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

Virtual Investor Update
October 8, 2021
## Today’s agenda

<table>
<thead>
<tr>
<th>Section</th>
<th>Presenter(s)</th>
<th>Position(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brief introduction</td>
<td>Lloyd M. Segal &amp; Maria Koehler, MD, PhD</td>
<td>President &amp; CEO, Repare Therapeutics, EVP &amp; CMO, Repare Therapeutics</td>
</tr>
<tr>
<td>Summary of AACR-NCI-EOTRC data and select case studies</td>
<td>Timothy Yap, MBBS, PhD, FRCP</td>
<td>Medical Director, Institute for Applied Cancer Science, Associate Professor, Department of Investigational Cancer Therapeutics, Division of Cancer Medicine, MD Anderson Cancer Center</td>
</tr>
<tr>
<td>RP-3500 next steps</td>
<td>Maria Koehler, MD, PhD, Timothy Yap, MBBS, PhD, FRCP</td>
<td>EVP &amp; CMO, Repare Therapeutics, MD Anderson Cancer Center</td>
</tr>
<tr>
<td>Concluding remarks</td>
<td>Lloyd M. Segal &amp; Maria Koehler, MD, PhD</td>
<td>President &amp; CEO, Repare Therapeutics, EVP &amp; CMO, Repare Therapeutics</td>
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<tr>
<td>Q&amp;A</td>
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</table>
REPARE participants

Lloyd M. Segal
President & CEO

Maria Koehler, MD, PhD
Chief Medical Officer

Mike Zinda, PhD
Chief Scientific Officer

Steve Forte
Chief Financial Officer

Joining for Q&A
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; the expected timing of program updates and data disclosures; the timing of filing INDs and other regulatory documents; 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 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 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 Quarterly Report on Form 10-Q filed with the SEC on August 12, 2021, 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

Lead clinical-stage candidate RP-3500, a potential best-in-class ATR inhibitor; currently in Phase 1/2 monotherapy and combination therapy

Robust pipeline of SL-based therapeutics; including RP-6306, our PKMYT1 inhibitor currently in Phase 1, and our Polθ inhibitor

Proprietary genome-wide CRISPR-enabled SNIPRx platform, focused on genomic instability and DNA damage repair

Powerful SL-based approach and proprietary platform provides differentiated patient selection insights

Cash, restricted cash and marketable securities of $301 million as of June 30, 2021
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>SL Pair</th>
<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>
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<tbody>
<tr>
<td><strong>Clinical</strong></td>
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<tr>
<td>ATR inhibitor RP-3500</td>
<td>ATM + 16 STEP² lesions</td>
<td>ATR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>▪ Q2 22 TRESR final MonoRx data</td>
<td>REPARE THERAPEUTICS</td>
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<tr>
<td>PKMYT1 inhibitor RP-6306</td>
<td>CCNE1, FBXW7 + others</td>
<td>PKMYT1</td>
<td></td>
<td></td>
<td></td>
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<td>▪ Q3 22 PARP combo early data</td>
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<tr>
<td><strong>Preclinical</strong></td>
<td></td>
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<td></td>
<td></td>
<td>▪ H2 22 early Phase 1 readout</td>
<td>REPARE THERAPEUTICS</td>
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<tr>
<td>Polθ inhibitor</td>
<td>BRCA1/2 + others</td>
<td>Polθ</td>
<td></td>
<td></td>
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<td>REPARE THERAPEUTICS</td>
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<tr>
<td><strong>Discovery</strong></td>
<td></td>
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<td></td>
<td></td>
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<td>▪ IND-enabling studies in H1 22</td>
<td>REPARE THERAPEUTICS</td>
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<tr>
<td>SNIPRx® platform</td>
<td>8 additional SL targets</td>
<td></td>
<td></td>
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<td>REPARE THERAPEUTICS</td>
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<td></td>
<td>Discovery and validation of new SL precision oncology targets</td>
<td>REPARE THERAPEUTICS</td>
</tr>
</tbody>
</table>
Expanding RP-3500 patient opportunity with STEP² selection tools*

Top 10 tumor types with highest prevalence of ATM deficiency

- Bladder Urothelial Carcinoma: 3.6%
- Pancreatic Adenocarcinoma: 3.4%
- Lung Adenocarcinoma: 2.8%
- Adrenocortical Carcinoma: 2.5%
- Rectum Adenocarcinoma: 2.4%
- Stomach Adenocarcinoma: 2.4%
- Breast Invasive Carcinoma: LumB: 2.4%
- Breast Invasive Carcinoma: LumA: 1.6%
- Breast Invasive Carcinoma: 1.4%
- Skin Cutaneous Melanoma: 1.3%

Top 10 tumor types with highest prevalence of ATM deficiency or STEP² genomic alterations

- Ovarian Serous Cystadenocarcinoma: 18.7%
- Uterine Corpus Endometrial Carcinoma: 17.6%
- Breast Invasive Carcinoma: Basal: 13.8%
- Stomach Adenocarcinoma: 10.9%
- Bladder Urothelial Carcinoma: 10.9%
- Breast Invasive Carcinoma: LumB: 9.1%
- Breast Invasive Carcinoma: 9.0%
- Lung Adenocarcinoma: 8.6%
- Colon Adenocarcinoma: 8.6%
- Cervical Squamous Cell Carcinoma: 8.5%

- Beyond ATM, 16 of 19 additional, mutually exclusive genomic alterations identified as SL with RP-3500 are eligible for recruitment into the ongoing trial
- Represents expanded, clinically relevant populations with unmet medical needs
- Average prevalence of ~2% (ATM) to ~10% (STEP² genes) across multiple tumors

* TCGA; Not weighted for tumor prevalence
RP-3500 clinical progress to-date

Global multicenter study designed for patients with recurrent tumors with ATM loss or loss of any of the additional 16 STEP² genes

- N=101 enrolled
- RP2D and schedule identified

Monotherapy: RP-3500
- dose escalation
- dose and schedule refinement

Dose decision/expansion phase: RP-3500
- ATM loss of function
- Signal seeking
- POC 3 arms
- STEP² gene alteration(s)
- Other STEP² gene alterations
- Potential registration-oriented development

Combination: RP-3500
- + Talazoparib
- dose escalation; safety/activity confirmation

Development in tumors with BRCA1/2 mutations and/or PARP-combination-specific STEP² gene alterations

ATTACC
- + Olaparib
- + Niraparib
Summary of AACR-NCI-EORTC data and select case studies
First-in-Human biomarker-driven Phase I TRESR trial of ATR inhibitor RP-3500 in patients with advanced solid tumors harboring synthetic lethal genomic alterations

Timothy A. Yap¹, Elizabeth Lee², David Spigel³, Elisa Fontana⁴, Martin Hojgaard⁵, Stephanie Lheureux⁶, Niharika Mettu⁷, Louise Carter⁸, Ruth Plummer⁹, Victoria Rimkunas¹⁰, Ian M. Silverman¹⁰, Adrian J. Fretland¹⁰, Danielle Ulanet¹⁰, Peter Manley¹⁰, Ezra Rosen¹¹

¹University of Texas MD Anderson Cancer Center, Houston, TX; ²Dana-Farber Cancer Institute, Boston, MA; ³Sarah Cannon Research Institute, Nashville, TN; ⁴Sarah Cannon Research Institute, London, UK; ⁵Copenhagen University Hospital, Herlev, Denmark; ⁶Princess Margaret Cancer Centre, Toronto, Canada; ⁷Duke University Medical Center, Durham, NC; ⁸The Christie NHS Foundation Trust, Manchester, UK; ⁹Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK; ¹⁰Repare Therapeutics, Cambridge, MA; ¹¹Memorial Sloan Kettering Cancer Center, New York, NY
I have the following financial relationships to disclose:

- **Employee of:** 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.

- **Grant/Research support (to Institution) from:** Repare, AstraZeneca, Artios, Bayer, Beigene, BioNTech, BMS, Clovis, Constellation, Cyteir, Eli Lilly, EMD Serono, Forbisch, F-Star, Artios, GlaxoSmithKline, Genentech, Haihe, ImmuneSensor, Ionis, Ipsen, Jounce, Karyopharm, K SQ, K yowa, Merck, Novartis, Pfizer, Ribon Therapeutics, Regeneron, Rubius, Sanofi, Scholar Rock, Seattle Genetics, Tesaro and Vivace.

- **Consultant for:** Repare, AstraZeneca, Almac, Aduro, Artios, Athen, Atrin, Axiom, Bayer, Bristol Myers Squibb, Calithera, Clovis, Cybrexa, EMD Serono, F-Star, GLG, Guidepoint, Ignyta, I-Mab, ImmuneSensor, Jansen, Merck, Pfizer, Roche, Schrodinger, Seattle Genetics, Varian, Zai Labs and ZielBio

- **Stockholder in:** Seagen

- **I will discuss the following off label use and/or investigational use in my presentation:** RP-3500
RP-3500: a potential best-in-class, highly selective inhibitor of ATR kinase

ATR inhibition is synthetically lethal with genomic alterations affecting DNA damage response

- ATR is a key mediator of cellular DNA damage response (DDR) and is activated in response to DNA replication stress
- A genome-wide CRISPR-based screening platform identified multiple synthetic lethal genomic alterations that predict for sensitivity to RP-3500 (STEP2* genes)
  - ATM, ATRIP, BRCA1/2, CHEK2, CDK12, CHTF8, FZR1, MRE11, NBN, PALB2, RAD17, RAD50, RAD51B/C/D, REV3L, RNASEH2A/B, SETD2

*STEP2 = SNIPRX** targeted expansion of patient populations
**SNIPRx = SyNthetic lethal Interactions for Precision Rx

RP-3500 is a potent and highly selective inhibitor of ATR

- Low nanomolar potency in biochemical (1.0 nM) and cell-based assays (0.33 nM)
- >2,000-fold selectivity over ATM, DNA-PK and PI3Ka
- Single agent activity in tumor models of different histologies and DDR defects

Roulston et al., ENA 2021, #PO54
First-in-human Phase 1/2 TRESR study design

Inclusion Criteria
- Patients ≥18yo with solid tumors resistant, refractory, and/or intolerant to standard therapy
- Tumors with centrally reviewed* deleterious STEP² alterations
- ECOG PS 0 or 1
- Hgb ≥9.5g/dL, Platelets ≥140K/uL, ANC ≥1.7K/uL

Module 1: single agent RP-3500
Primary endpoints:
- Safety and tolerability
- Recommended Phase 2 dose (RP2D), schedule
Other endpoints
- Pharmacokinetics
- Pharmacodynamics in paired tumor biopsies
- Preliminary antitumor activity
- Kinetics of circulating tumor DNA (ctDNA)

Presentation of early data from this ongoing study:
- TRESR initiated in July 2020
- Data cut-off date: August 15, 2021
- 101 patients included in this early dataset

*Central review performed by Precision Oncology Decision Support (PODS) Group at MDACC
# Phase 1/2 TRESR: patient characteristics

<table>
<thead>
<tr>
<th>All patients</th>
<th>N = 101</th>
</tr>
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<tbody>
<tr>
<td>Male</td>
<td>42</td>
</tr>
<tr>
<td>Female</td>
<td>59</td>
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<table>
<thead>
<tr>
<th>Median age, years (range)</th>
<th>63 (33-77)</th>
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<tr>
<td>≥65 yrs</td>
<td>46</td>
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<table>
<thead>
<tr>
<th>ECOG status</th>
</tr>
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<tbody>
<tr>
<td>0</td>
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<tr>
<td>1</td>
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<table>
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<tr>
<th>Lines of prior therapy</th>
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<tbody>
<tr>
<td>1-3</td>
</tr>
<tr>
<td>4 or more</td>
</tr>
<tr>
<td>Pending</td>
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<table>
<thead>
<tr>
<th>Prior Platinum</th>
<th>62</th>
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<tbody>
<tr>
<td>Prior PARP inhibitor</td>
<td>28</td>
</tr>
<tr>
<td>Prior PD-1/L1 inhibitor</td>
<td>20</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Tumor types</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovarian</td>
</tr>
<tr>
<td>Prostate</td>
</tr>
<tr>
<td>Breast</td>
</tr>
<tr>
<td>Pancreas</td>
</tr>
<tr>
<td>Sarcoma</td>
</tr>
<tr>
<td>Other*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Most common genotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATM</td>
</tr>
<tr>
<td>BRCA1</td>
</tr>
<tr>
<td>BRCA2</td>
</tr>
<tr>
<td>CDK12</td>
</tr>
<tr>
<td>Other STEP2**</td>
</tr>
</tbody>
</table>

*other tumor types: CRC, Bile Duct, GI, Endometrial, Lung, Ampullary, Appendix, HNSCC, Melanoma, Mesothelioma, Skin

**STEP2 genotypes: CHEK2, NBN, PALB2, RAD51C/B, RNASEH2, SETD2, FZR1
RP-3500 MTD/RP2D established at 160mg QD, 3d on/4d off schedule

Comprehensive assessment for RP-3500 MTD/RP2D

Single agent RP-3500 tested at multiple doses and schedules

- Adaptive BOIN design and sufficient cohort sizes to ensure confidence in MTD/RP2D decision
- Once daily (QD) and twice daily (BID)
- 5d on/2d off and 3d on/4d off; continuously and 2w on/1w off

DLTs: anemia, thrombocytopenia

MTD/RP2D of RP-3500: 160mg QD, 3d on/4d off
## RP-3500 treatment emergent adverse events

All grades, occurring in ≥10% of patients

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>5/2 Schedule (N=25)</th>
<th>3/4 Schedule (N=76)</th>
<th>All Patients (N=101)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>All Grade n (%)</td>
<td>Grade 3 n (%)</td>
<td>Grade 4 n (%)</td>
</tr>
<tr>
<td><strong>Any TEAE</strong></td>
<td>25 (100)</td>
<td>15 (60)</td>
<td>2 (8)</td>
</tr>
<tr>
<td><strong>Anemia</strong></td>
<td>19 (76)</td>
<td>11 (44)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Fatigue</strong></td>
<td>9 (36)</td>
<td>1 (4)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Decreased appetite</strong></td>
<td>6 (24)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Nausea</strong></td>
<td>6 (24)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Neutrophil count decreased</strong></td>
<td>5 (20)</td>
<td>2 (8)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Platelet count decreased</strong></td>
<td>7 (28)</td>
<td>2 (8)</td>
<td>1 (4)</td>
</tr>
<tr>
<td><strong>Diarrhea</strong></td>
<td>3 (12)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Abdominal pain</strong></td>
<td>3 (12)</td>
<td>0</td>
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MTD/RP2D established at 160mg QD, 3d on/4d off

**DLT**
Anemia is the most common cause of dose interruptions, modifications.

At the preferred 3/4 schedule, dose interruptions, reductions and transfusions were infrequent.

No discontinuations related to RP-3500 emergent adverse events.

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<tr>
<th></th>
<th>5/2 Schedule</th>
<th>3/4 Schedule</th>
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<tbody>
<tr>
<td></td>
<td>≥100 mg/day* (N=18)</td>
<td>≥100 mg/day* (N=75)</td>
</tr>
<tr>
<td># Cycles, mean (SD) [Range]</td>
<td>3.9 (2.62) [0, 10]</td>
<td>1.9 (1.72) [0, 8]</td>
</tr>
<tr>
<td>Subjects Exposed to RP-3500 n (%)</td>
<td></td>
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<tr>
<td>≥1 cycle</td>
<td>17 (94.4%)</td>
<td>57 (76.0%)</td>
</tr>
<tr>
<td>≥2 cycles</td>
<td>14 (77.8%)</td>
<td>37 (48.7%)</td>
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<tr>
<td>Interruptions n (%)</td>
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<tr>
<td>1</td>
<td>8 (44.0%)</td>
<td>16 (21.3%)</td>
</tr>
<tr>
<td>2</td>
<td>2 (11.1%)</td>
<td>3 (4.0%)</td>
</tr>
<tr>
<td>≥3</td>
<td>5 (27.8%)</td>
<td>2 (2.7%)</td>
</tr>
<tr>
<td>Dose Reductions, n (%)</td>
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</tr>
<tr>
<td>1</td>
<td>6 (33.3%)</td>
<td>10 (13.3%)</td>
</tr>
<tr>
<td>2</td>
<td>3 (16.7%)</td>
<td>1 (1.3%)</td>
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<tr>
<td>Transfusions, n (%)</td>
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</tr>
<tr>
<td>Cycle 1</td>
<td>4 (22.2%)</td>
<td>6 (8.0%)</td>
</tr>
<tr>
<td>Cycles 1-2</td>
<td>9 (50.0%)</td>
<td>9 (12.0%)</td>
</tr>
<tr>
<td>Cycles 1-3</td>
<td>12 (66.7%)</td>
<td>10 (13.2%)</td>
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</table>

*Data presented include only patients treated at therapeutic doses to allow more accurate representation of safety at the recommended dose range.
Pharmacokinetic profile RP-3500 exposures meet efficacy targets at ≥100mg

- Half-life is ~ 6 hrs
- Linear Cmax and AUC, consistent across all doses
- Doses ≥100 mg QD achieve predicted efficacious RP-3500 exposures
  - Once daily (QD) regimen selected over twice daily (BID) based on minimal differences in target coverage between these 2 regimens
  - Based on the results of the RP-3500 food effect study, RP-3500 can be given with and without food
RP-3500 Pharmacodynamics

Robust pathway modulation in paired tumor biopsies

Consistent and statistically significant on-treatment increases in DNA damage-induced γH2AX and p-KAP1 across tumor genotypes (N=21)

Enrollment Gene
- ATM
- BRCA1
- BRCA2
- CDK12
- PALB2
- RAD51B
- RAD51C
- SETD2

Baseline

On RP-3500 (Cycle 2)

γH2AX p < 0.0004*

p-KAP1 p < 0.003*

*Wilcoxon test
Early analysis of treatment duration

Therapy ongoing in 54* (54%) of 101 patients

- Early analysis of therapy duration shows clinical activity across tumor types and STEP2 alterations

- Responses** included:
  - CRPC (ATM, CDK12)
  - Ovarian, post-PARPi (4 BRCA1, 1 RAD51C)
  - ER+ breast (BRCA1)
  - HNSCC (BRCA1)
  - Melanoma (BRCA2)

- Copy number analysis of enrolled gene alterations is ongoing

---

*As of August 15, 2021

**Response Evaluation Criteria in Solid Tumors (RECIST); Prostate Cancer Working Group 3 (PCWG3); Gynecological Cancer InterGroup (GCIG)
Early efficacy observed with RP-3500 ≥100 mg/day

Broad spectrum of efficacy observed

- **Meaningful clinical benefit in 34 (49%) of 69 evaluable patients**
- **Across STEP2 gene alterations**
- **Across schedules & after PARPi failure**
  - **12 responses**: 8 RECISTv1.1 cPR/uPR, 2 pts by PCWG3 and 2 pts by GCIG (ATM, CDK12, BRCA1, BRCA2, RAD51B, RAD51C and FZR1)
  - **14 patients** ongoing SD ≥ 16 weeks
  - **8 patients** <16w on study: early significant decreases in tumor markers and tumor shrinkage (<30%)
- **Late responses also observed**: initial RECISTv1.1 partial response (PR) seen at week 16

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<thead>
<tr>
<th></th>
<th>5/2 Schedule ≥100 mg/day (N=18)</th>
<th>3/4 Schedule ≥100 mg/day (N=76)</th>
<th>All patients ≥100 mg/day (N=94)</th>
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<tbody>
<tr>
<td>Evaluate pts (≥1 post baseline scan)</td>
<td>17</td>
<td>52</td>
<td>69</td>
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<tr>
<td><strong>Best response</strong></td>
<td></td>
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<tr>
<td>RECISTv1.1</td>
<td>2 cPR*, 1uPR **</td>
<td>2 cPR; 3 uPR#</td>
<td>4 cPR; 4uPR</td>
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<td>PCWG3 PSA</td>
<td>1</td>
<td>1</td>
<td>2</td>
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<td>GCIG CA125</td>
<td>-</td>
<td>2</td>
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<td>SD (≥16w)</td>
<td>6</td>
<td>8</td>
<td>14</td>
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<td>SD (≥6w)&amp;</td>
<td>6</td>
<td>23</td>
<td>29</td>
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<td>PD</td>
<td>6</td>
<td>21</td>
<td>27</td>
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*1 patient with cPR required radiotherapy to brain lesions early in trial. No brain scan at study entry.
**Patient started on 5/2 schedule and changed to 3/4, later achieved uPR response on 3/4
#1 patient began on PARPi+RP3500 for 2 weeks, before transitioning to RP-3500 monotherapy.
& includes the SD>16w patients
Deep molecular responses in TRESR

Circulating tumor DNA (ctDNA) measured serially in 37 pts

- ctDNA, fragmented tumor DNA in circulating blood, may reflect the entire tumor genome as “liquid biopsies” at various time points to monitor tumor during treatment

- Published data suggest that early molecular responses in ctDNA may be correlated with patient benefit during treatment with anticancer drugs

- ctDNA best mean variant allele frequency (mVAF*) measures change in tumor burden

- RP-3500 data show early and significant decrease (>50%) in mVAFR** in tumors with multiple genotypes

* mVAF calculated as % decrease from baseline
** mVAFR is the mean variant allele frequency ratio (relative to baseline). mVAFR capped at +100%
Preliminary analysis suggests ctDNA response may predict clinical benefit

- RP-3500 patients with PRs showed early and frequently significant (>50%) reductions in mVAFR in ctDNA
- Analyses are ongoing to correlate ctDNA responses with clinical efficacy in order to evaluate the predictive power of serial ctDNA measurements

- ctDNA cohort = 37/101 enrolled patients
- mVAFR = mean variant allele frequency ratio as an indirect measure of tumor burden
Ovarian cancer with gBRCA1 mutation

Ongoing RECIST cPR*

Ongoing GCIG CA125 response

59 y/o female with 4 prior therapeutic regimens for metastatic ovarian cancer: Prior platinum, previous failure of PARP inhibitor (best response PD) and docetaxel + avastin (best response PD)

Baseline Week 12
T01 Lymph Node common iliac left
Baseline: 15.6 mm
Restage: 6.9 mm

T03 Vaginal Cuff
Baseline: 51.7 mm
Restage: 35.4 mm

*RECISTv1.1 PR was confirmed after 15th Aug data cut
CRPC with CDK12 mutation

Ongoing RECIST cPR

Ongoing PCWG3 PSA response

57 y/o male with CRPC received 6 prior regimens, incl. best response of PD on docetaxel, platinum/etoposide and Ipi/Nivo

Baseline Week 12

Common hepatic lymph node
Baseline: 32mm
Restage: 17mm

Retrocaval lymph node
Baseline: 22mm
Restage: 9mm

Left adrenal gland mass
Baseline: 44mm
Restage: 27mm
68 y/o male with CRPC, multiple bone metastases and lymph node disease, with disease progression on 2 prior regimens.
Summary – Early Phase 1/2 TRESR trial data

RP-3500 is safe and well tolerated, with mainly G1-2 anemia (only 21.8% G3 overall and 14.5% in chosen schedule)
- Likely off-target toxicities, e.g., fatigue or GI events, are infrequent (only up to 3% G3)

RP-3500 RP2D for further monotherapy evaluation is 160mg QD 3d on/4d off

Biomarker data confirm proof-of-mechanism across different tumors with multiple molecular backgrounds

Preliminary antitumor activity observed in patients with cancers harboring selected genomic alterations at doses ≥100mg
- Meaningful clinical benefit in 34 (49%) of 69 patients
  - 12 patients with objective tumor responses:
    - 8 RECIST V1.1: cPR/uPR (7 confirmed, 1 unconfirmed )
    - 2 PCWG3 PSA responses
    - 2 GCIG CA125 responses
  - 14 patients with ongoing RECIST v1.1 SD for at least 16 weeks
  - 8 patients <16 weeks on study: SD with early significant decreases in tumor markers and <30% tumor shrinkage
Conclusions

RP-3500 is in development as a potent, potentially best-in-class, highly selective ATR inhibitor.

The TRESR Phase 1/2 study is the largest biomarker-selected trial testing a single agent ATR inhibitor (N=101) and continues to enroll.

Early TRESR data provide clinical POC and validate Repare Therapeutics' SNIPRx platform for molecular selection of tumors for ATR inhibitor therapy.

Favorable and differentiated safety profile, along with promising and distinct early efficacy, offer a clear direction for further development of RP-3500.

Next steps include:

- TRESR Phase 2 expansion cohorts to open imminently.
- Combination studies are ongoing or will open shortly.
Acknowledgements

The patients and their families who make this trial possible

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- University of Texas MD Anderson Cancer Center
- Dana Farber Cancer Institute
- Sarah Cannon Research Institute/Tennessee Oncology
- Memorial Sloan Kettering Cancer Center
- Duke Cancer Institute
- Massachusetts General Hospital
- Rhode Island Hospital/Lifespan
- Princess Margaret Cancer Center
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- Newcastle Hospital NHS Foundation Trust
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- Rigshospitalet, Denmark

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The Repare Clinical Study Team

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Treximo (part of the ProPharma Group)

This Study is funded by Repare Therapeutics
RP-3500 next steps
Update on TRESR (as of Oct 6th)

**Update on TRESR Module 1**

Enrollment to the main component of TRESR Module 1 (RP2D determination) is closed

- Recruitment to Module 1 is now closed (goal 120 pts)
- Unchanged safety/tolerability profile as of Oct 6th
- Update of 4 patients with uPR reported as of AACR-NCI-EORTC 2021 meeting: 3 cPR, 1 uPR
- Final results of Module 1 expected to be reported in 2Q 2022 with expected 3-4 months follow up of all M1 patients

Additional Modules in TRESR anticipated to open imminently
## Additional details on clinical responders

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<th>Tumor type</th>
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<td>cCA-125***</td>
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* Initial 32 weeks on talazoparib combination, 23 w on therapy
** Approx. 8 Mo on therapy (SD last scan -26% on Sept 23rd)
*** On-Tx 15weeks: SD (-28.7% at last scan on 07Sep)
Monotherapy: RP-3500

- N=120 enrolled
- RP2D and schedule identified

Dose decision/expansion phase: RP-3500

- ATM loss of function
- STEP² gene alteration(s)
- Other STEP² gene alterations

Signal seeking POC 3 arms

Potential registration-oriented development

Combination: RP-3500

- + Talazoparib
dose escalation; safety/activity confirmation

Development in tumors with BRCA1/2 mutations and/or PARP-combination-specific STEP² gene alterations

ATTACC

- + Olaparib
- + Niraparib

Global multicenter study designed for patients with any recurrent tumor with ATM loss or loss of any of the additional 16 STEP² genes
RP-3500 TRESR study – Updates to upcoming Module 2

Global multi-center study:
- Phase 2 study with 3 distinct arms designed to deliver PoC
- Expected 4Q 2021 start
- Results will inform discussion with the FDA/EMA on next steps

- ATM loss of function
  - Selected ATM LoF patients
  - Less heavily pre-treated patients than in Module 1
- STEP² gene alteration(s)
  - Two STEP² genes
  - Focused tumor population enriched for these genes
- Other STEP² gene alteration(s)
  - Selected STEP² genes
  - Focused on those un/under-represented in Module 1
RP-3500 updated clinical trial program: additional modules

Trial results to date support expanded clinical development

**Module 1**
- **July 2020**
- **Monotherapy: RP-3500**
  - N=120 enrolled
  - RP2D and schedule identified
  - Dose escalation; safety/activity confirmation
  - Combination: RP-3500 + Talazoparib
  - Safety & preliminary efficacy of RP-3500 in combination with PARP Inhibitors - Ongoing

**Module 2**
- **Oct 6, 2021**
- **Dose decision/expansion phase: RP-3500**
  - 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**
- **Monotherpy: RP-3500**
  - Dose escalation; safety/activity confirmation

**Module 4**
- **Combination: RP-3500 + Gemcitabine**
  - Safety & preliminary efficacy
  - Expected start Q4 2021

**Module 5**
- **Combination: RP-3500 Pediatrics**
  - Safety & preliminary efficacy of RP-3500 in children – Expected start Q1 2022

- **ATTACC**
  - Olaparib
  - Niraparib

- **Potential registration-oriented development**
  - FDA
  - EMA
RP-3500 key clinical summary

Early TRESR data provide clinical POC and validate Repare Therapeutics' SNIPRx platform

Favorable and differentiated safety profile and distinct early activity, offer a clear direction for further development

RP-3500 RP2D for further monotherapy evaluation is 160mg QD 3d on/4d off

Biomarker data confirm proof-of-mechanism across different tumors with multiple molecular backgrounds

Preliminary results observed in tumors with selected genomic alterations continue to mature

Final efficacy and safety analysis from Module 1 expected in 2Q 22

Meaningful clinical benefit in 34 (49%) of 69 patients as of 15th August:

- **12 patients** with objective tumor responses:
  - 8 RECIST V1.1 cPR/uPR- 1 unconfirmed PR
  - 2 PCWG3 PSA responses
  - 2 GCIG CA125 responses
- **14 patients** with ongoing RECIST v1.1 SD for at least 16 weeks
- **8 patients** <16w on study: SD with early significant decreases in tumor markers and <30% tumor shrinkage
## Recent progress and upcoming anticipated milestones

### 2021

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Q&A Session