    - >10 mitoses/2 mm²
    - >10 mitoses/2 mm²

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234,000 new cases*

85% Non-Small Cell Lung Cancer

12% Small Cell Lung Cancer

2-3% Carcinoids

60% Adenoca

20% SCCa

10% NOS

10% LGC Undiff

High Grade

1-2+ necrosis

>10 mitoses/2 mm²

Non-Small Cell Lung Cancers

10% High Grade

60%

20%

10%

Adenoca SCCa NOS LGC Undiff

10% Intermed Grade

("Atypical carcinoids")

12%

3+ necrosis

>10 mitoses/2 mm²

Small Cell Lung Cancer

2-10 mitoses/2 mm²

10%

High Grade

10%

Low Grade

("Typical Carcinoids")

2-3%

Carcinoids

90%

0-1+ necrosis

<2 mitoses/2 mm²

Neuroendocrine Lung Cancers

1-2+ necrosis

>10 mitoses/2 mm²

0-1+ necrosis

<2 mitoses/2 mm²

Lung Cancer in the U.S. in 2018

234,000 new cases*

Non-Small Cell Lung Cancer
- 85%
  - 60% Adenoca
  - 20% SCCa
  - 10% NOS
  - 10% High Grade LGC Undiff
- 12% Small Cell Lung Cancer
- 2-3% Carcinoids

High Grade
- 3+ necrosis
- >10 mitoses/2 mm²

Neuroendocrine Lung Cancers
- 0-1+ necrosis
- 2-10 mitoses/2 mm²
- >10 mitoses/2 mm²
- <2 mitoses/2 mm²

Small Cell Lung Cancer: Staging

• Limited Disease (30-35% pts)
  – Disease confined to primary tumor, regional LNs (intrapulmonary, mediastinal and ipsilateral SCN)
  “Disease can be encompassed in a radiation field”

• Extensive Disease (65-70% pts)
  – Disease metastatic to contralateral lung, nodes or other organs (bones, liver, brain, etc.)
  – Pleural effusion
  “Disease can not be encompassed within a radiation field”
1. Platinum + Etoposide has been the standard 1st line treatment for SCLC for the past 35 years.

2. Cisplatin + etoposide / concurrent RT are the standard of care for Limited Stage SCLC.
<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment Details</th>
</tr>
</thead>
</table>
| JCOG 9511             | **Irino 60 mg/m²** days 1, 8, 15  
P 60 mg/m² day 1  
Q4 weeks x 6 cycles    |
|                       | **E 100 mg/m²** days 1 to 3  
P 80 mg/m² day 1  
Q3 weeks x 6 cycles    |
| North American/Australian Study | **Irino 65 mg/m²** days 1 and 8  
P 30 mg/m² days 1 and 8  
Q3 weeks x 4 cycles |
|                       | **E 120 mg/m²** days 1 to 3  
P 60 mg/m² day 1  
Q3 weeks x 4 cycles    |
## Comparison of Therapeutic Outcomes

<table>
<thead>
<tr>
<th>Result</th>
<th>JCOG 9511</th>
<th>N. American/Australian</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IP (n = 77)</td>
<td>EP (n = 77)</td>
</tr>
<tr>
<td></td>
<td>IP (n = 221)</td>
<td>EP (n = 110)</td>
</tr>
<tr>
<td>Overall RR</td>
<td>84.4% * (75-92%)</td>
<td>67.5% * (56-78%)</td>
</tr>
<tr>
<td></td>
<td>48%</td>
<td>43.6%</td>
</tr>
<tr>
<td>Stable</td>
<td>2.6%</td>
<td>20.8%</td>
</tr>
<tr>
<td></td>
<td>4.1%</td>
<td>7.3%</td>
</tr>
<tr>
<td>Progression</td>
<td>3.9%</td>
<td>11.7%</td>
</tr>
<tr>
<td></td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>NE for Response</td>
<td>9.1%</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>28.1%</td>
<td>29.1%</td>
</tr>
<tr>
<td>Median Survival</td>
<td>12.8 mos**</td>
<td>9.4 mos**</td>
</tr>
<tr>
<td></td>
<td>9.3 mos</td>
<td>10.2 mos</td>
</tr>
<tr>
<td>% 1 Yr Survival</td>
<td>58.4%</td>
<td>37.7%</td>
</tr>
<tr>
<td></td>
<td>35%</td>
<td>35.2%</td>
</tr>
<tr>
<td>% 2 Yr Survival</td>
<td>19.5%</td>
<td>5.2%</td>
</tr>
<tr>
<td></td>
<td>8%</td>
<td>7.9%</td>
</tr>
</tbody>
</table>

* p = .02
** p = .002
Comparison of Survival Outcomes

JCOG 9511

<table>
<thead>
<tr>
<th>Survival</th>
<th>Irino + P</th>
<th>Etop + CP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (95% c.i.)</td>
<td>12.8 m</td>
<td>9.4 m</td>
</tr>
<tr>
<td>% 1 yr</td>
<td>58.4%</td>
<td>37.7%</td>
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<tr>
<td>% 2 yr</td>
<td>19.5%</td>
<td>5.2%</td>
</tr>
</tbody>
</table>

N Amer / Aus

Comparison of Survival Outcomes

<table>
<thead>
<tr>
<th>Survival</th>
<th>Irino + P</th>
<th>Etop + CP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (95% c.i.)</td>
<td>9.3 m</td>
<td>10.2 m</td>
</tr>
<tr>
<td>% 1 yr</td>
<td>35%</td>
<td>35.2%</td>
</tr>
<tr>
<td>% 2 yr</td>
<td>8.0%</td>
<td>7.9%</td>
</tr>
</tbody>
</table>
S0124: IP vs EP in E-SCLC


671 Patients
Stratified: PS 0 vs 1/2, # met sites, LDH, wght loss

Randomized

N = 336

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

324 evaluable for Survival (ITT)
317 evaluable for toxicity

N = 335

Arm 2
Etoposide 100 mg/m² d 1,2,3
CDDP 80 mg/m² d 1
Q 3 weeks x 4 cycles

327 evaluable for Survival (ITT)
325 evaluable for toxicity
### S0124: IP vs EP in E-SCLC Toxicity

<table>
<thead>
<tr>
<th>Toxicity Type</th>
<th>IP (n = 317)</th>
<th>EP (n = 324)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Gr 3 / 4 ANC</td>
<td>19% / 15%</td>
<td>20% / 48%</td>
</tr>
<tr>
<td>% Gr 3 / 4 Thrombocytopenia</td>
<td>3.5% / &lt;1%</td>
<td>12% / 3%</td>
</tr>
<tr>
<td>% Gr 3 / 4 Anemia</td>
<td>5% / &lt;1%</td>
<td>11% / 1%</td>
</tr>
<tr>
<td>% Gr 3 / 4 Vomiting</td>
<td>10% / 0</td>
<td>9% / &lt;1%</td>
</tr>
<tr>
<td>% Gr 3 / 4 Diarrhea</td>
<td>18% / 1%</td>
<td>3% / 0%</td>
</tr>
<tr>
<td>% Gr 3 / 4 Dehydration</td>
<td>15% / 1%</td>
<td>8% / 0</td>
</tr>
<tr>
<td>% Gr 3 / 4 Any Toxicity</td>
<td>42% / 22%</td>
<td>29% / 53%</td>
</tr>
<tr>
<td>% Treatment-Related Deaths</td>
<td>4.1%</td>
<td>4.6%</td>
</tr>
</tbody>
</table>

S0124: IP vs EP in E-SCLC
Survival Outcome

**Progression Free Survival**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Events/N</th>
<th>Median (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDDP/CPT-11</td>
<td>313/324</td>
<td>5.7 (5.1 – 6.1)</td>
</tr>
<tr>
<td>CDDP/VP-16</td>
<td>314/327</td>
<td>5.2 (4.9 – 5.5)</td>
</tr>
</tbody>
</table>

**Overall Survival**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Events/N</th>
<th>Median (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDDP/CPT-11</td>
<td>288/324</td>
<td>9.9 (9.2 – 11.1)</td>
</tr>
<tr>
<td>CDDP/VP-16</td>
<td>285/327</td>
<td>9.1 (8.4 – 9.9)</td>
</tr>
</tbody>
</table>

1. Platinum + Etoposide has been the standard 1\textsuperscript{st} line treatment for SCLC for the past 20 years.

2. Cisplatin + etoposide / concurrent RT are the standard of care for Limited Stage SCLC.

3. PCI is the standard of care in responding SCLC pts.
META-ANALYSIS OF PCI IN SCLC

• 7 Randomized trials
  – PCI doses = 24 - 40 Gy in 8 - 20 fractions
  – Median follow-up = 5.9 yrs

• Results
  – Hazard ratio for death(PCI:Control) = 0.84
    • (16% reduction in mortality)
  – Overall survival @ 3 yrs = 20.7% vs 15.3%
  – Benefit (decrease in brain mets) was dose-dependent
PCI in SCLC

Proc ASCO 2007

Study Design

Chemotherapy (4-6 cycles)

No response

Any response

Random

PCI
20-30 Gy in 5-12 fractions

< 5 weeks

4-6 weeks

No PCI

Stratification:
- Institute
- Performance score
PCI in SCLC

Proc ASCO 2007

Symptomatic brain metastases

1 year: 14.6% vs. 40.4%

HR: 0.27 (0.16-0.44)  p<0.001

(months)

(months from moment of randomization)
PCI in SCLC
Proc ASCO 2007

**Failure-free survival**
- 8 months: 23.4% vs. 15.5%
- HR: 0.76 (0.59-0.96)  p=0.02

**Overall survival**
- 1 year: 27.1% vs. 13.3%
- HR: 0.68 (0.52-0.88)  p=0.003

Months from moment of randomization
1. Platinum + Etoposide has been the standard 1\textsuperscript{st} line treatment for SCLC for the past 20 years.

2. Cisplatin + etoposide / concurrent RT are the standard of care for Limited Stage SCLC.

3. PCI is the standard of care in responding SCLC pts.

4. No convincing evidence supports the substitution or addition of another cytotoxic agent, dose intensification or the addition of a biological agent (\textit{yet}).
SCLC: State of the Art

1. Platinum + Etoposide has been the standard 1st line treatment for SCLC for the past 20 years.

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3. PCI is the standard of care in responding SCLC pts.

4. No convincing evidence supports the substitution or addition of another cytotoxic agent, dose intensification or the addition of a biological agent (yet).

5. Topotecan is the reference standard for 2nd line treatment.
New Treatments in Development

- Rovalpituzumab tesirine
- Immunotherapy
Delta-like Protein 3 (DLL3): A Novel Target in Neuroendocrine Tumors

- An atypical inhibitory Notch ligand
- Induced by the key neuroendocrine transcription factor, ASCL1
- Expressed on both cancer stem and tumor cells, but not normal adult tissues
- Not prognostic of SCLC outcomes on standard therapy
- >85% of SCLC express DLL3
TRINITY: 2, Single-Arm Study of Rovalpituzumab tesirine in DLL3-Expressing, Relapsed/Refractory SCLC

**Key Eligibility Criteria**
- DLL3-positive* SCLC
- Relapsed or refractory disease
- ≥ 2 previous regimens
- ≥ 1 platinum-based regimen
- ECOG Performance Status 0-1
- Stable CNS metastases allowed

**Primary Endpoints**
- Objective response rate (ORR)
- Overall survival (OS)

**Secondary Endpoints**
- Duration of response (DOR)
- Clinical benefit rate (CBR)
- Progression-free survival (PFS)

**N = 339**
Rovalpituzumab tesirine 0.3 mg/kg IV Q6W x 2

- Re-treatment was permitted at progression
- Study was powered to detect a 25% best overall response rate in DLL3-high Pts with a Simon’s two-stage design
- Study size was increased to ensure adequate enrollment of 3L Pts

*Clinical trial mouse antibody-based immunohistochemistry assay.

CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; IHC, immunohistochemistry; IV, intravenous; q6w, every 6 weeks.
Trinity: Primary Endpoint Analyses

Change in Target Lesion(s) From Baseline
Investigator-assessed, N = 301 evaluable 3-7L patients

<table>
<thead>
<tr>
<th>Primary Endpoint</th>
<th>All Dosed (N = 339)</th>
<th>DLL3-High (N = 238)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR(^2): Investigator, % (95% CI)</td>
<td>18.0 (14.1, 22.5)</td>
<td>19.7 (14.9, 25.4)</td>
</tr>
<tr>
<td>ORR(^2): IRC, % (95% CI)</td>
<td>12.4 (9.1, 16.4)</td>
<td>14.3 (10.1, 19.4)</td>
</tr>
<tr>
<td>Median OS, Mo (95% CI)</td>
<td>5.6 (4.9, 6.1)</td>
<td>5.7 (4.9, 6.7)</td>
</tr>
</tbody>
</table>

1. Patients who had a baseline scan and at least 1 follow-up scan with an evaluable response.
2. Confirmed CR+PR per RECIST v1.1

Presented at: 2018 ASCO Annual Meeting

Presented By: David Carbone

Abstract # 8507
Responses are Enriched Among 3L Patients with High DLL3 Expression

P-value = 0.0074

IRC-Assessed Outcomes by DLL3 Status (%: 95% CI)

<table>
<thead>
<tr>
<th>DLL3 Status</th>
<th>ORR*</th>
<th>Best Overall Response Rate</th>
<th>CBR</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (N=177)</td>
<td>6%</td>
<td>16%</td>
<td>72%</td>
</tr>
<tr>
<td>Non-High (N=63)</td>
<td>14%</td>
<td>24%</td>
<td>57%</td>
</tr>
</tbody>
</table>

P-value based on two-sample t test; not adjusted for multiple testing.
*Confirmed CR+PR per RECIST v1.1
IRC-Assessed PFS & OS Among DLL3-High Patients, All Lines

**Progression-Free Survival**
- mPFS = 3.8 Mo

**Overall Survival**
- mOS = 5.7 Mo

Presented By David Carbone at 2018 ASCO Annual Meeting
### Summary of TEAEs

#### TEAEs, Any Grade ≥ 15% Patients

<table>
<thead>
<tr>
<th>TEAEs</th>
<th>All Patients, N = 339</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any n (%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>130 (38%)</td>
</tr>
<tr>
<td>Photosensitivity reaction</td>
<td>123 (36%)</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>109 (32%)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>104 (31%)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>103 (30%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>88 (26%)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>84 (25%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>83 (25%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>75 (22%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>59 (17%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>58 (17%)</td>
</tr>
<tr>
<td>Cough</td>
<td>55 (16%)</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>53 (16%)</td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>50 (15%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>49 (15%)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>49 (15%)</td>
</tr>
</tbody>
</table>

#### TEAEs, Grade 3/4 ≥ 10 Patients

<table>
<thead>
<tr>
<th>TEAEs</th>
<th>All Patients, N = 339</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any n (%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>38 (11%)</td>
</tr>
<tr>
<td>Photosensitivity reaction</td>
<td>23 (7%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>16 (5%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>15 (4%)</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>15 (4%)</td>
</tr>
</tbody>
</table>

- Serosal effusions were managed primarily through standard drainage procedures; steroids, NSAIDs, and colchicine also used
- History of effusions may be identified risk factor for Gr3+ Rova-T-related effusions
TRINITY: Conclusions

- Rovalpituzumab tesirine is active in 3L+ SCLC, where no current therapies are approved
  - ORR: 18% INV; 12% IRC

- 3L DLL3-High biomarker-selected Pts were most likely to respond and benefit
  - ORR: 20% INV; 16% IRC
  - Best Overall Response Rate: 29% INV; 24% IRC
  - Clinical Benefit Rate: 71% INV; 72% IRC
  - mOS: 5.6 Mo

- Adverse events were generally manageable

- Important identified risks were pleural/pericardial effusion, edema & photosensitivity

- Rovalpituzumab tesirine is being evaluated in 2 ongoing ph 3 studies (1st line maintenance, MERU; 2L, TAHOE), and Ph 1 studies in combination with chemotherapy (platinum/etoposide), nivolumab, and nivolumab/ipilimumab
New Treatments in Development

- Rovalpituzumab tesirine
- Immunotherapy
Immunotherapy in SCLC

- **Pembrolizumab**
  - Keynote 158

- **Nivolumab**
  - Checkmate 032

- **Atezolizumab**
  - Impower 133
KEYNOTE-158 (NCT02628067): Phase 2 Multicohort Study of Pembrolizumab for Advanced Solid Tumors

Patients
- Unresectable and/or metastatic SCLC
- Progression on or intolerance to standard therapy
- ECOG PS 0 or 1
- ≥1 measurable lesion
- Evaluable tumor sample for biomarker assessments
- No autoimmune disease or noninfectious pneumonitis

Pembrolizumab 200 mg IV Q3W

Treat for 2 years or until progression, intolerable toxicity, or study withdrawal

Survival follow-up

Primary endpoint: ORR (RECIST v1.1, central review)
Secondary endpoints: PFS, OS, duration of response, safety
Exploratory endpoints: Efficacy in biomarker subgroups
Response assessed every 9 weeks year 1; every 12 weeks thereafter

if SD or better when pembrolizumab discontinued and subsequently have PD, patients may be eligible to resume pembrolizumab for ≤1 year.
If clinically stable, patients are to remain on pembrolizumab until PD is confirmed on a second scan performed ≥4 weeks later.
The point estimate and exact Clopper-Pearson CI were calculated.

Presented By Hyun Chung at 2018 ASCO Annual Meeting
Antitumor Activity by PD-L1 Status  
(RECIST v1.1, Independent Central Review

Presented By Hyun Chung at 2018 ASCO Annual Meeting

<table>
<thead>
<tr>
<th></th>
<th>PD-L1–Positive N = 42</th>
<th>PD-L1–Negative N = 50</th>
<th>Overall N = 107</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, % (95% CI)</td>
<td>35.7 (21.6–52.0)</td>
<td>6.0 (1.3–16.5)</td>
<td>18.7 (11.8–27.4)</td>
</tr>
<tr>
<td>Best overall response, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>2 (5)</td>
<td>1 (2)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Partial response</td>
<td>13 (31)</td>
<td>2 (4)</td>
<td>17 (16)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>3 (7)</td>
<td>7 (14)</td>
<td>12 (11)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>22 (52)</td>
<td>29 (58)</td>
<td>62 (58)</td>
</tr>
<tr>
<td>Disease control, n (%)</td>
<td>18 (43)</td>
<td>10 (20)</td>
<td>32 (30)</td>
</tr>
</tbody>
</table>

*Only confirmed responses are included.  
Data cutoff date: January 15, 2018.
Overall Survival by Tumor PD-L1 Status (RECIST v1.1, Independent Central Review)

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Number of Events (%)</th>
<th>Median OS, mo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-L1-positive</td>
<td>42</td>
<td>23 (55)</td>
<td>14.9 (5.6–NR)</td>
</tr>
<tr>
<td>PD-L1-negative</td>
<td>50</td>
<td>38 (76)</td>
<td>5.9 (3.3–10.1)</td>
</tr>
</tbody>
</table>

Data cutoff date: January 15, 2018.

Presented By Hyun Chung at 2018 ASCO Annual Meeting
Immunotherapy in SCLC

• Pembrolizumab
  – Keynote 158

• Nivolumab
  – Checkmate 032

• Atezolizumab
  – Impower 133
Checkmate 032

Pts with ESCLC (n= 401) Stratified by TMB (Hi v Interm v Low)

Nivolumab 3 mg/kg Q2W

ORR 1 Yr PFS

All Pts | Hi TMB | Int TMB | Low TMB
---|---|---|---
ORR | 11% | 21% | 7% | 5%
1 Yr PFS | 21% | 3% | -

Nivolumab 1 mg/kg Q3W + Ipilumumab 3 mg/kg

ORR 1 Yr PFS

All Pts | Hi TMB | Int TMB | Low TMB
---|---|---|---
ORR | 22% | 46% | 16% | 22%
1 Yr PFS | 30% | 8% | 6%

Hellmann et al. WCLC, Yokohama, Japan, 10/2017
Immunotherapy in SCLC

- Pembrolizumab
  - Keynote 158

- Nivolumab
  - Checkmate 032

- Atezolizumab
  - Impower 133
Atezolizumab in SCLC

• IMpower 133: Phase III randomized, double-blind, placebo-controlled trial of carboplatin + etoposide +/- atezolizumab in ES-SCLC

• 403 patients, randomized 1:1

• June 25, 2018 Press Release: Study met it’s co-primary endpoints of statistically significant improvement in PFS and OS!
Ongoing pivotal studies and emerging strategies
NRG-LU005: Phase II/III randomized study of chemoradiation versus chemoradiation plus atezolizumab

**PATIENT POPULATION:** Limited stage SCLC

**STRATIFICATION**
- Radiation schedule (BID vs daily)
- Chemotherapy (cisplatin vs carboplatin)
- Sex
- ECOG Performance Status (0/1 vs 2)

**Platinum/etoposide x 4 cycles**
+ Thoracic RT 45 Gy bid or 66 Gy daily

**Platinum/etoposide x 4 cycles**
+ Thoracic RT 45 Gy bid or 66 Gy daily
+ Atezolizumab q3 weeks beginning with cycle 2

Atezolizumab q3 weeks for 1 year

**Anticipated Study Start Date:** 2018
CA184-310 (STIMULI): Phase 2 trial of consolidation nivolumab and ipilimumab in limited-stage SCLC after chemo-radiotherapy

N=260

Key Eligibility Criteria
- Histologically confirmed SCLC
- Untreated limited-stage disease (I-IIIB)
- ECOG PS ≤1
- No MPE
- No interstitial lung disease or pulmonary fibrosis

Primary Outcome Measures:
OS, PFS

Study Start Date: July 2014
Estimated Completion Date: January 2022

# Frontline immunotherapy trials in extensive stage SCLC

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMpower133</td>
<td>Treatment naïve SCLC</td>
<td>Carboplatin/Etoposide</td>
</tr>
<tr>
<td></td>
<td>Phase I/III</td>
<td>Vs.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carboplatin/Etoposide/Atezolizumab</td>
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<tr>
<td>KEYNOTE-604</td>
<td>Treatment naïve SCLC</td>
<td>Pembrolizumab/Etoposide/Platinum</td>
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<td>Phase I/III</td>
<td>Vs.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Etoposide/Platinum</td>
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<tr>
<td>Caspian Study</td>
<td>Treatment naïve SCLC</td>
<td>Etoposide/Platinum</td>
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<tr>
<td></td>
<td>Phase III</td>
<td>Vs.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Etoposide/Platinum + Durvalumab + Tremelimumab</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Etoposide/Platinum</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vs.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Etoposide/Platinum/Durvalumab</td>
</tr>
</tbody>
</table>
CheckMate 451: Phase 3 study of maintenance nivolumab ± ipilimumab in SCLC

Key eligibility criteria
- ED-SCLC
- Ongoing SD/PR/CR after 4 cycles of 1L PLT-CT
- No symptomatic CNS metastases
- Toxicities from prior therapy resolved to grade ≤1
- ECOG PS ≤1

N = 810

- Primary outcome measures:
  - OS, PFS
- Secondary outcome measures:
  - OS and PFS descriptive analyses: nivolumab vs nivolumab + ipilimumab

1L = first-line; CT = chemotherapy; CRT = chemoradiation therapy; CTLA-4 = cytotoxic T lymphocyte antigen-4; PD-1 = programmed-death 1; PD-L2 = PD ligand 2
PLT = platinum-based; *Where locally approved

Presented By Taofeek Owonikoko at 2018 ASCO Annual Meeting
CheckMate 331: Phase 3 study of nivolumab versus topotecan/amrubicin in relapsed SCLC

Key eligibility criteria
- SCLC
- Recurrence/PD after 1L PLT-CT or CRT (≥4 cycles)
- ECOG PS ≤1
- No symptomatic CNS metastases
- No prior therapy with anti-CTLA-4, anti-CD137, anti-PD-1/PD-L1/PD-L2

N = 480

- Primary outcome measures: OS
- Secondary outcome measures: PFS, ORR

Presented By Taofeek Owonikoko at 2018 ASCO Annual Meeting
SCLC: Take Home Message

• After 30 years, the SOC for the treatment SCLC is finally about to change, perhaps dramatically
  – Immune checkpoint inhibitors will have an important role to play in ~40% of patients with high PDL-1 or high TMB
    • FDA approval of atezolizumab is imminent; others will likely follow
  – CAR-T therapy can’t be much further behind
  – Targeted therapy (targeting DLL-3) is promising
    • Rovalpituzumab tesirine will likely obtain 3L FDA approval
Lung Cancer in the U.S. in 2018

234,000 new cases*

85% Non-Small Cell Lung Cancer

60% Adenocarcinoma

20% SCCa

10% NOS

12% Small Cell Lung Cancer

10% LGC Undiff

High Grade

10% Intermed Grade

("Atypical carcinoids")

2-3% Carcinoids

90% Low Grade

("Typical Carcinoids")

High Grade

1-2+ necrosis

>10 mitoses/2 mm²

Neuroendocrine Lung Cancers

3+ necrosis

>10 mitoses/2 mm²

0-1+ necrosis

2-10 mitoses/2 mm²

no necrosis

<2 mitoses/2 mm²

Incidence of NETs over time by site and disease stage

Annual age-adjusted incidence (# cases per 100,000 population), 1973-2004
Treatment Options

• Localized disease: surgery
Patient Survival Dependent on Extent of Disease

A

Survival Probability vs. Time (months)

Localized

Regional

Distant

Survival Probability vs. Time (months)

Median Survival (months)

<table>
<thead>
<tr>
<th>Color</th>
<th>Site</th>
<th>Localized</th>
<th>Regional</th>
<th>Distant</th>
</tr>
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<tbody>
<tr>
<td>Appendix</td>
<td>&gt;360</td>
<td>&gt;360</td>
<td>27</td>
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<tr>
<td>Cecum</td>
<td>135</td>
<td>107</td>
<td>41</td>
<td></td>
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<tr>
<td>Colon</td>
<td>261</td>
<td>36</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Duodenum</td>
<td>107</td>
<td>101</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>Gastric</td>
<td>154</td>
<td>71</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>50</td>
<td>14</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>227</td>
<td>154</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td>136</td>
<td>77</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Rectum</td>
<td>280</td>
<td>90</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Small bowel</td>
<td>111</td>
<td>105</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td>Thymus</td>
<td>110</td>
<td>68</td>
<td>40</td>
<td></td>
</tr>
</tbody>
</table>
Treatment Options

• Localized disease: surgery

• Locally advanced: Adjuvant chemotherapy +/- radiation
  – No good evidence supporting routine use
Treatment Options

- Localized disease: surgery

- Locally advanced: ?Adjuvant chemotherapy +/- radiation
  - No good evidence supporting routine use

- Metastatic disease:
  - Surgery (for “oligometastases”)

Kaplan-Meier Survival following Resection of Liver Metastases (stratified by margin status and hormonal function)

Proportion Surviving (%)

0 12 24 36 48 60 72 84 96 108 120
Survival (Months)

- R0/R1 & Hormonally Functional
- R0/R1 & Nonfunctional
- R2 & Hormonally Functional
- R2 & Nonfunctional

P < 0.008; log rank, overall

Treatment Options

• Localized disease: surgery

• Locally advanced: ?Adjuvant chemotherapy +/- radiation
  – No good evidence supporting routine use

• Metastatic disease:
  – Surgery (for “oligometastases”)
  – SSAs (octreotide and lanreotide)
SSAs Recommended for:

- All TCs and ACs with ‘Carcinoid” symptoms
  - Recommended 1st line option

- 70% of TCs or ACs have + SSRT status (+Octreotide scan)

- Randomized clinical trials in progress
Treatment Options

• Localized disease: surgery

• Locally advanced: ?Adjuvant chemotherapy +/- radiation
  – No good evidence supporting routine use

• Metastatic disease:
  – Surgery (for “oligometastases”)
  – SSAs (octreotide and lanreotide)
  – Targeted therapy (everolimus, sunitinib, bevacizumab)
  – Interferon
  – Chemotherapy (platinum + etoposide, temozolomide)
  – PRRT (for SSTR-expressing NETs)
    • 1/26/18 FDA approved $^{177}$LU-Dotatate for treatment of SSRT+ GEP-NETs
RADIANT 4 Study Design

Patients with well-differentiated (G1/G2), advanced, progressive, nonfunctional NET of lung or GI origin (N = 302)
- Absence of active or any history of carcinoid syndrome
- Pathologically confirmed advanced disease
- Enrolled within 6 months from radiologic progression

Endpoints:
- **Primary:** PFS (central)
- **Key Secondary:** OS
- **Secondary:** ORR, DCR, safety, HRQoL (FACT-G), WHO PS, NSE/CgA, PK

Stratified by:
- Prior SSA treatment (yes vs. no)
- Tumor origin (stratum A vs. B)*
- WHO PS (0 vs. 1)

Randomize

Everolimus 10 mg/day
N = 205

Placebo
N = 97

Treated until PD, intolerable AE, or consent withdrawal
Progression Free Survival

52% reduction in the relative risk of progression or death with everolimus vs placebo

HR = 0.48 (95% CI, 0.35-0.67); P < 0.00001

Kaplan-Meier medians

Everolimus: 11.0 months (95% CI, 9.23-13.31)
Placebo: 3.9 months (95% CI, 3.58-7.43)

P-value is obtained from the stratified one-sided log-rank test; Hazard ratio is obtained from stratified Cox model.
### PFS Benefit Across Multiple Patient Subgroups

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>No.</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prior SSA treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>157</td>
<td>0.52 (0.34-0.81)</td>
</tr>
<tr>
<td>No</td>
<td>145</td>
<td>0.60 (0.39-0.94)</td>
</tr>
<tr>
<td><strong>Tumor origin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stratum A</td>
<td>153</td>
<td>0.63 (0.40-1.02)</td>
</tr>
<tr>
<td>Stratum B</td>
<td>149</td>
<td>0.43 (0.28-0.66)</td>
</tr>
<tr>
<td><strong>WHO PS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>216</td>
<td>0.58 (0.41-0.84)</td>
</tr>
<tr>
<td>1</td>
<td>86</td>
<td>0.50 (0.28-0.91)</td>
</tr>
</tbody>
</table>

*Based on prognostic level, grouped as: **Stratum A** (better prognosis) - appendix, caecum, jejunum, ileum, duodenum, and NET of unknown primary). **Stratum B** (worse prognosis) - lung, stomach, rectum, and colon except caecum).

Hazard ratio obtained from unstratified Cox model.
NET, neuroendocrine tumors; SSA, somatostatin analogues; WHO PS, World Health Organization performance status.
Second interim OS analysis performed with 53% of information fraction favored the everolimus arm

Everolimus vs Placebo
HR = 0.73 (95% CI, 0.48-1.11); $P = 0.071$ (NS)*

*P-value boundary for significance = 0.0020.
P-value is obtained from the stratified log-rank test; Hazard ratio is obtained from stratified Cox model. Abbreviation: NS, not significant.
<table>
<thead>
<tr>
<th>Drug-related adverse events</th>
<th>Everolimus</th>
<th></th>
<th>Placebo</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 202</td>
<td>N = 98</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>All grades</td>
<td>Grade 3/4</td>
<td>All grades</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Stomatitis*</td>
<td>63%</td>
<td>9%</td>
<td>19%</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>31%</td>
<td>7%</td>
<td>16%</td>
<td>2%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>31%</td>
<td>3%</td>
<td>24%</td>
<td>1%</td>
</tr>
<tr>
<td>Infections†</td>
<td>29%</td>
<td>7%</td>
<td>4%</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>27%</td>
<td>1%</td>
<td>8%</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>26%</td>
<td>2%</td>
<td>4%</td>
<td>1%</td>
</tr>
<tr>
<td>Nausea</td>
<td>17%</td>
<td>1%</td>
<td>10%</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>16%</td>
<td>4%</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>16%</td>
<td>1%</td>
<td>6%</td>
<td>0</td>
</tr>
<tr>
<td>Asthenia</td>
<td>16%</td>
<td>1%</td>
<td>5%</td>
<td>0</td>
</tr>
<tr>
<td>Non-infectious pneumonitis‡</td>
<td>16%</td>
<td>1%</td>
<td>1%</td>
<td>0</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>15%</td>
<td>1%</td>
<td>4%</td>
<td>0</td>
</tr>
<tr>
<td>Cough</td>
<td>13%</td>
<td>0</td>
<td>3%</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>13%</td>
<td>1%</td>
<td>4%</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>11%</td>
<td>2%</td>
<td>5%</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>10%</td>
<td>1%</td>
<td>4%</td>
<td>1%</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>10%</td>
<td>3%</td>
<td>2%</td>
<td>0</td>
</tr>
</tbody>
</table>

Presented are drug-related adverse events in ≥10% of patients (safety set).
*Includes stomatitis, aphthous stomatitis, mouth ulceration, and tongue ulceration.
Treatment of Pulmonary Neuroendocrine Cancers: New Directions

• Mutations in TC and ACs
  – MEN1 (tumor suppressor) mutationally inactivated/deleted in 30-40% of cases
  – P53 mutations (exons 5-8) in ~20%

• Immunotherapy
  – PDL-1 expression and tumor mutational burden generally very low
  – MMR deficiencies in ~ 10% may identify a small subset of “responsive” patients

• ROVA-T (a DLL-3 antibody-drug conjugate)
  – Initially promising results in SCLC failed further follow-up primarily due to low efficacy and high toxicity
PNETS: Take Home Message

• Neuroendocrine cancers (including PNETS) are an increasing group of disease entities with an increasing need for medical oncology approaches

• As a group they have interesting differences from the more common medical oncology disease, but the approach is the same
  – Standard staging/diagnostics to define the extent of disease
  – Surgery remains the dominant treatment modality for localized and “oligometastatic” disease
  – Symptom management (flushing, diarrhea, heart disease) has high importance
  – New treatment options will be developed (keep abreast)
Back-up Slides
Dose-Intensity with Cytokine Support

<table>
<thead>
<tr>
<th>Investigators</th>
<th>Regimen</th>
<th>No. Pts.</th>
<th>RDI</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crawford et al, 1991</td>
<td>CAE +/- GCSF</td>
<td>101</td>
<td>NR</td>
<td>11.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>110</td>
<td></td>
<td>12.2</td>
</tr>
<tr>
<td>Hamm et al, 1991</td>
<td>CAE +/- GCSF</td>
<td>NR</td>
<td></td>
<td>89% (10)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>78% (0)</td>
</tr>
<tr>
<td>Fukuoka et al, 1992</td>
<td>CODE +/- GCSF</td>
<td>27</td>
<td>85%</td>
<td>14.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>26</td>
<td>76%</td>
<td>p&lt;.05</td>
</tr>
<tr>
<td>Trillet-Lenoir et al, 1993</td>
<td>CDE +/- GCSF</td>
<td>64</td>
<td>96%</td>
<td>13.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>66</td>
<td>88%</td>
<td></td>
</tr>
<tr>
<td>Miles et al, 1994</td>
<td>PE/IA +/- GCSF</td>
<td>23</td>
<td>84%</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>17</td>
<td>82%</td>
<td></td>
</tr>
<tr>
<td>Woll et al, 1995</td>
<td>VICE +/- GCSF</td>
<td>34</td>
<td>1.34</td>
<td>17.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>31</td>
<td>1.13</td>
<td>16.2</td>
</tr>
</tbody>
</table>
Small Cell Lung Cancer Treatment: Limited Disease

• Combination chemotherapy
  » EP (etoposide + cisplatin)
  » moderately intensive doses
  » no observed benefit of treatment >4-6 cycles

• Radiotherapy
  » increases survival by about 15-20%
  » most effective when given early and concurrently with chemotherapy
  » may increase morbidity/mortality of treatment
  » altered versus standard fractionation?
  » role of PCI?
## Meta-Analysis of Thoracic Radiotherapy in SCLC

<table>
<thead>
<tr>
<th>Trial</th>
<th>CT</th>
<th>RT</th>
<th>Timing</th>
<th>Start Day</th>
<th>No. Pts.</th>
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<tbody>
<tr>
<td>Copenhagen</td>
<td>CCMV</td>
<td>40/10,split</td>
<td>Con</td>
<td>43</td>
<td>145</td>
</tr>
<tr>
<td>Sydney</td>
<td>CAV</td>
<td>40/20</td>
<td>Seq</td>
<td>63</td>
<td>94</td>
</tr>
<tr>
<td>NCI</td>
<td>CMC/VAP</td>
<td>40/15</td>
<td>Con</td>
<td>1-3</td>
<td>97</td>
</tr>
<tr>
<td>SECSG I</td>
<td>CAV</td>
<td>40/14,split</td>
<td>Alt</td>
<td>29</td>
<td>295</td>
</tr>
<tr>
<td>London</td>
<td>VA/CM</td>
<td>40/20</td>
<td>Seq</td>
<td>85</td>
<td>138</td>
</tr>
<tr>
<td>SWOG</td>
<td>VME/CAV</td>
<td>48/22,split</td>
<td>Seq</td>
<td>85</td>
<td>103</td>
</tr>
<tr>
<td>SAKK</td>
<td>CAE/PAE</td>
<td>45/25,split</td>
<td>Seq</td>
<td>127</td>
<td>70</td>
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<tr>
<td>Uppsala</td>
<td>CAV/CMDV</td>
<td>40/20</td>
<td>Seq</td>
<td>77</td>
<td>57</td>
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<tr>
<td>CALGB</td>
<td>CAE/CAV</td>
<td>50/24</td>
<td>Con</td>
<td>1 or 64</td>
<td>426</td>
</tr>
<tr>
<td>ECOG</td>
<td>CCM</td>
<td>50/25</td>
<td>Seq</td>
<td>43</td>
<td>426</td>
</tr>
<tr>
<td>Okayama</td>
<td>CVMP/AE</td>
<td>40/20</td>
<td>Seq</td>
<td>30</td>
<td>56</td>
</tr>
<tr>
<td>SECSG</td>
<td>CAV</td>
<td>45/15,split</td>
<td>Con</td>
<td>1</td>
<td>322</td>
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<tr>
<td>GETCB</td>
<td>CAEC</td>
<td>32/8</td>
<td>Seq</td>
<td>224</td>
<td>36</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>2103</strong></td>
</tr>
</tbody>
</table>

# META-ANALYSIS OF TRT IN SCLC

Relationship to Patient Age

<table>
<thead>
<tr>
<th>Age</th>
<th>CT + RT</th>
<th>Pts.</th>
<th>Relative Risk (CT+RT : CT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 55</td>
<td>309</td>
<td>252</td>
<td></td>
</tr>
<tr>
<td>55 - 59</td>
<td>239</td>
<td>233</td>
<td></td>
</tr>
<tr>
<td>60 - 64</td>
<td>257</td>
<td>233</td>
<td></td>
</tr>
<tr>
<td>65 - 69</td>
<td>191</td>
<td>181</td>
<td></td>
</tr>
<tr>
<td>&gt; 70</td>
<td>113</td>
<td>86</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1109</td>
<td>985</td>
<td></td>
</tr>
</tbody>
</table>
### Pilot Studies Using Cisplatin/Etoposide + TRT in SCLC

<table>
<thead>
<tr>
<th>Group</th>
<th>No. Pts.</th>
<th>Sequence</th>
<th>No. CT Pre-TRT</th>
<th>Frctntrn</th>
<th>% Survival 2 Yr</th>
<th>5 Yr</th>
<th>5 Yr Local Failure(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SWOG</td>
<td>123</td>
<td>C</td>
<td>0</td>
<td>Daily</td>
<td>42</td>
<td>25</td>
<td>36</td>
</tr>
<tr>
<td>MSKCC-1</td>
<td>36</td>
<td>C</td>
<td>4</td>
<td>Daily</td>
<td>50</td>
<td>28</td>
<td>27</td>
</tr>
<tr>
<td>Penn</td>
<td>28</td>
<td>C</td>
<td>0</td>
<td>BID</td>
<td>54</td>
<td>36</td>
<td>3</td>
</tr>
<tr>
<td>ECOG-I</td>
<td>41</td>
<td>C</td>
<td>0</td>
<td>BID</td>
<td>36</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ECOG-II</td>
<td>41</td>
<td>A</td>
<td>0</td>
<td>BID</td>
<td>40</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>NCI/Navy</td>
<td>36</td>
<td>C</td>
<td>0</td>
<td>BID</td>
<td>65</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mayo</td>
<td>27</td>
<td>C</td>
<td>3</td>
<td>Split/BID</td>
<td>39</td>
<td>-</td>
<td>20</td>
</tr>
<tr>
<td>MSKCC-2</td>
<td>29</td>
<td>S</td>
<td>4</td>
<td>BID</td>
<td>19</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Cisplatin + Etoposide (PE) + Concurrent Thoracic Radiotherapy (TRT) [INT-0096] (Daily versus BID)

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>No. Pts.</th>
<th>SURVIVAL Median</th>
<th>2-yr</th>
<th>5-yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE x 4 + TRT 45 Gy (daily)</td>
<td>206</td>
<td>18.6 mos</td>
<td>40.9%</td>
<td>16%</td>
</tr>
<tr>
<td>PE x 4 + TRT 45 Gy (BID)</td>
<td>211</td>
<td>22.0 mos</td>
<td>46.1%</td>
<td>26%</td>
</tr>
</tbody>
</table>

p = 0.043
Cisplatin + Etoposide (PE) + Concurrent Thoracic Radiotherapy (TRT) [INT-0096] (Daily *versus* BID)

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>FAILURE RATES</th>
<th>Brain Mets</th>
<th>PCI +</th>
<th>PCI -</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Local</td>
<td>Local + DM</td>
<td>DM</td>
<td></td>
</tr>
<tr>
<td>PE x 4 + TRT</td>
<td>52%</td>
<td>23%</td>
<td>55%</td>
<td></td>
</tr>
<tr>
<td>45 Gy (daily)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p=0.058</td>
<td>p=0.006</td>
<td>p=NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>36%</td>
<td>6%</td>
<td>40%</td>
<td>31%</td>
</tr>
<tr>
<td>PE x 4 + TRT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45 Gy (BID)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
META-ANALYSIS OF PCI IN SCLC

• 7 Randomized trials
  – PCI doses = 24 - 40 Gy in 8 - 20 fractions
  – Median follow-up = 5.9 yrs

• Results
  – Hazard ratio for death(PCI:Control) = 0.84
    • (16% reduction in mortality)
  – Overall survival @ 3 yrs = 20.7% vs 15.3%
  – Benefit (decrease in brain mets) was dose-dependent
Small Cell Lung Cancer Treatment: Extensive Disease

- **Combination chemotherapy (4-6 cycles)**
  - EP (etoposide + cisplatin) *or* EC (carboplatin)
  - CAV (cyclophosphamide + vincristine + doxorubicin)

- **Radiotherapy**
  - no survival benefit
  - palliative only
Carboplatin + Etoposide *versus* Cisplatin + Etoposide in Previously Untreated SCLC

Kosmidis et al. (Hellenic Cooperative Oncol Group) *Semin Oncol* 21:23, 1994

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>No. of Pts.</th>
<th>LD *</th>
<th>ED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboplatin 300 mg/m² IV x d 1</td>
<td></td>
<td>41</td>
<td>31</td>
</tr>
<tr>
<td>Etoposide 100 mg/m² IV x d 1-3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cisplatin 50 mg/m² IV x d 1-2</td>
<td></td>
<td>41</td>
<td>30</td>
</tr>
<tr>
<td>Etoposide 100 mg/m² IV x d 1-3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* LD pts. received 45 Gy thoracic radiation concurrent with 4th cycle of chemotherapy.
* LD pts. achieving CR received 25 Gy PCI
## Carboplatin + Etoposide versus Cisplatin + Etoposide in Previously Untreated SCLC

### Efficacy

<table>
<thead>
<tr>
<th></th>
<th>No. Pts.</th>
<th>% Overall Response</th>
<th>% CR</th>
<th>Median TTP</th>
<th>2 Yr Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Carboplatin</strong></td>
<td>72</td>
<td>76%</td>
<td>29%</td>
<td>8.6 m</td>
<td>12.5%</td>
</tr>
<tr>
<td>Etoposide</td>
<td>(41 LD)</td>
<td>(86%)</td>
<td>(37%)</td>
<td>11.8 m</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(31 ED)</td>
<td>(64%)</td>
<td>(16%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cisplatin</strong></td>
<td>71</td>
<td>63%</td>
<td>30%</td>
<td>8.4 m</td>
<td>14%</td>
</tr>
<tr>
<td>Etoposide</td>
<td>(41 LD)</td>
<td>(73%)</td>
<td>(44%)</td>
<td>12.5 m</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(30 ED)</td>
<td>(50%)</td>
<td>(10%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Carboplatin + Etoposide *versus* Cisplatin + Etoposide in Previously Untreated SCLC

*Toxicity*

<table>
<thead>
<tr>
<th></th>
<th>Leukopenia</th>
<th>Thrombo</th>
<th>N / V</th>
<th>Neuro</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>No. Pts.</td>
<td>Gr 3</td>
<td>Gr 4</td>
<td>Gr 2</td>
</tr>
<tr>
<td>Carboplatin Etoposide</td>
<td>72</td>
<td>10.3%</td>
<td>6.8%</td>
<td>6%</td>
</tr>
<tr>
<td></td>
<td>p = .09</td>
<td></td>
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</tr>
<tr>
<td>Cisplatin Etoposide</td>
<td>71</td>
<td>37.5%</td>
<td>12.5%</td>
<td>4%</td>
</tr>
<tr>
<td></td>
<td>p = .001</td>
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<tr>
<td></td>
<td>p = .002</td>
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</table>