REPARE THERAPEUTICS

Insight that enriches. Precision that empowers.

Corporate Presentation

February 2024

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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 lunresertib (RP-6306) and camonsertib; 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, 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 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 Annual Report on Form 10-K filed with the SEC on February 28, 2024, 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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Developing Next-Generation Precision Oncology Medicines

Differentiated and wholly-owned clinical pipeline

- Lunresertib: First-in-class oral PKMYT1 inhibitor (Phase 1/2)
- Camonsertib: ATR inhibitor (Phase 1/2)
- RP-1664: First-in-class selective PLK4 inhibitor (Phase 1)

Proprietary CRISPR -enabled SNIPRx platform

- Focused on genomic instability and DNA damage repair
- Clinical trials enriched for patients with tumors carrying a network of synthetic lethal alterations (STEP[2])

Multiple clinical catalysts expected in 2024

- Ongoing combination trials
- New clinical entries (PLK4 and Polθ ATPase inhibitors)

Strong balance sheet

- Cash and investments of ~$223.6M[1] plus recent $40M milestone payment fund operations into mid-2026
- Multiple clinical catalysts in that timeframe

[1] *As of December 31, 2023.*

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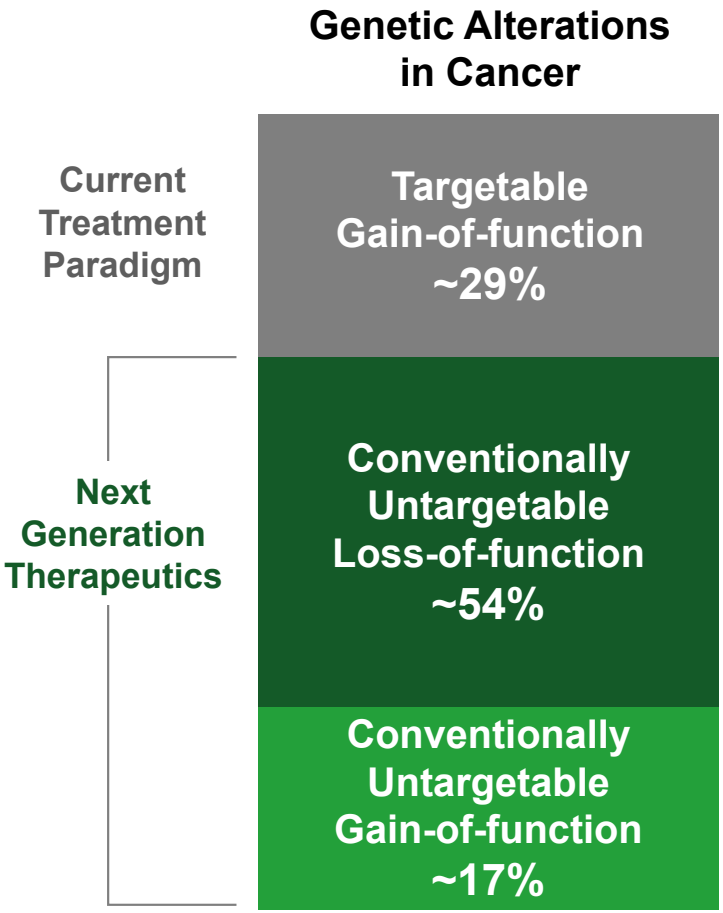
Targeting the untargetable through synthetic lethality



Specifically targeting and disrupting genes essential for cancer cell survival

SNIPRx identifies and targets necessary genes to induce synthetic lethality

- Highly targeted & tumor-type agnostic approach
- Exploiting cancer cell genomic instability, including DNA damage repair

Platform validated with established and expanding clinical-stage pipeline

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Expanding pipeline of precision oncology therapeutics

PROGRAM	TUMOR LESION	DRUG TARGET	PRECLINICAL	PHASE 1	PHASE 2	PHASE 3	RIGHTS
Lunresertib (RP-6306)	CCNE1, FBXW7 + others	PKMYT1	Ph2 CCTG ISTs	Ph1 MYTHIC: Mono + Camonsertib Combination Ph1 MAGNETIC: Gemcitabine Combination Ph1 MINOTAUR: FOLFIRI Combination Ph1 Carboplatin/paclitaxel Combination IST Ph1/1b Debio 0123 Combination (Debiopharm)			REPARE THERAPEUTICS
Camonsertib (RP-3500)	ATM + 16 STEP² lesions	ATR	Ph2 TAPISTRY (Roche) Ph1b/2 Morpheus-Lung (Roche) Ph1/2 TRESR: Mono (M1) + PARP (Talazoparib; M3) Combination Ph1/2 ATTACC: PARP (olaparib/niraparib) Combination Ph1/2 TRESR: Gemcitabine (M4) Combination				REPARE THERAPEUTICS
RP-1664	TRIM37-high	PLK4	Ph1 LIONS Monotherapy				REPARE THERAPEUTICS
RP-3467	BRCA1/2	Polθ ATPase					REPARE THERAPEUTICS
SNIPRx® Platform	Additional SL targets in advanced stages of development						REPARE THERAPEUTICS
	Discovery and validation of new SL precision oncology targets						Bristol Myers Squibb REPARE THERAPEUTICS

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Driving shareholder value through strategic collaborations

Roche	Bristol Myers Squibb
Global development and commercialization collaboration for Camonsertib	**Multi-target discovery collaboration leveraging SNIPRx® discovery platform**
$135M upfront	$65M upfront
~$1.2B potential milestones + royalties	~$3B potential milestones + royalties
50/50 U.S. co-development, profit/cost share and co-promotion option	Both SL targets and “undruggable” targets outside our focus
Concluding May 2024	Completed Nov 2023

Source: Company press releases.

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Proven experience in drug discovery and development

Leadership Team

Lloyd M. Segal
President & CEO
McKinsey & Company · PCP · CAPRION

Steve Forte, CPA
Chief Financial Officer
clementia · APTALIS

Michael Zinda, PhD
Chief Scientific Officer
AstraZeneca · Lilly

Maria Koehler MD, PhD
Chief Medical Officer
gsk · AstraZeneca · Pfizer

Cameron Black, PhD
Head of Discovery
MERCK · aneqpharma

Philip Herman
Chief Commercial, Portfolio Development Officer
-mAbs Therapeutics, Inc · Pfizer · santhera · Dyax

Kim A. Seth, PhD
Chief Business Officer
Pfizer · Goldman Sachs

Daniel Bélanger
Head of Human Resources
ADARE PHARMA SOLUTIONS · APTALIS

Scientific Founders

Daniel Durocher, PhD
- Developed CRISPR SL platform
- Deep DNA repair knowledge
- Lunenfeld-Tanenbaum Research Institute (LTRI) & professor at University of Toronto

Agnel Sfeir, PhD
- DDR and cancer pathway investigator
- Pioneer in Polθ, genome instability
- Professor, MSKCC

Frank Sicheri, PhD
- Globally recognized structural biologist, expert in eukaryotic cell signaling, drug mechanism of action
- LTRI & professor at University of Toronto

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Lunresertib (RP-6306)

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Lunresertib:
First-in-class, oral, small molecule, PKMYT1 inhibitor

Large, genomically defined potential patient population of ~90k addressable

- 50% RECIST response in camonsertib combination in gynecological tumors

Demonstrated anti-tumor activity

- Across multiple tumor types and genotypes
- POC in patients established
- Safe and well tolerated RP2D achieved

Repare discovered synthetic lethality of PKMYT1 inhibition

- Initially identified CCNE1 amplification
- STEP^2 screen identified additional genes – FBXW7 and PPP2R1A
- First and only PKMYT1 inhibitor in clinical trials

Validated preclinical synergy hypothesis and patient section approach from proprietary SNIPRx platform

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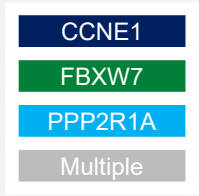
Large, genomically defined potential patient population

~90K addressable patients including ~65K among top tumors with genetic alterations largely mutually exclusive

Top New Advanced Tumor Cases (US+UK/EU4)

Tumor Type	Prevalence of Genes of Interest	Eligible Patients
Uterine	3.8% / 12.9% / 7.6% / 4.7% — 28.9%	7,000
Ovarian	19.0% — 20.0%	6,300
Stomach	10.2% / 6.4% — 17.7%	9,000
Colorectal	13.1% — 14.7%	24,500
Bladder	5.8% / 6.3% — 12.2%	6,200
Cervical	9.1% — 11.8%	1,300
Esophageal	7.1% / 3.3% — 11.5%	4,500
Sarcoma[1]	7.1% — 7.8%	1,200
Lung Squamous[2]	4.7% — 7.6%	5,300



** Based on estimated number of pts US+UK/EU4 treated in 1st line, advanced setting for diagnosed and new recurrent patients (CancerMPact®, Treatment Architecture, United States, 2021; accessed 5/19/23) and lesion prevalence (TCGA). [1] Soft Tissue Sarcoma only; [2] Squamous subtype of Non-Small Cell Lung Cancer only*

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Lunresertib: the first and only clinical PKMYT1 inhibitor

CCNE1 amplification synthetic lethal to PKMYT1 (Wee1 family protein kinase)

Regulates cell cycle and is part of DNA damage repair-related signaling

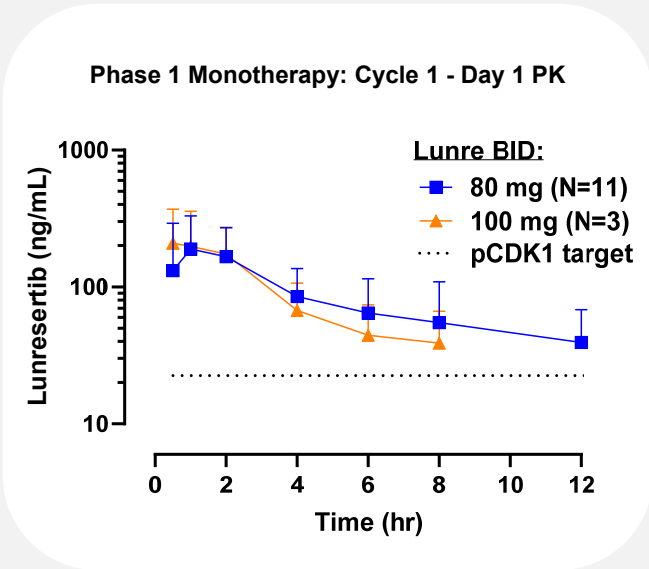
Inactivates CDK1 via phosphorylation of threonine14 (T14) holding the cell in S phase until ready to undergo mitosis

CCNE1 amp or **deleterious mutations in FBXW7 and PPP2R1A** result in an extended S phase and reliance on PKMYT1 activity

Inhibiting PKMYT1 in these genomic backgrounds **results in cell death** via mitotic catastrophe

Synergistic combinations enhance lunresertib anti-tumor activity

Target PK exposures achieved with lunresertib



Human PK exceeds the target exposure for inhibition of *p*CDK1 with half life of ~9 hours and similar QD and BID schedules

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Evolving broad trial program: sponsored and collaborative

Key inclusion criteria:

Recurrent solid tumors

CCNE1

amplification or

PPP2R1A

FBXW7

inactivating mutations

Lunresertib Combination Therapy

- **MAGNETIC: + Gemcitabine**
- **MYTHIC: + Camonsertib; + Debio 0123 (Wee1 inhibitor)**
- **MINOTAUR: + FOLFIRI**
- **IST: CCTG[1]**
- **IST: + Carbo/paclitaxel[2]**
- **4 collaboration trials in advanced discussion**

Determine RP2D dose / schedule

Progress to late-stage trials

Future Opportunities

Selected tumors with amplified CCNE1	Ovarian, Lung, Esophageal / Gastric
Selected tumors with FBXW7 loss	CRC, Other GI, Pan Tumor
Tumors with high rate of sensitivity genes	Endometrial, Bladder
Basket trial	Breast, Sarcoma, Bile Duct

[1] Canadian Clinical Trial Group (CCTG) collaborations include NCT05605509 and NCT05601440.

[2] SOC for 1st line ovarian cancer is carbo/paclitaxel (6 cycles) + PARPi maintenance therapy or carbo/paclitaxel with bevacizumab + bev maintenance therapy; this IST supports future potential 1st line combination studies as triplet therapy in patients with CCNE1 amplified tumors.

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Lunresertib:

MYTHIC Preliminary Phase 1 Trial Results (M1: Monotherapy) (M2: Camonsertib Combination Therapy)

CAMONSERTIB COMBINATION THERAPY

Safe, well tolerated, and promising anti-tumor activity across tumors and all lunresertib-sensitizing genomic alterations (N=59)

23.6% OR; 41.8% CBR in efficacy-evaluable patients (N=55)

33.3% OR; 50.0% CBR at preliminary RP2D range, across all tumors (N=18)

38.5% OR; 57.7% CBR in patients with heavily pre-treated gynecologic cancers (N=26); **50% RECIST response** at preliminary RP2D (N=10)

Preliminary recommended Phase 2 dose: Lunresertib 80mg twice daily and camonsertib 80mg once daily, **dose/schedule optimization ongoing**

MONOTHERAPY

Safe, well tolerated, and anti-tumor activity established (N=67)

Recommended Phase 2 dose: 80 mg twice daily in intermittent schedule

OR, overall response; CBR, clinical benefit rate; RP2D, recommended phase 2 dose.

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Lunre + cam responses across tumor types and genotypes

RECIST and tumor marker responses occurred early despite heavily pre-treated, relapsed/refractory patient population

Tumor type	Genotype	Response	Best % change in TL from BL	Therapy (weeks)	Lines of prior Tx/ prior platinum
Endometrial	*PPP2R1A/FBXW7*	cPR	-55.9	30.4	3/Y
	PPP2R1A/CCNE1	cPR	-53.0	18.1	2/Y
	FBXW7	cPR*	-100.0	11.1+	3/Y
	FBXW7	uPR	-39.6	16.0	3/Y
	FBXW7	uPR*	-44.7	11.4+	3/Y
Ovarian	*CCNE1*	cPR*	-70.2	21.4+	2/Y
	CCNE1†	cPR*	-30.8	12.6+	3/Y
	CCNE1	CA-125	-16.9	29.0+	9/Y
	CCNE1	CA-125	-23.1	37.0+	2/Y
	CCNE1	CA-125	13.6	12.9+	5/Y
Cervical	*PPP2R1A*	cPR*	-44.4	11.0+	1/Y
Colorectal	*FBXW7*	cPR	-43.3	27.6	3/Y
Bile duct	*CCNE1*	cPR	-35.0	28.1	2/Y
Breast	*FBXW7*‡	uPR	-43.8	18.1	2/N

** One response evaluable patient became uPR and four patients had responses confirmed after the Sept. 5, 2023 cutoff, data as of Oct. 6, 2023. Relevant patient tumor co-mutations †BRCA1 rearrangement and ‡BRCA2 biallelic loss. +Treatment ongoing. BL, baseline; cPR, confirmed partial response; RECIST, Response Evaluation Criteria in Solid Tumors; TL, target lesion; Tx, treatment; uPR, unconfirmed partial response.*

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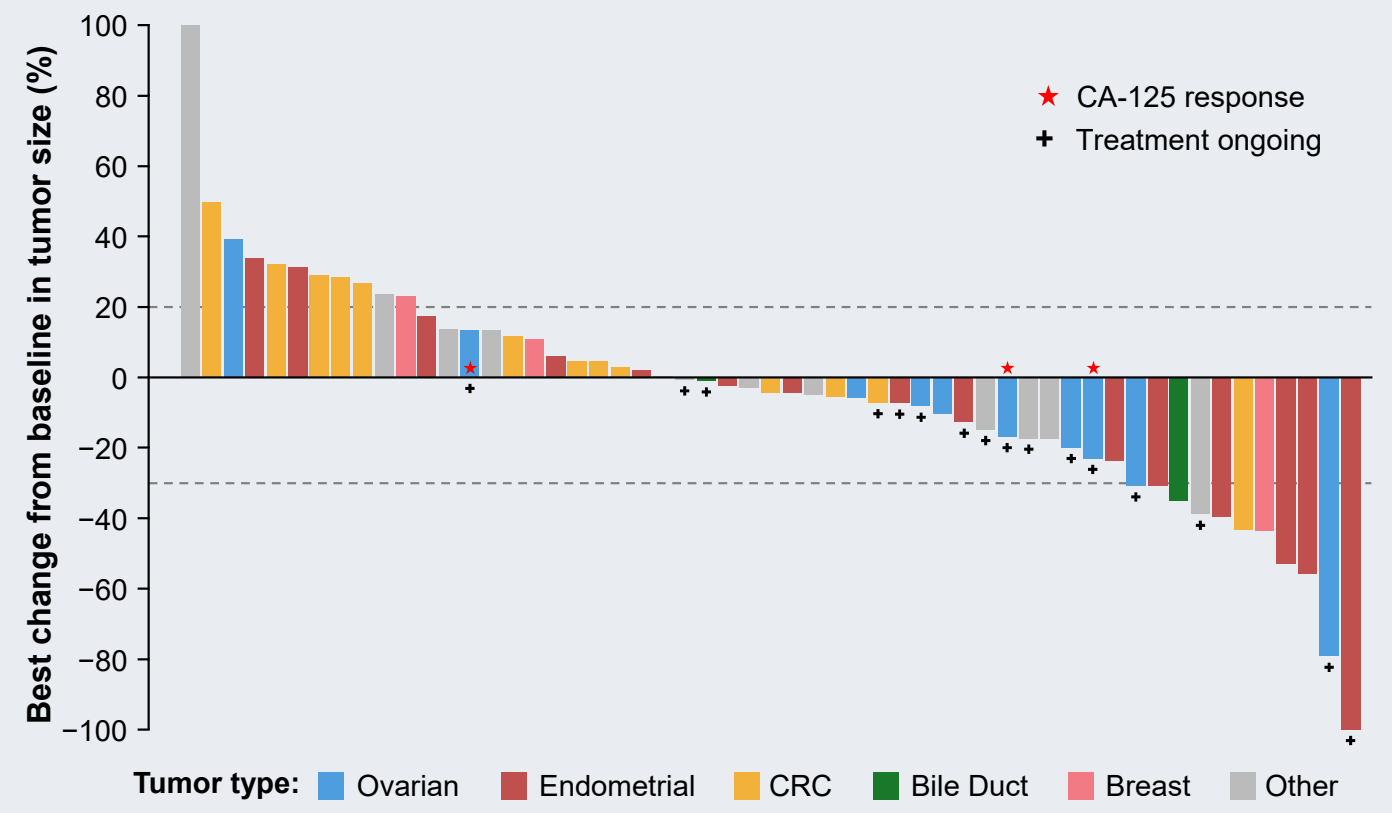
Frequent and deep tumor reductions with lunre + cam



- **In evaluable patients*, across all tumors/doses:**
  - OR: 23.6% (n=55)
  - CBR: 41.8% (n=55)
  - MRR: 50.0% (n=24)
- **At preliminary RP2D, across all tumors:**
  - OR: 33.3% (n=18)
  - CBR: 50.0% (n=18)

Efficacy evaluable patients only (≥1 post-baseline tumor assessment). Other tumor types include cervical (n=1), esophageal (n=1), GI (n=1), liver (n=1), lung (n=3), melanoma (n=1), osteosarcoma (n=1), pancreatic (n=2), and upper GI (n=1). CBR: overall response or time on treatment ≥ 16 wk w/o progression; CRC, colorectal cancer; RECIST, Response Evaluation Criteria in Solid Tumors (RECIST) Gynecologic Cancer InterGroup (GCIG); MRR, molecular response rate; OR, overall response based on RECIST or GCIG CA-125 response; RP2D, recommended phase 2 dose.

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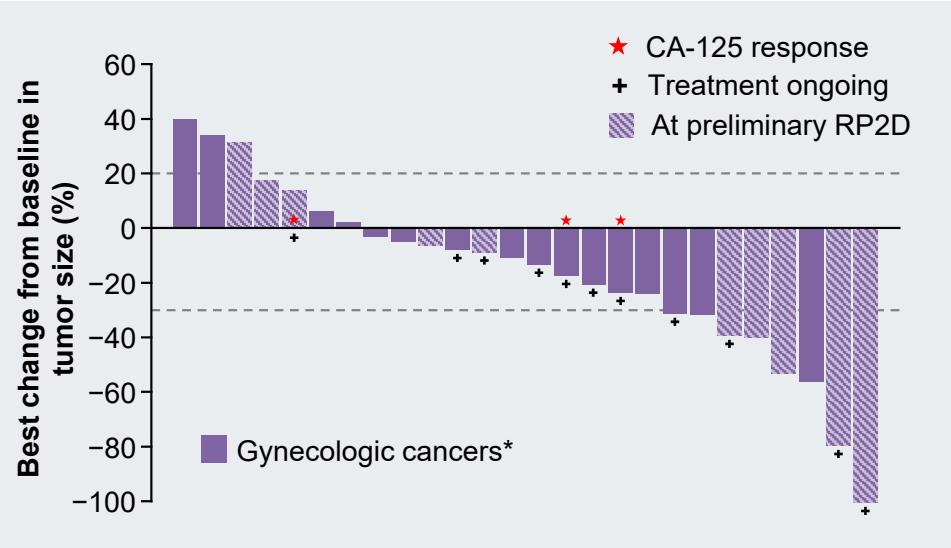
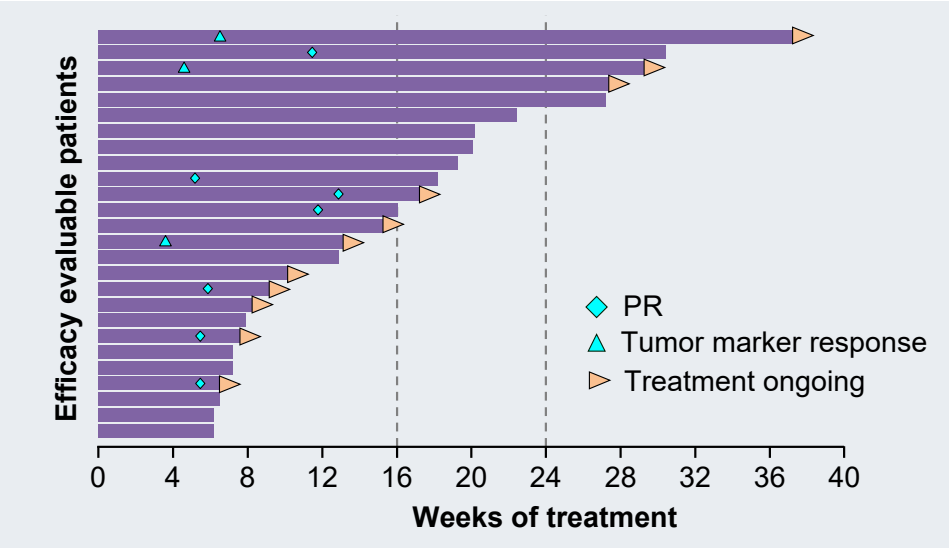
Combination treatment effective in gynecologic tumors

Meaningful tumor reductions and durable clinical benefit observed in heavily pre-treated patients





Across all doses (n=26):

- Overall response: 38.5%; RECIST Response: 26.9%
- CBR: 57.7%; MRR: 8/10 (80%)

At preliminary RP2D (n=10):

- Overall response: 60%; RECIST Response: 50%
- CBR: 70%

- Patients had 1-9 prior therapies (median=3); treatment ongoing in 11 patients; enrollment in expansion cohorts at RP2D continues

** Gynecologic cancers: ovarian, endometrial, and cervical cancers. Data represent the efficacy evaluable population (≥1 post-baseline tumor assessment). CBR, clinical benefit rate; OR, overall response based on RECIST or GCIG CA-125 response; MRR, molecular response rate; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors ; Gynecological Cancer InterGroup (GCIG); RP2D, recommended phase 2 dose.*

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Recurrent ovarian cancer response heralded by CA-125 decrease

Female
56 years old

High grade serous ovarian carcinoma

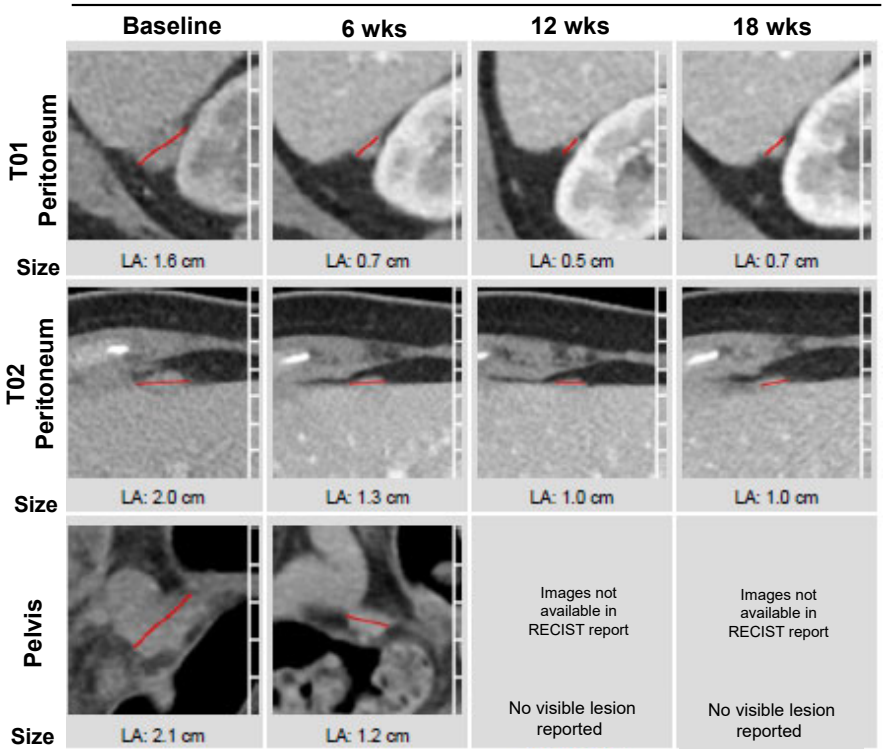
CCNE1
Amplification

TP53 mut

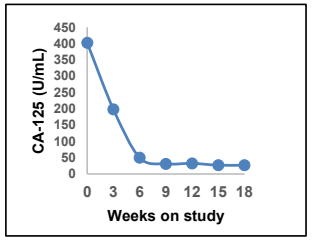
2 prior lines of therapy

RP2D:
Lunre 80mg BID 3/4
Cam 80mg QD 3/4

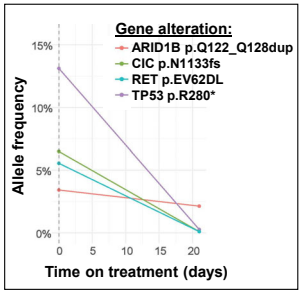
Tumor assessment



CA-125 dynamics



ctDNA dynamics



- **Overall response: cPR (RECIST)**
- **RECIST target lesion decrease -70.2%**
- **Therapy ongoing for >21 weeks**

3/4, 3 days on/4 days off; cPR, confirmed partial response; ctDNA, circulating tumor DNA; RECIST, Response Evaluation Criteria in Solid Tumors; QD, once daily; RP2D, recommended phase 2 dose.

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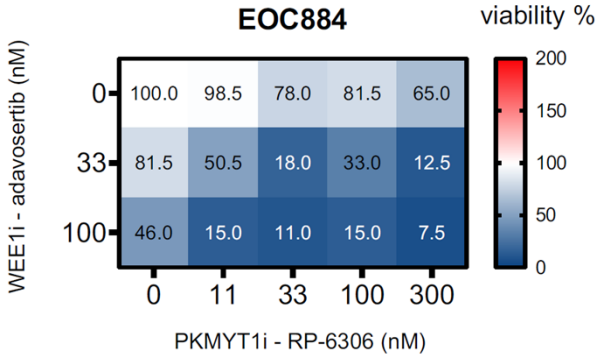
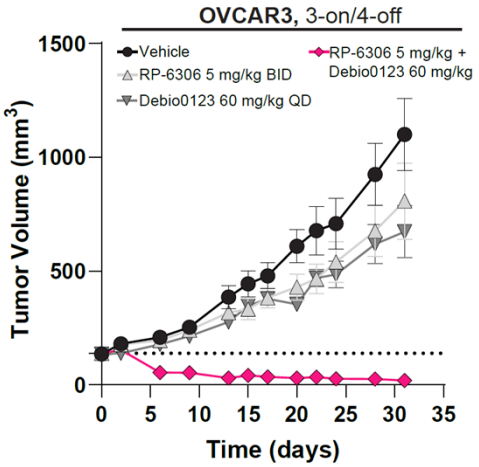
Debiopharm collaboration enables PKMYT1 + Wee1 leadership

Strong preclinical evidence of PKMYT1 + Wee1 inhibitor combination potential; Ph1/1b start in H1 2024



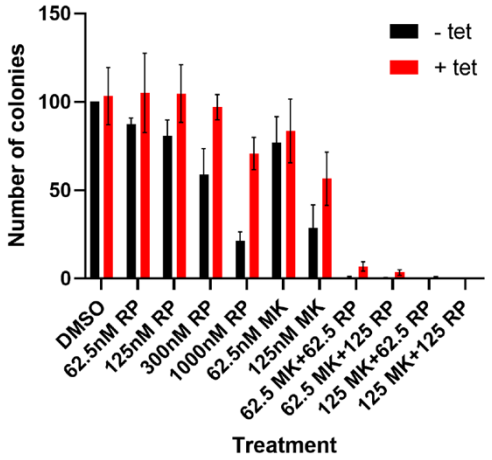
Combination synergistically eradicates ovarian cancer cells and organoid models at a low doses…

Benada et al., NAR Cancer, 2023.



…drives tumor regressions on intermittent schedule at doses below monotherapy EC_{50} …

Gallo et al., ANE 2023, Poster #A023.



… and overcomes resistance to MK-1775 (adavosertib) mediated by tet-induced Myt1 upregulation

Sokhi et al., AACR 2023, Poster #5511.

Camonsertib (RP-3500)

REPARE THERAPEUTICS

Camonsertib:
Potential best-in-class ATR inhibitor

Demonstrated synthetic lethal interaction of ATR and a network of genes identified by SNIPRx and STEP^2 process

Proof of concept established in Phase 1/2 monotherapy trial

Durable antitumor activity in combination with PARPi; meaningful clinical benefit in ovarian cancer

Global development and commercialization rights to be **wholly-owned** by Repare in May 2024

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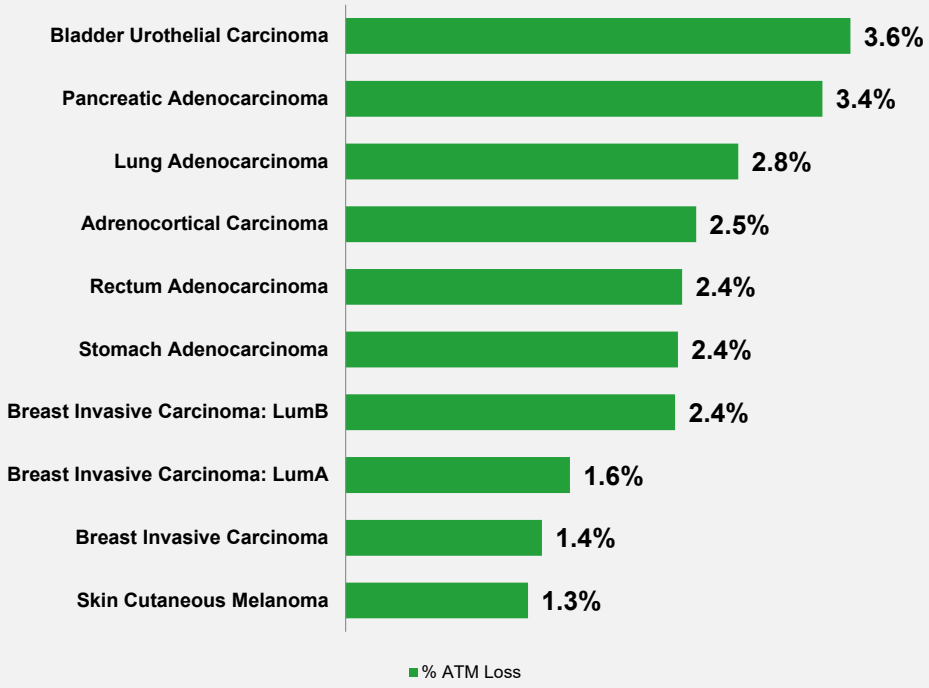
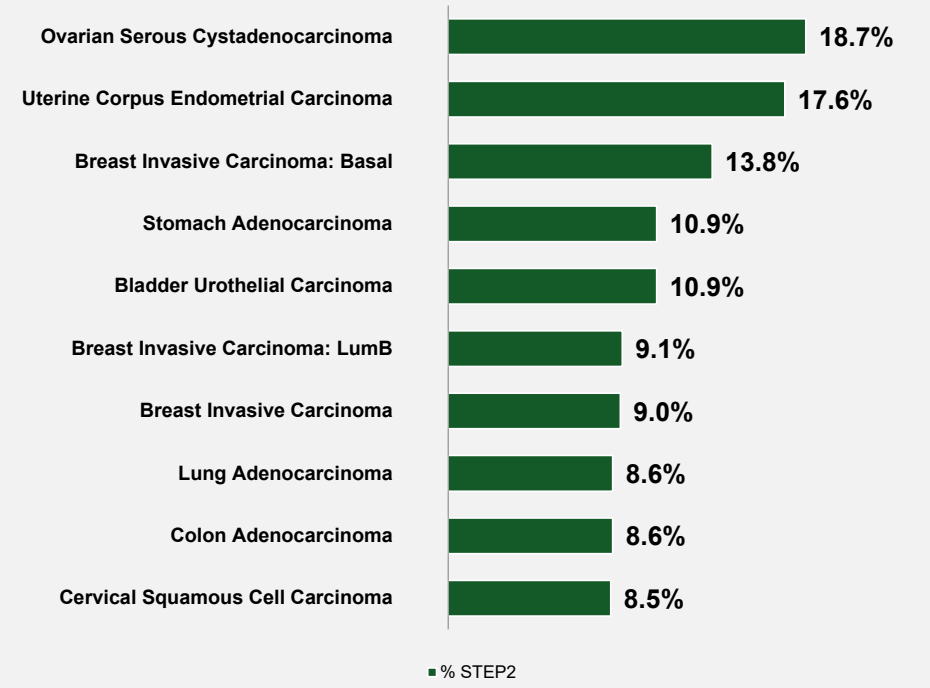
Potential across significant additional patient populations

Top 10 Tumor Types* with Highest Prevalence of ATM Deficiency



Top 10 Tumor Types* with Highest Prevalence of ATM Deficiency or STEP^2 Genomic Alterations



** TCGA; Not weighted for tumor prevalence*

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Camonsertib:

TRESR & ATTACC
Phase 1/2
Trial Results

COMBINATION THERAPY

Clinically meaningful anti-tumor activity in combination with all leading PARP inhibitors

Confirmed efficacy in **platinum- and PARPi-resistant cancers**

48% overall CBR (N=90) in patients with advanced solid tumors

32% OR; 58% CBR; ~7 months PFS in advanced ovarian cancer (N=19)

MONOTHERAPY

Favorable safety profile (N=120)

Proof-of-concept established in **ovarian cancer**

25% OR; 75% CBR; 8+ months PFS

Clinical benefit in patients with **BRCA1/2 mutations**

OR, overall response; CBR, clinical benefit rate; PFS, progression free survival

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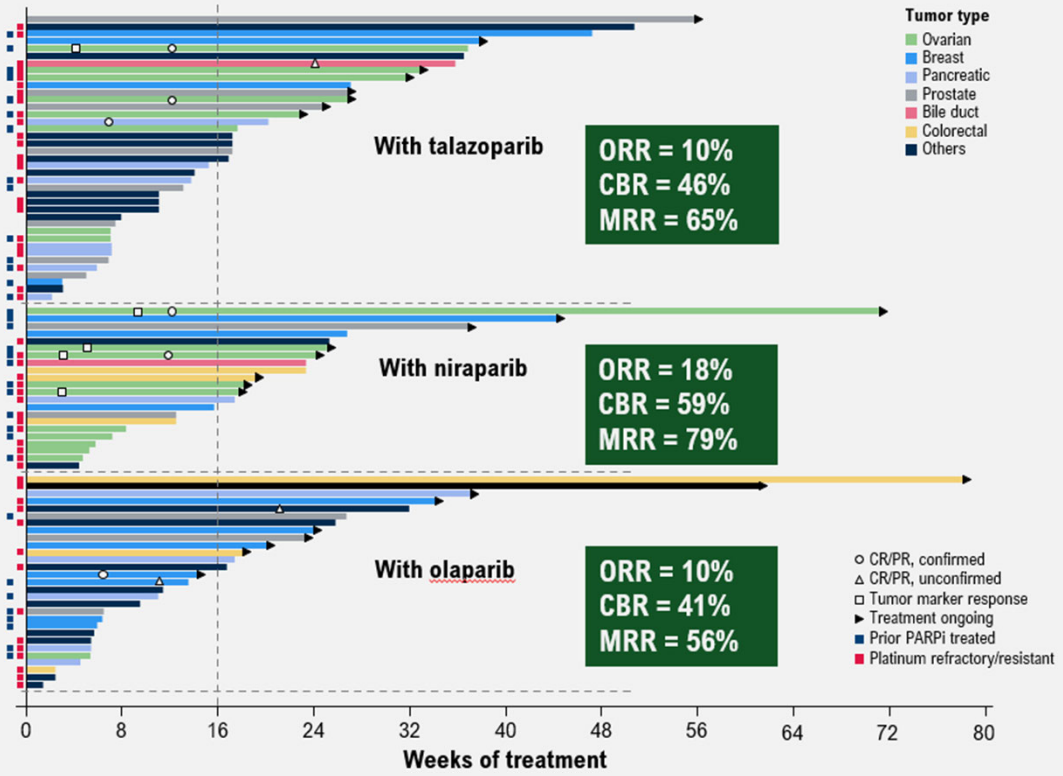
Durable clinical benefit observed with combination therapy

48% overall CBR
(N=90)

Benefit observed across multiple tumors, regardless of previous PARPi treatment

Similar benefit observed in patients with platinum-resistant tumors (ORR 12%, CBR 49%) and non-platinum-resistant tumors (ORR 13%, CBR 46%)

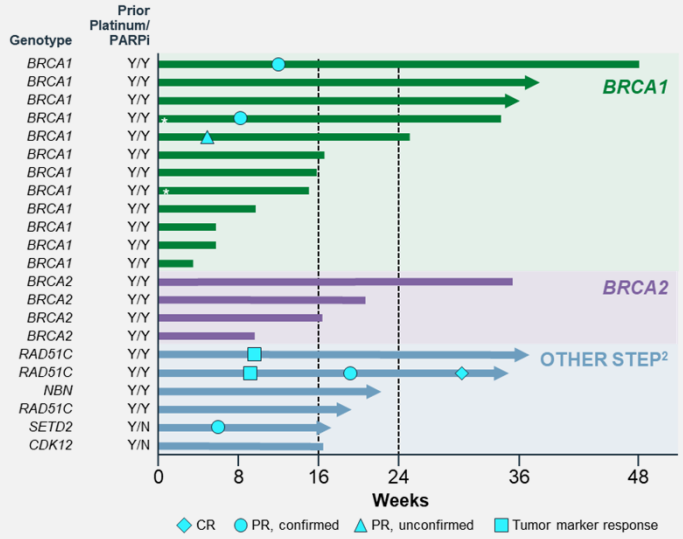


Included patients from efficacy analysis set.
ORR is based on overall response as best response of confirmed or unconfirmed CR or PR per RECIST v1.1 criteria or confirmed CA-125 response per Gynecological Cancer Intergroup; CBR is based on overall response or ≥16 weeks on treatment without progression; MRR is based on ctDNA molecular response as >50% decline in mVAF assessed by GuardantINFINITY or Tempus xF gene panel for patients with detectable somatic alterations.
CBR, clinical benefit rate; CR, complete response; PR, partial response; ORR, overall response rate; RECIST, Response Evaluation Criteria in Solid Tumors.

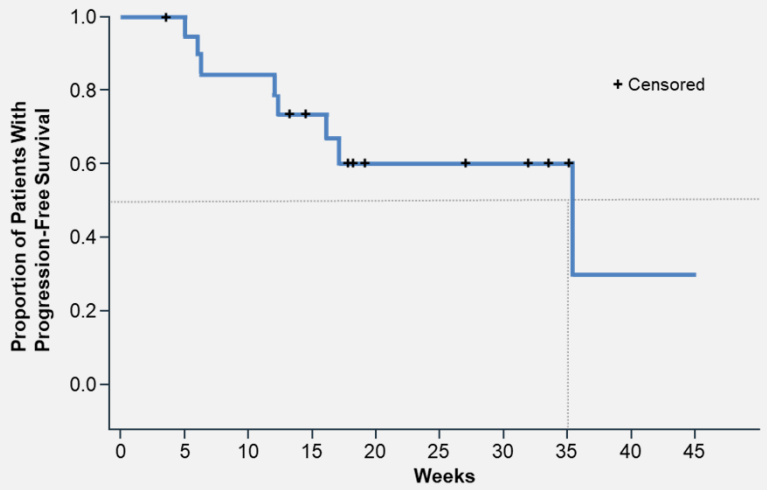
Anti-tumor activity in ovarian cancer with monotherapy

25%	35w	75%	90%	85%
Overall response (5/20*)	Median PFS	Clinical benefit rate (CBR)	(18/20) patients had prior PARPi	(17/20) patients platinum refractory/ resistant*

Time on Treatment (wk) – *Ovarian*



Time to Disease Progression or Death – *Ovarian*



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

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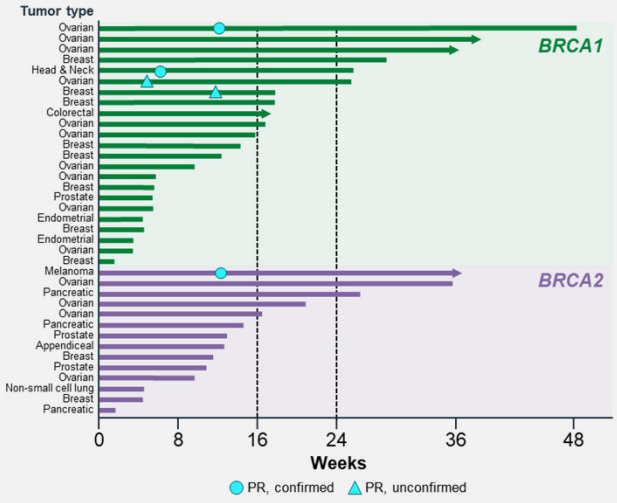
Monotherapy clinically relevant benefit in BRCA1/2 mutated patients

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

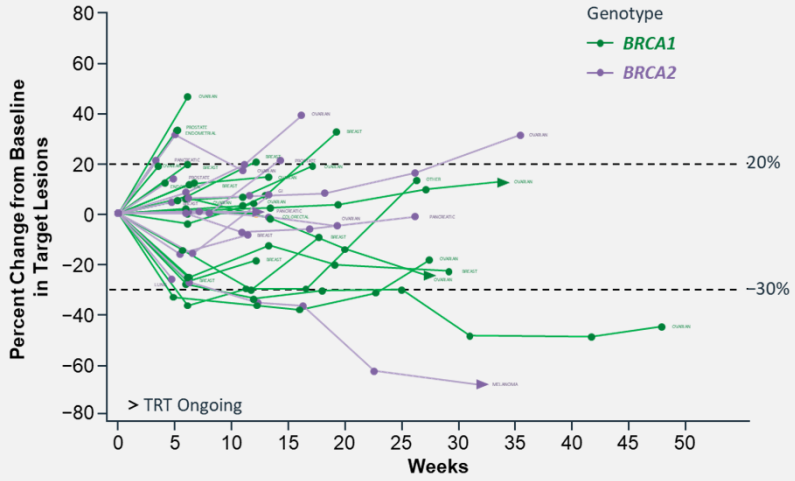
43%
CBR for BRCA1/2 tumors

48%
CBR for post-PARPi BRCA1/2 tumors

Time on Treatment (wk) – *BRCA1/BRCA2*
Module 1 subjects with > 100mg/day dose levels



Percent change from baseline in target lesions *(BRCA1/BRCA2)*
Module 1 subjects > 100mg/day dose levels



CBR (OR or ≥16w on therapy without progression) was 48% for BRCA1 population, and 36% for BRCA2

REPARE THERAPEUTICS

RP-1664

REPARE THERAPEUTICS

RP-1664

First-in-class, oral PLK4 inhibitor

FPI in 1H 2024

Highly potent, selective and **bioavailable** PLK4 inhibitor **synthetically lethal** with TRIM37 gain of function

Strong, dose-dependent anti-tumor activity as **monotherapy** across preclinical models

Trials to be initiated in 2024 in TRIM37-high **solid tumors** and **neuroblastoma**

~63K addressable patient population with limited treatment options; potential across multiple tumor types

REPARE THERAPEUTICS

High prevalence in patient populations with limited treatment options

~63K patients with TRIM37 amplification or overexpression, with ~53K among top tumors

Top TRIM37 Altered Tumors (New Advanced Cases, US+UK/EU4)

Tumor type	Prevalence of gene of interest	Eligible patients*
Neuroblastoma[1]	81.0%	<1,000
Breast: HER2+	29.6%	5,900
Breast: HR+/HER2-	17.9%	11,800
Breast: TNBC	12.8%	2,200
Lung Non-Squamous[2]	8.6%	19,300
Bladder	8.1%	4,100
Liver	7.4%	2,200
Lung Squamous[3]	6.7%	4,700
Soft Tissue Sarcoma	6.1%	<1,000
Esophageal	5.1%	2,000

**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*

REPARE THERAPEUTICS

Compelling synthetic lethal rationale for targeting PLK4

Biomarker-driven patient selection hypothesis for development of oral PLK4i for TRIM37-high tumors

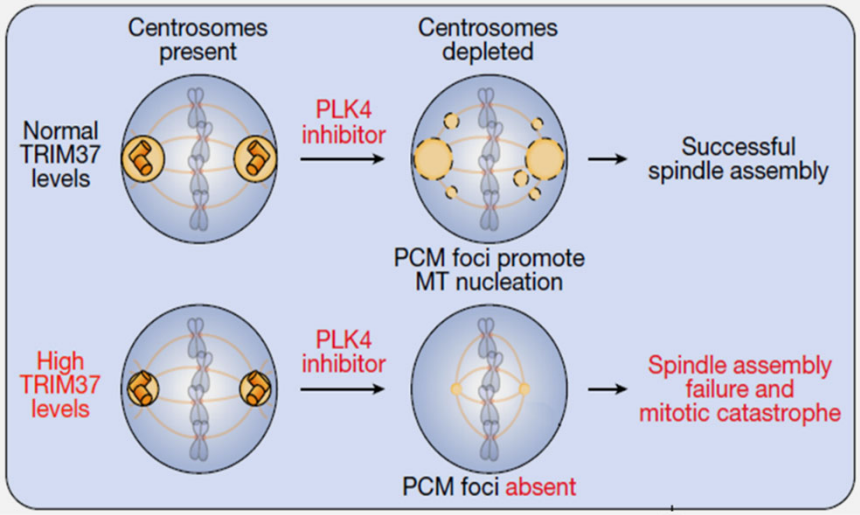
Centrosomes use centrioles and pericentriolar material (PCM) for mitotic spindle formation

Polo-Like Kinase 4 (PLK4) required for centriole creation in S-phase

TRIM37 (an E3 Ligase) reduces 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



Chapman/Holland Nature volume 585, pages 447–452 (2020)

REPARE THERAPEUTICS

Potential first-in-class oral PLK4 inhibitor

	Key Parameter	RP-1664
In vitro	PLK4 Enzyme IC_{50}	1 nM
	PLK4 cell binding IC_{50}	3 nM
	Cell proliferation in MCF7 / T47D (TRIM37 amp) EC_{50}	51 / 17 nM
	Cell-base selectivity vs AurA, AurB	>2000-fold
	Kinome screen at 90x PLK4 IC_{50}	8/280 kinases >50% inh
ADME	Human Hepatocyte Clearance (µL/min/10^6 cells)	2.2
	Rat PK (%F, $t_{1/2}$)	28%, 4h
	Monkey PK (%F, $t_{1/2}$)	96%, 9h

- **Highly potent, selective and orally bioavailable PLK4 inhibitor**
  - **~10x more potent than competitor molecules[1] with vastly improved selectivity vs AurB**
- **Clean in PanLabs safety pharmacology screen**

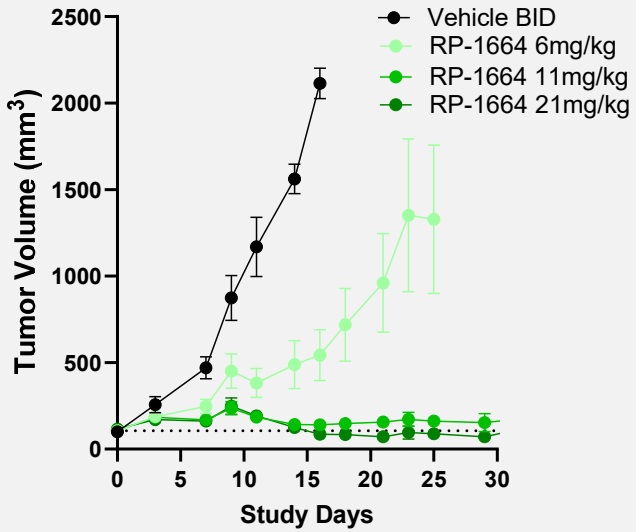
[1] CFI-400945 and EXEL-7871. *Source: internal data and Exelixis corporate presentation*

REPARE THERAPEUTICS

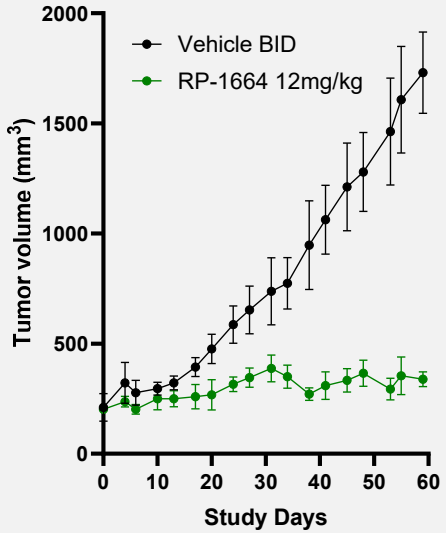
Robust monotherapy efficacy across solid tumor PDX/CDX models

Monotherapy drives tumor stasis to regression in TRIM37-high models

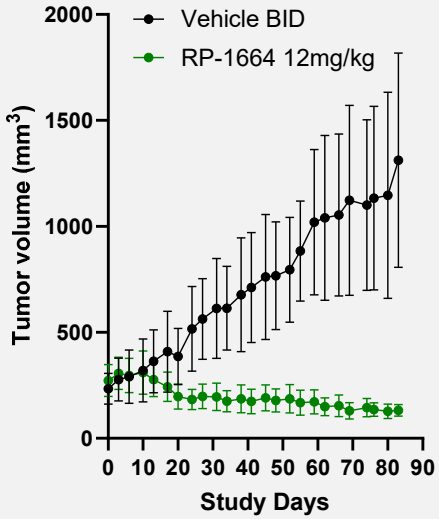
Breast (Triple Negative) CDX



Breast (ER positive) PDX



NSCLC PDX

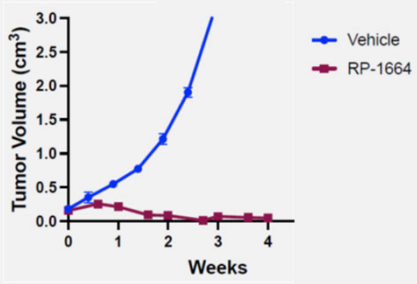


REPARE THERAPEUTICS

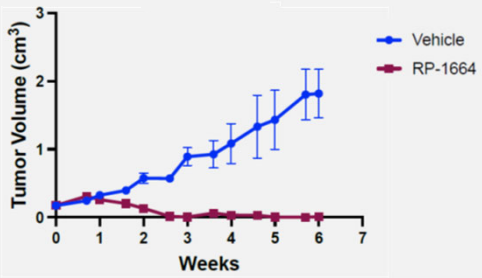
Highly efficacious as monotherapy in neuroblastoma models

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

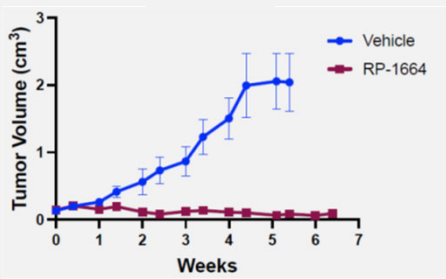
COG-N-424X



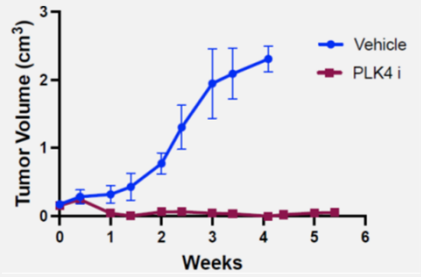
COG-N-421



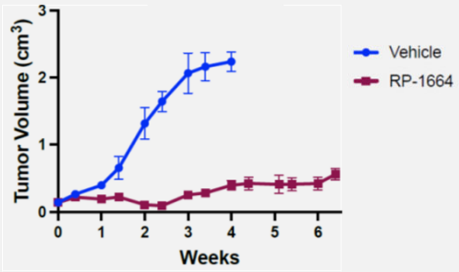
NBSD



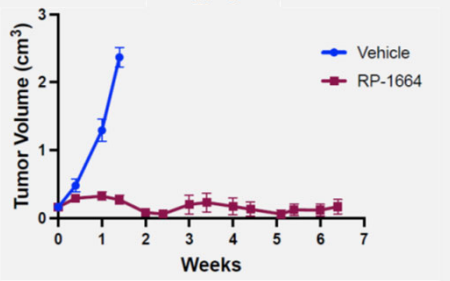
Felix



COG-N-453x



Ebc1



**J Maris and Y Mosse, CHOP*

REPARE THERAPEUTICS

RP-1664 Phase 1/2 monotherapy clinical development plan

Efficient RP-1664 Phase 1 plan enables early start for pediatric dose finding study in neuroblastoma and clear view on adult solid tumor opportunity

Phase 1 Trial

Adult and adolescent patients
with solid tumors **TRIM37-high** & additional biomarkers

Goal: Recommended Phase 2 dose & safety

Study start: Feb 2024

Phase 1b Expansion

Adult solid tumors

TRIM37-high

Phase 1/2 Investigation

High grade pediatric neuroblastoma

REPARE THERAPEUTICS

RP-3467

REPARE THERAPEUTICS

RP-3467

Potential best-in-class Polθ ATPase inhibitor

FPI in 2H 2024

Highly potent, selective Polθ ATPase inhibitor; inhibits DNA repair and is **synthetic lethal** with **BRCA loss**

Demonstrates compelling **combination efficacy** without added toxicity

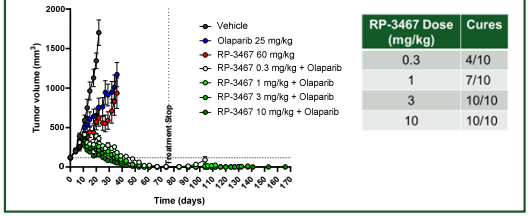
RP-3467 capable of **complete regressions** and synergies in **PARPi resistance** models

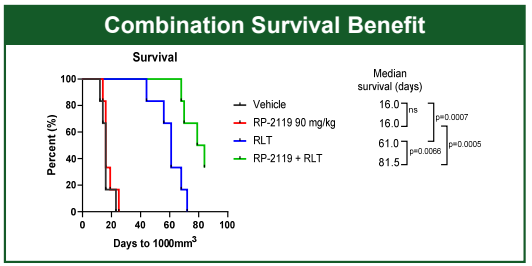
Global market segments comprise $16 billion in PARP inhibitors, RLT, and chemotherapy

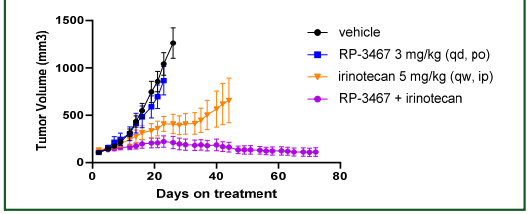
REPARE THERAPEUTICS

RP-3467 clinical plan: multiple potential Phase 1/2 trials

Phase 1 Trial	Phase 1/2 Trials	Preclinical Results	Global Market Segment
Initiation expected in H2 2024 **Goal: PK, safety and RP2D (recommended Phase 2 dose)**	**PARPi combination – PARP1/2 or PARP1** Deep/durable complete responses preclinically, with no additional toxicity	**HCT116 BRCA2 -/-**	**~$3 Billion**
	RLT combination Survival benefit preclinically in <u>unselected</u> tumor backgrounds, with no additional toxicity	**Combination Survival Benefit**	**~$8 Billion**
	Chemotherapy / ADC Payloads Well tolerated preclinically in combination with carboplatin and irinotecan, including topoisomerase ADC payloads	**HCT116 BRCA2 -/- (Irinotecan combo)**	**~$5 Billion**





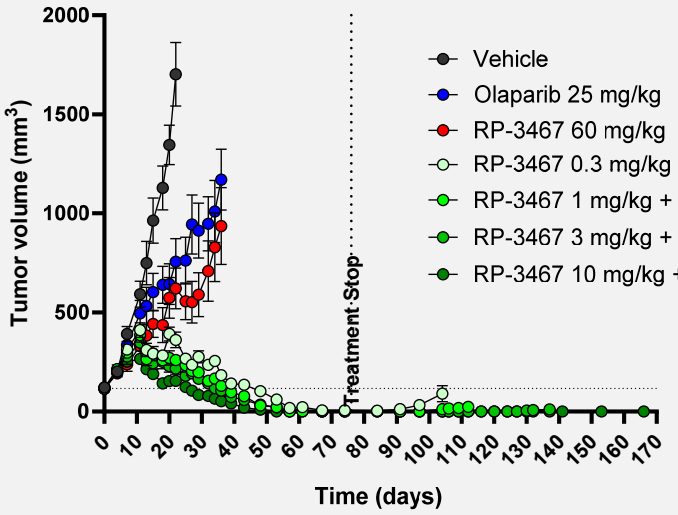


REPARE THERAPEUTICS

Profound, durable synergy with PARP inhibition

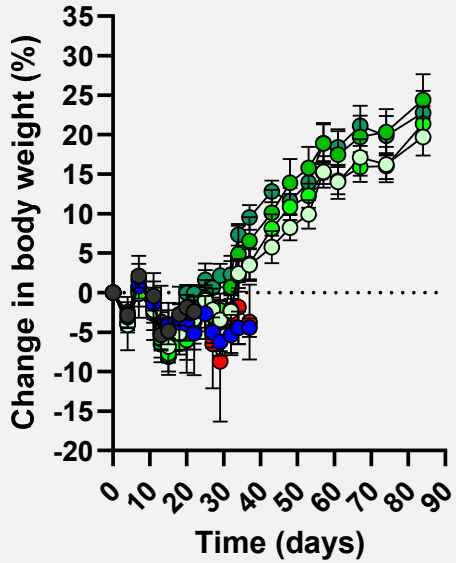
Deep/durable complete regressions across a wide dose range and extremely well tolerated

HCT116 BRCA2 -/-



RP-3467 Dose (mg/kg)	Cures
0.3	4/10
1	7/10
3	10/10
10	10/10

Body Weight



REPARE THERAPEUTICS

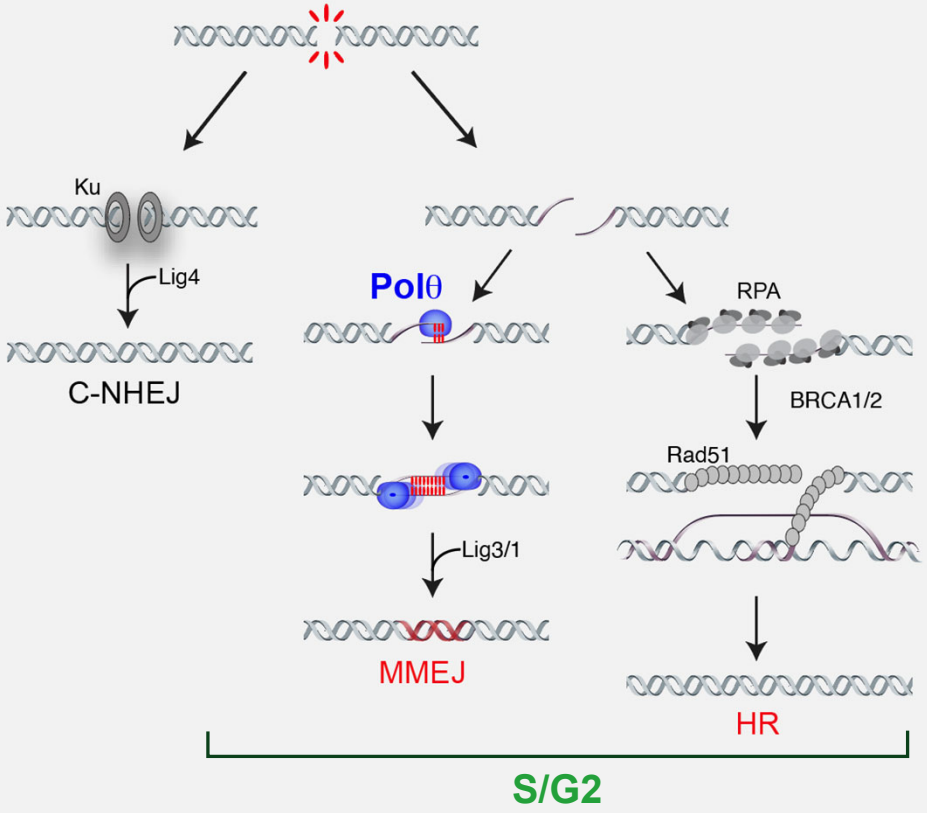
Polθ: uniquely promising therapeutic target

Polθ is a 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**



Recent evidence that MMEJ is the predominant repair pathway in mitosis

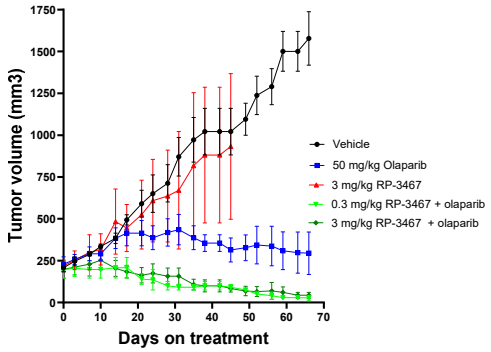
REPARE THERAPEUTICS

Target profile: potent, tolerable, capable of complete regressions

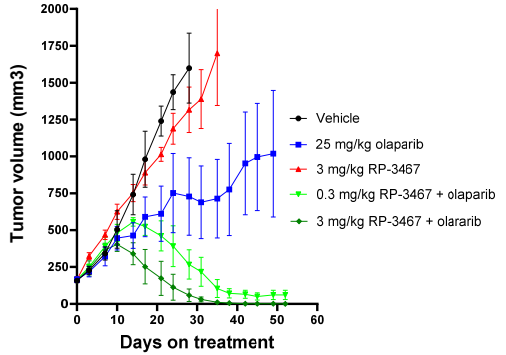
	Parameter	RP-3467
Potency	Polθ ATPase Enzyme IC_{50}	<0.25 nM
	CETSA cellular target engagement IC_{50}	5 nM
	Cell proliferation DLD1 / HCT116 (BRCA2mt) EC_{50}	4 / 7 nM
Selectiv.	Off-target ATPase (HELQ, WRN, BLM) IC_{50}	> 10 µM
	Off-target Polθ polymerase domain IC_{50}	> 100 µM
ADME	Human Hepatocyte Clearance (µL/min/10^6 cells)	2.1
	Rat PK (%F, $t_{1/2}$)	123%, 6h
	Monkey PK (%F, $t_{1/2}$)	60%, 3h

Complete regressions in PDX models at low doses

HBCx-22 (BRCA2null)



HBCx-10 (BRCA2null)



- Highly potent, selective and orally bioavailable Polθ ATPase inhibitor; clean PanLabs safety pharmacology screen
- RP-3467 demonstrated complete regressions in BRCA1/2 null PDX models, also synergy in a PARPi resistance model

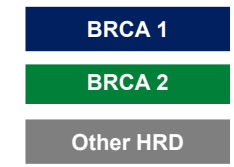
REPARE THERAPEUTICS

Addressing unmet need in critical patient populations

~26K among patients with PARP-naïve and PARP-treated tumors

PARP-naïve and PARP-treated (Treated Patients US+UK/EU4)*

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



** 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*

REPARE THERAPEUTICS

Upcoming milestones

1H 2024

RP-1664 (PLK4i)
clinical trial initiation

Initial **lunresertib + FOLFIRI** combination
Phase 1 data

Phase 1/1b **lunresertib + Debio 0123**
combination clinical trial initiation[1]

Regain rights to **camonsertib** in May

2H 2024

RP-3467 (Polθ ATPase inhibitor)
clinical trial initiation

Lunresertib + gemcitabine combination
Phase 1 data

Lunresertib + camonsertib combination
Phase 1 data (expansion cohorts)

[1] *Collaboration agreement with Debiopharm announced on January 4, 2024.*

Developing Next-Generation Precision Oncology Medicines

Differentiated and wholly-owned clinical pipeline

- Lunresertib: First-in-class oral PKMYT1 inhibitor (Phase 1/2)
- Camonsertib: ATR inhibitor (Phase 1/2)
- RP-1664: First-in-class selective PLK4 inhibitor (Phase 1)

Proprietary CRISPR -enabled SNIPRx platform

- Focused on genomic instability and DNA damage repair
- Clinical trials enriched for patients with tumors carrying a network of synthetic lethal alterations (STEP[2])

Multiple clinical catalysts expected in 2024

- Ongoing combination trials
- New clinical entries (PLK4 and Polθ ATPase inhibitors)

Strong balance sheet

- Cash and investments of ~$223.6M[1] plus recent $40M milestone payment fund operations into mid-2026
- Multiple clinical catalysts in that timeframe

[1] *As of December 31, 2023.*

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Insight that enriches. Precision that empowers.

Corporate Presentation

February 2024