Comprehensive Phase 1 Data From First-in-Human Phase 1/2 TRESR Study of RP-3500

Virtual Investor Update
April 11, 2022
Today’s agenda

Brief introduction
Lloyd M. Segal & Maria Koehler, MD, PhD
President & CEO, Repare Therapeutics; EVP & CMO, Repare Therapeutics

Summary of AACR presentation
Timothy Yap, MBBS, PhD, FRCP
Medical Director, Institute for Applied Cancer Science, Associate Professor, Department of Investigational Cancer Therapeutics, Division of Cancer Medicine, MD Anderson Cancer Center

A look into a few patients from TRESR
Maria Koehler, MD, PhD
EVP & CMO, Repare Therapeutics

Key conclusions from monotherapy Ph 1 of TRESR
Lloyd M. Segal & Maria Koehler, MD, PhD
President & CEO, Repare Therapeutics; EVP & CMO, Repare Therapeutics

Q&A
Repare participants

Lloyd M. Segal
President & CEO

Mike Zinda, PhD
Chief Scientific Officer

Maria Koehler, MD, PhD
Chief Medical Officer

Steve Forte
Chief Financial Officer
Disclaimer

Statements contained in this presentation regarding matters that are not historical facts are “forward-looking statements” within the meaning of the Private Securities Litigation Reform Act of 1995, as amended. Words such as "anticipates," "believes," "expects," "intends," "plans," "potential," "projects," "would" and "future" or similar expressions are intended to identify forward-looking statements. Each of these forward-looking statements involves substantial risks and uncertainties that could cause actual results to differ significantly from those expressed or implied by such forward-looking statements. Forward-looking statements contained in this presentation include, but are not limited to, statements regarding the initiation, timing, progress and results of our current and future preclinical studies and clinical trials, including specifically our clinical trials of RP-3500 and RP-6306; the expected timing of program updates and data disclosures; the timing of filing INDs and other regulatory documents, including the initiation of IND-enabling studies for our Polθ inhibitor program; the timing and likelihood of seeking regulatory approval for our product candidates; the competitive landscape for our product candidates; our ability to identify and develop additional product candidates using our SNIPRx platform; and our estimates regarding expenses, future revenue, capital requirements, cash runway and needs for additional financing.

These forward-looking statements reflect our current beliefs and expectations. Many factors may cause differences between current expectations and actual results, including the duration and impact of the ongoing COVID-19 pandemic and the evolving situation regarding the Omicron variant of COVID-19 on our business and market volatility, unexpected safety or efficacy data observed during preclinical or clinical studies, clinical site activation rates or clinical trial enrollment rates that are lower than expected, changes in expected or existing competition, changes in the regulatory environment, and unexpected litigation or other disputes. These and other risks are described more fully in our filings with the Securities and Exchange Commission (“SEC”), including the “Risk Factors” section of our Annual Report on Form 10-K filed with the SEC on February 28, 2022, and other documents we subsequently filed with or furnished to the SEC. All forward-looking statements contained in this presentation speak only as of the date on which they were made. Except as required by law, we assume no obligation to update any forward-looking statements contained herein to reflect any change in expectations, even as new information becomes available.

This presentation also contains estimates and other statistical data made by independent parties and by us relating to market size and growth and other data about our industry. This data involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates. Neither we nor any other person makes any representation as to the accuracy or completeness of such data or undertakes any obligation to update such data after the date of this presentation. In addition, projections, assumptions and estimates of our future performance and the future performance of the markets in which we operate are necessarily subject to a high degree of uncertainty and risk.

Solely for convenience, the trademarks and trade names in this presentation may be referred to without the ® and ™ symbols, but such references should not be construed as any indicator that their respective owners will not assert their rights thereto.
Leading clinical-stage precision oncology company focused on synthetic lethality

RP-3500, a potential best-in-class ATR inhibitor and RP-6306, a first-in-class PKMYT1 inhibitor both currently in clinical Ph 1 or Ph1/2 monotherapy and combination trials with multiple data readouts expected in 2022

Robust pipeline of SL-based therapeutics with our Polθ inhibitor program expected to initiate IND-enabling studies in H1 22 and a pipeline of pre-clinical opportunities we are pursuing

Proprietary genome-wide CRISPR-enabled SNIPRx platform, focused on genomic instability and DNA damage repair, and a powerful SL approach, enabling novel target identification and differentiated patient selection insights

Cash and marketable securities of $341.9 million as of December 31, 2021, funding Repare through 2023 and multiple clinical catalysts
Expert participant: Timothy Yap, MBBS, PhD, FRCP

Medical Oncologist and Physician-Scientist at the University of Texas, MD Anderson Cancer Center

- Associate Professor, Department for Investigational Cancer Therapeutics
- Medical Director of the Institute for Applied Cancer Science
- Associate Director of Translational Research in the Institute for Personalized Cancer Therapy
- Primary research focuses on the first-in-human and combinatorial development of molecularly targeted agents and immunotherapies, and their acceleration through clinical studies using novel predictive and pharmacodynamic biomarkers
- Main interests include the targeting of the DNA damage response with novel therapeutics, such as ATR and PARP inhibitors, as well as the development of novel immuno-therapeutics
- BSc degree in Immunology and Infectious Diseases and MD from Imperial College London, UK
## Robust pipeline of SL-based precision oncology therapeutics

<table>
<thead>
<tr>
<th>Tumor lesion</th>
<th>Drug target</th>
<th>Discovery</th>
<th>IND-Enabling</th>
<th>Phase 1/2</th>
<th>Registration-directed</th>
<th>Anticipated milestones</th>
<th>Rights</th>
</tr>
</thead>
</table>
| ATR inhibitor      | ATM + 16 STEP² lesions | ATR TRESR: Monotherapy                                                    | TRESR: PARP (talazoparib) Combination       |                                               | Q1 22 start TRESR Phase 2 monotherapy and Phase 1 pediatric trials | ▪ Q1 22 start TRESR Phase 2 monotherapy and Phase 1 pediatric trials  
                              |             | ATTACC: PARP (olaparib/niraparib) Combination                            | TRESR: Gemcitabine Combination              |                                               | Q2 22 comprehensive TRESR monotherapy data  
                              |             |                                               | TRESR: Gemcitabine Combination |                                               | H2 22 PARPi combination initial data (targeting Q3)  
| Clinical           |             |                                           |                                               |                                               | H2 22 early Phase 1 readout                              |                                                                                     |        |
| PKMYT1 inhibitor   | CCNE1, FBXW7 + others | PKMYT1 MYTHIC: Monotherapy                                                 | MAGNETIC: Gemcitabine Combination           |                                               |                                                                 | H2 22 early Phase 1 readout                                                                 |        |
| RP-6306            |             |                                           | MINOTAUR: FOLFIRI Combination              |                                               |                                                                 |                                                                                     |        |
| Preclinical        | Polθ inhibitor | BRCA1/2 + others Polθ                                                       |                                             |                                               | IND-enabling studies in H1 22                            |                                                                                     |        |
| Discovery          | SNIPRx® platform | Several additional SL targets in advanced stages of development           |                                             |                                               |                                                                 |                                                                                     |        |
|                    |             | Discovery and validation of new SL precision oncology targets             |                                             |                                               |                                                                 |                                                                                     |        |
RP-3500 updated clinical trial program: additional modules

Trial results to date support expanded clinical development

Module 1  July 2020
Monotherapy: RP-3500
- dose escalation
- dose and schedule refinement

Module 2  October 2021
Dose decision/expansion phase: RP-3500
- N=120 enrolled
- RP2D and schedule identified
- Signal seeking
- POC 3 arms
- ATM loss of function
  - Selected ATM LoF patients
  - Less pre-treated patients
- STEP2 gene alteration(s)
  - Two STEP2 genes
  - Focused tumor population enriched for these genes
- Other STEP2 gene alterations
  - Selected STEP2 genes
  - Focused on those un-or-under-represented in Module 1

Module 3  May 2021
Combination: RP-3500 + Talazoparib
- dose escalation; safety/activity confirmation
Safety & preliminary efficacy of RP-3500 + PARPi
Ongoing

Module 4  December 2021
Combination: RP-3500 + Gemcitabine
- dose escalation; safety/activity confirmation
Safety & preliminary efficacy of RP-3500 + Gemcitabine
Ongoing

Module 5
Monotherapy: RP-3500 Pediatrics
- dose escalation; safety/activity confirmation
Safety & preliminary efficacy of RP-3500 in children
Recruiting

ATTACC  August 2021
- + Olaparib
- + Niraparib

Module 4  December 2021
Combination: RP-3500 + Gemcitabine
- dose escalation; safety/activity confirmation
Safety & preliminary efficacy of RP-3500 + Gemcitabine
Ongoing

Module 5
Monotherapy: RP-3500 Pediatrics
- dose escalation; safety/activity confirmation
Safety & preliminary efficacy of RP-3500 in children
Recruiting

FDA  EMA

Potential registration-oriented development
Summary of AACR presentation
Speaker Disclosures: Timothy Yap, MD

I have the following financial relationships to disclose:

**Employment**
University of Texas MD Anderson Cancer Center, where I am Medical Director of the Institute for Applied Cancer Science, which has a commercial interest in DDR and other inhibitors (IACS30380/ART0380 was licensed to Artios)

**Grant/Research support (to the Institution)**
Acrivon, Artios, AstraZeneca, Bayer, Beigene, BioNTech, Blueprint, BMS, Clovis, Constellation, Cyteir, Eli Lilly, EMD Serono, Forbius, F-Star, Artios, GlaxoSmithKline, Genentech, Haihe, ImmuneSensor, Ionis, Ipsen, Jounce, Karyopharm, KSQ, Kyowa, Merck, Mirati, Novartis, Pfizer, Ribon Therapeutics, Regeneron, Repare, Rubius, Sanofi, Scholar Rock, Seattle Genetics, Tesaro, Vivace and Zenith

**Consultant for**

**Stockholder in**
Seagen
Study population and endpoints

Phase 1/2 TRESR (Treatment Enabled by SNIPRx) study (NCT04497116)

Inclusion Criteria
- Patients ≥18yo with solid tumors after failure of/intolerant to standard therapy
- Tumors with centrally reviewed* deleterious STEP2 alterations
- ECOG PS 0 or 1
- Hemoglobin ≥9.5g/dL, platelets ≥140K/uL, absolute neutrophil count (ANC) ≥1.7K/uL

120 patients in safety cohort
99 patients evaluable for efficacy (≥1 post-baseline scan, RP-3500 >100mg/day)

Primary endpoints
- Safety and tolerability
- Recommended phase 2 dose (RP2D) and schedule

Clinical outcomes
- Overall Response (OR; RECIST1.1 confirmed/unconfirmed complete [CR]/partial response [PR], prostate specific antigen [PSA] or CA125 response)
- Clinical benefit rate (CBR; OR or ≥16w on therapy without progression)
- Progression-free survival (PFS)

Translational analyses
- Antitumor activity in genomic subsets
- Impact of gene zygosity on clinical outcomes
- Patient selection methods for ataxia telangiectasia-mutated (ATM) tumors
- ctDNA

*Precision Oncology Decision Support (PODS; MDACC); STEP2: SNIPRx targeted expansion of patient populations
### Patient characteristics: Diverse, heavily pretreated population

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All Patients, N=120</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex, n (%)</strong></td>
<td>Male: 49 (41)</td>
</tr>
<tr>
<td></td>
<td>Female: 71 (59)</td>
</tr>
<tr>
<td><strong>Age (y), median (range)</strong></td>
<td>63 (30–77)</td>
</tr>
<tr>
<td>≥65 years, n (%)</td>
<td>54 (45)</td>
</tr>
<tr>
<td><strong>ECOG status, n (%)</strong></td>
<td>0: 56 (47)</td>
</tr>
<tr>
<td></td>
<td>1: 64 (53)</td>
</tr>
<tr>
<td><strong>Lines of prior systemic therapy, n (%)</strong></td>
<td>≤3: 69 (57.5)</td>
</tr>
<tr>
<td></td>
<td>4 or more: 51 (42.5)</td>
</tr>
<tr>
<td><strong>Prior platinum</strong></td>
<td>81 (67.5)</td>
</tr>
<tr>
<td><strong>Prior PARP inhibitor</strong></td>
<td>39 (32.5)</td>
</tr>
<tr>
<td><strong>Prior PD-1/L1 inhibitor</strong></td>
<td>28 (23.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tumor Types, n</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovarian</td>
<td>22</td>
</tr>
<tr>
<td>Prostate</td>
<td>21</td>
</tr>
<tr>
<td>Breast</td>
<td>17</td>
</tr>
<tr>
<td>Pancreas</td>
<td>13</td>
</tr>
<tr>
<td>Other&lt;sup&gt;1&lt;/sup&gt;</td>
<td>47</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Most Common Genotypes, n</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ATM</strong></td>
<td>44</td>
</tr>
<tr>
<td><strong>BRCA1</strong></td>
<td>25</td>
</tr>
<tr>
<td><strong>BRCA2</strong></td>
<td>15</td>
</tr>
<tr>
<td><strong>CDK12</strong></td>
<td>9</td>
</tr>
<tr>
<td><strong>RNAseH2</strong></td>
<td>5</td>
</tr>
<tr>
<td><strong>PALB2</strong></td>
<td>5</td>
</tr>
<tr>
<td><strong>SETD2</strong></td>
<td>5</td>
</tr>
<tr>
<td><strong>Other&lt;sup&gt;2&lt;/sup&gt;</strong></td>
<td>12</td>
</tr>
</tbody>
</table>

ECOG, Eastern Cooperative Oncology Group; PARP, poly (ADP-ribose) polymerase; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1

<sup>1</sup>Ampullary, appendix, bile duct, colorectal, endometrial, gastrointestinal, head and neck squamous cell carcinoma, lung, melanoma, mesothelioma, sarcoma, skin

<sup>2</sup>NBN, RAD51B/C, CHEK2 (not STEP2)
## Treatment-related adverse events (TRAE)

**Expected, manageable anemia; potentially best in class safety profile at well studied doses**

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>5d on/2d off (N=25)</th>
<th>3 d on/4 d off (N=95)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 3 N (%)</td>
<td>Grade 4 N (%)</td>
</tr>
<tr>
<td>Any TRAE</td>
<td>14 (56.0)</td>
<td>1 (4.0)</td>
</tr>
<tr>
<td>Anemia</td>
<td>13 (52.0)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1 (4.0)</td>
<td>0</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>3 (12.0)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>2 (8.0)</td>
<td>1 (4.0)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>White blood cell count decreased</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Detailed safety analysis at 3/4 schedule at various dose levels reported at AACR-NCI-EORTC, December 2021 (Yap et al., oral presentation, #4950) and ESMO-TAT, March 2022 (Fontana et al, oral presentation #202)

No incidences of Gr4 anemia reported. * 2/3 with documented “outlier” high exposure. ** at 200mg non-tolerated dose level. No Grade 5 TRAE reported
Monotherapy results in median duration of treatment of ~8 months

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Genotype</th>
<th>Response</th>
<th>Prior PARP</th>
<th>Prior Platin</th>
<th>Prior Tx lines</th>
<th>Wks on Tx</th>
<th>Max % reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovarian</td>
<td>gBRCA1</td>
<td>RECIST cPR</td>
<td>Y</td>
<td>Y</td>
<td>6</td>
<td>48</td>
<td>49.3</td>
</tr>
<tr>
<td></td>
<td>BRCA1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>RECIST cPR</td>
<td>Y</td>
<td>Y</td>
<td>4</td>
<td>38</td>
<td>32.5</td>
</tr>
<tr>
<td></td>
<td>gBRCA1</td>
<td>RECIST uPR</td>
<td>Y</td>
<td>Y</td>
<td>5</td>
<td>28&lt;sup&gt;b&lt;/sup&gt;</td>
<td>38.3</td>
</tr>
<tr>
<td></td>
<td>gRAD51C</td>
<td>RECIST CR</td>
<td>Y</td>
<td>Y</td>
<td>3</td>
<td>35+</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>gRAD51C</td>
<td>CA-125</td>
<td>Y&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Y</td>
<td>5</td>
<td>37+</td>
<td>12.5</td>
</tr>
<tr>
<td></td>
<td>SETD2</td>
<td>RECIST cPR</td>
<td>N</td>
<td>Y</td>
<td>4</td>
<td>17+</td>
<td>70</td>
</tr>
<tr>
<td>CRPC</td>
<td>ATM</td>
<td>RECIST cPR</td>
<td>N</td>
<td>N</td>
<td>2</td>
<td>30</td>
<td>33.7</td>
</tr>
<tr>
<td></td>
<td>ATM</td>
<td>PSA</td>
<td>N</td>
<td>N</td>
<td>7</td>
<td>56+</td>
<td>29.8</td>
</tr>
<tr>
<td></td>
<td>gATM</td>
<td>PSA&lt;sup&gt;d&lt;/sup&gt;</td>
<td>N</td>
<td>N</td>
<td>3</td>
<td>30+</td>
<td>N/A&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>CDK12</td>
<td>RECIST cPR</td>
<td>N</td>
<td>Y</td>
<td>6</td>
<td>27</td>
<td>31.9</td>
</tr>
<tr>
<td>Breast</td>
<td>BRCA1</td>
<td>RECIST uPR</td>
<td>N</td>
<td>N</td>
<td>7</td>
<td>18</td>
<td>30.4</td>
</tr>
<tr>
<td>Melanoma</td>
<td>BRCA2</td>
<td>RECIST cPR</td>
<td>Y</td>
<td>N</td>
<td>5</td>
<td>36+</td>
<td>68.5</td>
</tr>
<tr>
<td>HNSCC</td>
<td>BRCA1</td>
<td>RECIST cPR</td>
<td>N</td>
<td>Y</td>
<td>1</td>
<td>26</td>
<td>36.7</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>ATM</td>
<td>RECIST uPR&lt;sup&gt;e&lt;/sup&gt;</td>
<td>N</td>
<td>Y</td>
<td>2</td>
<td>53+</td>
<td>32.1</td>
</tr>
</tbody>
</table>

<sup>a</sup> Pt switched to RP-3500 monotx after 3w PARPi+RP-3500 (not included in M1 efficacy population); cPR while on RP-3500 monotx. <sup>b</sup> 5/7 non-target lesions disappeared; sustained reduction in TLs after brain progression. <sup>c</sup> 2 prior PARPi. <sup>d</sup> Non-measurable disease; >90% PSA decrease. <sup>e</sup> RECIST uPR on 22Mar2022 at 53 wks of Tx (data cutoff of 14Feb2022). + indicates treatment ongoing at time of data cut cPR, confirmed partial response; uPR, unconfirmed partial response; CR, complete response; CRPC, castration-resistant prostate cancer; PSA, prostate specific antigen; HNSCC, head and neck squamous cell carcinoma. Duration of response: time from start of response (RECIST or PSA/CA-125 response) to tumor progression. Median based on Kaplan-Meier estimate.
Clinically relevant benefit in advanced, platinum-and PARPi pretreated ovarian cancer

Overall Response (5/20*)

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Prior Platinum/ PARPi</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1</td>
<td>Y/Y</td>
</tr>
<tr>
<td>BRCA1</td>
<td>Y/Y</td>
</tr>
<tr>
<td>BRCA1</td>
<td>Y/Y</td>
</tr>
<tr>
<td>BRCA1</td>
<td>Y/Y</td>
</tr>
<tr>
<td>BRCA1</td>
<td>Y/Y</td>
</tr>
<tr>
<td>BRCA1</td>
<td>Y/Y</td>
</tr>
<tr>
<td>BRCA1</td>
<td>Y/Y</td>
</tr>
<tr>
<td>BRCA1</td>
<td>Y/Y</td>
</tr>
<tr>
<td>BRCA1</td>
<td>Y/Y</td>
</tr>
<tr>
<td>BRCA1</td>
<td>Y/Y</td>
</tr>
<tr>
<td>BRCA1</td>
<td>Y/Y</td>
</tr>
<tr>
<td>BRCA2</td>
<td>Y/Y</td>
</tr>
<tr>
<td>BRCA2</td>
<td>Y/Y</td>
</tr>
<tr>
<td>BRCA2</td>
<td>Y/Y</td>
</tr>
<tr>
<td>BRCA2</td>
<td>Y/Y</td>
</tr>
<tr>
<td>RAD51C</td>
<td>Y/Y</td>
</tr>
<tr>
<td>RAD51C</td>
<td>Y/Y</td>
</tr>
<tr>
<td>NBN</td>
<td>Y/Y</td>
</tr>
<tr>
<td>RAD51C</td>
<td>Y/Y</td>
</tr>
<tr>
<td>SETD2</td>
<td>Y/N</td>
</tr>
<tr>
<td>CDK12</td>
<td>Y/N</td>
</tr>
</tbody>
</table>

Time on Treatment (wk) – Ovarian

- **BRCA1**
- **BRCA2**
- **OTHER STEP**

**Platinum refractory/resistant: progression on platinum or a platinum-free interval of <6 mo. CBR: OR or ≥16w on therapy without progression**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Prior Platinum/ PARPi</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1</td>
<td>Y/Y</td>
</tr>
<tr>
<td>BRCA1</td>
<td>Y/Y</td>
</tr>
<tr>
<td>BRCA1</td>
<td>Y/Y</td>
</tr>
<tr>
<td>BRCA1</td>
<td>Y/Y</td>
</tr>
<tr>
<td>BRCA1</td>
<td>Y/Y</td>
</tr>
<tr>
<td>BRCA1</td>
<td>Y/Y</td>
</tr>
<tr>
<td>BRCA1</td>
<td>Y/Y</td>
</tr>
<tr>
<td>BRCA1</td>
<td>Y/Y</td>
</tr>
<tr>
<td>BRCA1</td>
<td>Y/Y</td>
</tr>
<tr>
<td>BRCA1</td>
<td>Y/Y</td>
</tr>
<tr>
<td>BRCA1</td>
<td>Y/Y</td>
</tr>
<tr>
<td>BRCA1</td>
<td>Y/Y</td>
</tr>
<tr>
<td>BRCA1</td>
<td>Y/Y</td>
</tr>
<tr>
<td>BRCA1</td>
<td>Y/Y</td>
</tr>
<tr>
<td>BRCA1</td>
<td>Y/Y</td>
</tr>
<tr>
<td>BRCA1</td>
<td>Y/Y</td>
</tr>
<tr>
<td>BRCA2</td>
<td>Y/Y</td>
</tr>
<tr>
<td>BRCA2</td>
<td>Y/Y</td>
</tr>
<tr>
<td>BRCA2</td>
<td>Y/Y</td>
</tr>
<tr>
<td>BRCA2</td>
<td>Y/Y</td>
</tr>
<tr>
<td>RAD51C</td>
<td>Y/Y</td>
</tr>
<tr>
<td>RAD51C</td>
<td>Y/Y</td>
</tr>
<tr>
<td>NBN</td>
<td>Y/Y</td>
</tr>
<tr>
<td>RAD51C</td>
<td>Y/Y</td>
</tr>
<tr>
<td>SETD2</td>
<td>Y/N</td>
</tr>
<tr>
<td>CDK12</td>
<td>Y/N</td>
</tr>
</tbody>
</table>

25% Overall Response (5/20*)

1 CR
3 PRs by CA125
1 CA125 response

75% CBR
35 weeks Median PFS

90% (18/20) of patients had prior PARPi
85% (17/20) of patients were platinum refractory/resistant**

*2 additional pts are included in the swim plot that started Tx on PARPi combination for ≤3w and switched to monoTx; duration of Tx calculated from start of monoTx.

**Platinum refractory/resistant: progression on platinum or a platinum-free interval of <6 mo. CBR: OR or ≥16w on therapy without progression
Clinically relevant benefit in patients with BRCA1/2 mutated tumors

14%  
Overall response in BRCA1/2 (RECIST, 5/37)

Responders included patients with ovarian (2), breast, head and neck squamous cell carcinoma, and melanoma (1 each)

43%  
CBR for BRCA1/2 tumors

48%  
CBR for post-PARPi BRCA1/2 tumors

CBR (OR or ≥16w on therapy without progression) was 48% for BRCA1 population, and 36% for BRCA2
Durable clinical benefit in patients with ATM LOF tumors

12% Overall response (4/34)

3 responders: prostate cancer (1 RECIST, 2 PSA), and 1 pancreatic cancer (RECIST)

29% Received RP-3500 for at least 6 months (10/34)

44% CBR for ATM population

17 weeks Median PFS

Clinical benefit rate (CBR; OR or at least 16w on therapy without progression)
Anti-tumor activity is largest in tumors with biallelic loss of function (LOF)

Biallelic gene LOF is an emerging biomarker for synthetic lethal therapies
(Not reported by routine clinical NGS assays)

47% vs. 15%
CBR significantly higher in biallelic tumors (p=0.02)
Longer PFS for biallelic (17 weeks) vs non-biallelic (11 weeks) for all subjects (not shown)

Central NGS assay, SNiPDX, (poster #2801) determines biallelic LOF, germline status and CHIP alterations in TRESR

Further analysis in additional patients ongoing; Confirmation in prospective studies required
Conclusions

RP-3500 monotherapy is well tolerated
- Mechanism based anemia is well controlled

RP-3500 monotherapy: durable responses and clinical benefit in several tumor types/genomic alterations
- Overall clinical benefit rate (CBR) was 43%
- In recurrent ovarian cancer (90% with prior PARPi; 85% platinum-refractory/resistant), OR was 25%, CBR was 75%, and median PFS was 35 weeks
- In BRCA1/2 tumors previously treated with a PARP inhibitor, CBR was 48% and responses were seen beyond hereditary breast and ovarian cancers
- Biallelic LOF has the potential to enrich for patients most likely to benefit from RP-3500

Multiple clinical trials with RP-3500 alone or in combination are ongoing
A look into a few patients from TRESR
69-year-old female with pancreatic cancer and gATM LOF
Late response (RECIST PR, wk 54) after slow, sustained decline in target lesion sum

- Prior therapies (2 lines)
  - FOLFIRINOX (8 cycles)
  - Nivolumab and cabiralizumab (for 5 mo)
- Enrolled at 60 BID (3d on, 4d off);
  - no dose/schedule change required
- CA 19-9 tumor marker >50% reduction starting at wk 9
- Patient remains on therapy (54+ wks)
73-year-old patient with prostate cancer and ATM biallelic LOF
Slow decline in the size of target lesions with 29.8% decrease at last follow-up

- **Castrate resistant prostate cancer**
- **Prior therapies (7 lines)**
  - Anti-hormonals, taxanes
  - Ipilimumab + nivolumab + RT (clinical trial)
- **Enrolled at 120 QD (5/2)**
  - Switch to 120 QD (3/4) at Cycle 5 (wk 16)
  - Remains on treatment (61+ wks)
- **PSA response (wk 11)**
  - PSA fluctuations due to multiple treatment breaks secondary to complications of adrenal insufficiency

**ctDNA kinetics**
- **Molecular response** with sustained ≥90% ctDNA decline
74-year-old patient with prostate cancer and gATM LOF

Early PSA response week 3 and continuous decrease in PSA

- Castrate resistant prostate cancer
- Prior 3 lines of antihormonal therapy
- Enrolled at 160 QD (3/4), 2 wks on/1 wk off
  - No changes in dose/schedule
  - Remains on tx (35+ wks)
- Patient had no measurable disease
  - Bone metastases only
- Early PSA response (wk 3), and continued decline (>90%) to sustained normal levels at week 19

ctDNA kinetics
- Week 6 ctDNA decline of detectable somatic TP53 mutation
77-year-old patient with ovarian cancer and gRAD51C LOF
Quick CA125 response followed by RECIST PR at 19 wks, and CR at 32 wks

- Prior therapies (4 lines)
  - Including platinum and PARP inhibitor
  - Refractory to last line of platinum

- Enrolled at 160 QD (3/4), 2 wks on/1 wk off
  - No changes in dose/schedule
  - Remains on tx (40+ wks) in CR

- Quick CA-125 response by wk 6 (82% decrease)

- RECIST CR at week 32

*CR in target lesion, but 1 peritoneal non-target lesion remained*
74-year-old patient with ovarian cancer and gBRCA1 biallelic LOF

RECIST PR at week 12

- Prior therapies (6 lines)
  - Including platinum and 2 PARP inhibitors

- Enrolled at 160 QD (3/4)
  - Switch to 120 QD (3/4) at Cycle 6 (wk 15)
  - Remained on treatment for 48 wks

- PR (RECIST1.1) response at wk 12
  - PD at week 48 due to new peritoneal lesion, not measurable
Key Conclusions from Monotherapy Ph 1 of TRESR
**RP-3500: Potentially best-in-class ATRi**

- **Potentially best-in-class safety profile confirmed with larger cohort and longer observation time**
  - Long-term tolerability further show; anemia non-cumulative, no new adverse safety findings
  - Potency/selectivity/PK differentiation increasingly clear

- **Large trial size (N=120) allowed for comprehensive assessment of dose and schedule**
  - Multiple dose/schedules rigorously tested to maximize patient benefit and evaluate tumors/molecular alterations to convincingly see a path to further development

- **POC in ovarian cancer clearly demonstrated – engagement with regulator(s) in near-term**
  - 25% OR, 75% CBR and PFS 8+mo in PARPi and platinum pretreated patients with ovarian cancer
  - Several long/deep ovarian cancer tumor responses (BRCA1, SETD2, RAD51c)

- **Early data supports further exploration of POC for ATM and STEP\(^2\) alterations**
  - Current data suggests need for further efficacy exploration – meaningful CBR noted in early data
  - Tools identified to potentially better select ATM LOF and improve clinical outcomes
  - Additional validation of STEP\(^2\) platform opportunities beyond ATM and BRCA1 LOF
Summary of monotherapy data in today’s AACR TRESR trial update

Mature data in 120 patients establish clinical path forward:

**Early POC for monotherapy in ovarian cancer**
- 25% OR and 75% CBR in tumors with multiple STEP² alterations
- recurring after PARPi/platinum therapy
- clear rationale for future trials

**Long term clinical benefit a clear pattern in tumors with ATM LOF**
- tumor response seen in 2 pts at >40 weeks
- overall CBR 44%

**Significant benefit in ATM LOF tumors if genomically selected**
- pertinent patient selection now demonstrated
- new tools and approaches to be further tested in current/future trials

**Monotherapy efficacy seen in multiple tumors**
- in several genomic alterations
- continue to validate and further explore the SNIPRx platform

**Well tolerated safety profile**
- unchanged with longer-term dosing
- right compound, right dose and schedule, right patients increasingly clear

Next steps for RP-3500 development to be discussed with regulatory agencies in the near term
Q&A Session