Insight that enriches. Precision that empowers.

RP-1664 & RP-3467 Update Conference Call
November 15, 2023
Agenda

Welcome & Introduction
Lloyd M. Segal, President & CEO

RP-1664 (PLK4 inhibitor) & RP-3467 (Polθ inhibitor)
Michael Zinda, Ph.D., EVP, Chief Scientific Officer, and, Phil Herman, EVP, Chief Commercial & Portfolio Development Officer

Upcoming Catalysts
Lloyd M. Segal, President & CEO

Q&A
Repare Therapeutics Leadership
Disclaimer

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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 COVID-19 pandemic 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 Quarterly Report on Form 10-Q filed with the SEC on November 9, 2023, 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.

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## Expanding pipeline of precision oncology therapeutics

<table>
<thead>
<tr>
<th>PROGRAM</th>
<th>TUMOR LESION</th>
<th>DRUG TARGET</th>
<th>PRECLINICAL</th>
<th>PHASE 1</th>
<th>PHASE 2</th>
<th>PHASE 3</th>
<th>RIGHTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Camonsertib (RP-3500/ RG6526)</td>
<td>ATM + 16 STEP2 lesions</td>
<td>ATR</td>
<td>Ph2 TAPISTRY</td>
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<td>Ph1b/2 Morpheus-Lung</td>
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<td>Roche</td>
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<td>Ph1/2 TRESR: Mono + PARP (talazoparib) Combo</td>
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<td>Ph1/2 ATTACC: PARP (olaparib/niraparib) Combo</td>
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<td>Ph1/2 TRESR: Gemcitabine Combo</td>
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<tr>
<td>Lunresertib (RP-6306)</td>
<td>CCNE1, FBXW7 + others</td>
<td>PKMYT1</td>
<td>Ph2 CCTG ISTs</td>
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<td>Ph1 MYTHIC: Mono + Camonsertib Combo</td>
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<td>Ph1 MAGNETIC: Gemcitabine Combo</td>
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<td></td>
<td>Ph1 MINOTAUR: FOLFIRI Combo</td>
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<td></td>
<td></td>
<td></td>
<td>Ph1 Carbo/valin/paclitaxel Combo IST</td>
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<tr>
<td>RP-1664 PLK4 Inhibitor</td>
<td>TRIM37-high</td>
<td>PLK4</td>
<td></td>
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<tr>
<td>RP-3467 Polθ Inhibitor</td>
<td>BRCA1/2</td>
<td>Polθ</td>
<td></td>
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<tr>
<td>SNIPRx® Platform</td>
<td>Additional SL targets in advanced stages of development</td>
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<td>Discovery and validation of new SL precision oncology targets</td>
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</tbody>
</table>

Focus of today’s presentation
## Overview of our next 2 clinical programs

<table>
<thead>
<tr>
<th>PROGRAM</th>
<th>FIRST PATIENT ENROLLMENT GOAL</th>
<th>TREATMENT APPROACH</th>
<th>CLINICAL OPPORTUNITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>RP-1664 PLK4 Inhibitor</td>
<td>1H 2024</td>
<td>Monotherapy</td>
<td>~63K addressable patient population for TRIM37-high solid tumors (US+UK/EU4)*</td>
</tr>
</tbody>
</table>
| RP-3467 Polθ Inhibitor | 2H 2024 | Combination therapy (PARPi, RLTs, and ADCs) | Global Market Segments**:  
~$3B PARPi  
~$8B RLTs  
~$5B ADCs |

*Based on estimated number of pts available for 1st line treatment in the advanced setting (CancerMPact®, Patient Metrics, 2022; accessed 8/18/23) and lesion prevalence

<table>
<thead>
<tr>
<th>Highly potent, selective and bioavailable PLK4 inhibitor synthetic lethal with TRIM37 amplification &amp; overexpression (TRIM37-high)</th>
<th>Strong, dose-dependent anti-tumor activity as monotherapy across preclinical models</th>
</tr>
</thead>
<tbody>
<tr>
<td>Will be initially investigated in TRIM37-high solid tumors and neuroblastoma</td>
<td>~63K addressable patient population with limited treatment options; Potential across multiple tumor types</td>
</tr>
</tbody>
</table>

**RP-1664**

Potential first-in-class, oral PLK4 inhibitor

FPI in 1H 2024
Addressing unmet need in critical patient populations

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Prevalence of tumors</th>
<th>Eligible patients*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuroblastoma</td>
<td>81.0%</td>
<td>&lt;1,000</td>
</tr>
<tr>
<td>Breast: HER2+</td>
<td>29.6%</td>
<td>5,900</td>
</tr>
<tr>
<td>Breast: HR+/HER2-</td>
<td>17.9%</td>
<td>11,800</td>
</tr>
<tr>
<td>Breast: TNBC</td>
<td>12.8%</td>
<td>2,200</td>
</tr>
<tr>
<td>Lung Non-Squamous</td>
<td>8.6%</td>
<td>19,300</td>
</tr>
<tr>
<td>Bladder</td>
<td>8.1%</td>
<td>4,100</td>
</tr>
<tr>
<td>Liver</td>
<td>7.4%</td>
<td>2,200</td>
</tr>
<tr>
<td>Lung Squamous</td>
<td>6.7%</td>
<td>4,700</td>
</tr>
<tr>
<td>Soft Tissue Sarcoma</td>
<td>6.1%</td>
<td>&lt;1,000</td>
</tr>
<tr>
<td>Esophageal</td>
<td>5.1%</td>
<td>2,000</td>
</tr>
</tbody>
</table>

*Based on estimated number of pts available for 1st line treatment in the advanced setting (CancerMPact®, Patient Metrics, 2022; accessed 8/18/23) and lesion prevalence (TCGA; GENIE-Neuroblastoma Only). 1 Represents only gene amplification for high risk Neuroblastoma; 2 Non-Squamous subtype of Non-Small Cell Lung Cancer only; 3 Squamous subtype of Non-Small Cell Lung Cancer only

~63K patients across tumor types; ~53K among top tumors
Compelling synthetic lethal rationale for targeting PLK4

- Centrosomes use centrioles and pericentriolar material (PCM) to initiate mitotic spindle formation
- Polo-Like Kinase 4 (PLK4) is necessary for centriole creation in S-phase
- TRIM37 (an E3 Ligase) negatively affects PCM stability; excess TRIM37 depletes PCM, increasing cell reliance on centrioles for spindle assembly
- Thus, PLK4 inhibition is harmful in cells with high TRIM37 and low PCM
- Validated in two 2020 *Nature* publications

- Biomarker-driven patient selection hypothesis for development of oral PLK4i for TRIM37-high tumors
**Potential first-in-class oral PLK4 inhibitor**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>RP-1664</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In vitro</strong></td>
<td></td>
</tr>
<tr>
<td>PLK4 Enzyme IC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>1 nM</td>
</tr>
<tr>
<td>PLK4 cell binding IC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>3 nM</td>
</tr>
<tr>
<td>Cell proliferation in MCF7 / T47D (TRIM37 amp) EC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>51 / 17 nM</td>
</tr>
<tr>
<td>Cell-base selectivity vs AurA, AurB</td>
<td>&gt;2000-fold</td>
</tr>
<tr>
<td>Kinome screen at 90x PLK4 IC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>8/280 kinases &gt;50% inh</td>
</tr>
<tr>
<td><strong>ADME</strong></td>
<td></td>
</tr>
<tr>
<td>Human Hepatocyte Clearance (µL/min/10&lt;sup&gt;6&lt;/sup&gt; cells)</td>
<td>2.2</td>
</tr>
<tr>
<td>Rat PK (%F, t&lt;sub&gt;1/2&lt;/sub&gt;)</td>
<td>28%, 4h</td>
</tr>
<tr>
<td>Monkey PK (%F, t&lt;sub&gt;1/2&lt;/sub&gt;)</td>
<td>96%, 9h</td>
</tr>
</tbody>
</table>

- Highly potent, selective and orally bioavailable PLK4 inhibitor
- Clean in PanLabs safety pharmacology screen
PLK4 inhibition is synthetic lethal with TRIM37-high tumors

- PLK4 inhibition selectively inhibited TRIM37-high cells
Potent PLK4 inhibition and downstream modulation of centrioles

- PLK4 inhibition leads to centriole depletion, p21 activation and ultimately cell death in TRIM37-high cells.
Cell lines with TRIM37-high are more sensitive to PLK4 inhibition

- Published SL hypothesis confirmed in house across a panel of cell lines with and without TRIM37-high
Robust monotherapy activity across PDX/CDX models

- Monotherapy drives tumor stasis to regression in TRIM37-high models
Deep monotherapy regressions in TRIM37-high models

- High risk neuroblastoma (>80% TRIM37-high) provides a biomarker-enriched monotherapy opportunity
Highly efficacious as monotherapy in neuroblastoma models

- Neuroblastoma PDX and CDX models (all TRIM37-high) conducted at Children’s Hospital of Philadelphia demonstrate deep and prolonged monotherapy regressions in 5 of 6 evaluable models

*J Maris and Y Mosse, CHOP
In vivo activity seen across a range of doses and schedules

### CHP-134 Neuroblastoma CDX Model

- Continuous and intermittent dosing delivered similar monotherapy efficacy using a chow formulation to mimic predicted human PK

### MCF7 CDX (ER+PR+HER2-) Model
Clinical PD biomarkers established

- Modulation of key downstream biomarkers confirmed with clinical assays available for evaluation of PD biomarkers in tumor and/or surrogate tissue during planned Phase 1 trials

<table>
<thead>
<tr>
<th>Untreated</th>
<th>RP-1664</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal centrioles</td>
<td>No centrioles</td>
</tr>
<tr>
<td>Abnormal mitoses</td>
<td>Rosette; Monopolar mitoses</td>
</tr>
<tr>
<td>Upregulation p21</td>
<td></td>
</tr>
</tbody>
</table>
Phase 1 monotherapy trial in neuroblastoma and adult tumors

- Efficient Phase 1 plan enabling early start for pediatric dose finding study in neuroblastoma and clear view on adult solid tumor opportunity.
RP-1664: Key takeaways and next steps

- Large market opportunity with significant unmet need across multiple tumor types
  - ~63K addressable patient population with limited treatment options
  - High risk neuroblastoma (>80% TRIM37-high) provides a biomarker-enriched opportunity

- Monotherapy-only development plan
  - Potential first-in-class highly potent and selective, oral inhibitor
  - Clear signal for monotherapy tumor regressions in preclinical models

- Expect to initiate Phase 1 clinical trial in 1H 2024
  - Focused, capital-efficient Phase 1 trial
  - Confirm strength of signal for future Phase 2 in solid tumors and facilitate quick start of neuroblastoma development
RP-3467
**Potential best-in-class Polθ inhibitor**

RP-3467 demonstrates compelling combination activity without added toxicity

<table>
<thead>
<tr>
<th>PARPi Combination</th>
<th>RLT Combination</th>
<th>Chemotherapy/ADC Payloads</th>
</tr>
</thead>
<tbody>
<tr>
<td>Durable complete responses preclinically, with no additional toxicity</td>
<td>Survival benefit preclinically in unselected tumor backgrounds, with no additional toxicity</td>
<td>Well tolerated preclinically in combination with chemotherapy, including topoisomerase ADC payloads</td>
</tr>
</tbody>
</table>

~$3 Billion global market segment for PARP inhibitors

~$8 Billion global market segment for RLTs

~$5 Billion global market segment for ADCs

Polθ is a promising therapeutic target

Polθ

- Unique, multifunctional DNA polymerase with ATP-dependent DNA helicase activity
- Required for microhomology-mediated end joining (MMEJ), a key mechanism of double-strand DNA break repair
- Uniquely active to repair double-strand DNA breaks during mitosis
- Minimally expressed in normal tissue and knockout animals have no significant phenotype
Protein structures enabled discovery of polymerase and helicase inhibitors

- Helicase and polymerase domains are both essential for Polθ cellular activity
- Repare has generated potent and selective Polθ inhibitors against both the helicase and polymerase domain
Repare Polθ helicase inhibitors demonstrate superior cell potency

- 100-1000X fold better cellular potency than could be achieved with polymerase-class inhibitors
- Repare has prioritized Helicase domain inhibitors to target potential best-in-class opportunity
RP-3467 is a potential best-in-class Polθ inhibitor

<table>
<thead>
<tr>
<th>Parameter</th>
<th>RP-1664</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polθ ATPase Enzyme IC$_{50}$</td>
<td>&lt;0.25 nM</td>
</tr>
<tr>
<td>CETSA cellular target engagement IC$_{50}$</td>
<td>5 nM</td>
</tr>
<tr>
<td>Cell proliferation DLD1 / HCT116 (BRCA2mt) EC$_{50}$</td>
<td>4 / 7 nM</td>
</tr>
<tr>
<td>Off-target ATPase (HELQ, WRN, BLM) IC$_{50}$</td>
<td>&gt; 10 µM</td>
</tr>
<tr>
<td>Off-target Polθ polymerase domain IC$_{50}$</td>
<td>&gt; 100 µM</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human Hepatocyte Clearance (µL/min/10$^6$ cells)</td>
<td>2.1</td>
</tr>
<tr>
<td>Rat PK (%F, t$_{1/2}$)</td>
<td>123%, 6h</td>
</tr>
<tr>
<td>Monkey PK (%F, t$_{1/2}$)</td>
<td>60%, 3h</td>
</tr>
</tbody>
</table>

- Highly potent, selective and orally bioavailable Polθ helicase inhibitor
- Clean on PanLabs safety pharmacology screen
Inhibits DNA repair and is synthetic lethal with BRCA2 loss

- Demonstrates potent *in vitro* cellular target engagement and activity
- Huge synthetic lethal window – no effect on BRCA2 WT cells
- Suppresses *in vivo* growth of a BRCA2 null tumor
Rationale for synergy between Polθi and PARPi

- PARPi + Polθi combination synergizes to kill homologous recombination deficient tumor cells
Addressing unmet need in critical patient populations

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Prevalence of gene of interest</th>
<th>PARP-naïve opportunity (1L)</th>
<th>PARP-resistant Opportunity (2L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovarian</td>
<td></td>
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<tr>
<td>Castrate-Resistant</td>
<td>10.7% 5.6% 6.4% 22.7%</td>
<td>7,700</td>
<td>3,500</td>
</tr>
<tr>
<td>Prostate</td>
<td>5.9% 8.2%</td>
<td>5,100</td>
<td>2,400</td>
</tr>
<tr>
<td>HER2- Breast**</td>
<td>3.7%</td>
<td>2,900</td>
<td>1,600</td>
</tr>
<tr>
<td>Pancreatic**</td>
<td>2.6%</td>
<td>1,700</td>
<td>500</td>
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</table>

*Based on estimated number of drug treated pts in the advanced setting likely to be naïve to PARP inhibitor treatment or previously treated with a PARP inhibitor (CancerMPact®, Patient Metrics, 2022; accessed 9/25/23) and lesion prevalence (TCGA; Riaz, N. et al. Pan-cancer analysis of bi-allelic alterations in homologous recombination DNA repair genes. Nat Commun 8, 857 (2017)). Other HRD gene mutations include: BRIP1, ATM, RAD51B, RAD51C, RAD51D, PALB2, BARD1, CDK12, CHEK1, CHEK2, FANCL, RAD54L. **Includes germline BRCA1/2 only

~25K among key tumor segments
Synergizes with both PARP1/2 and PARP1-selective inhibitors

- Opportunities with PARP1/2 standard-of-care and potential with emerging PARP1-selective agents
Profound, durable synergy with PARP inhibition

- Deep/durable complete regressions across a wide dose range and extremely well tolerated
No added hematological toxicity in combination over Olaparib alone

5 weeks co-administration of human clinical PK equivalent dose of Olaparib with RP-3467 up to 10mg/kg in CD1 mice

- Extremely well tolerated combination at relevant Olaparib doses
Complete regressions in PDX models

- Complete regression in BRCA1/2 null PDX models
- Synergy in a PARPi resistance model (data not shown)
Polθ is a radio-sensitizing agent

- Cancer cells often transfer radiation-induced DSBs generated in S/G2 into mitosis
- Polθ-directed MMEJ is the only known pathway for repairing DSBs during mitosis
- Polθ inhibitors could be prime radio-sensitizing agents for use in the clinic

- Radioligand therapy market is substantial with a commercial value currently estimated at approximately $8B and projected to exceed $13B by 2030*

Polθi sensitizes *unselected* tumors to Radioligand Therapy

- Inhibition of Polθ sensitizes tumors, irrespective of genetic background, to RLT
- HRD gene loss would be expected to further enhance synergy

Homologous recombination proficient tumors treated with one dose of RLT and 4 weeks of Polθi
Synergizes with dsDNA break inducing chemotherapy

- Synergistic efficacy supports opportunity to combine with chemotherapies
- ADC payload combinations are a key focus (e.g. Topoisomerase inhibitors)
- Clean tolerability profile suggests no overlapping toxicities
Clear *in vivo* combination benefit with chemo – No additional tox

- Sensitizes to carboplatin and irinotecan and is well tolerated in combination (no changes in BW over single agents alone)
Phase 1 clinical trial initiation expected in 2H 2024

- Primary Goal: PK, safety and recommended Phase 2 dose

Multiple potential Phase 1/2 studies

- PARPi combination – PARP1/2 or PARP1
- RLT combination
- ADC combination(s)
RP-3467: Key takeaways and next steps

- Polθ inhibition was extremely well tolerated preclinically as a monotherapy and in combination

- Compelling preclinical combination activity with select DNA damaging agents
  - Durable complete responses in combination with PARPi, with no additional toxicity
  - Survival benefit in combination with RLT in unselected tumor backgrounds, with no additional toxicity
  - Well tolerated in combination with chemotherapy, including topoisomerase ADC payloads

- Differentiation potential with modalities in large market segments
  - ~$3B PARPi
  - ~$8B RLTs
  - ~$5B ADCs

- Expect to initiate Phase 1 clinical trial in 2H 2024
Upcoming Catalysts
Upcoming milestones

2H 2023

Camonsertib Phase 2  
TAIPISTRY trial FPI

Lunresertib + carboplatin/paclitaxel  
combination Phase 1  
IST initiation

1H 2024

RP-1664 (PLK4i)  
clinical trial initiation

Initial lunresertib + FOLFIRI  
combination Phase 1 data

2H 2024

RP-3467 (Polθi)  
clinical trial initiation

Lunresertib + gemcitabine  
combination Phase 1 data

Lunresertib + camonsertib  
combination Phase 1 data  
(expansion cohorts)
Insight that enriches. Precision that empowers.

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