WHAT IS NEW IN SMALL CELL LUNG CANCER?

NOVEL TARGETS IN SCLC

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SCLC, where are we?

- Accounts for ~15% of newly diagnosed lung cancer
- Predominately associated with tobacco smoking
- Rapid doubling times and early propensity to metastasize
- Initial sensitivity to CT with 60-80% RR
SCLC, where are we?

- 1st-line treatment for both LD and ED: platinum/etoposide x 4-6 cycles
- For patients with LD
  - Early TRT (<30 days from CT start) should be added to CT
  - PCI for patients with CR/PR
- 2nd-line: topotecan or re-induction
- No new agents approved in over 20 years
- No targeted agents approved
Novel targets in SCLC

- Review paper:

- I will not cover immunotherapy
Genomic Analysis of SCLC

- Hot spot mutations
  - TP53, RB1, PIK3CA, CDKN2A, PTEN
  - RAS family regulators (RAB37, RASGRF1, RASGRF2)
  - Chromatin modifiers (EP300, DMBX1, MLL2, MED12, etc.)

- Hot spot mutations PLUS q-score
  - RUNX1T1, CDYL, RIMS2

- Gene families and pathways
  - PI3K pathway, Notch and Hedgehog, glutamate receptor family, DNA repair/checkpoint, SOX family

- Focal amplifications
  - MYC, SOX2, SOX4, KIT

- Recurrent translocations and fusion genes
  - Recurrent: RLF—MYCL1
  - Kinase fusions

Circos plot whole genome SCLC
22 significantly mutated genes


EUROPEAN LUNG CANCER CONFERENCE 2016
Comprehensive genomic analysis identifies SOX2 as a frequently amplified gene in small-cell lung cancer

Charles M Rudin\textsuperscript{1,8}, Steffen Durinck\textsuperscript{2,3,8}, Eric W Stawiski\textsuperscript{2,3,8}, John T Poirier\textsuperscript{1,8}, Zora

Proteomic Profiling Identifies Dysregulated Pathways in Small Cell Lung Cancer and Novel Therapeutic Targets Including PARP1

Lauren Averett Byers\textsuperscript{1}, Jing Wang\textsuperscript{2}, Monique B. Nilsson\textsuperscript{1}, Junya Fujimoto\textsuperscript{3}, Pierre
SCLC: comprehensive mutation analysis program at MSKCC

- Prospectively testing of SCLC biopsies genotyping with Sequenom and NGS

- Sequenom (n=32 samples): AKT1E17-mut (n=1) and PIK3CA E542K-mut (n=1)

- NGS (n=25 samples): loss of RB1 (N=18 mutations; N=4 deletions); TP53-mut (N=24), MLL3 (N=9), and EPHA 5 (N=9); and amplifications of CDKN2C (N=5), MYCL1 (N=3), SOX2 (N=2), and FGFR1 (N=1, confirmed by FISH)
Clinical correlation of extensive-stage SCLC genomics

- 50 SCLC tumors examined
- TP53 (86%) and RB1 (58%), the two most frequently mutated genes
- Other mutated genes (>10% pts), involved in epigenetic regulation / mTOR pathway
- Low-frequency of targetable mutations, including RICTOR, FGFR1, KIT and RET
Comprehensive genomic profiles of SCLC

- 110 SCLC genomes sequenced
- Nearly all tumors analyzed had inactivation of TP53 and RB1
- Uncommonly, SCLC tumors exhibited kinase gene mutations
- Inactivating mutations in NOTCH family genes found in 25% of SCLC
  - Activation of NOTCH signaling in SCLC mouse model reduced the number of tumors and extended the survival

*George Nature 15*
NOTCH pathway

- Delta-like ligand 3 (DLL3)
  - Inhibits NOTCH pathway activation
  - One of several NOTCH ligands possibly associated with neuroendocrine phenotype and contribute to neuroendocrine tumorigenesis

- Rovalpituzumab tesirine is an antibody drug conjugate that targets the atypical Notch ligand DLL3 on the cell surface and then delivers the DNA-damaging agent pyrrolobenzodiazepine dimer toxin
Rovalpituzumab tesirine, a delta-like protein 3 (DLL3)-targeted antibody drug conjugate (ADC), in SCLC. Phase I Trial in recurrent pts after 1 or 2 previous lines

DLL3 is a dominant inhibitor of Notch signaling

- Normally expressed during development in the Golgi
- Aberrantly expressed in SCLC tumor-initiating cells
- Interacts with and inhibits Notch1 in cis
- May mediate Notch inhibition downstream of ASCL1

Kume et al., J Angiogen Res 2009

Drug-to-Antibody Ratio (DAR) = 2

Phase I study of a delta-like protein 3 (DLL3)-targeted antibody drug conjugate, rovalpituzumab tesirine, in pts with relapsed and refractory SCLC

**Study population: 73 SCLC pts enrolled**

<table>
<thead>
<tr>
<th>Baseline Characteristic (SCLC)</th>
<th>Total (%) or Median (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>61 (44-81)</td>
</tr>
<tr>
<td>Male</td>
<td>41 (56%)</td>
</tr>
<tr>
<td><strong>Disease Characteristics</strong></td>
<td></td>
</tr>
<tr>
<td>ECOG 0/1</td>
<td>19 (26%) / 53 (73%)</td>
</tr>
<tr>
<td>Refractory/“Resistant”/“Sensitive”*</td>
<td>9 (12%) / 23 (32%) / 39 (53%)</td>
</tr>
<tr>
<td>Prior CNS metastases</td>
<td>20 (27%)</td>
</tr>
<tr>
<td><strong>Prior Therapies</strong></td>
<td></td>
</tr>
<tr>
<td>Prior therapies: 1/2</td>
<td>40 (55%) / 33 (45%)</td>
</tr>
<tr>
<td>Cisplatin/Carboplatin + Etoposide</td>
<td>45 (62%) / 28 (38%)</td>
</tr>
<tr>
<td>Topotecan</td>
<td>8 (11%)</td>
</tr>
<tr>
<td>Prior Radiation</td>
<td>60 (82%)</td>
</tr>
</tbody>
</table>

* “Resistant” = Clinical benefit on 1L; began 2L in < 90 days
  “Sensitive” = Clinical benefit on 1L; began 2L in ≥ 90 days
## Related AEs occurring in > 10% of patients

### Phase 1b Expansion Cohorts (7/6/15 cutoff)

<table>
<thead>
<tr>
<th># Patients Enrolled</th>
<th>25</th>
<th>40</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose/Schedule</strong></td>
<td>0.2 Q3W</td>
<td>0.3 Q6W</td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>Gr 3/4</td>
</tr>
<tr>
<td><strong>Fatigue</strong></td>
<td>24%</td>
<td>4%</td>
</tr>
<tr>
<td><strong>Thrombocytopenia</strong></td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Decreased Appetite</strong></td>
<td>0%</td>
<td>4%</td>
</tr>
<tr>
<td><strong>Rash Maculo-Papular</strong></td>
<td>12%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Oedema Peripheral</strong></td>
<td>16%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Anaemia</strong></td>
<td>12%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Erythema</strong></td>
<td>8%</td>
<td>4%</td>
</tr>
<tr>
<td><strong>Serosal Effusions</strong></td>
<td>16%</td>
<td>12%</td>
</tr>
<tr>
<td><strong>Nausea</strong></td>
<td>20%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Vomiting</strong></td>
<td>8%</td>
<td>0%</td>
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RP2D
Rova-T: best response data in evaluable patients
0.2 mg/kg q3w and 0.3 mg/kg q6w cohorts (n=60)

- 20% ORR
- 57% Anti-Tumor Activity
- 70% Clinical Benefit Rate

Rova-T: best response data in evaluable DLL3+ patients
0.2 mg/kg q3w and 0.3 mg/kg q6w cohorts (n=28)

- 39% ORR
- 71% Anti-Tumor Activity
- 75% Clinical Benefit Rate

\[^{3}Pts\; whose\; target\; lesions\; were\; noted\; as\; SD\; or\; better\; by\; RECIST\; had\; clinical\; progression\]
## Results support biomarker-guided phase II studies

### Overall response rates

<table>
<thead>
<tr>
<th></th>
<th>Topotecan†</th>
<th>Rova-T; SC16LD6.5 All Pts &amp; dose levels</th>
<th>DLL3+ Ph 1b Cohorts</th>
</tr>
</thead>
<tbody>
<tr>
<td>2nd Line</td>
<td>17%</td>
<td>22%</td>
<td>40%</td>
</tr>
<tr>
<td>3rd Line</td>
<td>No Approved Drug</td>
<td>17%</td>
<td>38%</td>
</tr>
<tr>
<td>Sensitive to C/E</td>
<td>23%</td>
<td>24%</td>
<td>62%</td>
</tr>
<tr>
<td>Resistant to C/E</td>
<td>9%</td>
<td>14%</td>
<td>20%</td>
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**Durability of Response at RP2D (0.3 mg/kg q6w): 182+ days**

**Duration of response by dosing cohort**

<table>
<thead>
<tr>
<th>Dose &amp; Regimen</th>
<th>Objective Responses</th>
<th># Remaining Progression Free</th>
<th>Mean DOR (Range)</th>
<th># Alive</th>
<th>Mean OS (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.2q3w</td>
<td>5</td>
<td>0</td>
<td>88 (68-130)</td>
<td>1</td>
<td>184+ (113-255)</td>
</tr>
<tr>
<td>0.3q6w</td>
<td>7</td>
<td>6</td>
<td>182+ (50-332)†</td>
<td>7</td>
<td>227+ (104-367)†</td>
</tr>
<tr>
<td>0.4q3w</td>
<td>2</td>
<td>0</td>
<td>164†</td>
<td>1</td>
<td>437+</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>14</strong></td>
<td><strong>6</strong></td>
<td></td>
<td><strong>9</strong></td>
<td></td>
</tr>
</tbody>
</table>

†DOR and OS excluding 3 new responses observed within last 30 days that have not yet been confirmed
†1 patient censored due to subsequent chemo prior to signs of progression

**Rova-T swimmer plot for DLL3+ patients**

![Graph showing duration of response by dosing cohort](image.png)
An open-label, single-arm, phase 2 Study evaluating the efficacy, safety and pharmacokinetics of Rovalpituzumab Tesirine (SC16LD6.5) for third-line and later treatment of subjects with relapsed or refractory delta-like protein 3-expressing SCLC (TRINITY)

- Histologically confirmed SCLC with documented PD after at least 2 prior systemic regimens, including at least one platinum-based regimen

- DLL3-expressing SCLC based on central IHC assessment of banked or otherwise representative tumor tissue. Positive is defined as staining in ≥ 1% of tumor cells

- ECOG PS of 0 or 1

- Estimated enrollment, 154 pts
NOTCH inhibitors in SCLC

- OMP-59R5, a fully human IgG2 antibody, inhibits signaling of NOTCH 2 / 3 receptors

- Phase Ib/II study of OMP-59R5 in combination with etoposide/platinum in untreated ED-SCLC showed promise with 13/16 (81%) attaining a PR and 3 achieving SD
PARP pathway

- Treatment for SCLC relies on DNA-damaging agents (CT, RT); inhibition of DNA damage repair, logical approach

- PARP inhibition, activity in preclinical models and in a subset of SCLC pts

- Single activity of veliparib and synergy with platinum/etoposide demonstrated in cell lines and animal models
  - Phase II trial of platinum/etoposide +/- veliparib ongoing

- Randomized phase II trial of olaparib vs placebo as maintenance after CT, recruitment closed

- Talazoparib, single agent activity in SCLC in a phase I trial
Temozolomide/veliparib

- SCLC, characterized by frequent aberrant methylation and epigenetic silencing of the MGMT gene

- Temozolomide phase II in 62 pts with relapsed SCLC *(Pietanza, CCR 12)*
  - 20% ORR (23%, sensitive group / 13%, refractory cohort)
  - Pts with tumor demonstrating MGMT promoter methylation responded better to treatment

- Phase II comparing temozolomide/veliparib vs temozolomide/placebo, ongoing
Hedgehog pathway

- Hedgehog signaling pathway frequently disrupted in SCLC
  - Occurs in cell-autonomous manner, independent of the lung microenvironment
  - May play a significant role in the development and proliferation of SCLC
  - Inhibition of hedgehog pathway decreases cell growth

- Ongoing trials of hedgehog inhibitors in SCLC, GDC-0449, IPI-926, LDE225
Aurora kinases

- Aurora kinases comprise a family of protein kinases that play a critical role in the mitotic process.

- Aurora kinase inhibitors effective in SCLC cell lines bearing MYC amplification, which occurs in 3-7% of SCLC pts.

- Phase II of alisertib in SCLC:
  - RR 21%, 19% in sensitive relapse and 27% in resistant relapse
  - PFS 2.6 mo in the sensitive and 1.4 mo in the resistant relapse
  - Ongoing randomized phase II trial comparing paclitaxel alone to paclitaxel/alisertinib in SCLC pts who progress after etoposide/platinum (NCT02038647)
Fibroblast growth factor receptor signaling pathway

- FGFR1 gene amplified in 5-6% of pts with SCLC
- High levels of serum FGF2 associated with poor prognosis in SCLC
- Efficacy of ponatinib being studied in a biomarker-driven trial (NCT01935336)
- Phase II trial to analyze lucitanib in pts with lung cancer, ongoing (NCT02109016)
PIK3CA

- Whole exon sequencing and copy number analysis on Japanese pts with SCLC detected genetic alterations in the PI3K/AKT/mTOR pathway in 36% of the tumors
Transcriptional addictions of SCLC

- High-throughout cellular screen of a diverse chemical library discovered that SCLC is sensitive to THZ1, a covalent inhibitor of CDK7
  - THZ1 may represent a prototype drug for tailored SCLC therapy

- In SCLC, evaluation of online databases and cell lines showed 30-40% have copy number gain for JAK1/2
  - AZD1480 (which targets JAK1/2/3) has single-agent activity / synergy with CT
RET

- An activating M918T RET somatic mutation identified in a metastatic SCLC tumor specimen (Davir JTO 14)

- A subpopulation of pts with SCLC may derive benefit from TKIs targeting RET
Novel targets in SCLC: summary

- Nearly uniform loss of function of TP53 and RB1
  - Not targetable at present

- Too many genetic alterations/pathways (mostly tumor suppressor genes)

- A number of potentially targetable molecular pathways have been identified
  - NOTCH most promising target

- GENOMICS and IMMUNOTHERAPY investigation required also in SCLC!!
Thanks!!

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