REAL-WORLD MULTIOMIC CHARACTERIZATION OF SMALL CELL LUNG CANCER SUBTYPES TO REVEAL DIFFERENTIAL EXPRESSION OF CLINICALLY RELEVANT BIOMARKERS


Abstract # 8508
Background and Methods

• Small cell lung cancer (SCLC) can be classified into four subtypes (SCLC-A, SCLC-N, SCLC-Y, and SCLC-P) based on the dominant expression of four lineage-defining transcription factors (ASCL1, NEUROD1, YAP1, or POU2F3 respectively) 1.
  • Emerging data suggests YAP1 expression is associated with an inflamed T cell gene expression profile 2.
  • SCLC has significant intra-tumor heterogeneity mediated by MYC-driven activation of NOTCH signaling 3.

• We conducted comprehensive molecular profiling of 437 small cell lung neuroendocrine tumors (including 7.3% high-grade neuroendocrine lung carcinomas) using next-generation DNA sequencing (592-gene panel), RNA sequencing (whole transcriptome), and immunohistochemistry at Caris Life Sciences (Phoenix, AZ).

• Tumors were categorized into 5 subtypes (SCLC-A/N/Y/P and -mixed) based on the relative expression of the four transcription factors.

• Differences in gene expression and key signature scores 4-7 in SCLC subtypes were analyzed. Significance was tested by Chi-square, Fisher’s exact test, or Mann-Whitney U test.

## RESULTS: BASELINE CHARACTERISTICS

### Table 1: Patient demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All SCLC Subtypes</th>
<th>SCLC-A</th>
<th>SCLC-N</th>
<th>SCLC-Y</th>
<th>SCLC-P</th>
<th>Mixed</th>
<th>P-value (test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total, N cases (%)</td>
<td>437 (100%)</td>
<td>156 (35.7%)</td>
<td>77 (17.6%)</td>
<td>92 (21.1%)</td>
<td>28 (6.4%)</td>
<td>84 (19.2%)</td>
<td>-----</td>
</tr>
<tr>
<td>Median Age, years (SD)</td>
<td>66 (9.44)</td>
<td>63 (9.26)</td>
<td>70 (8.03)</td>
<td>65.5 (11.01)</td>
<td>67.5 (7.44)</td>
<td>64.5 (9.28)</td>
<td>36-90+</td>
</tr>
<tr>
<td>Female/Male, N cases - (% Female/% Male)</td>
<td>221/216 (50.6%/49.4%)</td>
<td>77/79 (50.6%/49.4%)</td>
<td>37/40 (48.1%/51.9%)</td>
<td>46/46 (50.0%/50.0%)</td>
<td>12/16 (42.9%/57.1%)</td>
<td>47/37 (56.0%/44.0%)</td>
<td>P=0.0164*</td>
</tr>
<tr>
<td>Metastatic/Primary, N cases - (% Metastatic/% Primary)</td>
<td>294/143 (67.3%/32.7%)</td>
<td>113/43 (72.4%/27.6%)</td>
<td>54/23 (70.1%/29.9%)</td>
<td>42/50 (45.7%/54.3%)</td>
<td>21/7 (75.0%/25.0%)</td>
<td>64/20 (76.2%/23.8%)</td>
<td>P=3.99e-5**</td>
</tr>
</tbody>
</table>

Notes: *Pairwise comparisons found significantly different age distribution between ASCL1 and NEUROD1 subtypes only. **Pairwise comparisons found the proportion of metastatic specimens to be significantly lower in YAP1 compared to each other subtype (no other comparisons were statistically significant).

---

**Figure 1:** Clinically relevant biomarkers of response to immunotherapy

<table>
<thead>
<tr>
<th>dMMR/MSI-High</th>
<th>TMB-High (&gt;=10)</th>
<th>PD-L1 (SP142)</th>
<th>PD-L1 (22c3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>dMMR/MSI-High</td>
<td>TMB-High (&gt;=10)</td>
<td>PD-L1 (SP142)</td>
<td>PD-L1 (22c3)</td>
</tr>
<tr>
<td>(n=424)</td>
<td>(n=411)</td>
<td>(n=314)</td>
<td>(n=106)</td>
</tr>
</tbody>
</table>

- **dMMR/MSI-High:** Deficient-mismatch repair / high-microsatellite instability
- **TMB:** Tumor mutational burden

**Figure 2:** Characteristics of small cell lung cancer from CNS metastasis

- **N=14, CNS: Central Nervous System**

- **Subtype: SCLC-N (n=5), SCLC-Y (n=2), SCLC-P (n=0), Mixed (n=4)**

- **Proportion of CNS Metastases**
  - SCLC-A (n=3): 21.4%
  - SCLC-N (n=5): 35.7%
  - SCLC-Y (n=2): 14.3%
  - SCLC-P (n=0): 0.0%
  - Mixed (n=4): 28.6%
RESULTS: KEY CORRELATIONS OF THERAPEUTIC SIGNIFICANCE

Top: Spectrum of gene expression and signature scores in the SCLC subtypes (n=437)
Bottom: Median expression of key genes in SCLC subtypes

Sonam Puri

#ASCO21 Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.
RESULTS: GENOMIC ALTERATIONS IN SMALL CELL LUNG CANCER

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>SCLC Subtypes (N = 437 samples)</th>
<th>Alteration Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP53</td>
<td>SCLC-A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SCLC-N</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SCLC-Y</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SCLC-P</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mixed</td>
<td></td>
</tr>
</tbody>
</table>

Most frequently altered genes:
- RB1
- TP53
- NF1
- KMT2D
- PTEN
- ARID1A

Other DDR genes:
- ATM
- BRCA2
- CHEK2
- RAD50
- BRCA1
- PALB2
- BARD1
- MRE11
- BRIP1
- NBN

**SCLC Subtypes**
- SCLC-A
- SCLC-N
- SCLC-Y
- SCLC-P
- Mixed

**Biomarkers**
- SCLC-A
- SCLC-N
- SCLC-Y
- SCLC-P
- Mixed

**EGFR mutation**
- Total
- SCLC-N
- SCLC-A
- SCLC-Y
- SCLC-P
- Mixed

- **E746_A750del**
  - Total: 4
  - SCLC-N: 3
  - SCLC-A: 0
  - SCLC-Y: 0
  - SCLC-P: 1

- **E746_S752delinsV**
  - Total: 1
  - SCLC-N: 0
  - SCLC-A: 1
  - SCLC-Y: 0
  - SCLC-P: 0

- **L747_P753delinsS**
  - Total: 1
  - SCLC-N: 0
  - SCLC-A: 0
  - SCLC-Y: 1
  - SCLC-P: 0

- **V843I**
  - Total: 1
  - SCLC-N: 1
  - SCLC-A: 0
  - SCLC-Y: 0
  - SCLC-P: 0

- **L858R**
  - Total: 1
  - SCLC-N: 1
  - SCLC-A: 0
  - SCLC-Y: 0
  - SCLC-P: 0

- **E709K**
  - Total: 1
  - SCLC-N: 1
  - SCLC-A: 0
  - SCLC-Y: 0
  - SCLC-P: 0

- **G719A**
  - Total: 1
  - SCLC-N: 1
  - SCLC-A: 0
  - SCLC-Y: 0
  - SCLC-P: 0

- **G719C**
  - Total: 1
  - SCLC-N: 1
  - SCLC-A: 0
  - SCLC-Y: 0
  - SCLC-P: 0

- **L747_A755delinsAN**
  - Total: 1
  - SCLC-N: 0
  - SCLC-A: 0
  - SCLC-Y: 0
  - SCLC-P: 1

Note: 3 SCLC-NEUROD1 samples harbored 2 concurrent EGFR mutations.

Left: **RB1** mutation frequency was highest in ASCL1 (79.2%) and lowest in YAP1 (49.4%) subgroup.
Right: **EGFR**-sensitizing mutations (L858R and Exon 19 deletions) were recurrent (5.2%, n = 4) in the SCLC-N tumor subtype.

**DDR**: DNA damage Repair

---

Sonam Puri

#ASC21 | Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.
CONCLUSIONS

• Our analysis represents the largest real-world dataset of human SCLC tumors profiled by NextGen DNA and whole transcriptomic sequencing.

• The differential expression of immune genes and predictive biomarkers across transcriptionally defined SCLC subtypes may inform therapeutic vulnerabilities for rational and personalized treatment approaches in SCLC.
  - SCLC-Y Subtype is associated with the highest median expression of key immunogenic gene and tumor micro-environment cell population signatures; may predict response to immunotherapy.
  - Highest median expression of SLFN11 and SSTR2 genes was observed in SCLC-N subtype, while MYC gene expression was highest in SCLC-P.

• Further prospective studies are warranted to validate the utility of SCLC subtyping to predict patient response or distinct therapeutic vulnerabilities.