DDR and cell cycle vulnerabilities

Lauren Averett Byers, MD

SCLC Research Consortium Meeting
National Cancer Institute
16 March 2018
NCI Funded SCLC Projects

• NIH/NCI R01-CA207295
  – Therapeutic strategies for targeting PARP1 in small cell lung cancer

• NIH/NCI U01-CA213273
  – Novel therapeutic approaches for enhancing antitumor immunity and overcoming PD-1/PD-L1 inhibitor resistance in SCLC
    • Project 1: DNA damage response (DDR) inhibition to enhance anti-PD1/PDL1 response

• UTSW/MDACC Lung SPORE
Are there distinct molecular profiles that translate into specific therapeutic vulnerabilities?

Wang and Byers, Cancer Discovery 2013
Rewiring of Small Cell Lung Cancer promotes increased expression of DDR proteins
DNA Damage Response (DDR) – a therapeutic vulnerability in SCLC?

Cardnell et al. CCR, 2013
Feng et al AACR-NCI-EORTC 2014
CHK1 Inhibition in Small-Cell Lung Cancer Produces Single-Agent Activity in Biomarker-Defined Disease Subsets and Combination Activity with Cisplatin or Olaparib

Triparna Sen¹, Pan Tong², C. Allison Stewart¹, Sandra Cristea³,⁴, Aly Valliani¹, David S. Shames⁵, Abena B. Redwood⁶, You Hong Fan¹, Lerong Li², Bonnie S. Glisson¹, John D. Minna⁷, Julien Sage⁸,⁹, Don L. Gibbons¹⁰, Helen Piwnica-Worms⁸, John V. Heymach¹¹, Jing Wang², and Lauren Averett Byers¹
Targeting a non-oncogene addiction to the ATR/CHK1 axis for the treatment of small cell lung cancer

Fabian Doerr\(^1,2,3\), Julie George\(^4\), Anna Schmitt\(^1,2\), Filippo Beleggia\(^1,2\), Tim Rehkämper\(^1,2\), Sarah Hermann\(^1,2\), Yvon Walter\(^6\), Jean-Philip Weber\(^7\), Roman K. Thomas\(^4,6,9\), Maike Wittersheim\(^8\), Reinhard Büttner\(^9\), Thorsten Persigehl\(^7\) & H. Christian Reinhardt\(^1,2\)

Scientific Reports, Nov 2017

ATRi (VE-822), Chk1i (PF-477736)

ATRi sensitivity in human cell lines

VX970

AZD6738

Carl Gay, IASLC Targeted Therapy Mtg 2018
Targeting AXL and mTOR Pathway Overcomes Primary and Acquired Resistance to WEE1 Inhibition in Small-Cell Lung Cancer

Biomarkers of Primary WEE1 resistance

Biomarkers of Acquired WEE1 resistance

Wee1 + AXL inhibition combination (WEE1 resistant model)
Growing number of PARP, ATR, Chk1, Wee1 and other DDR inhibitors in clinical trials

Bunn, J Thorac Oncol 2016

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Table 1 DDR-targeted therapy clinical trials in SCLC (list includes ongoing trials as of 12/2017)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment</th>
<th>Indication</th>
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</thead>
<tbody>
<tr>
<td>NCT02327016 Phase 1: veliparib alone; phase 2: veliparib + topotecan</td>
<td>Relapsed/refractory ES-SCLC</td>
<td></td>
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<tr>
<td>NCT02734004 Phase 1/2; MEDI4736 (anti-PD-L1) in combination with olaparib</td>
<td>Advanced solid tumors including ES-SCLC cohort</td>
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<tr>
<td>NCT02283690 Phase 1: carboplatin/etoposide +/- veliparib</td>
<td>Treatment-naïve ES-SCLC</td>
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<tr>
<td>NCT02799992 Phase 1/2: CRXL101 (camptothecin nanoparticle) + olaparib</td>
<td>Relapsed/refractory ES-SCLC</td>
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<tr>
<td>NCT01642251 Phase 1/2: cisplatin/etoposide +/- veliparib</td>
<td>Treatment-naïve ES-SCLC</td>
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<tr>
<td>NCT02498613 Phase 2: olaparib + cediranib (anti-VEGFR TKI)</td>
<td>Advanced solid tumors including ES-SCLC cohort</td>
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<tr>
<td>NCT02446704 Phase 2: olaparib + TMZ</td>
<td>Relapsed/refractory ES-SCLC</td>
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<tr>
<td>NCT03096882 Phase 2: olaparib monotherapy</td>
<td>Relapsed/refractory ES-SCLC harboring HR mutations</td>
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<tr>
<td>NCT02511759 Phase 1b: olaparib + AZD1775 (WEE1 inhibitor)</td>
<td>Advanced solid tumors including ES-SCLC cohort</td>
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<tr>
<td>ATR Inhibitor trials including SCLC</td>
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<tr>
<td>NCT02487095 Phase 1/2: topotecan + VX970</td>
<td>Advanced small cell cancers</td>
<td></td>
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<tr>
<td>NCT02589522 Phase 1: VX 970 + WBRT</td>
<td>Brain metastases from tumors</td>
<td></td>
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<tr>
<td>NCT02229923 Phase 1: AZD6738 +/- RT</td>
<td>Advanced solid tumors</td>
<td></td>
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<tr>
<td>NCT02723864 Phase 1: veliparib + VX-970 + cisplatin</td>
<td>Advanced solid tumors</td>
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<tr>
<td>NCT02595303 Phase 1: VX-970 + irinotecan</td>
<td>Advanced solid tumors</td>
<td></td>
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<tr>
<td>NCT02157792 Phase 1: VX-970 + chemotherapy</td>
<td>Advanced solid tumors</td>
<td></td>
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<tr>
<td>NCT03169956 Phase 1: BAY189544 monotherapy</td>
<td>Advanced solid tumors</td>
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<tr>
<td>CHK inhibitor trials including SCLC</td>
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<tr>
<td>NCT02735980 Phase 2: prexasertib monotherapy</td>
<td>Relapsed/refractory ES-SCLC</td>
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<tr>
<td>NCT02797984 Phase 1: SRA757 monotherapy</td>
<td>Advanced solid tumors</td>
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<tr>
<td>NCT02797977 Phase 1: SRA737 + gemcitabine +/- cisplatin</td>
<td>Advanced solid tumors</td>
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<tr>
<td>NCT02873975 Phase 2: prexasertib monotherapy</td>
<td>Advanced solid tumors with HR deficiency or replicative stress</td>
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<tr>
<td>NCT03057145 Phase 1: prexasertib + olaparib</td>
<td>Advanced solid tumors</td>
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<tr>
<td>Wee1 inhibitor trials including SCLC</td>
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<tr>
<td>NCT02482311 Phase 1: AZD1775 monotherapy</td>
<td>Advanced solid tumors including ES-SCLC cohort</td>
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<tr>
<td>NCT02511795 Phase 1b: AZD1775 + olaparib</td>
<td>Relapsed/refractory ES-SCLC</td>
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<tr>
<td>NCT02593019 Phase 2: AZD1775 monotherapy</td>
<td>Relapsed/refractory ES-SCLC with MYC amplifications or CDKN2A + TP53 mutations</td>
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<tr>
<td>NCT02889907 Phase 2: AZD1775 monotherapy</td>
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</table>

Sen, Gay, and Byers. TLCR 2018
Combination of Temozolomide with the PARP inhibitor Veliparib improves outcomes in relapsed SCLC

Recurrent SCLC patients
- 1-2 prior regimens
- 104 pts treated

Clinical Outcomes
- Higher Response Rate in Veliparib/TMZ arm (39% vs. 14%)
- Higher Overall Survival with combination in patients with biomarker-positive (SLFN11 ≥ 1%) tumors

Pietanza and Byers, et al, ASCO 2016; World Lung Cancer Conference 2017
NSCLC – Genomic Pie Slices

- MAP2K1
- NRAS
- ROS1 fusions
- KIF5B-RET
- ALK fusions
- EGFR
- KRAS
- Unknown

SCLC – Evolving Proteomic Landscape

- PARP inhibitor, chemotherapy
- EMT
- SLFN11
- Other
- DLL3
- cMYC
- AXL inhibitor
- Chk1 inhibitor, Aurora Kinase Inhibitor
- Rova-T

Pao, Hutchinson; Nat Med 2012
Protein expression of TTF1 and cMYC define distinct molecular subgroups of small cell lung cancer with unique vulnerabilities to aurora kinase inhibition, DLL3 targeting, and other targeted therapies

Robert J. Cardnell¹, Lerong Li², Triparna Sen¹, Rasha Bara¹, Pan Tong², Junya Fujimoto³, Abbie S. Ireland⁴, Matthew R. Guthrie⁴, Sheila Bheddah⁵, Upasana Banerjee¹, Nene N. Kalu¹, You-Hong Fan¹, Scott J. Dylla⁵, Faye M. Johnson¹,⁶, Ignacio I. Wistuba³, Trudy G. Oliver⁴, John V. Heymach¹, Bonnie S. Glisson¹, Jing Wang²,⁴,* and Lauren A. Byers¹,⁶,*
Protein expression of TTF1 and cMYC define distinct molecular subgroups of small cell lung cancer with unique vulnerabilities to aurora kinase inhibition, DLL3 targeting, and other targeted therapies

Targets for non-NE SCLC (TTF1-low/MYC-high)  
*e.g.,* Aurora, PLK, Chk1

Low DLL3 expression in TTF1-low SCLC

SCLC patient tumors (Rovalpituzumab tesirine Clinical Trials)

<table>
<thead>
<tr>
<th>TTF1 (IHC)</th>
<th>DLL3 (IHC)</th>
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<tbody>
<tr>
<td>Positive</td>
<td>21</td>
</tr>
<tr>
<td>Negative</td>
<td>0</td>
</tr>
<tr>
<td>p=0.031</td>
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</table>

<table>
<thead>
<tr>
<th>DLL3</th>
<th>TTF1</th>
</tr>
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<tbody>
<tr>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>+, 0</td>
<td>3</td>
</tr>
<tr>
<td>+, -</td>
<td>2</td>
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</tbody>
</table>
Eventually, …doctors will be able to target more types of cancer with combination treatments, including antibodies that remove immunological barriers.

“I think they will be like bacon…Bacon is good on everything.”

-Elfriede Noessner, German Cancer Research Center for Environmental Health
PARP inhibition increases PDL1 expression and may activate innate immune response.

**Olaparib increases PDL1 (SCLC)**

Byers, IASLC Santa Monica 2018 (unpublished data) Adapted from Mouw et al.

Jiao et al, CCR 2017
Co-targeting PARP1 (olaparib) and PD-L1 causes significant tumor regression in SCLC model

Naoto Morikawa, John Heymach
Co-targeting CHK1 and PD-L1 causes significant tumor regression in SCLC model

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**Chk1i increases PDL1**

- **SCLC tumors (B6129F1)**
  - p< 0.001
  - FC= 3.07

- **PDL1 protein (RPPA)**

- **Tumor volume mm^3±SEM**

- **Days elapsed**

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**Co-targeting CHK1 and PD-L1 causes significant tumor regression in SCLC model**

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**Sen et al, WCLC 2017**
CTC-derived xenograft models (CDXs)

Junya Fujimoto, John Heymach, Hai Tran, Ignacio Wistuba
MDACC Lung Moon Shot Program (unpublished)
CDX in vivo response matches clinical response of patient to chemotherapy

Allison Stewart, Carl Gay (Byers Lab), unpublished
Single cell RNAseq analysis of CDX models to explore tumor heterogeneity

Allison Stewart, Carl Gay, Yuanxin Xi, Jing Wang, unpublished; Funded by SWOG/JAX Pilot
L-MYC is associated with tumor propagation in SCLC

Jahchan et al., 2016

Allison Stewart, Carl Gay, Yuanxin Xi, Jing Wang, unpublished
Conclusion

- Activity of DNA damage response (DDR) and cell cycle inhibitors observed in SCLC models (e.g., PARP1, Chk1, Wee1, ATR inhibitors), many now in the clinic

- Candidate biomarkers for specific DDR inhibitors identified, with initial validation of SLFN11 in TMZ-veliparib treated patients (CTEP/NCI trial)

- DDR-IO combinations enhance anti-tumor effect in syngeneic and spontaneous GEMM models, warrant further investigation in the clinic

- CTC-derived xenograft models (CDXs) provide an opportunity for increasing the number of drug resistant models for translational research

- Single cell RNAseq data reveals intra-tumoral heterogeneity. Contribution of tumor heterogeneity to resistance is being further investigated.
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