Immunotherapy targets for SCLC

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Disclosures: Advisory boards for BMS, Merck, Genentech, AZ, G1 Therapeutics, EMD-Serono, GSK, Boehringer-Ingelheim, Spectrum
An apparent paradox: despite its high TMB, SCLC has a relatively immunosuppressed phenotype

Compared to NSCLC, reduced levels of HLA, death receptors, and low checkpoint targets

Denning, Wistuba, Heymach et al, unpublished..
Proposed mechanisms for immunosuppressed phenotype

Decreased Antigen Presentation (HLA, B2M, TAP-1)


Increase in suppressive cell populations (T regs, suppressive myeloid pop.)

(Antonia et. al. CCR. 2006)
## Proposed mechanisms for immunosuppressed phenotype

Decrease in cytokines that support T cell expansion  
(Fischer et. al. Ann Oncol. 1995)

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Controls (n = 44)</th>
<th>SCLC LD (n = 36)</th>
<th>SCLC ED (n = 22)</th>
<th>NSCLC M0 (n = 66)</th>
<th>NSCLC M1 (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1α</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (pg/ml)</td>
<td>145</td>
<td>164</td>
<td>124</td>
<td>215</td>
<td>158</td>
</tr>
<tr>
<td>95% CI</td>
<td>119–171</td>
<td>114–214</td>
<td>64–183</td>
<td>168–262</td>
<td>119–197</td>
</tr>
<tr>
<td>P-value</td>
<td>0.9</td>
<td>0.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-1β</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Mean (ng/ml)</td>
<td>1461</td>
<td>2016</td>
<td>1372</td>
<td>1702</td>
<td>1609</td>
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<tr>
<td>95% CI</td>
<td>1112–1810</td>
<td>1304–2729</td>
<td>605–239</td>
<td>1369–2035</td>
<td>989–2229</td>
</tr>
<tr>
<td>P-value</td>
<td>0.66</td>
<td>0.066</td>
<td></td>
<td></td>
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<tr>
<td>IL-2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (ng/ml)</td>
<td>3086</td>
<td>1480</td>
<td>1153</td>
<td>1426</td>
<td>1470</td>
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<tr>
<td>95% CI</td>
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<td>988–1972</td>
<td>770–1537</td>
<td>1023–1827</td>
<td>909–2033</td>
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<tr>
<td>P-value</td>
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<td>0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0002</td>
</tr>
<tr>
<td>IFNa</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (U/ml)</td>
<td>152</td>
<td>61</td>
<td>54</td>
<td>78</td>
<td>45</td>
</tr>
<tr>
<td>95% CI</td>
<td>86–218</td>
<td>41–80</td>
<td>24–84</td>
<td>57–99</td>
<td>32–60</td>
</tr>
<tr>
<td>P-value</td>
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<td>0.0003</td>
<td>0.005</td>
<td>0.005</td>
<td>0.0002</td>
</tr>
<tr>
<td>IFNy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (ng/ml)</td>
<td>71240</td>
<td>37297</td>
<td>21619</td>
<td>50702</td>
<td>43945</td>
</tr>
<tr>
<td>95% CI</td>
<td>53652–88829</td>
<td>24723–49871</td>
<td>12244–30993</td>
<td>40568–60838</td>
<td>27743–60148</td>
</tr>
<tr>
<td>P-value</td>
<td>0.001</td>
<td>0.0001</td>
<td>0.045</td>
<td>0.012</td>
<td></td>
</tr>
<tr>
<td>IFNγ</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (ng/ml)</td>
<td>995</td>
<td>1140</td>
<td>745</td>
<td>1228</td>
<td>935</td>
</tr>
<tr>
<td>95% CI</td>
<td>776–1214</td>
<td>647–1632</td>
<td>296–1195</td>
<td>863–1593</td>
<td>694–1176</td>
</tr>
<tr>
<td>P-value</td>
<td>0.47</td>
<td>0.012</td>
<td>0.9</td>
<td>0.9</td>
<td>0.8</td>
</tr>
</tbody>
</table>
Immune status in SCLC is important

PD-L1 expression correlated to longer survival in SCLC patients

Could be indicative of active T cells and the presence of IFN-γ

Ishii et. al. J Thorac Onc. 2014
Nivo or Nivo/Ipi for recurrent SCLC (Checkmate 32)


<table>
<thead>
<tr>
<th></th>
<th>ORR</th>
<th>mPFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>N3</td>
<td>10%</td>
<td>1.4m</td>
</tr>
<tr>
<td>N1+I3</td>
<td>23%</td>
<td>2.6m</td>
</tr>
<tr>
<td>N3+I1</td>
<td>19%</td>
<td>1.4m</td>
</tr>
</tbody>
</table>
U01: Novel therapeutic approaches for enhancing antitumor immunity in SCLC (Heymach/Byers/Sage)

**Aim 1. DDR inhibition to increase neoantigen expression and anti-PD-1/PD-L1 response**
1A: DDR targeting to increase the expression of tumor associated neoantigen
1B: DDR targeting ± PD-1/PD-L1 inhibition in SCLC
1C. Effect of DDR inhibition on immune infiltration and markers in SCLC patients

**Aim 2. CDK4/6 inhibition to protect immune cells from chemotherapy-induced cytotoxicity and enhance anti-PD-1/PD-L1 response**
2A. CDK4/6 inhibition to protect immune cells from chemotherapy-induced cytotoxicity
2B. CDK4/6 inhibition ± immunotherapy in syngeneic and allograft SCLC models
2C. CDK4/6 inhibition to protect immune cells from chemotherapy in SCLC patients

**Aim 3. Co-activation of anti-tumorigenic macrophages to enhance T-cell based immunotherapies**
3A. CD47 blockade and chemo combinations to suppress the growth of SCLC
3B. CD47 and T-cell checkpoint blockade to enhance the efficacy of single therapies in models of SCLC

**Cores:**
- Preclinical Models Team (GEMMs, Human cell lines, allografts)
- Immune/Genomic Profiling Team
- Biostats/Bioinformatics team
CAR-T cells for SCLC

Warren Denning  Laurence Cooper  Denise Crossland
If endogenous T cell elicitation is difficult due to an 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
CARs under consideration for SCLC

- 50% of patients detectable auto-antibodies to at least 1 target (Robertson et. al. CCR. 2011.)

  p53           SOX2
  CAGE          Hu-D
  NY-ESO-1      CD56
  GBU4-5        GD2
  Annexin I    GD3

- Other potential targets include DLL3
CD56 is an attractive target

**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>Distribution of NCAM in malignant tissues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignoma</td>
</tr>
<tr>
<td>Neuroblastoma</td>
</tr>
<tr>
<td>Rhabdomyosarkoma</td>
</tr>
<tr>
<td>Glioma</td>
</tr>
<tr>
<td>Astrocytoma</td>
</tr>
<tr>
<td>Small cell lung cancer</td>
</tr>
<tr>
<td>Multiple myeloma</td>
</tr>
<tr>
<td>Acute myeloid leukemia</td>
</tr>
</tbody>
</table>

(Jensen et al. CL. 2007)
CAR Design

2nd Gen CAR

Importance

Antigen binding

Flexibility & “Reach”

Molecular Association

Co-stimulation

Activation

scVf

CD56R

scaffold

IgG Fc

transmembrane domain

CD3z

signaling domain

CD28

CD3z

(Adapted Gilham et. al. Trends: Mol Med. 2012.)
Schema for generation of T-CARs via Sleeping Beauty system (Cooper et al)

PBMCs

Sleeping Beauty Transposase + pCAR

Nucleofection

Selection via artificial APC

K562 AaPC

Proliferation with IL-2/IL-21

Cryopreservation (Release & In-process testing)

Infusion

Car expressing T cells

99% 52% 46%

CD3  CD4  CD8

(Singh, Moyes, Huls, Cooper. Cancer Gene Therapy. 2015)
CD56R-CAR T cells inhibit tumor growth in CD56+ neuroblastoma model
CD56R-CAR T cells inhibit tumor growth in a CD56+, but not CD56-, SCLC model

Denning et al, Oncogene, in press
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*
CDK4/6 inhibition arrests hematopoietic cells and other Rb-intact cells, but not Rb-deficient tumor cells, at G1 phase.
CDK4/6 inhibition may protect **Rb-intact** cells from chemotherapy toxicity without diminishing the therapeutic effect in SCLC **Rb mutant** tumors.

**Rb-deficient SCLC**

Chemotherapy → High chemo-toxicity

Antitumor efficacy

Chemotherapy → Reduced chemo-toxicity in Rb-intact cells

Antitumor efficacy not reduced
1\textsuperscript{st}-line SCLC complete blood counts (CBCs): no clinically relevant myelotoxicity

Robust myelopreservation: mean CBCs above clinically relevant cytopenia thresholds for all blood lineages, no febrile neutropenia

Data from Rocha Lima et al., ASCO 2017
The CDK4/6 inhibitor G1T28 enhances chemotherapy protection of all blood lineages *in vivo*
CDK4/6 inhibition by G1T28 protects peripheral CD4+ and CD8+ cells from cisplatin-induced cytotoxicity *in vivo*.

Guijarro et al, (Heymach lab) unpublished
The CDK4/6 inhibitor G1T28 enhanced chemotherapy toxicity and protect TILs in vivo

Guijarro et al, (Heymach lab) unpublished
### Three ongoing POC trials in extensive–stage SCLC

| Setting        | Combination                                      | Phase                          | Total # Patients | Primary Endpoints | Secondary Endpoints | Current Status                           |
|----------------|--------------------------------------------------|================================|------------------|-------------------|---------------------|------------------------------------------|
| 1st-line       | carboplatin (AUC=5) and etoposide (100 mg/m²)    | 1b: open label                 | 96               | myelo-preservation: e.g. FN, transfusions | ORR, PFS, OS         | 2a enrollment completed; top-line data expected in 1Q18 |
|                |                                                  | 2a: randomized (1:1), placebo-controlled | 1b: 19 2a: 77    |                   |                     |                                          |
| 2nd/3rd-line   | topotecan (0.75 mg/m² and 1.5 mg/m²)             | 1b: open label                 | ~ 120            | myelo-preservation: e.g. FN, transfusions | ORR, PFS, OS         | 2a enrollment completion anticipated 2Q18; top-line data expected 4Q18 |
|                |                                                  | 2a: randomized (2:1), placebo-controlled | 1b: 32 2a: ~ 90  |                   |                     |                                          |
| 1st-line       | carboplatin/etoposide/atezolizumab               | 2: randomized (1:1), placebo-controlled | ~ 100            |                   | ORR, PFS, myelo-preservation | enrollment completion anticipated 3Q18 |

Open-label data: no febrile neutropenia (FN) in 51 patients, >250 cycles chemo (historical FN rates ~ 30% with topotecan)
1\textsuperscript{st}-line SCLC: trilaciclib does not compromise efficacy of chemo

Data from Rocha Lima et al., ASCO 2017

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Evaluable</th>
<th>Trilaciclib dose (mg/m(^2))</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8</td>
<td>200</td>
<td>Carboplatin AUC = 5 on Day 1 and etoposide 100 mg/m(^2) on Days 1-3</td>
</tr>
<tr>
<td>2</td>
<td>9</td>
<td>240</td>
<td></td>
</tr>
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</table>

Best % tumor change from baseline

<table>
<thead>
<tr>
<th>Evaluable</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
<th>ORR</th>
<th>CBR</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td>1</td>
<td>14</td>
<td>1</td>
<td>1</td>
<td>88%</td>
<td>94%</td>
</tr>
</tbody>
</table>

Literature* etop/carb efficacy (n=387)
- 52% ORR (only 1 CR)
- 75% CBR

*Target lesion change consistent with PR at cycle 2; best response was PD due to occurrence of new lesions at cycle 2

Data from Rocha Lima et al., ASCO 2017
Trilaciclib/EP/atezolizumab in 1st-line SCLC

**INDUCTION PHASE (4x 21-day cycles)**
- Carboplatin + Etoposide + Atezolizumab + Trilaciclib
- Carboplatin + Etoposide + Atezolizumab + Placebo

**MAINTENANCE PHASE**
- Atezolizumab
- Atezolizumab

- Phase 2, randomized (1:1), global, double-blind, placebo-controlled
- Key objectives: PFS, OS, RR, safety in newly diagnosed ES SCLC patients
- Sample size: 100 patients
- NCT03041311
G1 Therapeutics Announces Positive Trilaciclib Phase 2a Topline Data Showing Robust Myelopreservation Benefits in Patients with Small Cell Lung Cancer

- 77 1L ES SCLC patients, EP+/- trilaciclib. Primary endpoint: myelopreservation
- Improved myelopreservation endpoints including G3/4 Heme AEs
- ORR trilaciclib 66.7%, placebo 62.2% (p=0.6759)
- PFS trilaciclib 6.2 months, placebo 5.0 months (hazard ratio 0.6, p=0.06)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>EP(1) + placebo Patients</th>
<th>EP + trilaciclib Patients</th>
<th>% Reduction</th>
<th>P-value (2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with Gr 3/4 Hematologic TEAEs</td>
<td>27 (73.0%)</td>
<td>9 (23.7%)</td>
<td>67.5%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Patients with Gr 3/4 Neutropenia</td>
<td>30 (81.1%)</td>
<td>15 (39.5%)</td>
<td>51.3%</td>
<td>0.0002</td>
</tr>
<tr>
<td>Patients with Gr 4 Neutropenia</td>
<td>16 (43.2%)</td>
<td>2 (5.3%)</td>
<td>87.7%</td>
<td>0.0001</td>
</tr>
<tr>
<td>Patients with Gr 4 Neutropenia in Cycle 1</td>
<td>13 (35.1%)</td>
<td>1 (2.6%)</td>
<td>92.6%</td>
<td>0.0003</td>
</tr>
<tr>
<td>Cycles with Febrile Neutropenia</td>
<td>5</td>
<td>1</td>
<td>80.8%</td>
<td>0.1542</td>
</tr>
<tr>
<td>Patients with Febrile Neutropenia</td>
<td>3 (8.1%)</td>
<td>1 (2.6%)</td>
<td>67.9%</td>
<td>0.2773</td>
</tr>
<tr>
<td>Patients with G-CSF Administration</td>
<td>24 (64.9%)</td>
<td>4 (10.5%)</td>
<td>83.8%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Patients with Chemotherapy Cycle Delays</td>
<td>25 (67.6%)</td>
<td>15 (39.5%)</td>
<td>41.6%</td>
<td>0.0170</td>
</tr>
<tr>
<td>Patients with Chemotherapy Dose Reductions</td>
<td>13 (35.1%)</td>
<td>3 (7.9%)</td>
<td>77.5%</td>
<td>0.0033</td>
</tr>
</tbody>
</table>

G1 Therapeutics press release, 3/5/2018
Short-term exposure to small-molecule inhibitors of CDK4/6 significantly enhances T-cell activation, contributing to antitumor effects in vivo.

CDK4/6 inhibition augments the response to PD-1 blockade in multiple in vivo murine syngeneic models.
CDK4/6 inhibitor trilaciclib: the bottom line

In preclinical models:
  - Causes G1 arrest in Rb-intact but not Rb-deficient cells
  - Given *before* chemo, protects HSPCs, peripheral and tumor infiltrating CD4+ and CD8+ lymphocytes from chemotherapy-induced cytotoxicity in vivo
  - Mitigates bone marrow exhaustion;
  - Enhances the efficacy of chemotherapy in SCLC models
  - Ongoing studies for enhancing IO with chemo, RT

Clinical testing:
  - Promising clinical results for myelopreservation
  - Three randomized trials:
    - 1L: EP+/- trila
    - 2L: topotecan+/- trila
    - 1L: EP+atezo, +/- trila
CD47-blocking immunotherapies stimulate macrophage-mediated destruction of small-cell lung cancer

Kipp Weiskopf,1,2,3 Nadine S. Jahchan,3,4,5 Peter J. Schnorr,1,2,3 Sandra Cristea,3,4,5 Aaron M. Ring,1,2,3,6,7 Roy L. Maute,1,2,3 Anne K. Vollmer,1,2,3,8 Jens-Peter Vollmer,1,2,3 Jie Liu,1,2,3 Jing Shan Lim,3,4,5 Dian Yang,3,4,5 Garrett Seitz,3,4,5 Thuyen Nguyen,3,4,5 Di Wu,3,6,7 Kevin Jude,2,3,6,7 Heather Guerston,9 Amira Barkal,1,2,3 Francesca Trapani,10 Julie George,11 John T. Poirier,12 Eric E. Gardner,12 Linde A. Miles,12 Elisa de Stanchina,12 Shane M. Lofgren,3,4,5 Hannes Vogel,13,11 Monte M. Winslow,5,13 Caroline Dive,10 Roman K. Thomas,14 Charles M. Rudin,12 Matt van de Rijn,10 Ravindra Majeti,1,2,3 K. Christopher Garcia,1,3,6,7 Irving L. Weissman,1,2,3,12 and Julien Sage1,4,5

NCI-H82 GFP-Luciferase

C

PBS

Anti-CD47

Radiance (p/s/cm²/sr x 10⁹)

D

Total flux (photons/s)

4 17 31 46

Days after engraftment

NS

PBS Anti-CD47

E

Treatment (d4)

0 25 50 75 100

Days after engraftment

125

P < 0.0001

Weiskopf et al, JCI, 2016
Genetic ablation of Cd47 inhibits SCLC growth in vivo

Weiskopf et al, JCI, 2016
Immunotherapy targets for SCLC: the bottom line

• Despite high TMB, SCLC typically has a more immunosuppressed phenotype than NSCLC
  – DDR agents may “warm up” cold tumors

• PD1+CTLA4 has activity in ES SCLC, especially in TMB high group

• CAR-T cells targeting CD56 demonstrate preclinical activity. Other CAR-Ts being developed.

• CDK4/6 inhibition a promising strategy for myelopreservation and potentially enhancing IO when given with chemo or RT.

• CD47 another potential target.
Acknowledgements

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Irene Guijarro (CDK4/6i)
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Haifa Hamdi
Fahao Zhang

Cooper Lab
Denise Crossland
Sonny Ang
Simon Olivares
Natalya Belousova
Alan Guerrero
Ana Korngold

Byers lab
Sage lab

Minna lab
UTSW

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• U01 (Heymach/Byers/Sage)
• UTSW/UTMDACC Lung SPORE Grant 5 P50 CA070907
• Lung Cancer Moon Shot
• Lung Cancer Research Foundation
• NIH Cancer Center Support Grant CA016672
Combination treatment of CDK4/6 inhibitors synergize anti–PD-1 antibody–induced antitumor immunity through T cells

Treatment schedule: The mice were treated with either CDK4/6 inhibitor [trilaciclib (Trila.) or palbociclib (Palb.), 100 mg/kg] intermittently (3 days on, 4 days off) with or without PD-1 antibody (200 μg/mouse, 3 times a week) as indicated starting from day 3 (MC38) or day 7 (CT26).
High mutation burden in SCLC – but discordant immunotherapy response

Alexandrov et al., 2013; Schumacher and Schreiber 2015