Translational Studies in Small Cell Lung Cancer

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Disclosures

- **Research Funding**
  - Lilly Oncology
  - Oncomed

- **Stock**
  - Andarix

- **“Borrowed Slides”**
  - Charlie Rudin
  - Lee Krug
  - Cathy Pietenza
  - Host of others
Overview

- DNA damage repair
  - PARP
  - Chk 1
- Notch
- Immunotherapy
  - Checkpoint inhibitors
  - Vaccines
  - CAR-T
DNA DAMAGE
DNA Repair: PARP Inhibitors

**Eastern Cooperative Oncology Group**

**Phase II Schema**

**Experimental Arm (D):**
- Veliparib 100 mg bid po Days 1-7
- Etoposide 100 mg/m² in 500 ml NS Days 1-3
- Cisplatin 75 mg/m² in 250 ml NS Day 1
- Every cycle for 4 cycles

**Control Arm (E):**
- Placebo 100 mg bid po Days 1-7
- Etoposide 100 mg/m² in 500 ml NS Days 1-3
- Cisplatin 75 mg/m² in 250 ml Day 1
- Every cycle for 4 cycles

**Stratification:**
1. Gender (M vs. F)
2. LDH ≤ upper limits of normal or > ULN
3. SCLC by histology
4. Extensive stage disease
5. ECOG PS: 0-1
6. Adequate hepatic, renal and marrow function
7. Eligibility criteria met

**Phase II Acrual Goal = 150**
- Cycle = 3 weeks (21 days)
- IV doses are based on actual weight

1. On days of chemotherapy, the morning veliparib/placebo dose is to be administered AFTER premedications for etoposide, prior to etoposide IV.
2. Recommended Phase II Dose (RP2D) - dose for Phase II was determined in Phase I portion of the study.
Temozolamide and PARP inhibitor for relapsed SCLC

Increased response observed with MGMT promoter methylation in tumors (38% vs. 7%; P = 0.08)

DNA Repair: CHK1 Inhibition

Nothing new under the sun…
LY2606368 in SCLC

Objectives: Pt sensitive H0 = 20%, H1 = 35%
Pt refractory H0 = 5%, H1 = 15%
NOTCH
• Complicated, multifaceted pathway. Involved in multiple aspects of differentiation and cellular function, including neuronal development.
• Notch receptors modified by addition of sugars. “fringe effect”: lunatic, manic and radical.
• Ligands: Delta (DLL1,3,4); Jagged
• Target:
  – Function
  – expression
Tarextumab (TRXT, OMP-59R5, anti-Notch2/3) is a fully human IgG2 that was originally identified by binding to Notch2.

- Inhibits the signaling of both Notch2 and Notch3 receptors
- Excellent preclinical activity in combination with platinum
Notch 2/3 targeting

• Phase I reported at ASCO 2015
• Longer survival in pts with elevated Notch 3 expression
• Randomised Phase II trial in progress.

**PINNACLE Ph2:**

- EP¹ x 6 + Tarextumab
- EP¹ x 6 + Placebo

- Ph2 ED-SCLC (Unselected) N=135
- 1:1
- To PD

¹ EP: Etoposide + cisplatin or carboplatin (physician choice in Ph2: Cis or Carbo)
Antibody-Drug Conjugate: Targeting DLL3

DLL3 is a dominant inhibitor of Notch signaling

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

Rovalpituzumab Tesirine (Rova-T; SC16LD6.5)

Drug-to-Antibody Ratio (DAR) = 2

DLL3 expression in SCLC by IHC

Vanderbilt: 60% High Expression (DLL3+)
Case Western: 22% Medium Expression

Rudin WCLC 2015
RovaT: Phase I/II Trial

80 pts enrolled

- 73 (91%) SCLC, 7 (9%) LCNEC
- 41 (51%) 2nd line, 39 (49%) 3rd line
- 1st line response: 45 (58%) sensitive, 33 (42%) resistant *
- Mean age 62 yr; 59% male/41% female; ECOG 0/1: 27%/73% *
- 50 (63%) provided archived tumor sample; 70% with “high” DLL3
- 68 (85%) pts in expansion cohorts
  - 0.3 mg/kg q6w
  - 0.2 mg/kg q3w

* Information unavailable for 2 Pts

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

<table>
<thead>
<tr>
<th># Patients Enrolled</th>
<th>Z5</th>
<th>40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose/Schedule</td>
<td>0.2 Q3W</td>
<td>0.3 Q6W</td>
</tr>
<tr>
<td>Fatigue</td>
<td>24%</td>
<td>4%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>Decreased Appetite</td>
<td>0%</td>
<td>4%</td>
</tr>
<tr>
<td>Rash Maculo-Papular</td>
<td>12%</td>
<td>0%</td>
</tr>
<tr>
<td>Oedema Peripheral</td>
<td>16%</td>
<td>0%</td>
</tr>
<tr>
<td>Anaemia</td>
<td>12%</td>
<td>0%</td>
</tr>
<tr>
<td>Erythema</td>
<td>8%</td>
<td>4%</td>
</tr>
<tr>
<td>Serosal Effusions</td>
<td>16%</td>
<td>12%</td>
</tr>
<tr>
<td>Nausea</td>
<td>20%</td>
<td>0%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>8%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Rudin, WCLC 2015
RovaT: Response

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>Total</td>
<td>14</td>
<td>6</td>
<td></td>
<td>9</td>
<td></td>
</tr>
</tbody>
</table>

* DOR and OS excluding 3 new responses observed within last 60 days that have not yet been confirmed
*1 patient censored due to subsequent chemor prior to signs of progression

Overall response rate

<table>
<thead>
<tr>
<th></th>
<th>Topotecan</th>
<th>Rova-T: SC16LD6.5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Pts &amp; dose levels</td>
<td>DLL3+ Ph 1b Cohorts</td>
</tr>
<tr>
<td>2nd Line</td>
<td>17%</td>
<td>22%</td>
</tr>
<tr>
<td>3rd Line</td>
<td>No Approved Drug</td>
<td>17%</td>
</tr>
<tr>
<td>Sensitive to C/E</td>
<td>23%</td>
<td>24%</td>
</tr>
<tr>
<td>Resistant to C/E</td>
<td>9%</td>
<td>14%</td>
</tr>
</tbody>
</table>

Durability of Response at RP2D (0.3 mg/kg q6w): 182+ days
IMMUNOTHERAPY
Regulation of immune response
Global Mutational Spectrum of SCLC

8.88 mutations/Mb
(7.4 mutations/Mb in protein changing genes)

CTLA-4 Inhibitor: Ipilimumab

• Ipilimumab is a humanized IgG1 monoclonal antibody against CTLA-4

• By blocking the inhibitory signal provided by CTLA-4, this class of antibodies can prolong the activation and proliferation of tumor-directed cytotoxic T cells, thus promoting an anti-tumor immune response

Spigel DR & Socinski MA. JTO. 2013;8:587.
Phase II Study of Ipilimumab in Lung Cancer

First-line Stage IIIb/IV NSCLC (n=204) ED-SCLC (n=130)

<table>
<thead>
<tr>
<th>Randomize</th>
<th>1:1:1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concurrent IPI + Pac/Carbo</td>
<td></td>
</tr>
<tr>
<td>Phased* IPI + Pac/Carbo</td>
<td></td>
</tr>
<tr>
<td>Control p + Pac/Carbo</td>
<td></td>
</tr>
</tbody>
</table>

Treatment Phase

C: chemotherapy doublet (Pac 175mg/m²)/Carbo (AUC=6); IPI: Ipilimumab (10 mg IV); p: Placebo

*Phased: 2 doses of paclitaxel/carboplatin given prior to start of ipilimumab

Note: Steroids were given as premedication for chemotherapy

Adopted from BMS.

Phase II Study of Ipilimumab in SCLC

- Phased schedule:
  - Significantly improved irPFS
  - Trend for improved OS

- No trend for concurrent schedule

Phase III Study of Ipilimumab in SCLC (NCT01450761)

Study population:
• ED SCLC
• Brain mets allowed if stable
• Measurable disease not required

Primary end-point: OS

Approximately 210 sites
33 countries
1100 subjects
Programmed Cell Death Protein (PD-1)

- Inhibitory receptor induced when T cells are activated
- Limits activity of T cells in peripheral tissue during an inflammatory response to infection
- Limits autoimmunity
- Ligands are PDL-1 and PDL-2
- Blocking PD-1 prevents interaction with PD-L1 and PD-L2, restoring antitumor T-cell function

Analysis of PD-L1 Expression

- Samples: archival or newly obtained core or excisional biopsy of a nonirradiated lesion
- Immunohistochemistry: performed at a central laboratory using a prototype assay and the 22C3 antibody clone (Merck)
- Positivity: membranous PD-L1 expression in ≥1% of tumor and associated inflammatory cells or positive staining in stroma
- SCLC cohort: of 147 evaluable samples, 42 PD-L1 positive (28.6%)

Examples of PD-L1 Staining in SCLC Specimens from KEYNOTE-028

Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic, n (%)</th>
<th>N = 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>60.5 (41–80)</td>
</tr>
<tr>
<td>Male</td>
<td>14 (58.3)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>13 (54.2)</td>
</tr>
<tr>
<td>Asian</td>
<td>3 (12.5)</td>
</tr>
<tr>
<td>Not specified</td>
<td>8 (33.3)</td>
</tr>
<tr>
<td>ECOG performance status</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>7 (29.2)</td>
</tr>
<tr>
<td>1</td>
<td>17 (70.8)</td>
</tr>
<tr>
<td>Stable brain metastases</td>
<td>3 (12.5)</td>
</tr>
</tbody>
</table>

Histology

- Small cell | 23 (95.8) |
- Neuroendocrine | 1 (4.2) |

Type of prior therapy

- Chemotherapy | 24 (100) |
- Radiotherapy | 1 (4.2) |
- Investigational TKI | 1 (4.2) |
- Other investigational therapy | 1 (4.2) |

Specific prior therapy

- Carboplatin + etoposide | 24 (100) |
- Irinotecan or topotecan | 11 (46.8) |
- Taxane | 7 (29.2) |

Antitumor Activity

(RECIST v1.1, Investigator Review)

<table>
<thead>
<tr>
<th>Best Overall Response</th>
<th>n</th>
<th>%</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>0</td>
<td>0</td>
<td>0.0-14.2</td>
</tr>
<tr>
<td>Partial response</td>
<td>7</td>
<td>29.2</td>
<td>12.6-51.1</td>
</tr>
<tr>
<td>Stable disease</td>
<td>1</td>
<td>4.2</td>
<td>0.1-21.1</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>10</td>
<td>41.7</td>
<td>22.1-63.4</td>
</tr>
<tr>
<td>No assessmentb</td>
<td>6</td>
<td>25.0</td>
<td>9.8-46.7</td>
</tr>
</tbody>
</table>

Objective response rate: 29.2% (95% CI, 12.6–51.1)
Disease control rate: 33.3% (95% CI, 15.6–55.3)
Anti-PD-1/L1 therapies have clear activity in SCLC. Other trials reported at ASCO with nivolumab +/- Ipilimumab.

*No relationship between PD-L1 and response (at least in this small series and with this assay).
Checkpoint Inhibition Studies in SCLC

- A Phase 1/2, Open-label Study of Nivolumab Monotherapy or Nivolumab Combined with Ipilimumab in Subjects with Advanced or Metastatic Solid Tumors [NCT01928394]
- A Phase I/2 Study to Evaluate MEDI4736 [NCT01693562]
- A Phase I Study of MEDI4736 (Anti-PD-L1 Antibody) in Combination With Tremelimumab (Anti-CTLA-4 Antibody) in Subjects With Advanced Solid Tumors [NCT02261220]
- Phase I Trial of MK-3475 and Concurrent Chemo/Radiation for the Elimination of Small Cell Lung Cancer [NCT02402920]
- Pembrolizumab in Treating Patients With Extensive Stage Small Cell Lung Cancer After Completion of Combination Chemotherapy [NCT02359019]
VACCINES
Cell Surface Antigens of SCLC

- N-acetyl Galactosamine
- Galactose
- Fucose
- Glucose
- N-acetyl-Neuraminic acid

Glycocalyx (100):
- GM2
- GD2
- GD3
- FUC
- GM1
- Globo H
- sLeα

Membrane (100):
- Glycolipids
- KSA
- Glycoproteins

Polysialic Acid

Glycocalyx:

- 1.3-2 KD
- 40 KD
- 150 KD

Embryonic NCAM
Gangliosides in SCLC

Past Failures: SILVA Trial

Giaccone et al, J Clin Oncol 2005

Limited SCLC
PR or CR after chemo/RT
PCI optional

Observation

N=258

BEC-2 (2.5 mg) + BCG intradermal injections
weeks 0, 2, 4, 6, 10

N=257

OS

PFS

Surv Based on Imm Resp

Giaccone et al, J Clin Oncol 2005
Gangliosides in SCLC

Fucosyl-GM1: Background

- Ganglioside isolated from bovine thyroid gland.
- Identified by immunofluorescence using the monoclonal antibody F12 in 19/21 human SCLC tumors.
- Detected in culture media from SCLC cell lines, and in tumor extracts and serum of nude mouse xenografts.
- Detected in the serum of 6/20 patients with extensive stage SCLC but not in NSCLC patients or volunteers.

Macher, Biochim Biophys Acta, 1979
Brezicka, Cancer Res, 1989
Vangsted, Cancer Res, 1991

Courtesy of L. Krug
Prevalence of fucosyl GM1 by IHC (BMS analyses)
- ~50% (12 positive/24 total samples)

Prevalence of fucosyl GM1 in SCLC in the literature
- ~70% (89 positive/124 total samples)
First-in-class fully human IgG1 mAb

High affinity and dose-dependent saturable binding to FucGM1 -- No binding to GM1

Optimized for enhanced ADCC by elimination of fucosylation on Fc domain

Gangliosides in SCLC
Anti-FucGM1 mAB BMS-986012

DMS79 SCLC Xenograft Model

Tumor volume (mm\(^3\))

Days Post Implantation

= Dosing

(\text{median, n=9})

Vehicle
Isotype 3mg/kg
BMS-986012, 0.01 mg/kg
BMS-986012, 0.1 mg/kg
BMS-986012, 0.3 mg/kg
BMS-986012, 1 mg/kg
BMS-986012, 3 mg/kg
Gangliosides in SCLC
Phase I/II Trial with BMS-986012

Phase I Dose Escalation
Eligibility: Ext or limited SCLC
At least 1 prior chemo regimen

Primary endpoint: Safety

<table>
<thead>
<tr>
<th>Dose level</th>
<th>BMS-986012 IV Q3W</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>160</td>
</tr>
<tr>
<td>3</td>
<td>400</td>
</tr>
<tr>
<td>4</td>
<td>1000</td>
</tr>
</tbody>
</table>

Phase II Expansion
Eligibility: Relapsed SCLC
One prior chemo regimen

Primary Endpoint: Response rate

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Group</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Refractory, MTD</td>
<td>22</td>
</tr>
<tr>
<td>B</td>
<td>Refractory, dose below MTD</td>
<td>22</td>
</tr>
<tr>
<td>C</td>
<td>Sensitive, MTD</td>
<td>28</td>
</tr>
<tr>
<td>D</td>
<td>Sensitive, dose below MTD</td>
<td>28</td>
</tr>
</tbody>
</table>

Supported by Bristol-Myers Squibb

Participating sites: MSKCC, Duke, Cross Cancer Institute, Monash Cancer Centre
CAR-T CELLS
If endogenous T cell elicitation is difficult due to the immunosuppressive microenvironment, then ex vivo T cell culture expansion should be considered.

Chimeric antigen receptor T cells provide advantages:
- HLA-independent
- Does not require stimulation by host immune system
- Targets SCLC antigens

Adapted from J. Heymach
Potential CARs for SCLC

- 50% of patients detectable auto-antibodies to at least 1 target (e.g. p53, NY-ESO-1, CD56, SOX-2 etc).
- CD56 (NCAM) selected as initial candidate for CARs
  - highly expressed in SCLC and other malignancies
  - also expressed in neuronal tissue, lower expression in skeletal muscle, NK cells, and T cells (potential fratricide)
  - ADCs have been tested with CD56

<table>
<thead>
<tr>
<th>Malignoma</th>
<th>% NCAM positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuroblastoma</td>
<td>≈100%</td>
</tr>
<tr>
<td>Rhabdomyosarkoma</td>
<td>≈100%</td>
</tr>
<tr>
<td>Glioma</td>
<td>≈100%</td>
</tr>
<tr>
<td>Astrocytoma</td>
<td>≈100%</td>
</tr>
<tr>
<td>Small cell lung cancer</td>
<td>≈100%</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>78%</td>
</tr>
<tr>
<td>Acute myeloid leukemia</td>
<td>53%</td>
</tr>
</tbody>
</table>

Robertson et. al. CCR. 2011
CD56R-CAR T cells control SCLC growth in vivo

Early experiments (low dose CARs, 1 CAR: 20 tumor cells) indicate CAR T cells may control even well established tumors

(Denning unpublished data) 2015, presented MSKCC
Concerns

CD56 is expressed on WT tissues (on target, off tissue)
*Damage to the brain and other neural tissue possible similar to autoimmune already displayed in some SCLC patients.*

Natural Killer cells loss
*Would patient become more susceptible to viral infections or NK cells act as a “decoy” reducing CD56R-CAR killing at tumor site.*

Antigen loss
*Intense selection by CAR T cells may allow rapid generation of tumor escape variants most likely due to antigen loss.*
General Comments: Clinical Trial Design Issues

• Traditional designs
  – Combination with existing regimens: PE vs. PE + X (front line)
  – Second line in combination or against: Topo vs. Topo + X or Topo vs. X

• Problems
  – Requires excellent PS
  – Fails to recognize the real world presentation (very sick)
  – Fails to exploit the value of current therapy (high RR)

• Suggest
  – Consolidation design:
    – PE -> X vs. PE
Conclusions

• Improved understanding of SCLC biology has led to the identification of new targets/strategies.
• Notch targeting and immunotherapy are most advanced.
• Clinical trial design should be optimized for this disease