Targeting ATR and other DNA repair proteins
Replicative stress is a SCLC hallmark

1. Loss of growth suppressors (TP53 and RB1 ~100%)
2. Sustained proliferation (e.g. MYC amplification)
3. Genomic instability (↑↑ mutations, ↑PARP)

Thomas and Pommier. Sci Transl Med 2016
DNA damage response

Sulli et al. Nature Reviews Cancer 2012
Synthetic lethal siRNA screen → Depletion of ATR was a top candidate gene for camptothecin synthetic lethality

ATR inhibition abrogated the S-phase replication elongation checkpoint and the replication origin-firing checkpoint induced by camptothecin
PARPi-resistant BRCA1-deficient cells

Gene profiling and inhibitor screening → ATR promotes RAD51 loading to DSBs and stalled forks → controls BRCA1-independent HR and fork protection

ATR inhibition disrupted the rewired HR and replication fork protection pathways - resensitizing resistant cells to PARPi
ATR inhibitors in clinical trials

- Berzosertib (VX-970; M6620; VE-822)- Phase II
- AZD6738- Phase II
- BAY1895344- Phase I
ATR inhibitors- phase I trials

- **VX-970 (M6620; VE-822)**- Phase I/II
  - Well tolerated in patients
  - No dose-limiting toxicities
  - Limited anti-tumor activity as monotherapy

- **AZD6738**- Phase I

- **BAY1895344**- Phase I
Phase I trial of VX-970 (M6620) and topotecan

Patients with advanced cancers and progressive disease after ≥ 1 chemotherapy

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Topotecan (days 1-5), mg/m² IV</th>
<th>M6620, mg/m² IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>140 on day 5</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>140 on days 2 and 5</td>
</tr>
<tr>
<td>3</td>
<td>1.25</td>
<td>140 on days 2 and 5</td>
</tr>
<tr>
<td>4</td>
<td>1.25</td>
<td>210 on days 2 and 5</td>
</tr>
</tbody>
</table>

21-day cycles
γH2AX, a sensitive marker for DNA double-strand breaks

Increasing number and intensity of γH2AX foci in hair follicles

Reduced ATR-dependent phosphorylation of H2AX

Cytotoxicity related to replication
Toxicities were predictable and manageable

Most Common (≥ 10%) Treatment-Related Adverse Events (maximum grade, all cycles)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>All (N = 21)</th>
<th>1* (n = 6)</th>
<th>2† (n = 6)</th>
<th>3‡ (n = 3)</th>
<th>4§ (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>≥ Grade 3</td>
<td>All</td>
<td>≥ Grade 3</td>
<td>All</td>
</tr>
<tr>
<td>Anemia</td>
<td>21</td>
<td>8 (38)</td>
<td>6</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>21</td>
<td>9 (43)</td>
<td>4</td>
<td>3 (14)</td>
<td>8</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>19</td>
<td>11 (52)</td>
<td>6</td>
<td>2 (10)</td>
<td>6</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>17</td>
<td>11 (52)</td>
<td>5</td>
<td>2 (10)</td>
<td>6</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>16</td>
<td>5 (24)</td>
<td>4</td>
<td>1 (5)</td>
<td>5</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>2</td>
<td>1 (5)</td>
<td>1</td>
<td>1 (5)</td>
<td>1</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>3</td>
<td>1 (5)</td>
<td>1</td>
<td>1 (5)</td>
<td>1</td>
</tr>
<tr>
<td>ALT increase</td>
<td>3</td>
<td>1 (5)</td>
<td>2</td>
<td>1 (5)</td>
<td>1</td>
</tr>
<tr>
<td>AST increase</td>
<td>4</td>
<td>1 (5)</td>
<td>2</td>
<td>1 (5)</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>13</td>
<td>1 (5)</td>
<td>4</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Vomiting</td>
<td>8</td>
<td></td>
<td>1</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Anorexia</td>
<td>6</td>
<td></td>
<td>1</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5</td>
<td>1 (5)</td>
<td>1</td>
<td>2</td>
<td>2</td>
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<tr>
<td>Fever</td>
<td>2</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucositis oral</td>
<td>2</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
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<td></td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2</td>
<td></td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infusion-related reaction</td>
<td>2</td>
<td></td>
<td>2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Topotecan 1 mg/m² days 1 to 5; M6620 140 mg/m² day 5.
†Topotecan 1 mg/m² days 1 to 5; M6620 140 mg/m² days 2 and 5.
‡Topotecan 1.25 mg/m² days 1 to 5; M6620 140 mg/m² days 2 and 5.
§Topotecan 1.25 mg/m² days 1 to 5; M6620 210 mg/m² days 2 and 5.
Efficacy: VX-970 and topotecan

<table>
<thead>
<tr>
<th>All evaluable pts</th>
<th>19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial response, n (%)</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Stable disease, n (%)</td>
<td>8 (42)</td>
</tr>
<tr>
<td>Progressive disease, n (%)</td>
<td>9 (47)</td>
</tr>
</tbody>
</table>
Efficacy in SCLC: VX-970 and topotecan

All 5 SCLC patients had chemotherapy-refractory relapses

Median PFS SCLC- 10.2 months (95% CI, 1.4 to 10.2 months)
6-month PFS probability- 60.0% (95% CI, 12.6% to 88.2%)
Response to VX-970 and topotecan in refractory SCLC

Before treatment

5 months after treatment

Patient remains on treatment at 13 months
Seven of the eight patients with SD had prolonged SD (≥3 months); Median, 9 months (3-12)
Phase I Study of ATR Inhibitor M6620 in Combination With Topotecan in Patients With Advanced Solid Tumors


Phase II is enrolling SCLC patients
Updated responses- Phase I/II

Responses in 1/3 sensitive and 6/8 refractory SCLC

Unpublished data
Predictive biomarkers of response - MYC?

In vivo, MYC-driven SCLC rapidly relapse following chemotherapy

Mollaoglu. Cancer Cell 2017

Reduced levels of ATR completely prevented the development of MYC-induced lymphomas and pancreatic tumors


Are resistant SCLCs responding to ATRi/topotecan MYC amplified?
Predictive biomarkers of response- SLFN11- tumors?

Are resistant SCLCs responding to ATRi/topotecan SLFN11 negative?

Murai, Pommier. Mol cell 2018
Chemotherapy resistance in SCLC may arise from multiple mechanisms—rewiring of HR, suppression of SLFN11, others...

ATR inhibition may disrupt the rewired HR in platinum-refractory SCLC cell—could render them sensitive to topotecan

ATR inhibition was tolerable in patients—no additive toxicities with topotecan

Preliminary data indicates efficacy of the combination in refractory SCLC—are these tumors MYC driven/SLFN11 negative?
WEE1
- AZD1775 monotherapy (NCT02593019)
- AZD1775 in MYC Amplified or CDKN2A Mutated plus TP53 Mutated SCLC (NCT02688907)
- AZD1775 plus olaparib in MYC or CCNE1 amplified SCLC (NCT02511795)

ATR
- VX970 plus topotecan (NCT02487095)
- AZD6738 plus olaparib (NCT03428607)

CHK1
- Prexasertib monotherapy (NCT02735980)

DNA-PK
- M3814 plus cisplatin/ etoposide (NCT03116971)
Acknowledgements

Patients and Families

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Research nurses

Christophe Redon  Yves Pommier  Jane Trepel