REPARE THERAPEUTICS

Precision oncology medicines powered by synthetic lethal insights

Corporate Presentation

Marc 2025

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REPARE THERAPEUTICS

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 H2 2025**

Runway into late-2027, with $153 million in cash and investments at Y/E 2024

Currently exploring partnerships across the portfolio, including lunre+camo

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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)**			▪ **3Q'25:** Initial POLAR topline data
RP-1664	**TRIM37-high**	**PLK4**	**Monotherapy (LIONS)**			▪ **3Q'25:** Initiate pediatric neuroblastoma Ph1/2 ▪ **4Q'25:** Initial LIONS topline data ▪ **Mid-2026:** LIONS completion and POC readout
Lunresertib / camonsertib	**CCNE1, FBXW7 + PPP2R1A**	**PKMYT1 / ATR**	**WEE1i Combination** (Debiopharm)			▪ **2Q'25:** Complete Lunre+WEE1i enrollment
			Lunre+Camo (MYTHIC)		**Seeking partnering opportunities**	

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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

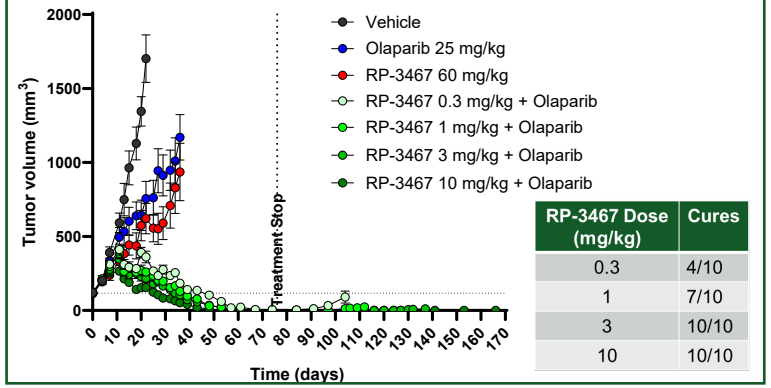
RLT Combination

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

Chemotherapy / ADC Payloads

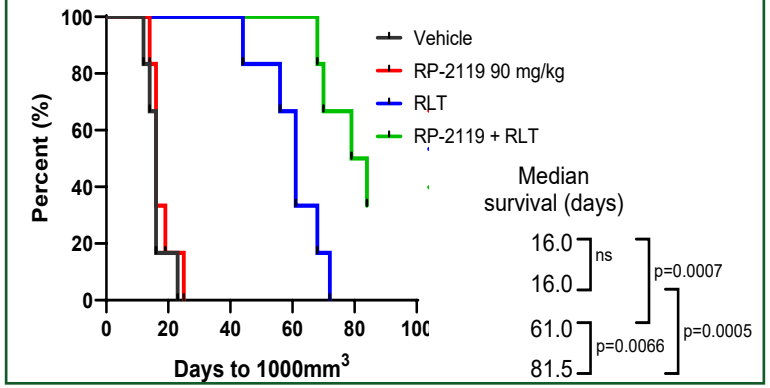
- Well tolerated preclinically with carboplatin/irinotecan, including topoisomerase ADC payloads
- ~$5B global market segment

HCT116 BRCA2 -/-

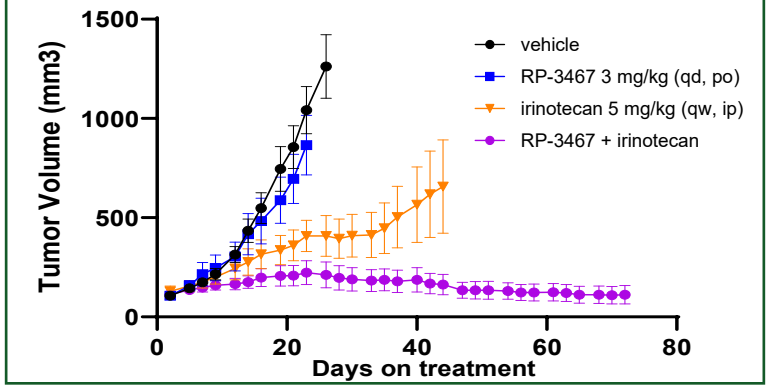


RP-3467 Dose (mg/kg)	Cures
0.3	4/10
1	7/10
3	10/10
10	10/10

Combination Survival Benefit



HCT116 BRCA2 -/- (Irinotecan)



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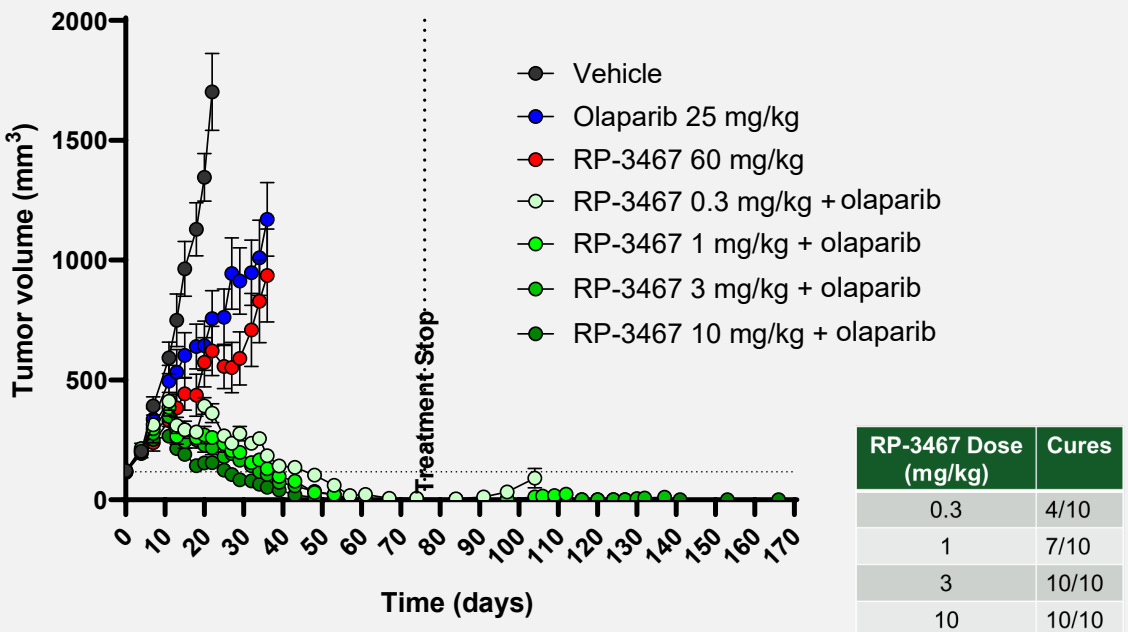
Profound, durable synergy observed with PARP inhibition

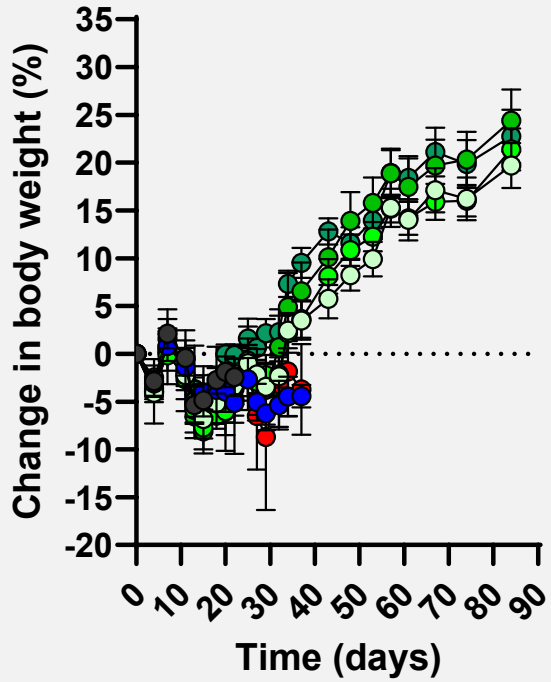
Deep/durable complete regressions observed across a wide dose range and well tolerated

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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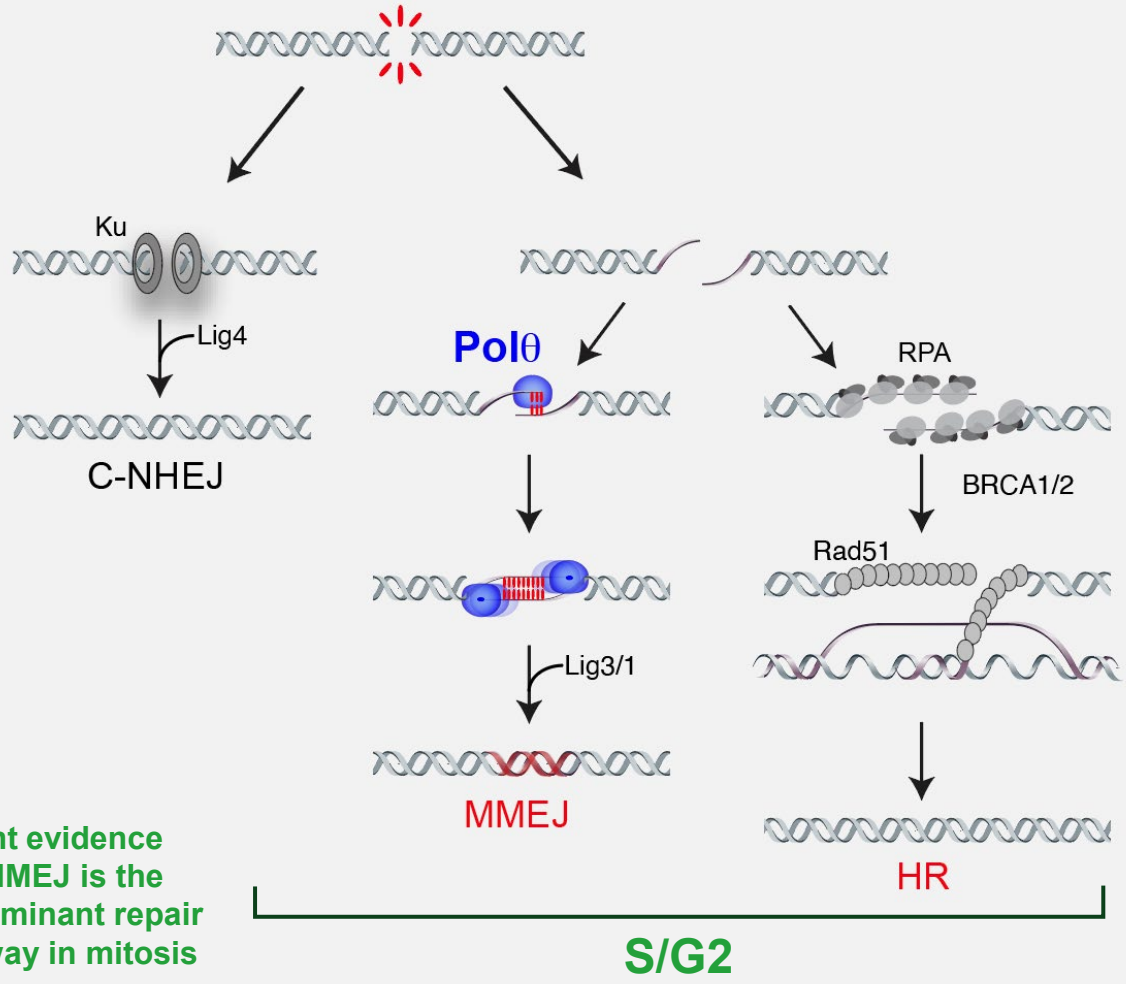
Polθ: uniquely promising therapeutic target

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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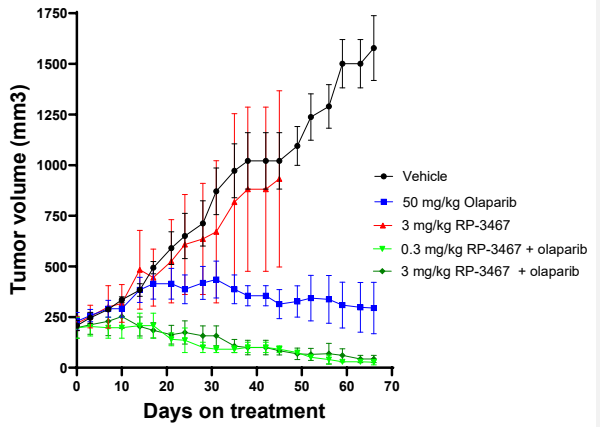
Target profile: potent, tolerable, capable of complete regressions

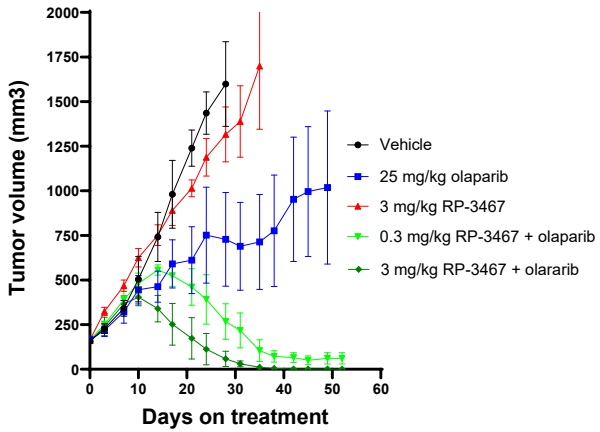
	Parameter	RP-3467
Potency	Polθ ATPase Enzyme IC_{50}	<0.25 nM
	CETSA cellular target engagement IC_{50}	5 nM
	Cell proliferation DLD1 / HCT116 (BRCA2mt) EC_{50}	4 / 7 nM
Selectiv.	Off-target ATPase (HELQ, WRN, BLM) IC_{50}	> 10 µM
	Off-target Polθ polymerase domain IC_{50}	> 100 µM
ADME	Human Hepatocyte 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: 3Q'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

Phase 1 ongoing in solid tumors and neuroblastoma; **Phase 1/2 study** in high-risk **pediatric neuroblastoma** expected 3Q'25

~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

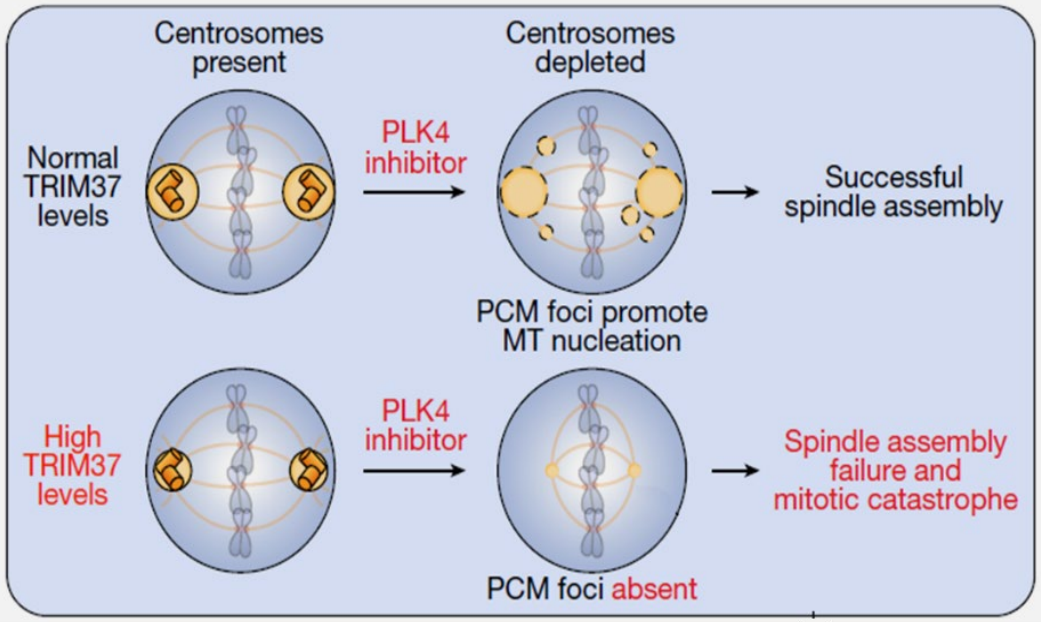
Centrosomes use centrioles and pericentriolar material (PCM) for mitotic spindle formation

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**

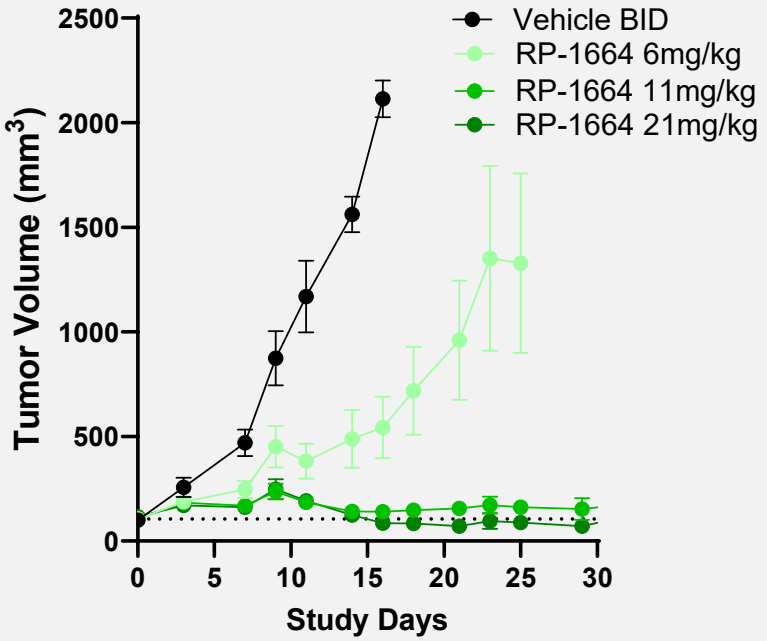
	Key Parameter	RP-1664
In vitro	PLK4 Enzyme IC_{50}	1 nM
	PLK4 cell binding IC_{50}	3 nM
	Cell proliferation in MCF7 / T47D (TRIM37 amp) EC_{50}	51 / 17 nM
	Cell-base selectivity vs AurA, AurB	>2000-fold
	Kinome screen at 90x PLK4 IC_{50}	8/280 kinases >50% inh
ADME	Human Hepatocyte Clearance (µL/min/10^6 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*

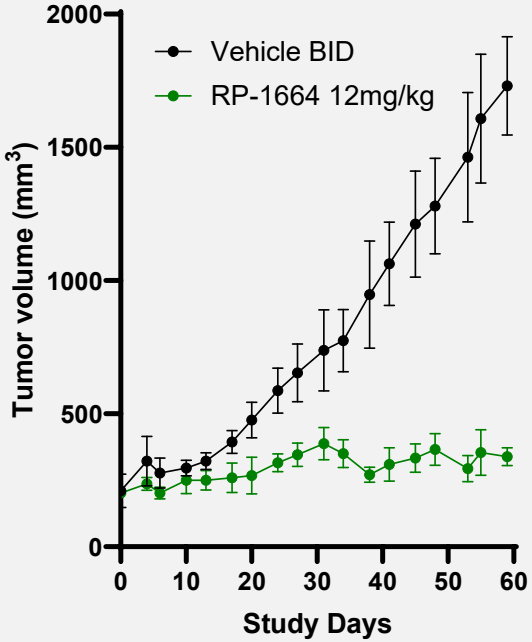
Robust monotherapy efficacy across solid tumor PDX/CDX models

Monotherapy drives tumor stasis to regression in TRIM37-high models

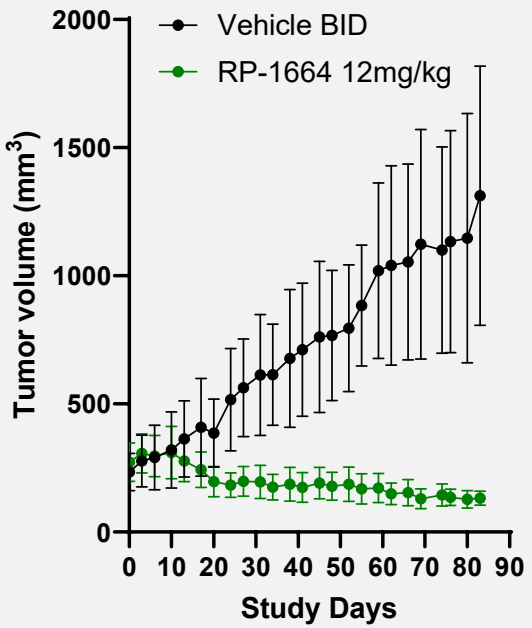
Breast (Triple Negative) CDX



Breast (ER positive) PDX



NSCLC PDX



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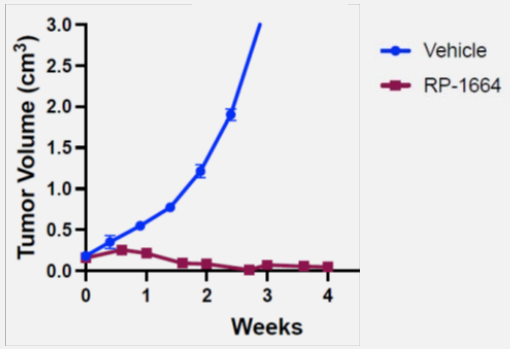
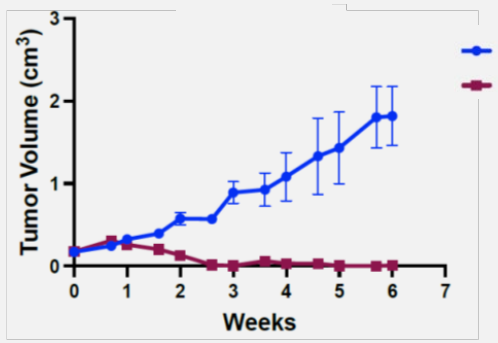
Highly efficacious as monotherapy in neuroblastoma models

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

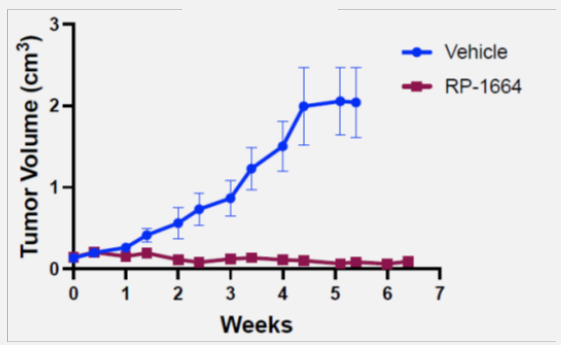
COG-N-424X



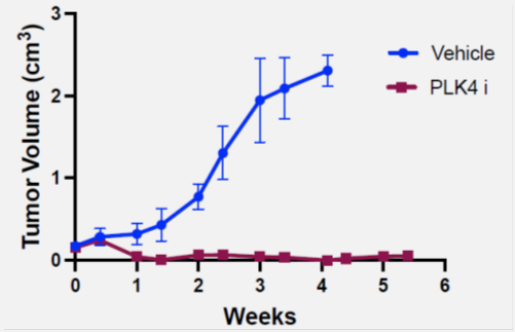
COG-N-421



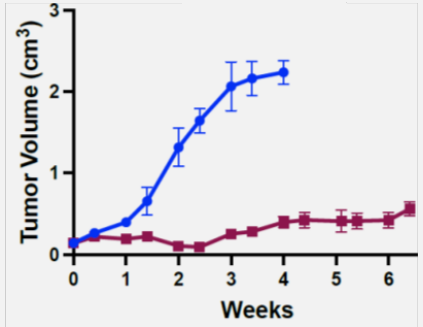
NBSD



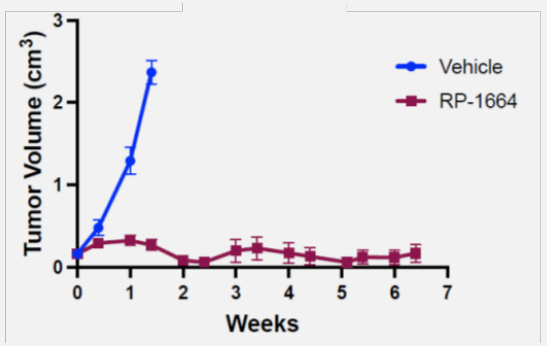
Felix



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

Study start: *Expected Q3 2025*

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

Lunresertib + Camonsertib

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Lunresertib

First PKMYT1 inhibitor to enter clinical trials

Camonsertib

Potential best-in-class ATR inhibitor

Registration ready program with US and EU regulatory support, prepared to launch **pivotal study** pending strategic partnership

Lunre+camo achieved POC in 2L EC and **3L PROC** with nearly half of patients maintaining PFS at 24 weeks, comparing favorably to historic controls

Lunresertib disrupts cell cycle regulation and camonsertib targets DNA damage response pathways to bring **tolerable and effective** synthetic lethal combination to clinic

Global market segments comprise **~$3 billion** in lead indications (EC and PROC) with upside from expansion opportunities by 2030

Full MYTHIC Lunresertib and Camonsertib Clinical Data Update presented on December 12, 2024 available on Company website or at link above.

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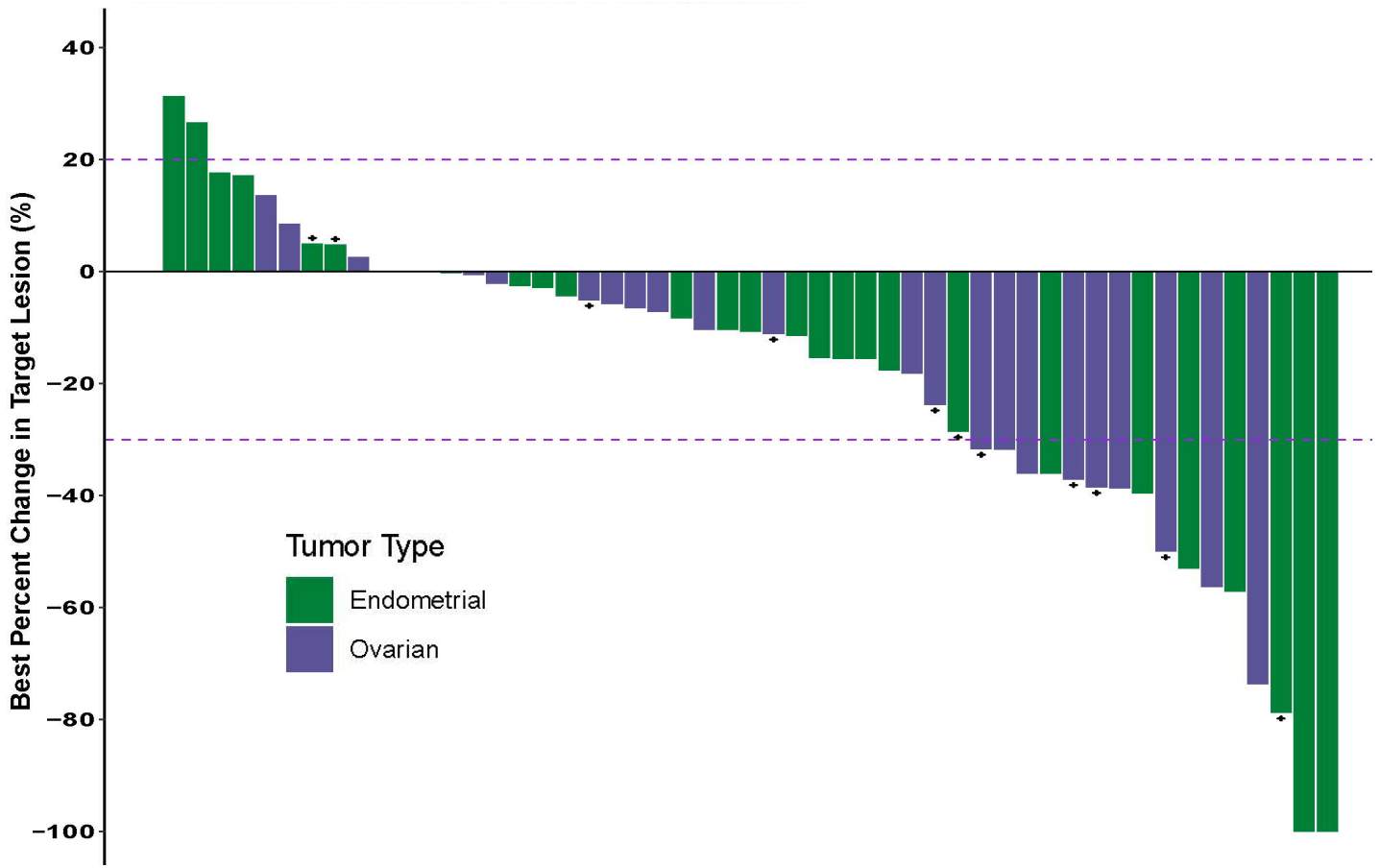
Significant overall efficacy observed with lunre+camo in gyn tumors

Tumor shrinkage with lunre+camo in recurrent gynecologic cancers



In efficacy-evaluable patients with EC or PROC at RP2D:

- **73%** of patients had tumor shrinkage
- **31%** (16/51) response rate (confirmed and unconfirmed)

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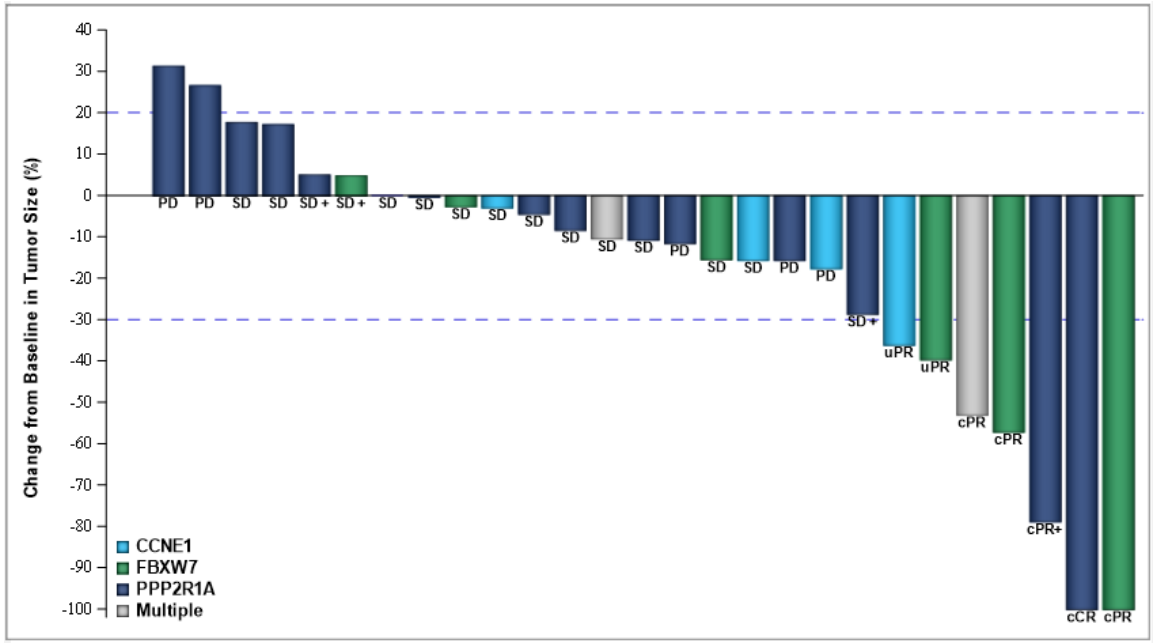
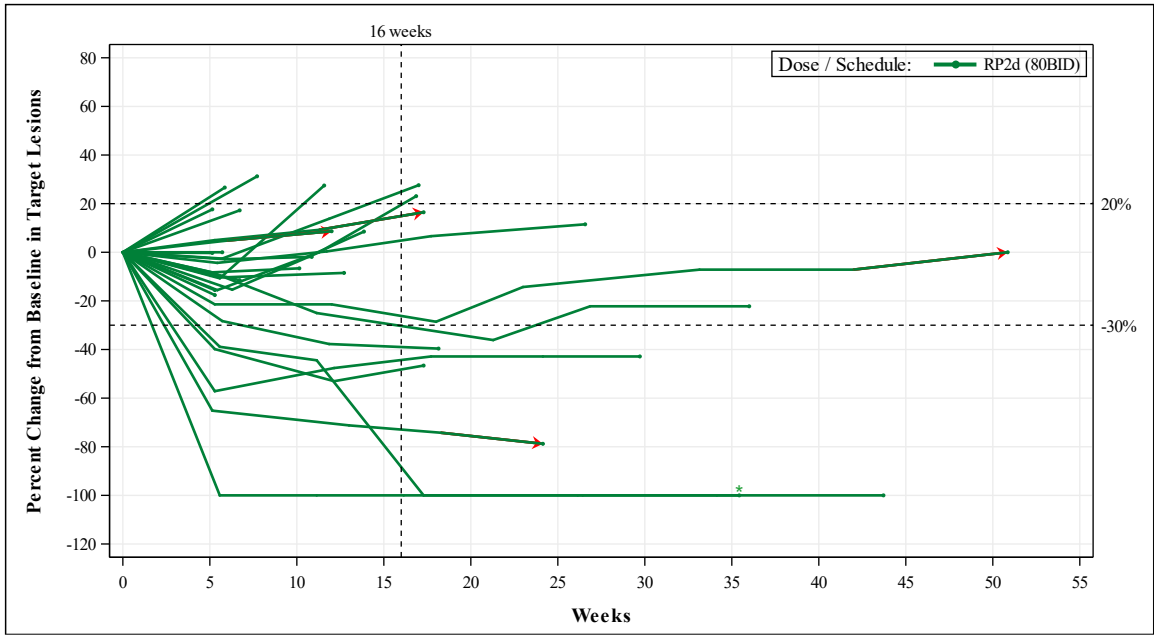
EC: Deep and durable responses across all lunre BM+ subsets

70% of patients experienced tumor shrinkage



ORR (conf.+ unconf.), %	25.9%
ORR (conf.), %	18.5%
CR	1 (3.7%)
PR	4 (14.8%)

Durable responses observed across histologies and biomarkers



Time to response (Range)	5-21 weeks

Duration of response up to ~30 weeks

Abbreviations: ORR, overall response rate**; conf.,** confirmed**; unconf.,** unconfirmed**; CR,** complete response**; PR,** partial response**; DOR,** duration of response; **PD**, progressive disease; **SD**, Stable disease.
Note: * Time of progression for one of two patients with 100% target lesion reduction

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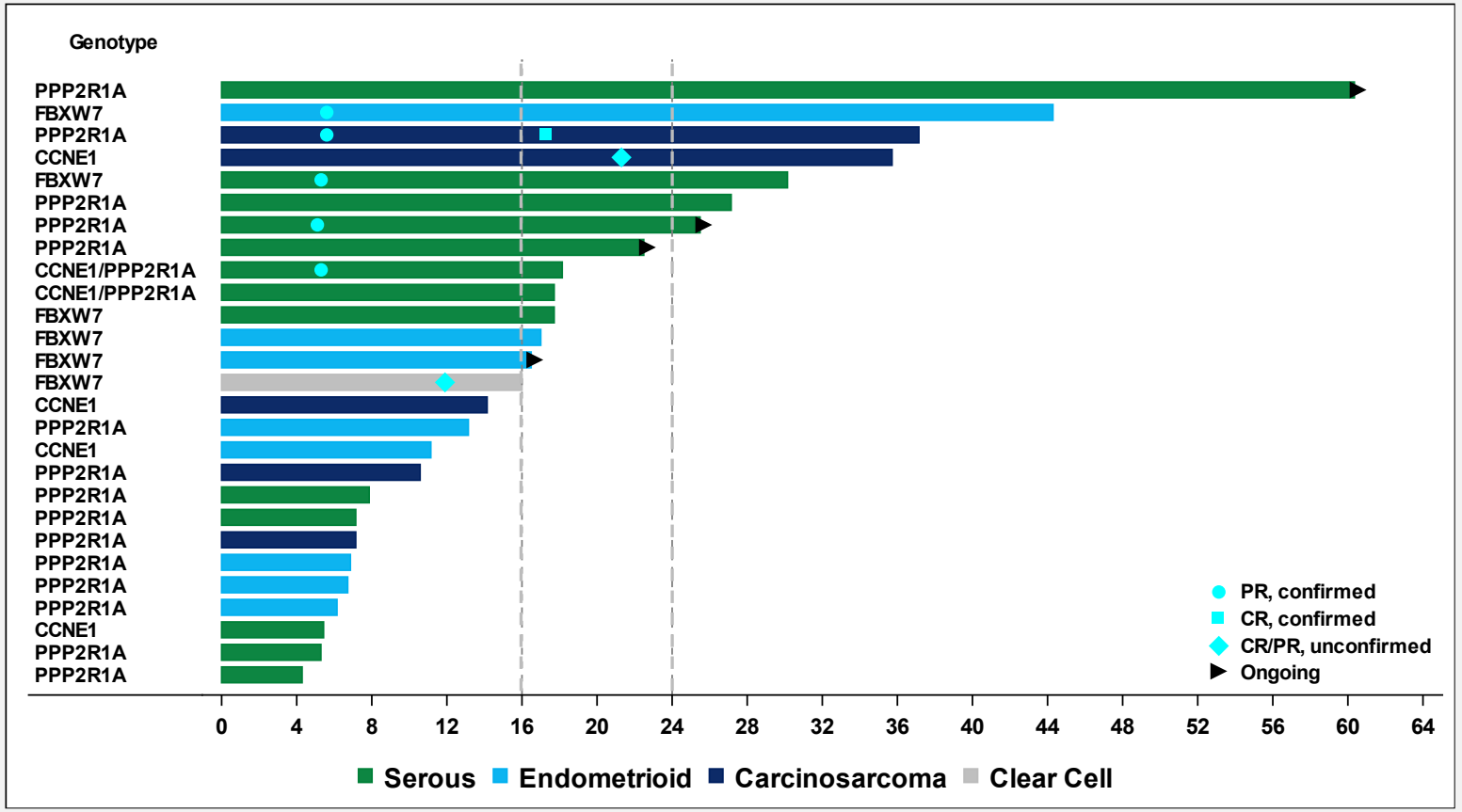
EC: Meaningful clinical benefit of across histological subtypes

Duration of treatment on lunre+camo



- **Progression-free rate (KM) at 24 wks is 43% (95% CI: 21-63%):**
  - Similar to emerging ADCs with comparable or less prior ICI treatment[1]
- **CBR of 48.1%**
- **Patterns of benefit reflect MOA:**
  - Long-term benefit in patients despite tumor reductions not meeting RECIST response
  - Continuous slow reductions in tumor burden and late PRs

Abbreviations: KM; Kaplan Meier estimate. **CBR**, clinical benefit rate defined as having CR, PR, or at least 16 weeks treatment without PD.

Reference: 1. Bradley R. Corr et al. Efficacy and safety of sacituzumab govitecan in patients with advanced/metastatic endometrial cancer: updated results from TROPiCS-03, ESMO2024. Note that cross-trial comparisons are not based on head-to-head studies and are presented for informational purposes; no direct comparisons are being made.

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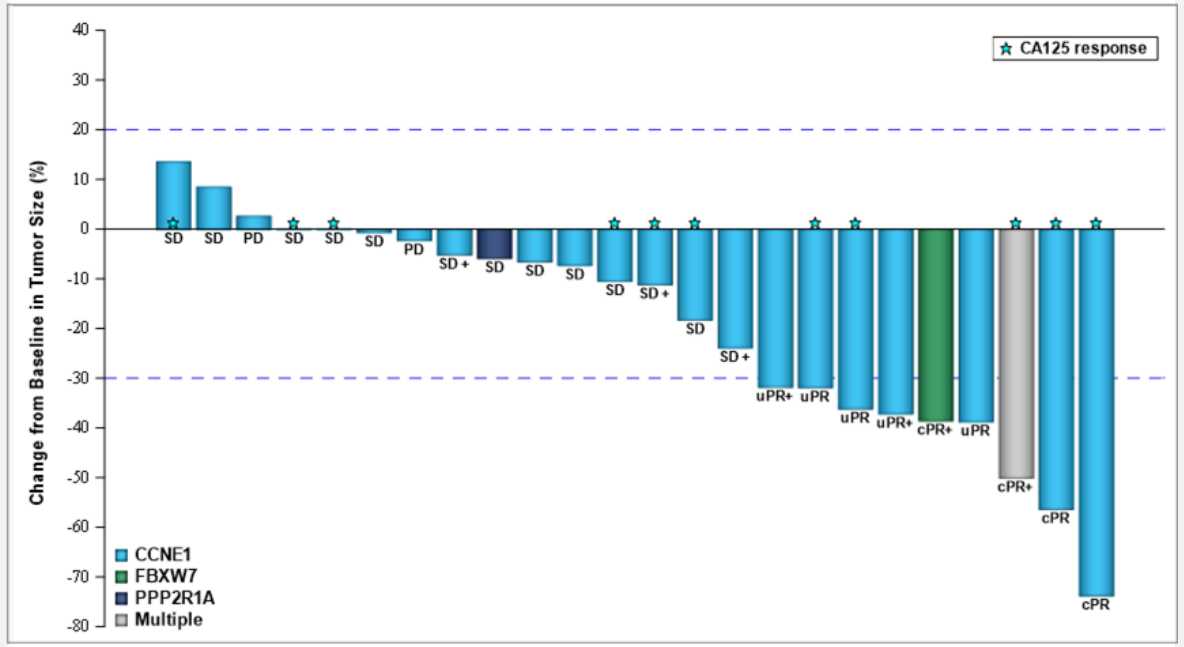
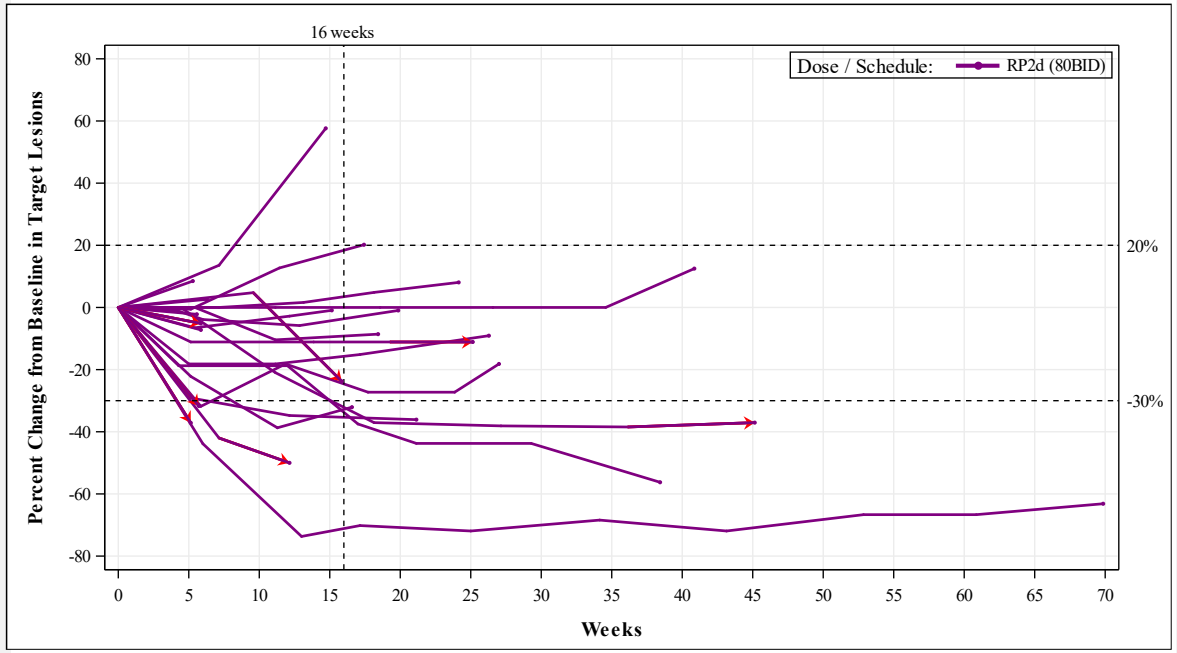
PROC: Strong efficacy in lunre BM+ tumors

75% of patients experienced tumor shrinkage



ORR (conf.+ unconf.), %	37.5%
ORR (conf.), %	16.7%
PR	4 (16.7%)

Durable responses observed across subtypes and genetic alterations



Time to response (Range)	5-18 weeks

Duration of response up to ~64 weeks

Note: +, denotes treatment ongoing

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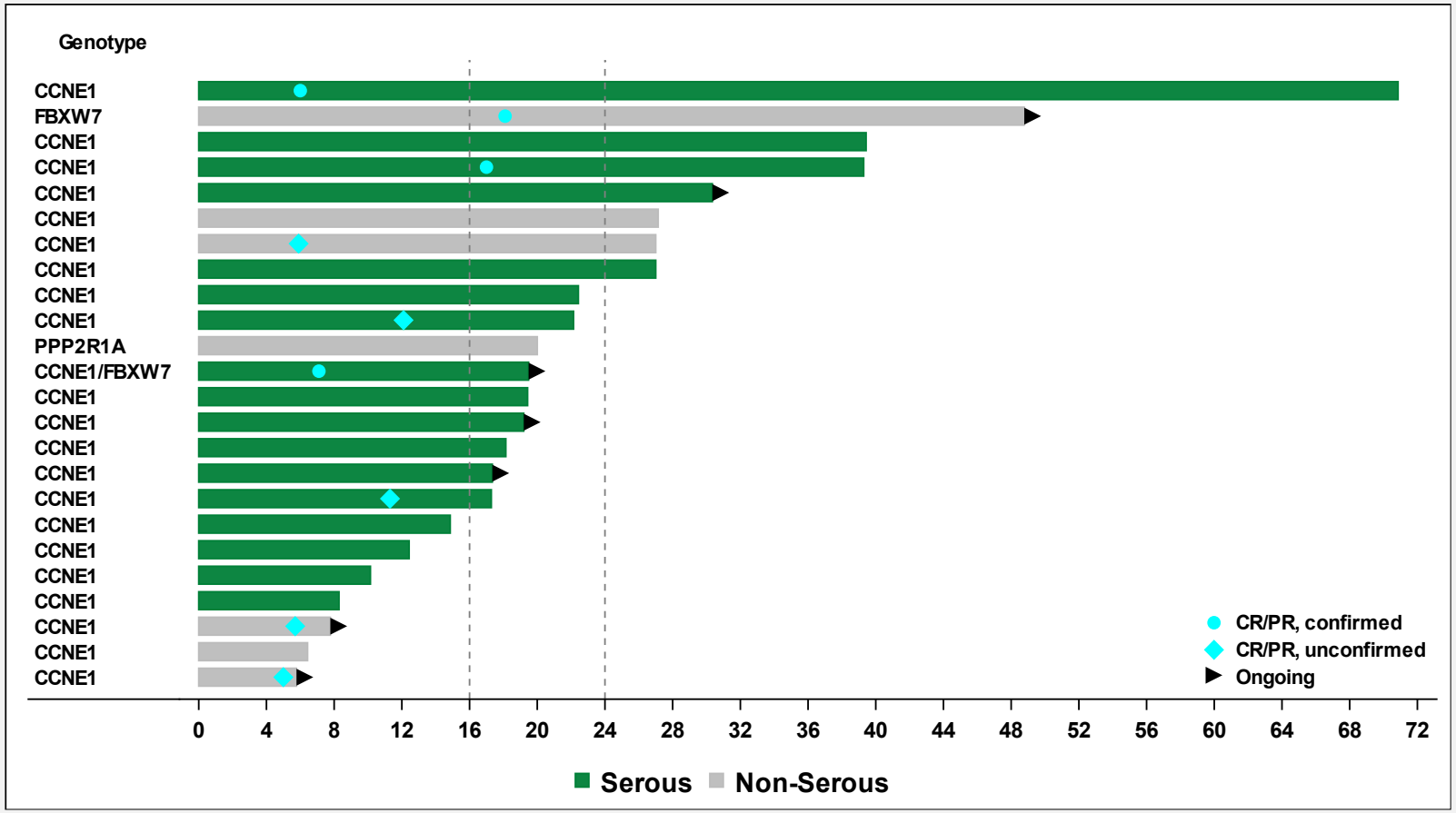
PROC: Compelling clinical benefit rate of 79% observed

Duration of treatment on lunre+camo



- **Progression-free rate (KM) at 24 weeks was 45% (95% CI: 22-66%)**
- **Pattern of benefit reflects unique lunre+camo MoA:**
  - Long-term benefit in patients when tumor reductions did not meet response definition
  - Continuous slow reductions in tumor burden, late and/or unconfirmed PRs
  - CA-125 responses predict clinical benefit
- **Treatment ongoing in 29% of patients; 4 additional patients with first scan pending**

CBR, %	**79%**
PFS (%) at 24-weeks (90% CI)	45% (22-66%)
TRT ongoing w/o PD, n (%)	29%

Abbreviations: CBR, clinical benefit rate defined as having CR, PR, or at least 16 weeks treatment without PD.
Note: Modified efficacy population defined as those treated patients with at least one post-baseline tumor assessment

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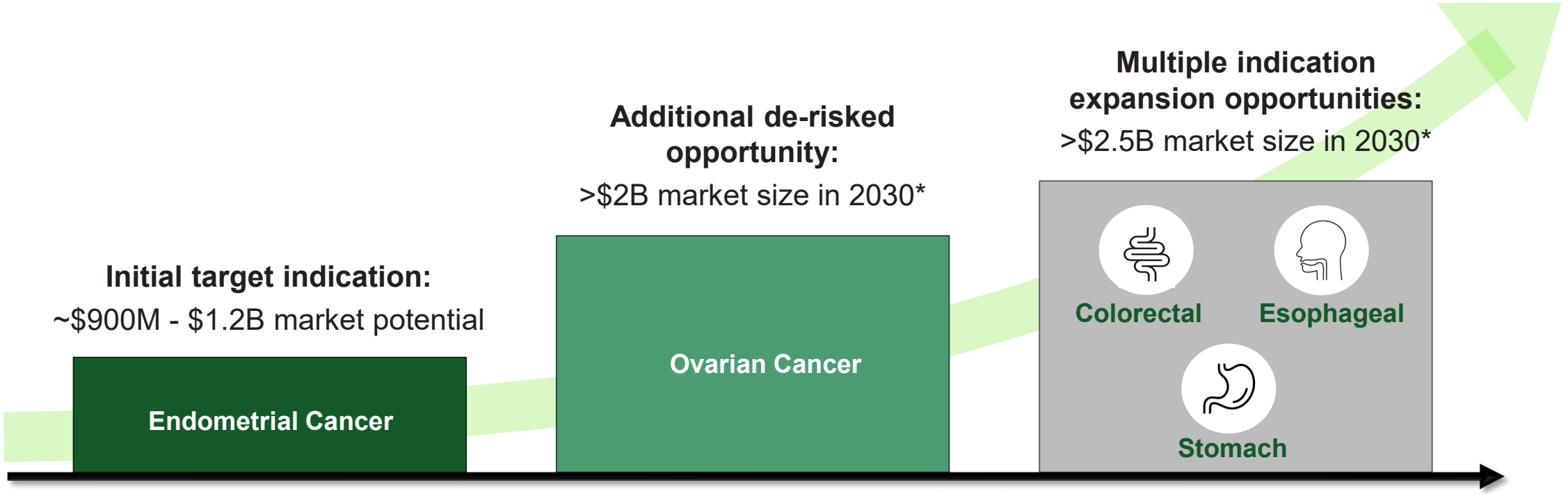
Seeking to partner lunre+camo for pivotal development

Significant market potential across multiple opportunities



*Indication global sales forecast in 2030 for approved therapies and projected approved therapies (**EvaluatePharma**), 75% factor for US/EU4/UK, Lunre segment ~29% of $7B Market for Ovarian, ~16% of $16B Market across multiple indication expansion opportunities.

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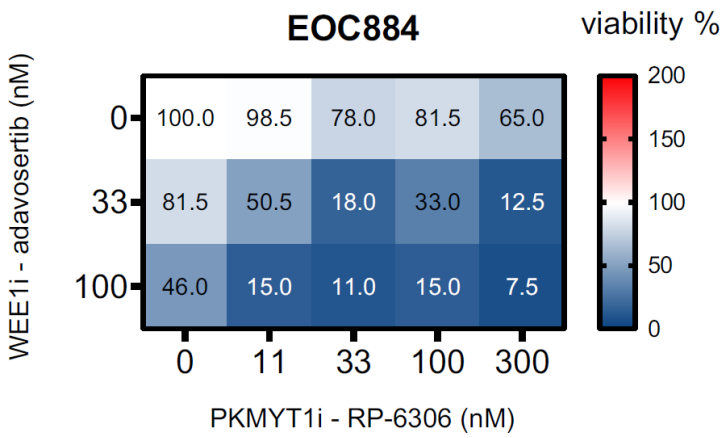
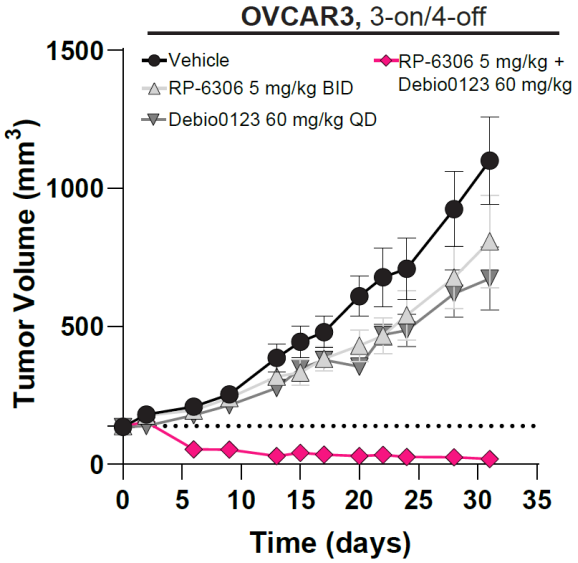
Lunre+Debio 0123 1st clinical trial inhibiting PKMYT1 + WEE1

Strong preclinical evidence of PKMYT1 + WEE1 inhibitor combination potential; Ph1/1b now enrolling



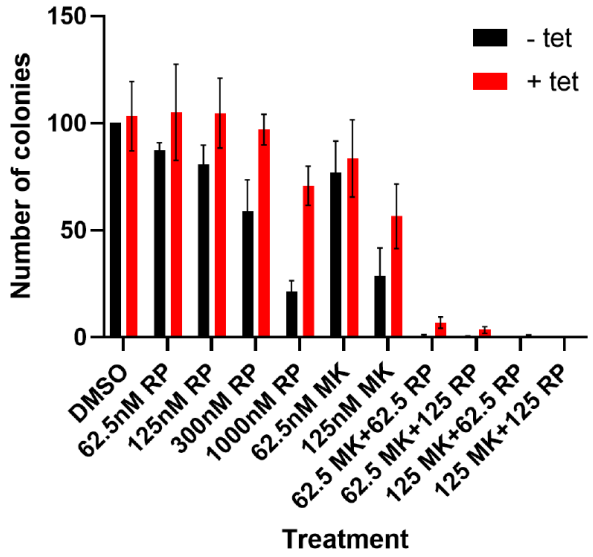
Combination synergistically eradicates ovarian cancer cells and organoid models at a low doses…

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.

Key upcoming milestones

	2Q'25	3Q'25	4Q'25	2026
RP-1664 (PLK4i)		Initiate pediatric neuroblastoma Ph1/2	Initial LIONS topline data	LIONS completion and POC readout
RP-3467 (Polθi)		Initial POLAR topline data		
Lunresertib / Camonsertib	Complete Lunre+WEE1i enrollment			

Financial Summary

$153M

Unaudited as of Dec 31, 2024

Cash runway into mid-2027

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RepareRx.com