REPARE THERAPEUTICS

Precision oncology medicines powered by synthetic lethal insights

Corporate Presentation

August 2025

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Repare's mission is to apply synthetic lethal biology to bring practice-changing, precision therapies to patients who need them

Two ongoing wholly-owned Phase 1/2 programs – **Polθ** ATPase inhibition in oncology combinations and **PLK4** inhibition in neuroblastoma, both with **initial readouts expected in Q4 2025**

Runway through 2027, with $109.5 million in cash and investments at June 30, 2025

Currently exploring strategic alternatives and partnerships across the portfolio

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Advancing pipeline of wholly-owned precision oncology therapeutics

Program	Tumor lesion	Drug target	Preclinical	Ph 1/2	Pivotal/Ph 3	Next Milestones
RP-3467	BRCA1/2	Polθ ATPase	Monotherapy & PARPi Combination (POLAR)			▪ **4Q'25:** Initial POLAR topline data
RP-1664	TRIM37-high	PLK4	Monotherapy (LIONS)			▪ **4Q'25:** Initial LIONS topline data

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RP-3467

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RP-3467

Potential best-in-class Polθ ATPase inhibitor

FPI in Oct 2024

Highly potent, selective Polθ ATPase inhibitor inhibits DNA repair and is **synthetic lethal** with **BRCA loss** – currently enrolling in both monotherapy and in combination with olaparib

Demonstrates compelling preclinical potential for **combination efficacy** without added toxicity

Demonstrated **complete regressions** and synergies in **PARPi resistance** preclinical models

Global market segments addressable >$16 billion across PARP inhibitors, RLT, and chemotherapy combinations

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

PARPi combination – PARP1/2 or PARP1

- Deep/durable complete responses preclinically, with no additional toxicity
- ~$3B global market segment

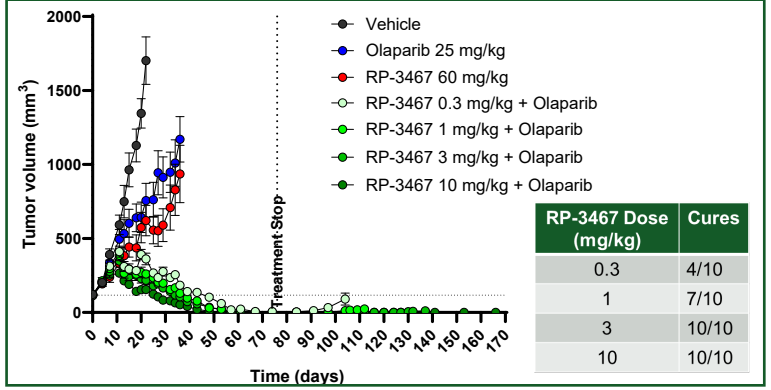
RLT Combination

- Survival benefit preclinically in **unselected tumor** backgrounds, with no additional toxicity
- ~$8B global market segment

Chemotherapy / ADC Payloads

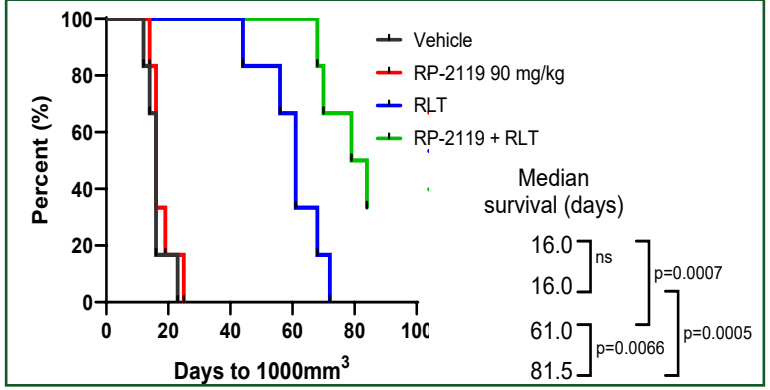
- Well tolerated preclinically with carboplatin/irinotecan, including topoisomerase ADC payloads
- ~$5B global market segment

HCT116 BRCA2 -/-

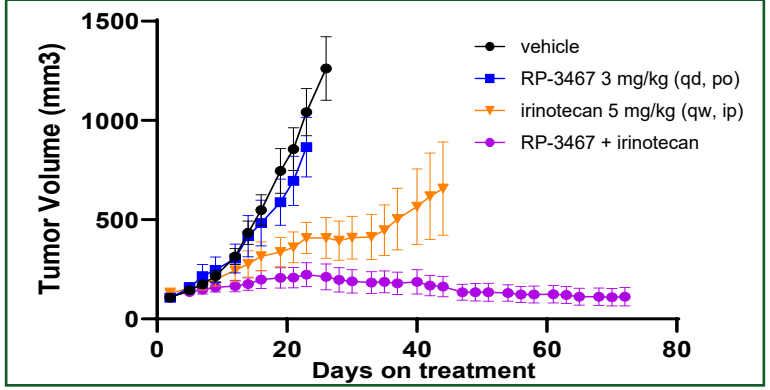


RP-3467 Dose (mg/kg)	Cures
0.3	4/10
1	7/10
3	10/10
10	10/10

Combination Survival Benefit



HCT116 BRCA2 -/- (Irinotecan)



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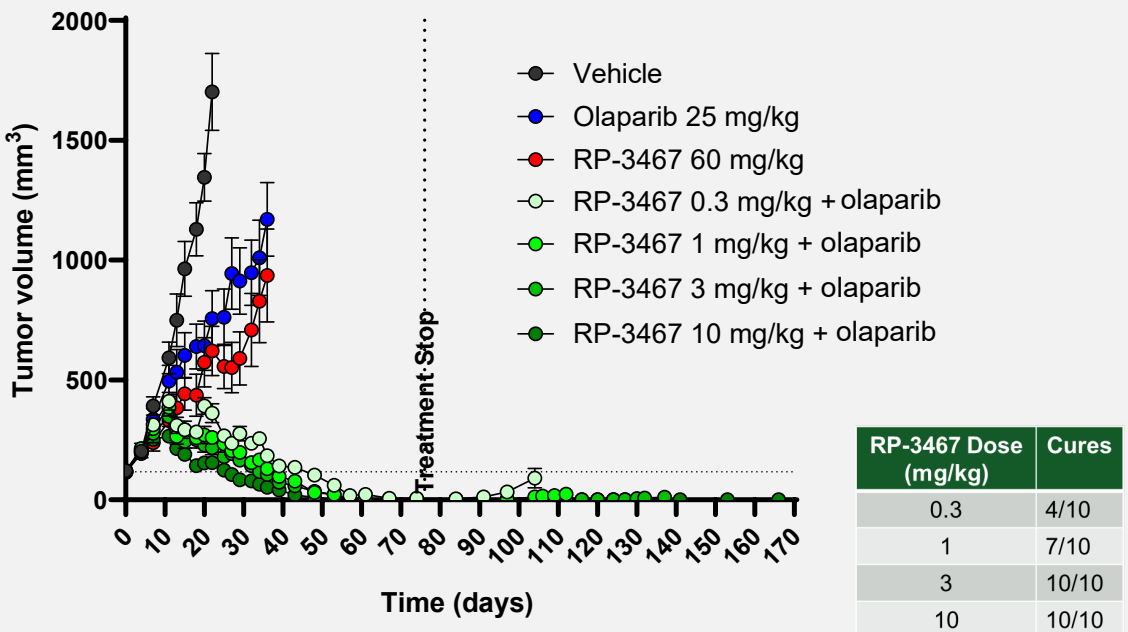
Profound, durable synergy observed with PARP inhibition

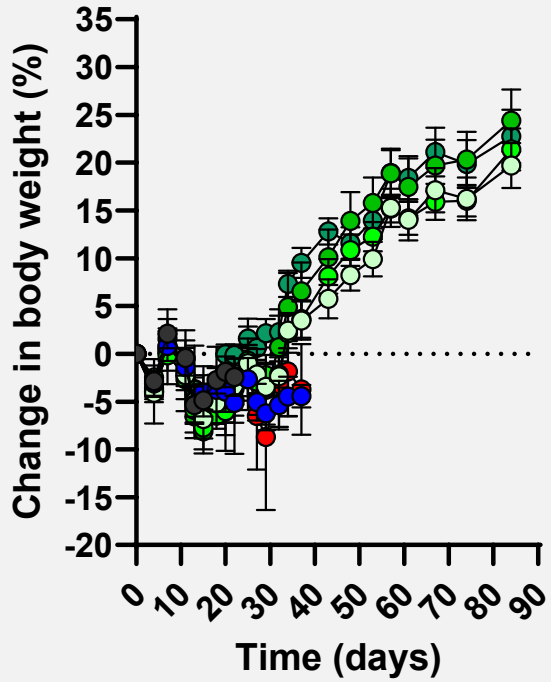
Deep/durable complete regressions observed across a wide dose range and well tolerated

HCT116 BRCA2 -/-



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

Body Weight



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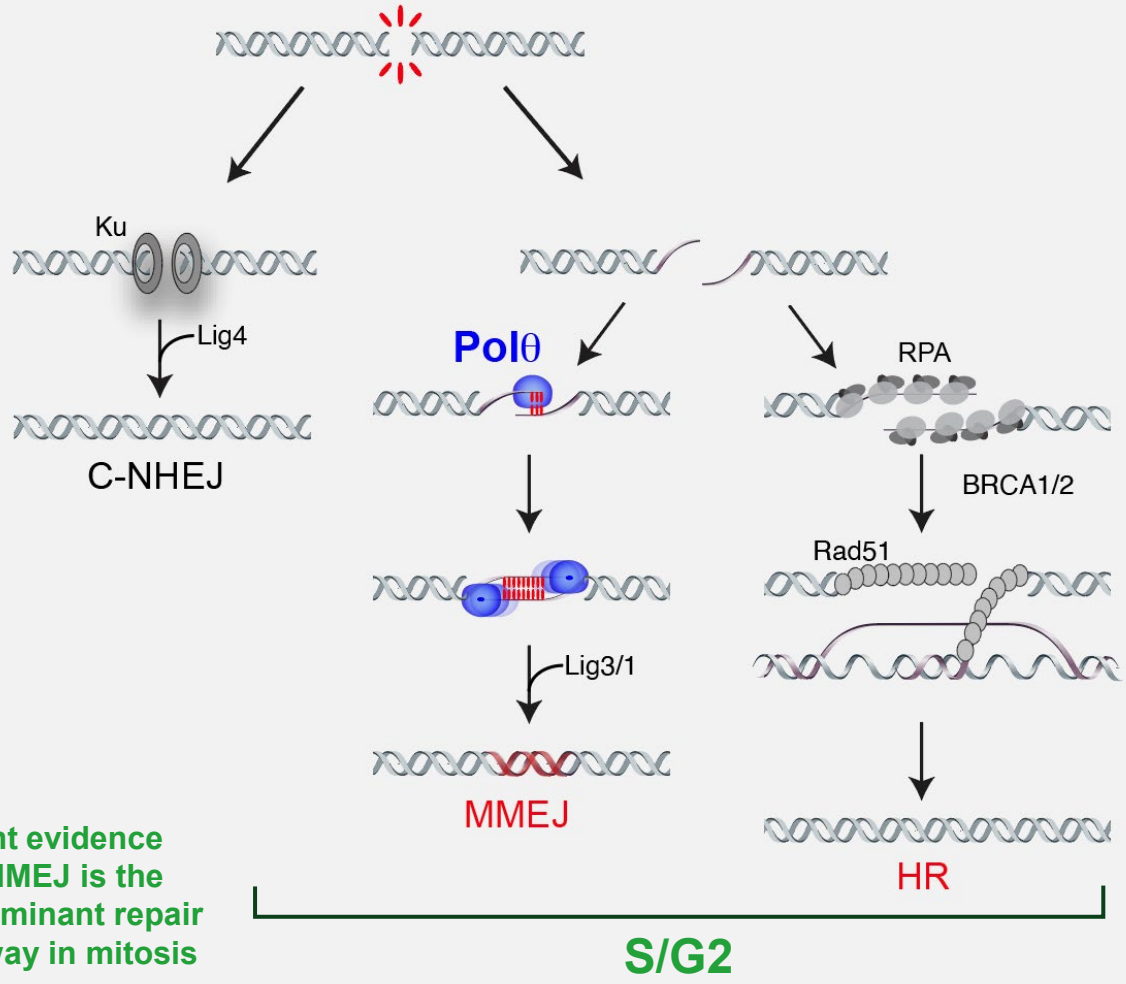
Polθ: uniquely promising therapeutic target

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

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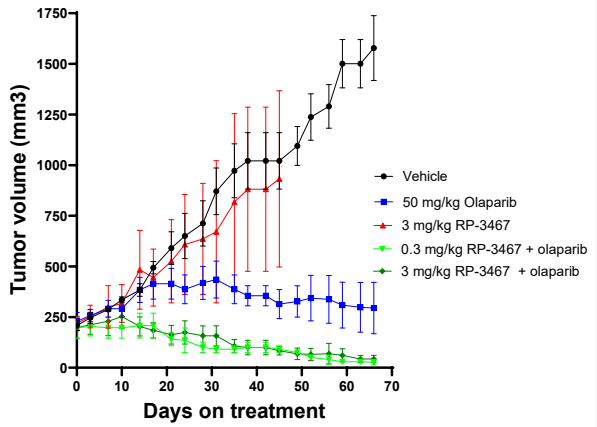
Target profile: potent, tolerable, capable of complete regressions

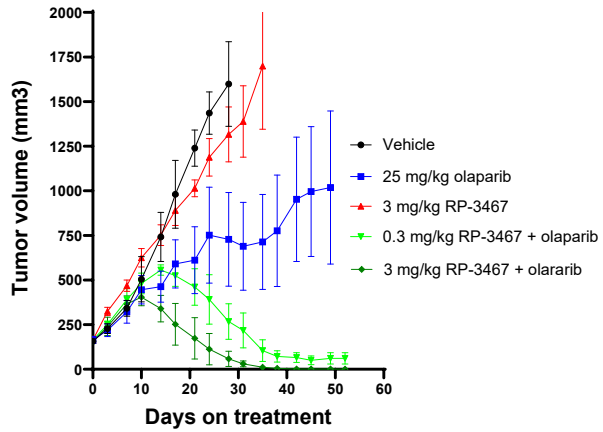
	Parameter	RP-3467
Potency	Polθ ATPase Enzyme IC_{50}	<0.25 nM
	CETSA cellular target engagement IC_{50}	5 nM
	Cell proliferation DLD1 / HCT116 (BRCA2mt) EC_{50}	4 / 7 nM
Selectiv.	Off-target ATPase (HELQ, WRN, BLM) IC_{50}	> 10 µM
	Off-target Polθ polymerase domain IC_{50}	> 100 µM
ADME	Human Hepatocyte 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

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RP-3467 Phase 1 clinical development plan

Efficient RP-3467 Phase 1 plan includes monotherapy and combination with the PARP inhibitor, olaparib, to provide Proof of Concept for future combinations

Phase 1 Trial (POLAR)

Adult patients
with solid tumors with eligible tumor biomarkers

Objective: PK, safety, and RP2D

Study started: Oct 2024

Expected Data Readout: 4Q'25

Arm 1: Monotherapy
dose escalation

Arm 2: RP-3467 combination with olaparib
200-300 mg BID, daily

POLAR clinical trial (NCT06560632) details available at clinicaltrials.gov or link.

RP-1664

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RP-1664

First-in-class,
oral PLK4 inhibitor

FPI in Feb 2024

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

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

Completed enrolment of 29 patients in Phase 1 trial in solid tumors and neuroblastoma

~63K addressable patient population with **TRIM37-high** tumors, initial focus on **pediatric neuroblastoma (>80% TRIM37-high)** – with potential additional opportunities in TRIM37-high breast and lung cancers

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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 TRIM37 alterations	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*

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Compelling synthetic lethal rationale for targeting PLK4

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

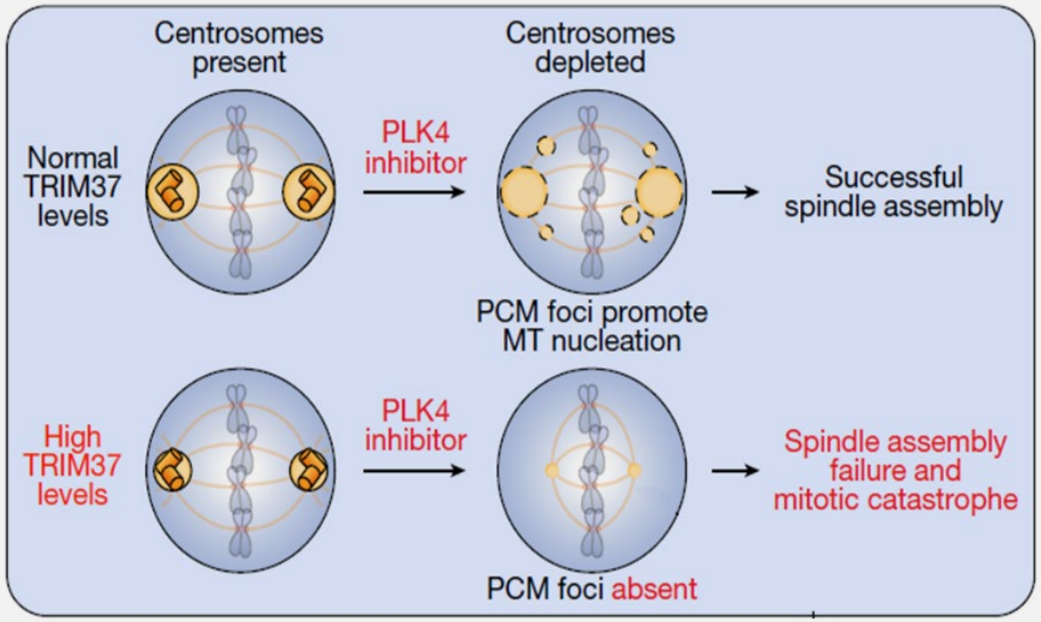
Centrosomes use centrioles and pericentriolar material (PCM) for mitotic spindle formation

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)

Source: Holland AJ Nature 2020; Oegema K Nature 2020.

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Potential first-in-class oral PLK4 inhibitor

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

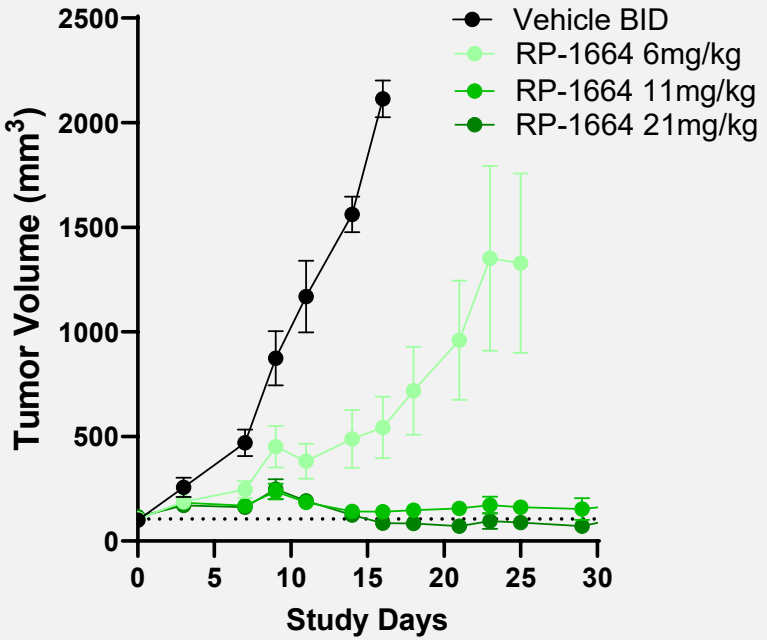
	Key Parameter	RP-1664
In vitro	PLK4 Enzyme IC_{50}	1 nM
	PLK4 cell binding IC_{50}	3 nM
	Cell proliferation in MCF7 / T47D (TRIM37 amp) EC_{50}	51 / 17 nM
	Cell-base selectivity vs AurA, AurB	>2000-fold
	Kinome screen at 90x PLK4 IC_{50}	8/280 kinases >50% inh
ADME	Human Hepatocyte Clearance (µL/min/10^6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

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

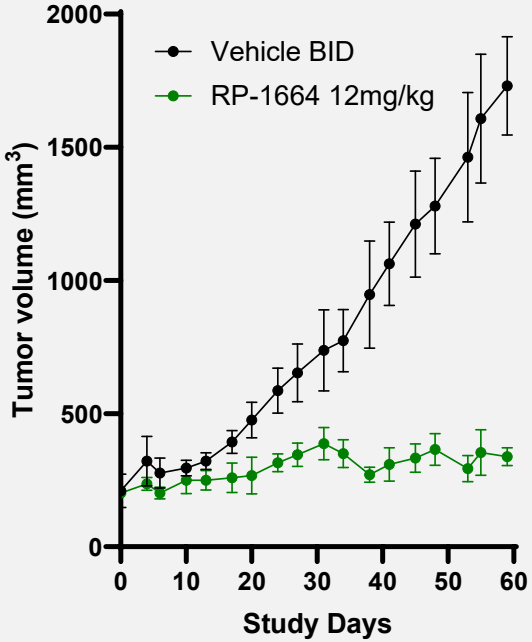
Robust monotherapy efficacy across solid tumor PDX/CDX models

Monotherapy drives tumor stasis to regression in TRIM37-high models

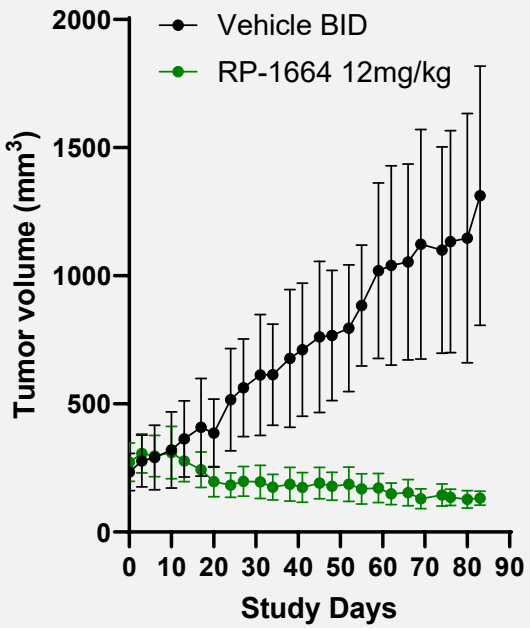
Breast (Triple Negative) CDX



Breast (ER positive) PDX



NSCLC PDX



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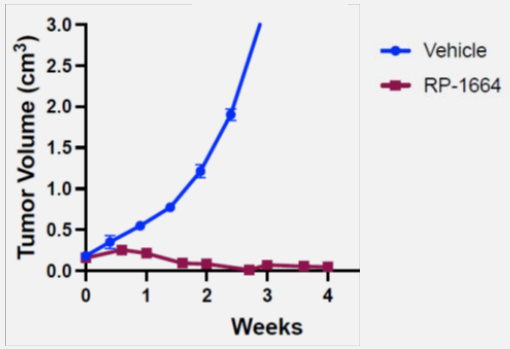
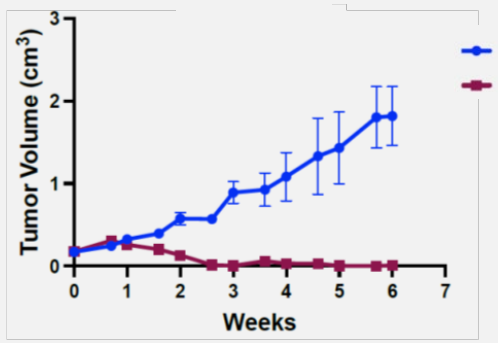
Highly efficacious as monotherapy in neuroblastoma models

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

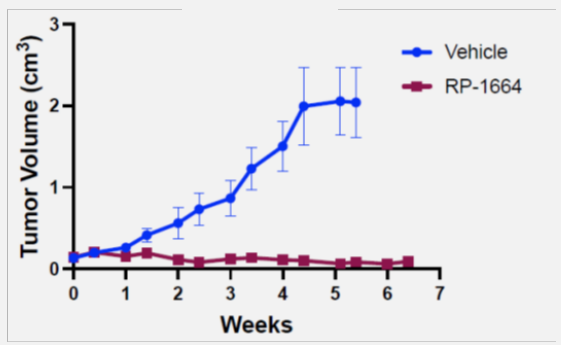
COG-N-424X



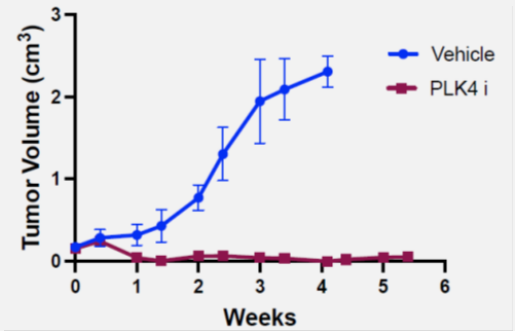
COG-N-421



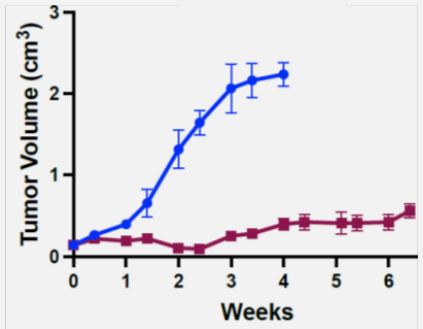
NBSD



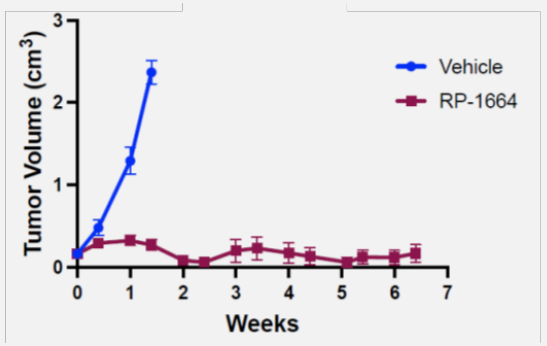
Felix



COG-N-453x



Ebc1



*J Maris and Y Mosse, CHOP

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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 (LIONS)

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

Objective: RP2D & safety

Study started: Feb 2024

Phase 1b Expansion

Adult solid tumors – select histologies

TRIM37-high

Phase 1/2 Investigation

High-risk pediatric neuroblastoma

LIONS clinical trial (NCT06232408) details available at clinicaltrials.gov or link.

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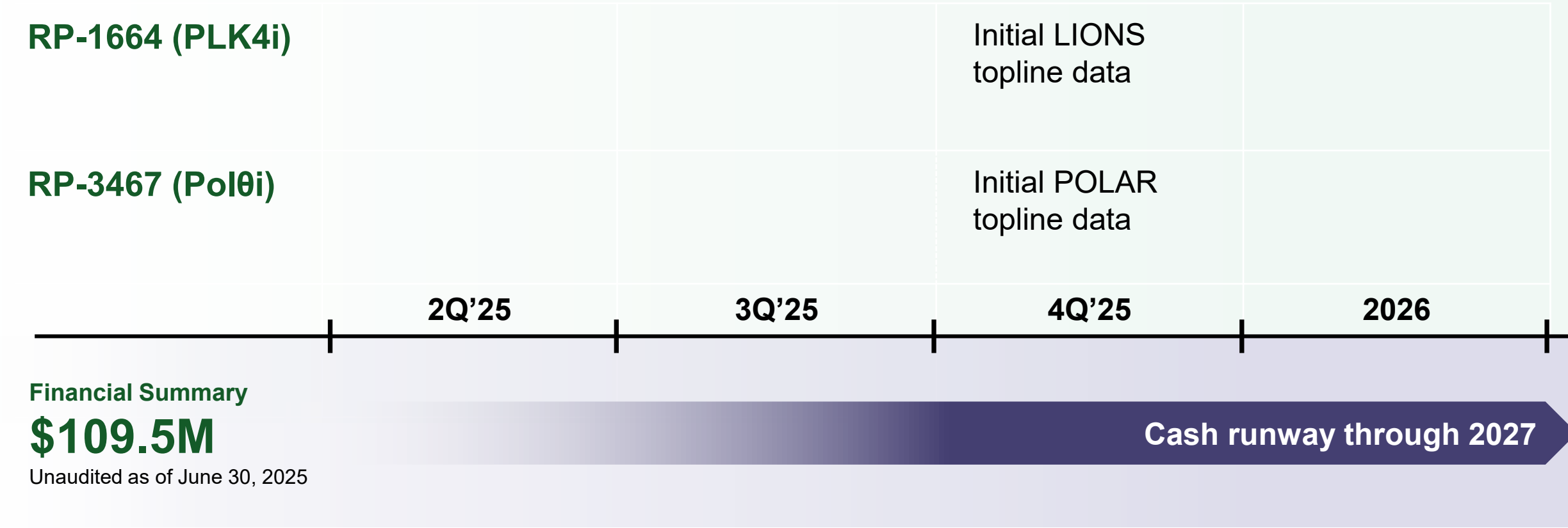
Key upcoming milestones



Financial Summary

$109.5M

Unaudited as of June 30, 2025

Cash runway through 2027

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