REPARE THERAPEUTICS

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

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Disclaimer

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 design, objectives, initiation, timing, progress and results of our current and future preclinical studies and clinical trials, including specifically our clinical trials of RP-1664 and RP-3467; the clinical and market opportunity for RP-1664 and RP-3467; the tolerability, efficacy and clinical progress of RP-1664 and RP-3467; the potential of RP-1664 as a first-in-class oral PLK4 inhibitor and RP-3467 as a best-in-class Polθ inhibitor; the expected timing of program updates and data disclosures; the competitive landscape for our product candidates.

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

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

Focus of today's presentation

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Overview of our next 2 clinical programs

PROGRAM	FIRST PATIENT ENROLLMENT GOAL	TREATMENT APPROACH	CLINICAL OPPORTUNITY
RP-1664 ***PLK4 Inhibitor***	**1H 2024**	**Monotherapy**	**~63K addressable patient population for TRIM37-high solid tumors (US+UK/EU4)***
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*

** PARPi and ADC market estimate: Decision Resources Group, RLT market estimate: *Ostuni E and Taylor MRG (2023) Commercial and business aspects of alpha radioligand therapeutics. Front.Med.9:1070497. doi:10.3389/fmed.2022.1070497*

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RP-1664

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RP-1664

Potential first-in-class, oral PLK4 inhibitor

FPI in 1H 2024

Highly potent, selective and bioavailable PLK4 inhibitor synthetic lethal with TRIM37 amplification & overexpression (TRIM37-high)

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

Will be initially investigated in TRIM37-high solid tumors and neuroblastoma

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

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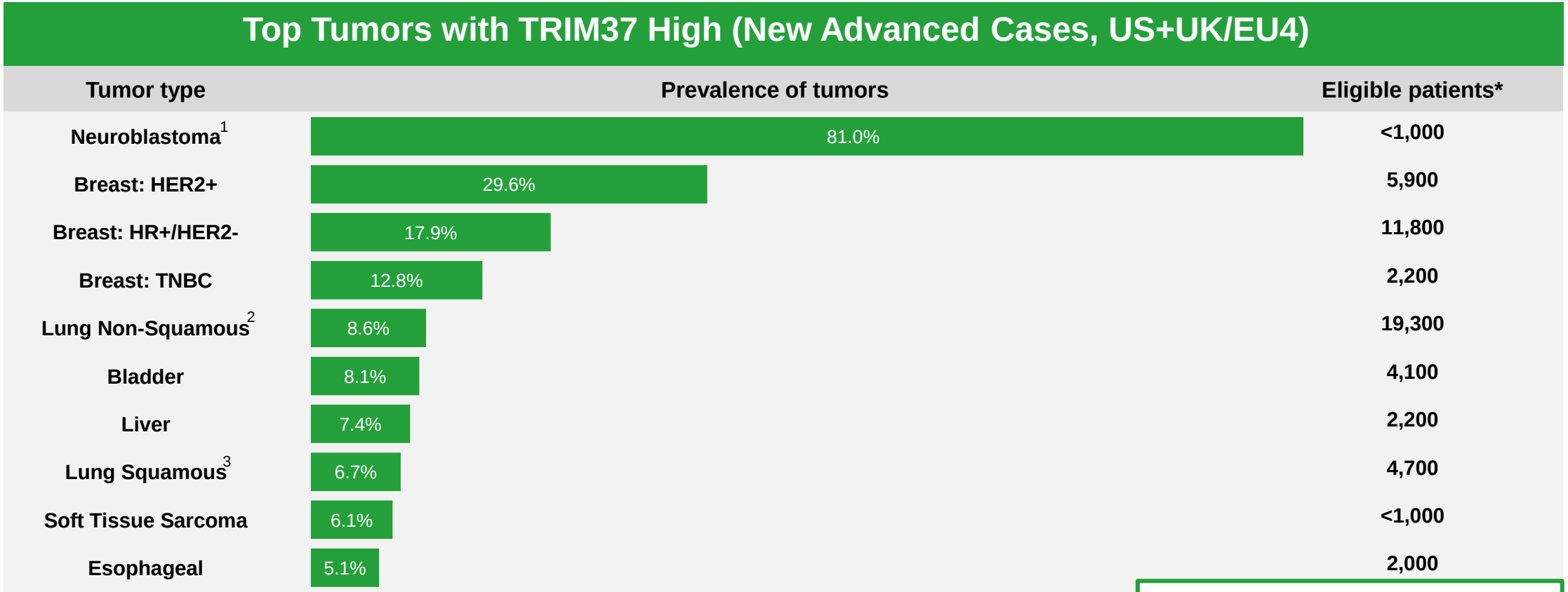
Addressing unmet need in critical patient populations

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



Tumor type	Prevalence of tumors	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

~63K patients across tumor types**;** ~53K among top tumors

**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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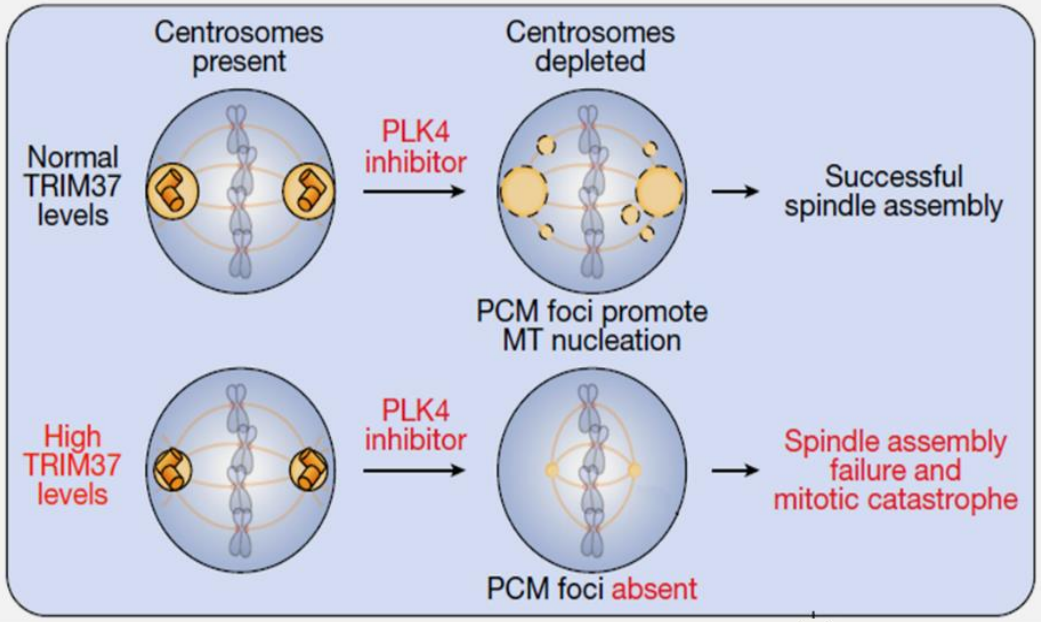
Compelling synthetic lethal rationale for targeting PLK4



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

- 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**

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Potential first-in-class oral PLK4 inhibitor

	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
- Clean in PanLabs safety pharmacology screen

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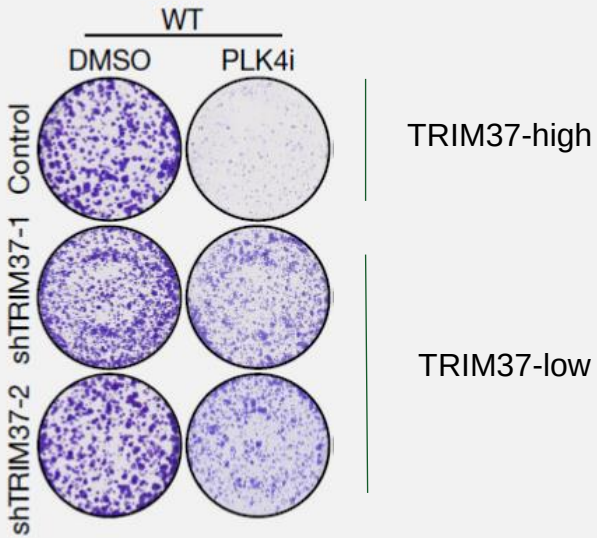
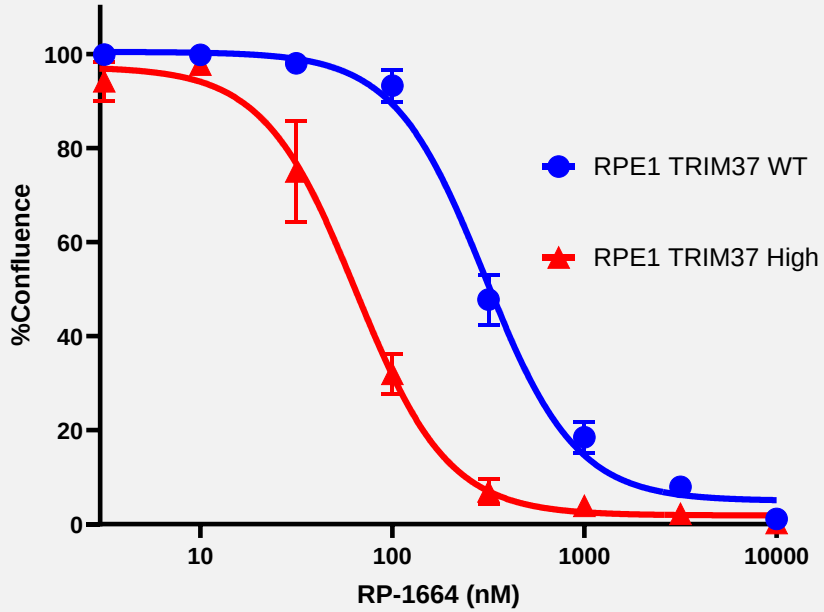
PLK4 inhibition is synthetic lethal with TRIM37-high tumors

MCF7 (*TRIM37*-high)



RPE1 Isogenic Cell Lines



- **PLK4 inhibition selectively inhibited TRIM37-high cells**

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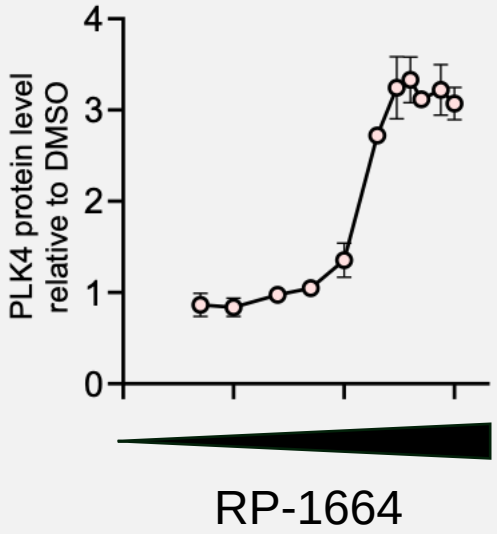
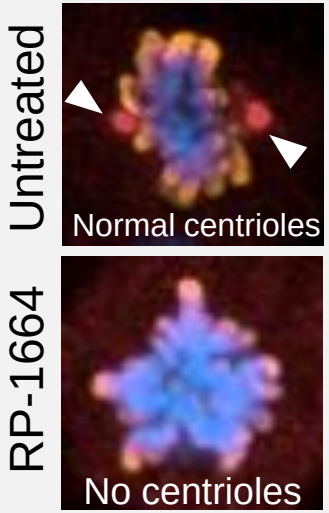
Potent PLK4 inhibition and downstream modulation of centrioles

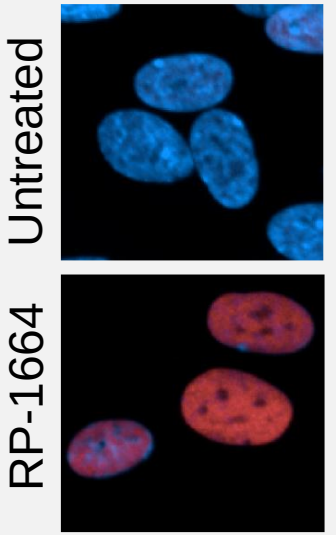
PLK4 Inactivation



Abnormal Centriole Numbers & Aberrant Mitosis



p21 Up-regulation



DAPI: DNA (Blue)
P21 (Red)

- **PLK4 inhibition leads to centriole depletion, p21 activation and ultimately cell death in TRIM37-high cells**

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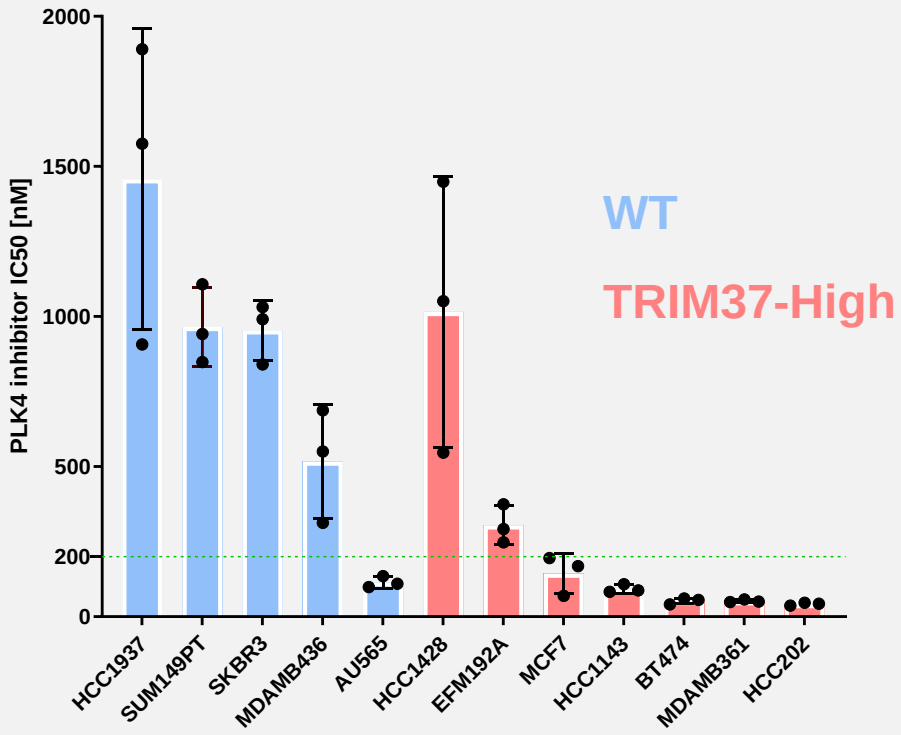
Cell lines with TRIM37-high are more sensitive to PLK4 inhibition

TRIM37-high vs WT Cell Panel



- Published SL hypothesis confirmed in house across a panel of cell lines with and without TRIM37-high

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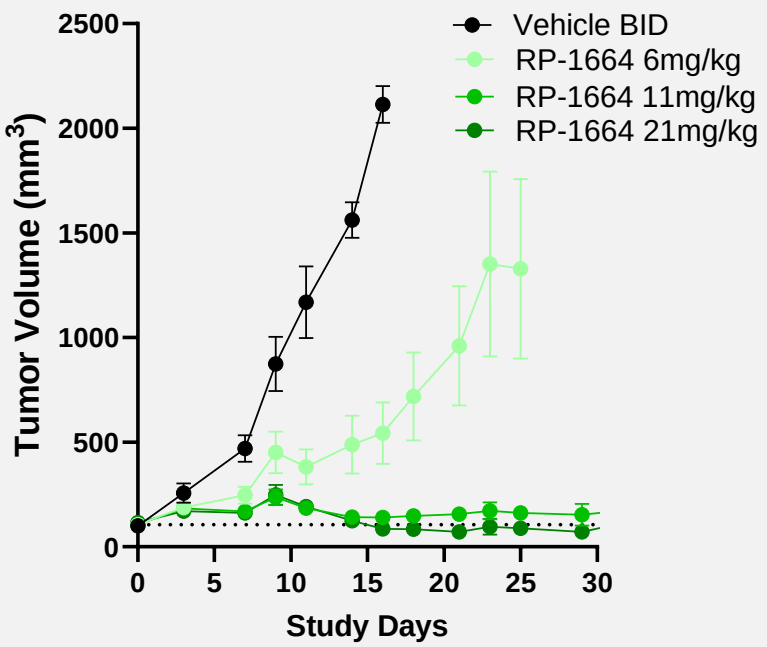
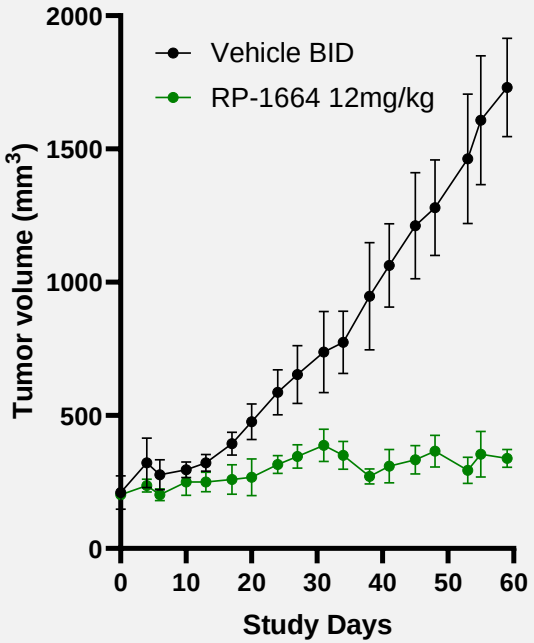
Robust monotherapy activity across PDX/CDX models

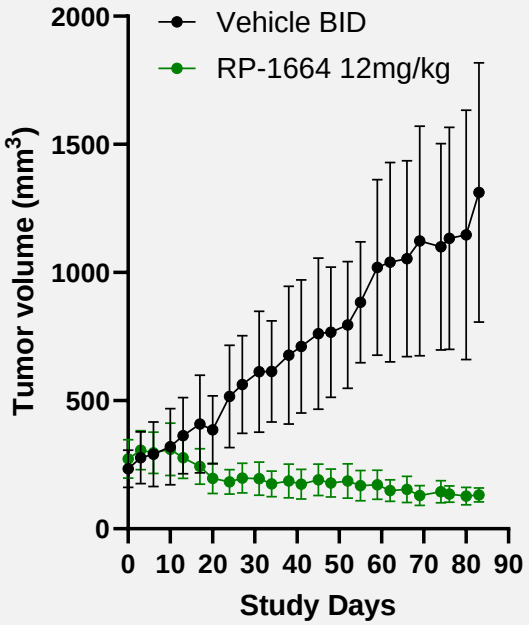
Breast (Triple Negative) CDX



Breast (ER positive) PDX



NSCLC PDX



- **Monotherapy drives tumor stasis to regression in TRIM37-high models**

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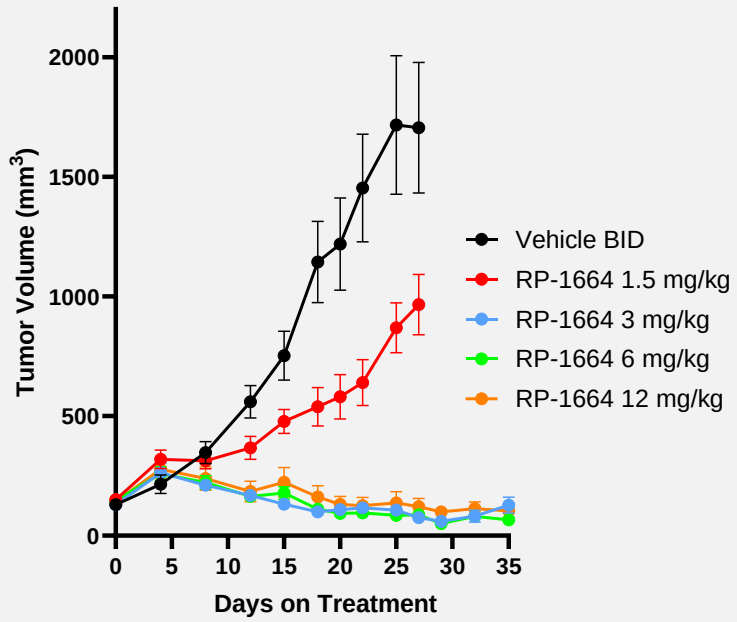
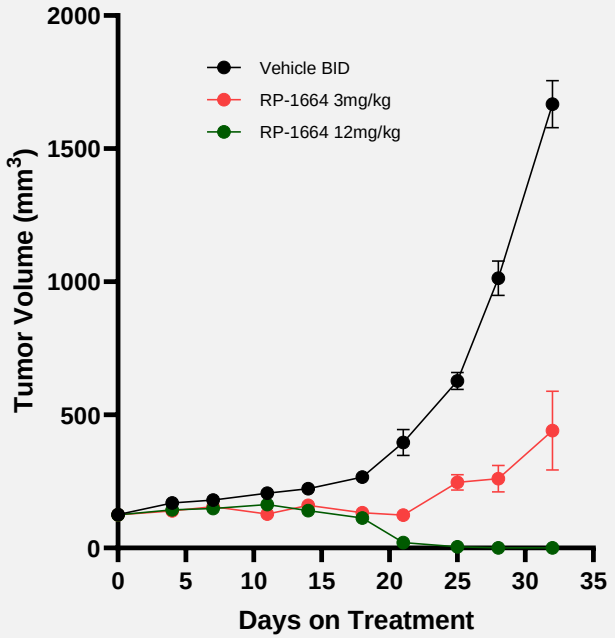
Deep monotherapy regressions in TRIM37-high models

CHP-134 Neuroblastoma CDX Model



IMR32 Neuroblastoma CDX Model



- **High risk neuroblastoma (>80% TRIM37-high) provides a biomarker-enriched monotherapy opportunity**

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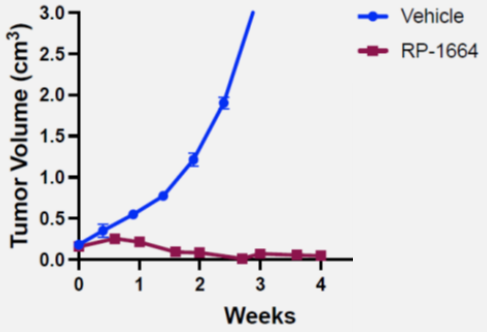
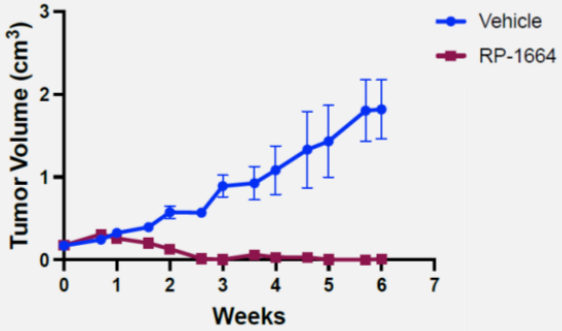
Highly efficacious as monotherapy in neuroblastoma models

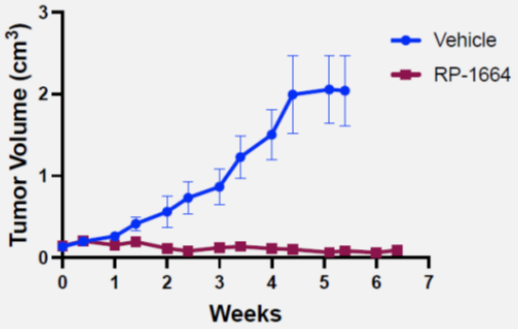
PDX1



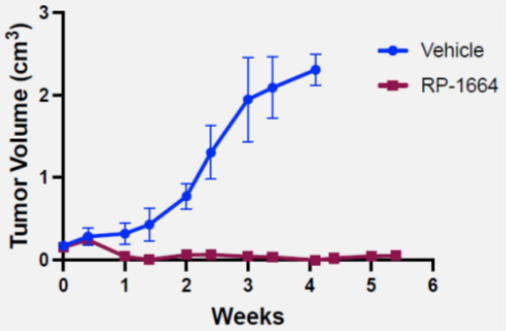
PDX2



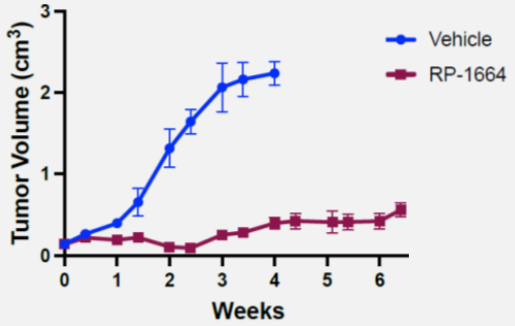
CDX1



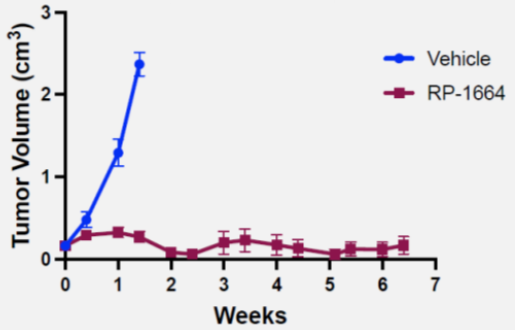
PDX3



PDX4



CDX2



- **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*

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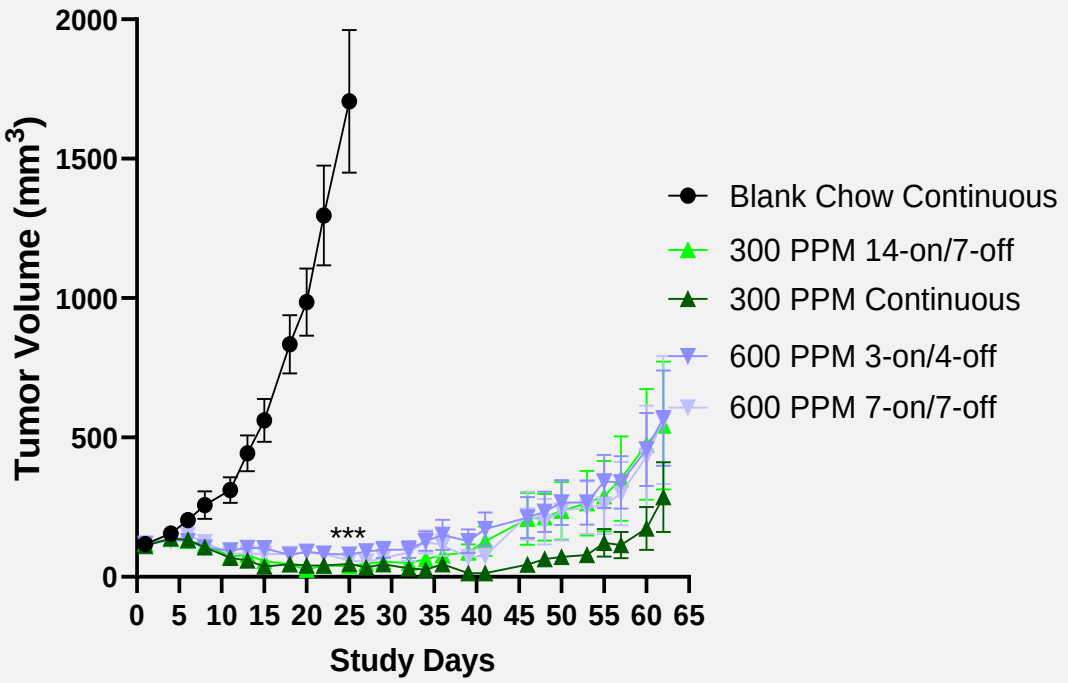
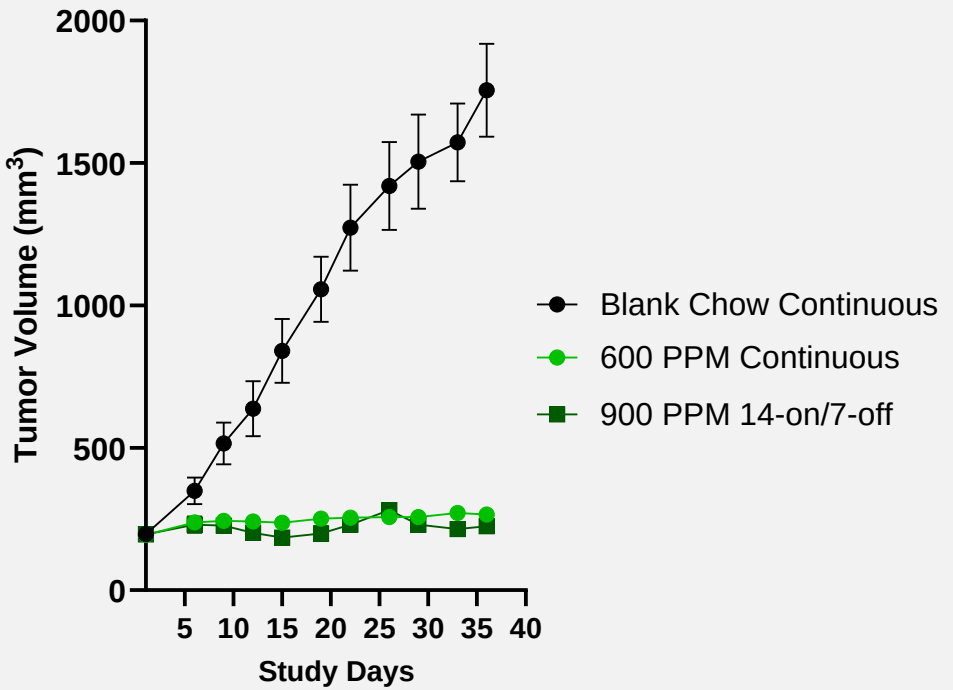
In vivo activity seen across a range of doses and schedules

CHP-134 Neuroblastoma CDX Model



MCF7 CDX (ER+PR+HER2-) Model



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

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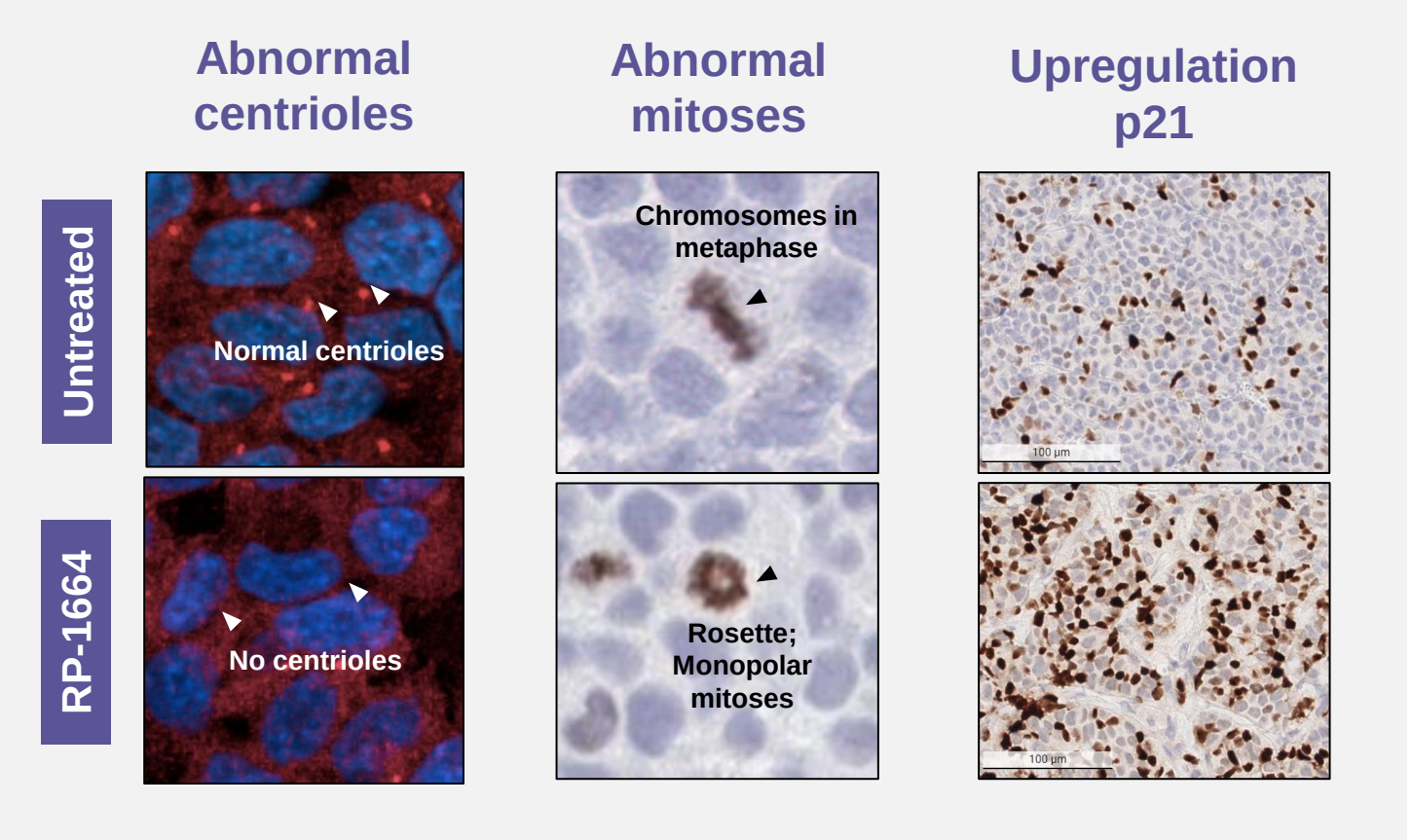
Clinical PD biomarkers established



- **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**

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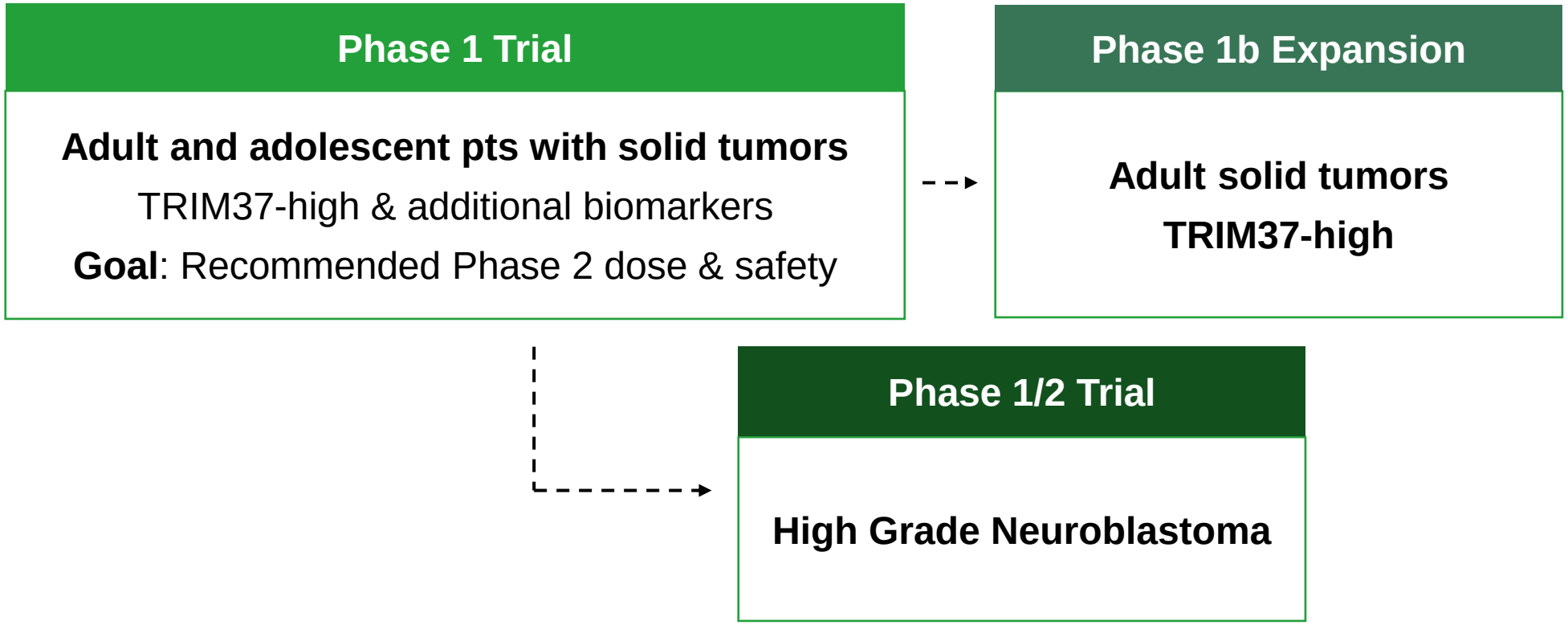
Phase 1 monotherapy trial in neuroblastoma and adult tumors



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

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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

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Potential best-in-class Polθ inhibitor

RP-3467 demonstrates compelling combination activity without added toxicity

PARPi Combination	RLT Combination	Chemotherapy/ADC Payloads
Durable complete responses preclinically, with no additional toxicity	**Survival benefit preclinically in unselected tumor backgrounds, with no additional toxicity**	**Well tolerated preclinically in combination with chemotherapy, including topoisomerase ADC payloads**
~$3 Billion global market segment for PARP inhibitors	**~$8 Billion** global market segment for RLTs	**~$5 Billion** global market segment for ADCs

* PARPi and ADC market estimate: Decision Resources Group, RLT market estimate: *Ostuni E and Taylor MRG (2023) Commercial and business aspects of alpha radioligand therapeutics. Front.Med.9:1070497. doi:10.3389/fmed.2022.1070497*

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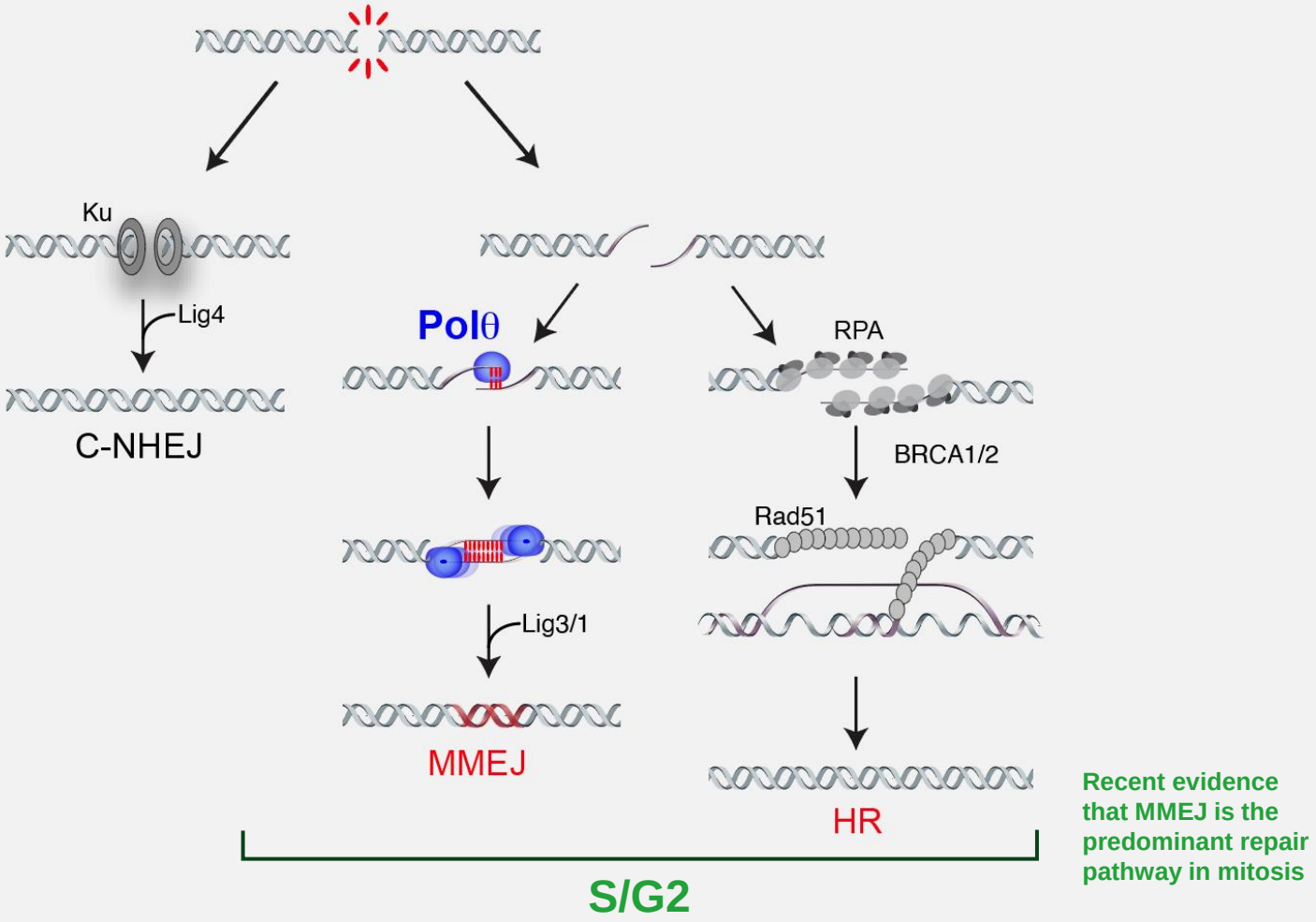
Polθ is a promising therapeutic target



Recent evidence that MMEJ is the predominant repair pathway in mitosis

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

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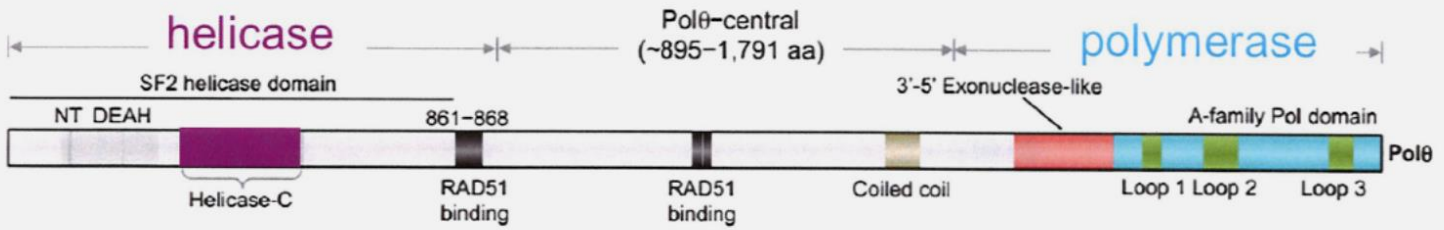
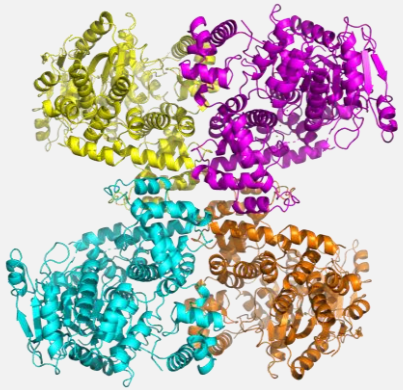
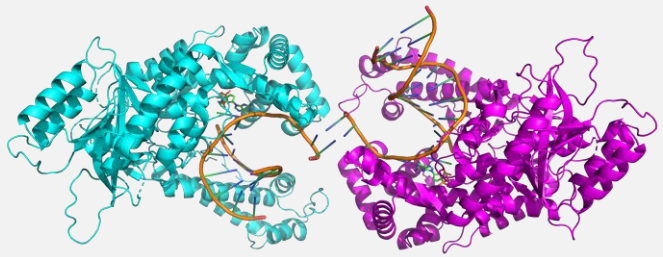
Protein structures enabled discovery of polymerase and helicase inhibitors





N-Terminal Helicase-Like Domain
Single-Particle Cryo-EM: **2.4 Angstroms**



C-Terminal DNA Polymerase Domain
X-ray Crystallography: **2.0 Angstroms**

- **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**

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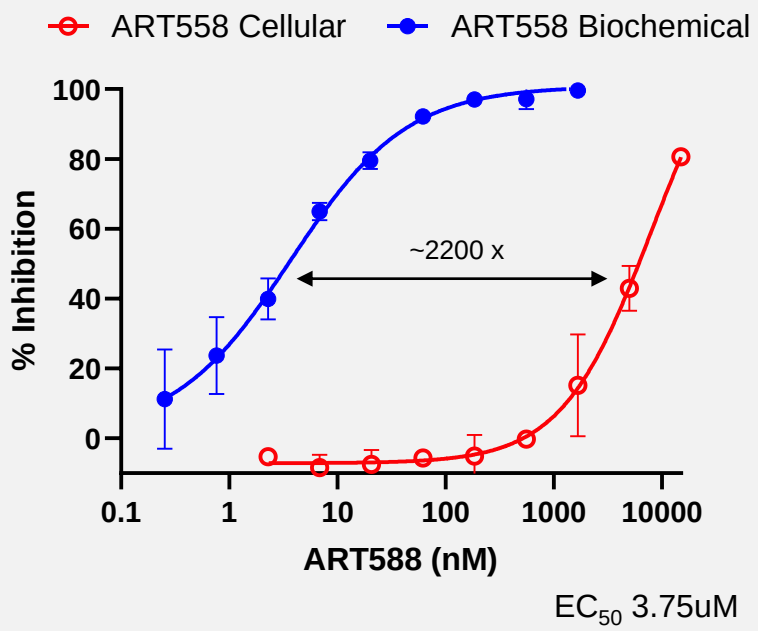
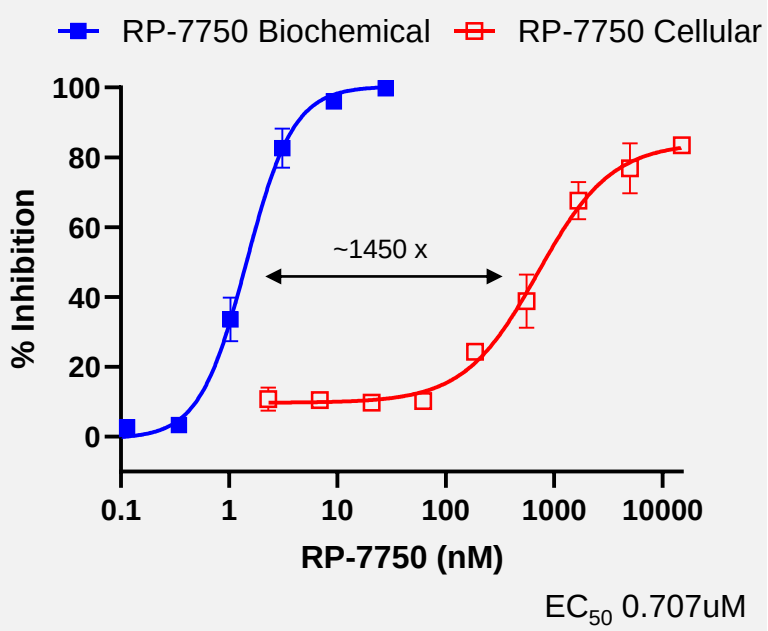
Repare Polθ helicase inhibitors demonstrate superior cell potency

Published Polymerase Inhibitior



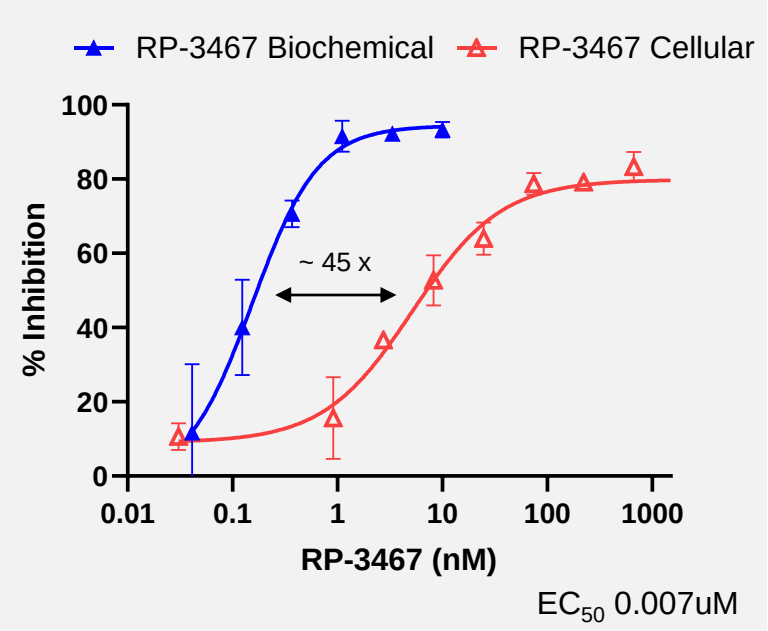
EC_{50} 3.75uM

Repare Polymerase Inhibitior



EC_{50} 0.707uM

Repare Helicase Inhibitor (RP-3467)



EC_{50} 0.007uM

- **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**

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RP-3467 is a potential best-in-class Polθ inhibitor

	Parameter	RP-1664
In vitro	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
	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

- Highly potent, selective and orally bioavailable Polθ helicase inhibitor
- Clean on PanLabs safety pharmacology screen

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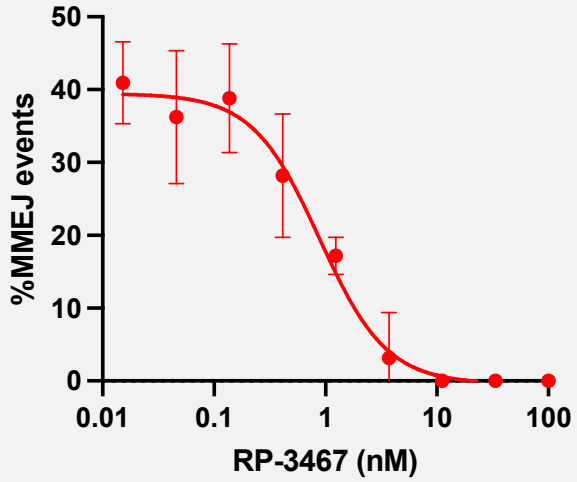
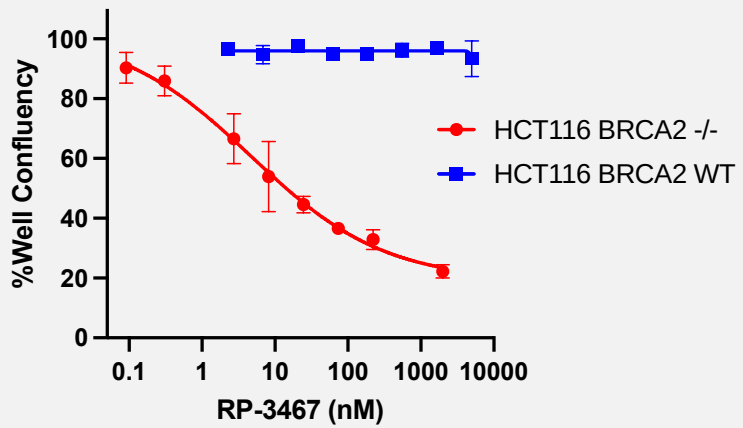
Inhibits DNA repair and is synthetic lethal with BRCA2 loss

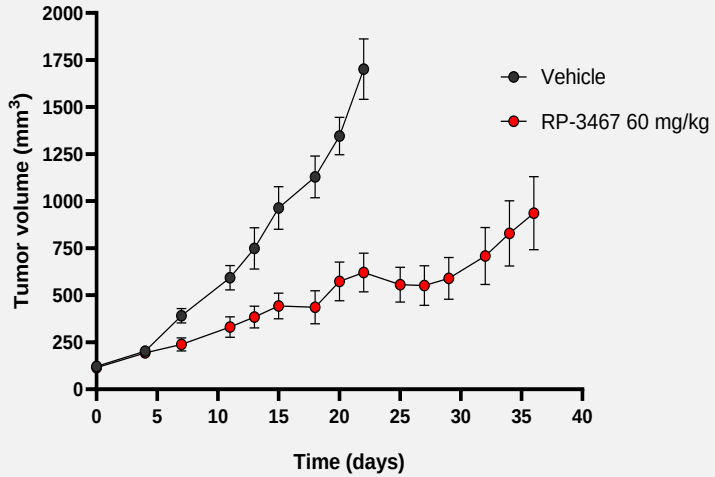
Inhibition of DNA Repair



Cell Proliferation HCT116 Isogenic



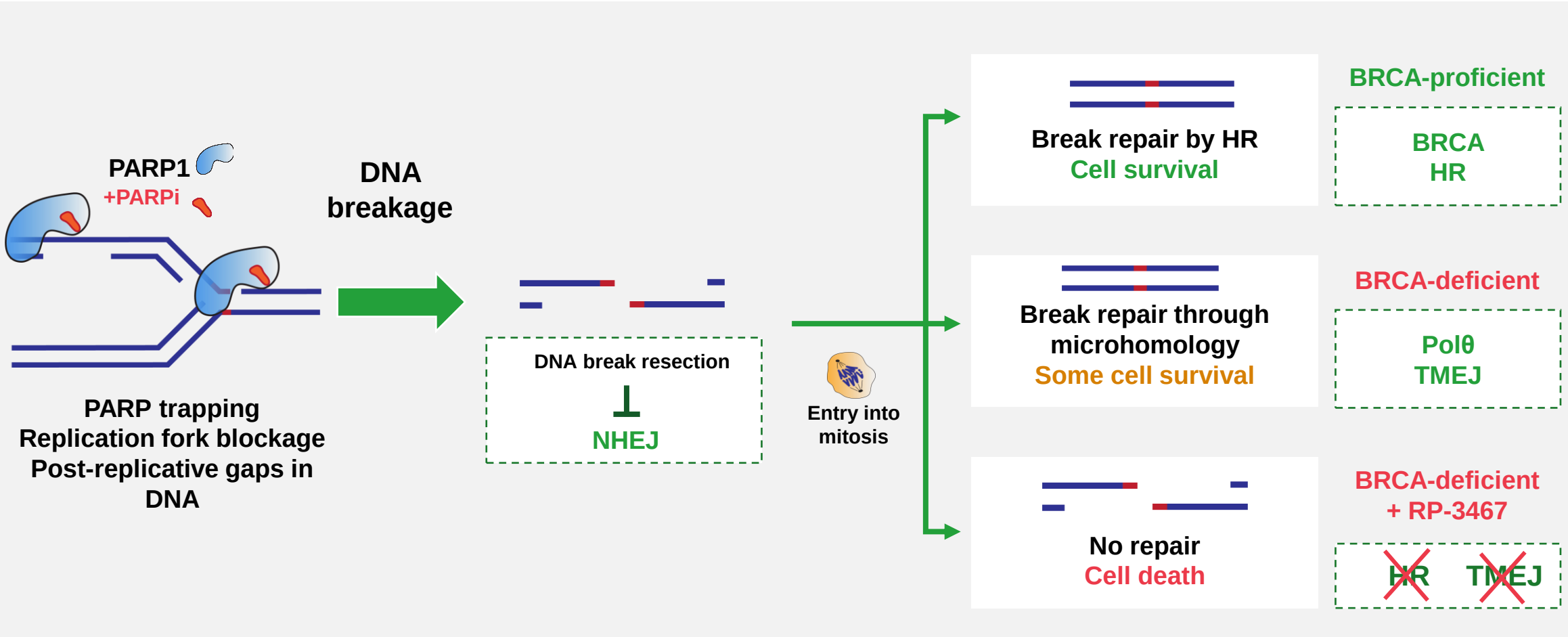
HCT116 BRCA2 -/- *in vivo* Activity



- **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**

REPARE THERAPEUTICS

Rationale for synergy between Polθi and PARPi



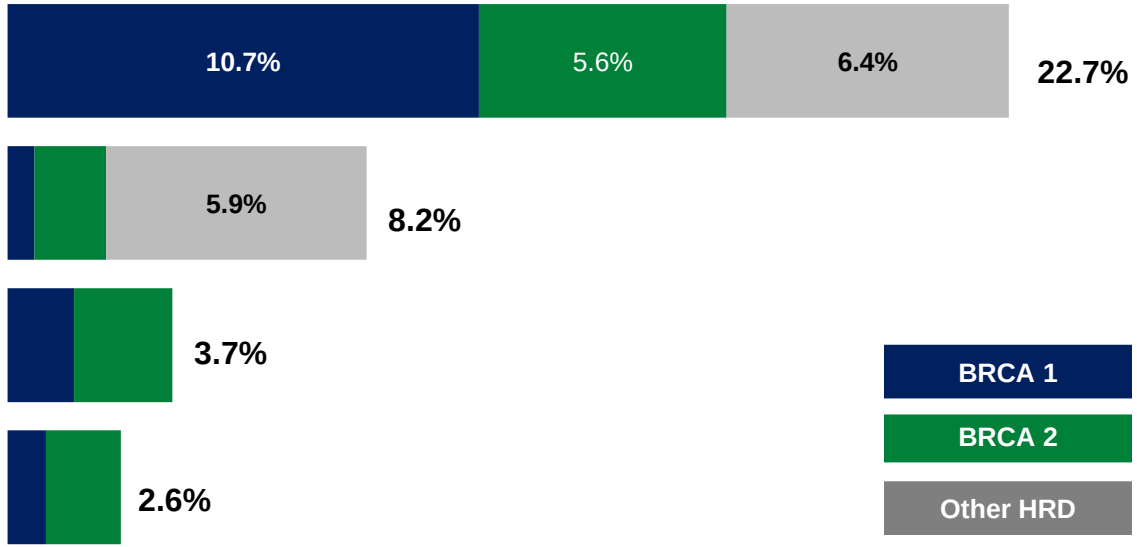
- PARPi + Polθi combination synergizes to kill homologous recombination deficient tumor cells

REPARE THERAPEUTICS

Addressing unmet need in critical patient populations

Key PARP-Naïve and PARP-Treated Market Segments (Treated Patients US+UK/EU4)*

Tumor type	Prevalence of gene of interest	PARP-naïve opportunity (1L)	PARP-resistant 0pportunity (2L)
Ovarian	22.7%	7,700	3,500
Castrate-Resistant Prostate	8.2%	5,100	2,400
HER2- Breast**	3.7%	2,900	1,600
Pancreatic**	2.6%	1,700	500



~25K among key tumor segments

** 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*

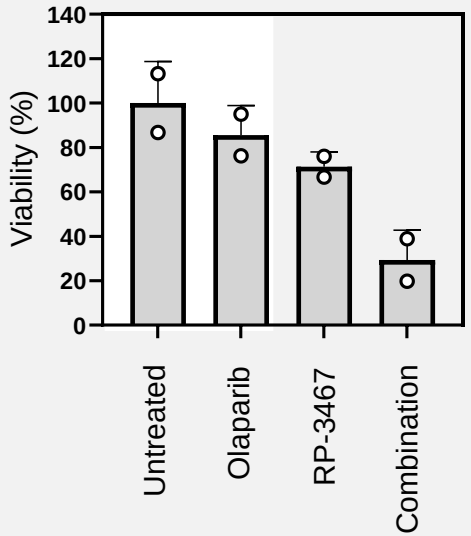
REPARE THERAPEUTICS

Synergizes with both PARP1/2 and PARP1-selective inhibitors

PARP1/2

Combo RP-3467 & Olaparib

HCT-116 BRCA2-/-

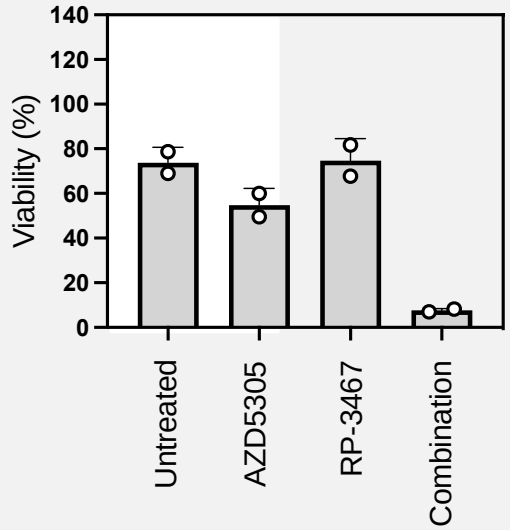


Olaparib: 1.25 nM
PolQi RP-3467: 1.23 nM

PARP1 Selective

Combo RP-3467 & AZD5305

HCT116 BRCA2-/-



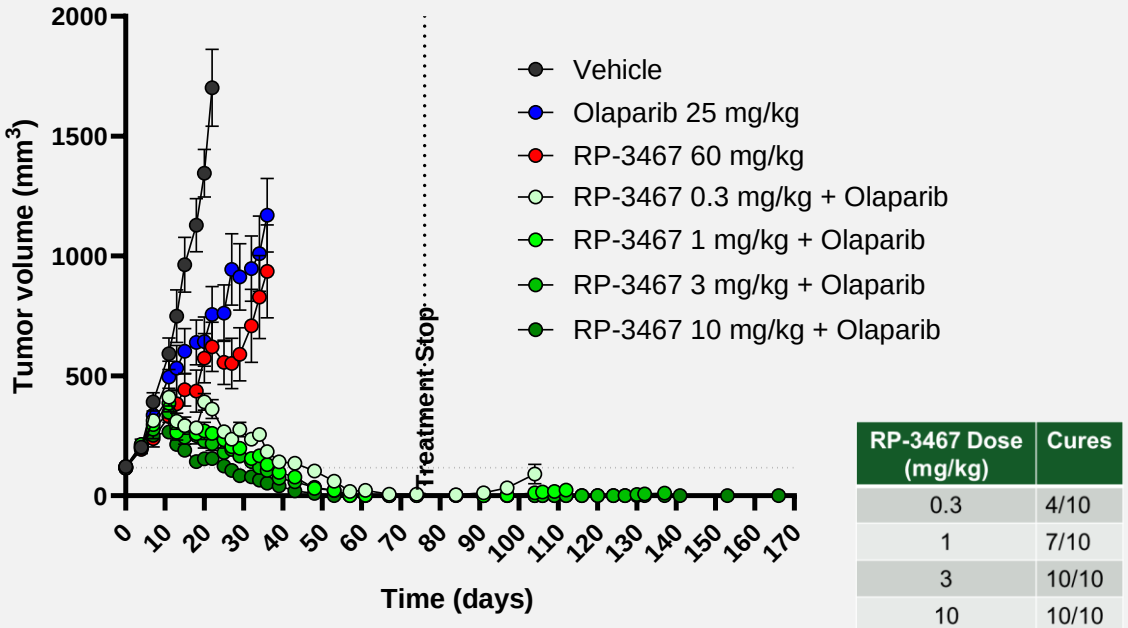
AZD5305: 0.37 nM
PolQi RP-3467: 1.23 nM

- **Opportunities with PARP1/2 standard-of-care and potential with emerging PARP1-selective agents**

REPARE THERAPEUTICS

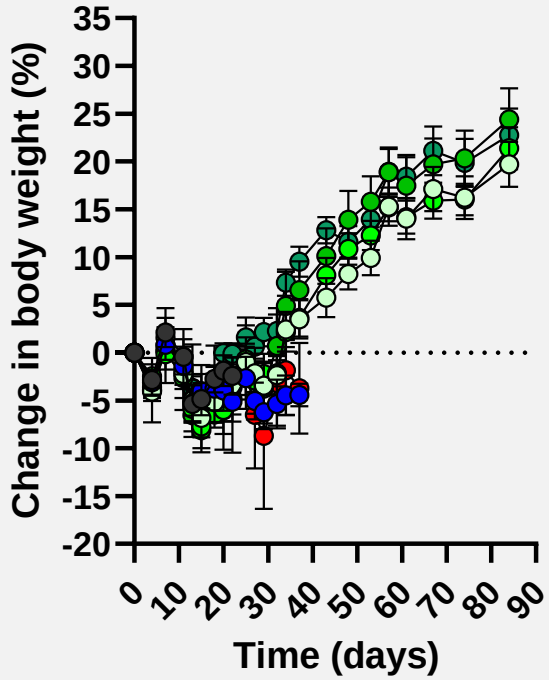
Profound, durable synergy with PARP inhibition

HCT116 BRCA2 -/-



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

Body Weight



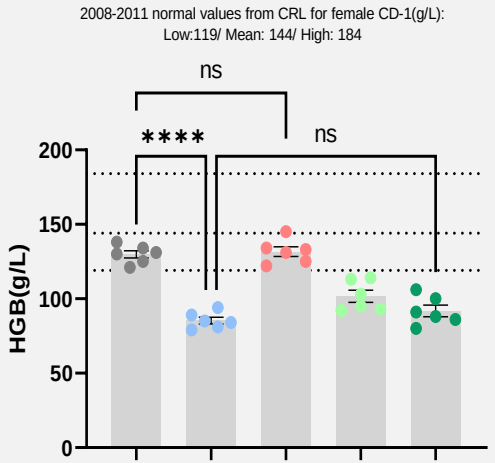
- **Deep/durable complete regressions across a wide dose range and extremely well tolerated**

REPARE THERAPEUTICS

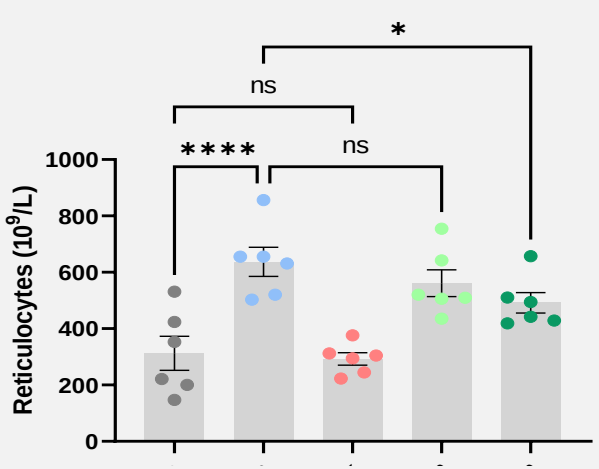
No added hematological toxicity in combination over Olaparib alone

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

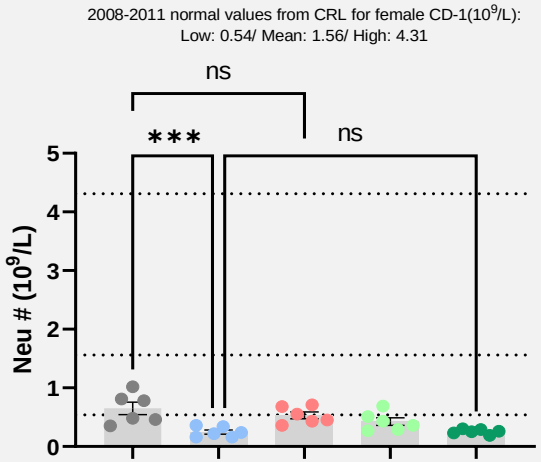
HGB (Hemoglobin)



RET (Reticuloyte)



NEUT (Neutrophil)



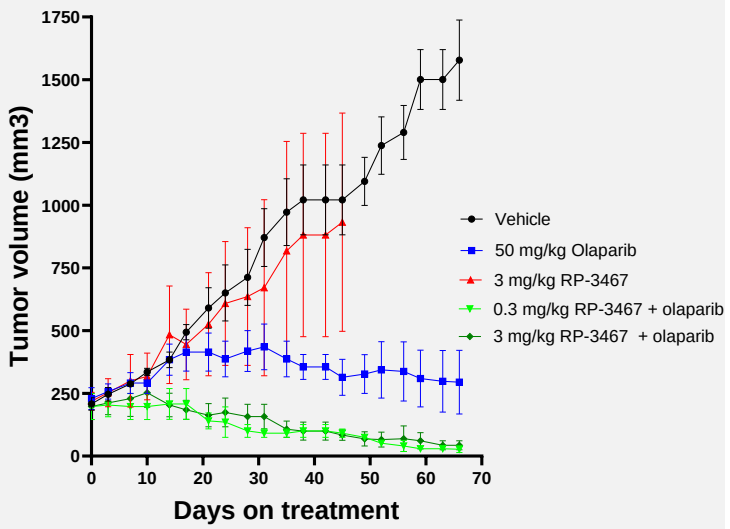
Vehicle QD PO + Ctrl chow — Vehicle QD PO + Olaparib chow 3000ppm — RP13467 10 mpk QD PO + Ctrl chow — RP13467 1 mpk QD PO + Olaparib chow 3000ppm — RP13467 10 mpk QD PO + Olaparib chow 3000ppm

- **Extremely well tolerated combination at relevant Olaparib doses**

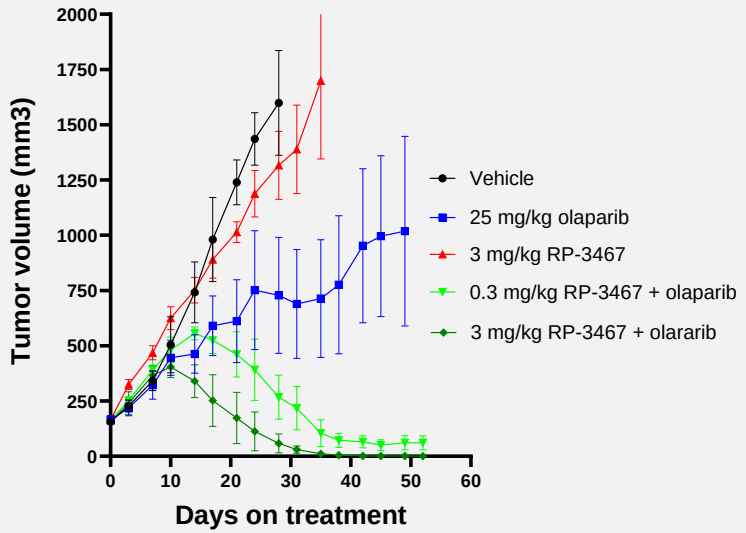
REPARE THERAPEUTICS

Complete regressions in PDX models

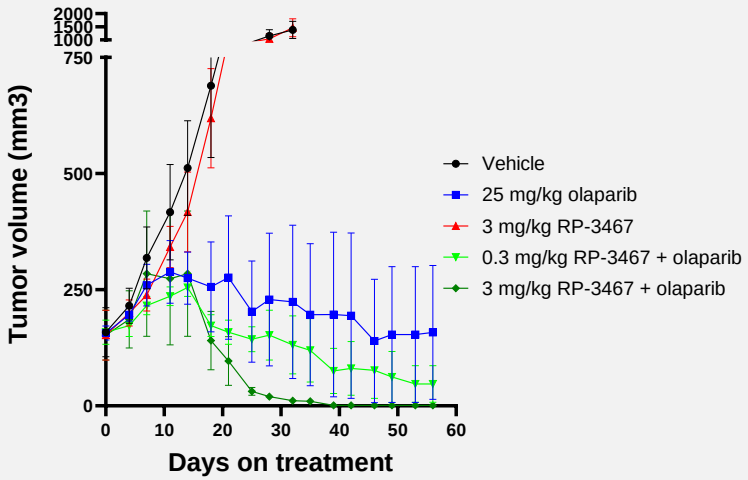
HBCx-22 (BRCA2null)



HBCx-10 (BRCA2null)



T400 (BRCA1null)

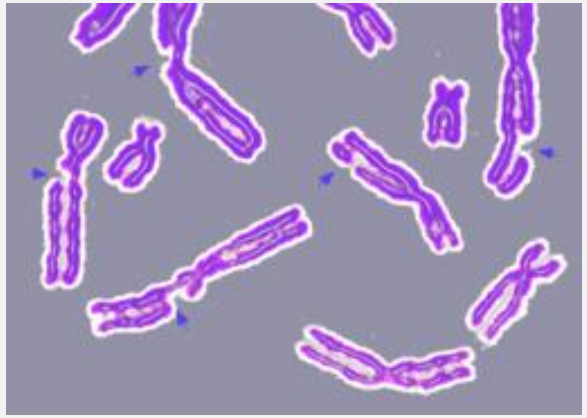


- **Complete regression in BRCA1/2 null PDX models**
- **Synergy in a PARPi resistance model (data not shown)**

REPARE THERAPEUTICS

Polθ is a radio-sensitizing agent

Mitotic IR-treated chromosomes with DSBs



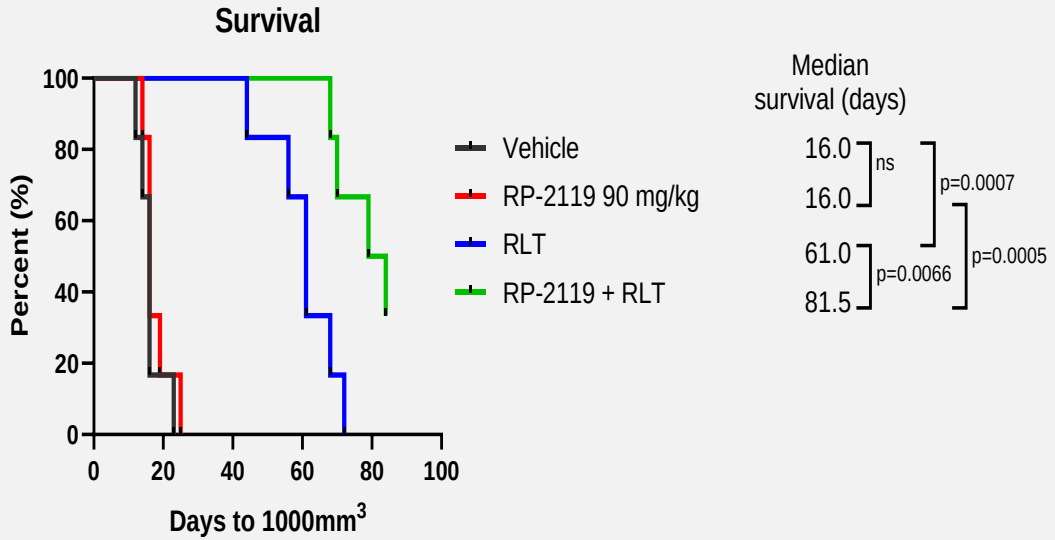
- **Cancer cells often transfer radiation-induced DSBs generated in S/G2 into mitosis**
- **Polθ-directed MMEJ is the only known pathway for repairing DSBs during mitosis**
- **Polθ inhibitors could be prime radio-sensitizing agents for use in the clinic**

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

** Source: Ostuni E and Taylor MRG (2023) Commercial and business aspects of alpha radioligand therapeutics. Front.Med.9:1070497. doi:10.3389/fmed.2022.1070497*

Polθi sensitizes *unselected* tumors to Radioligand Therapy

Combination Survival Benefit



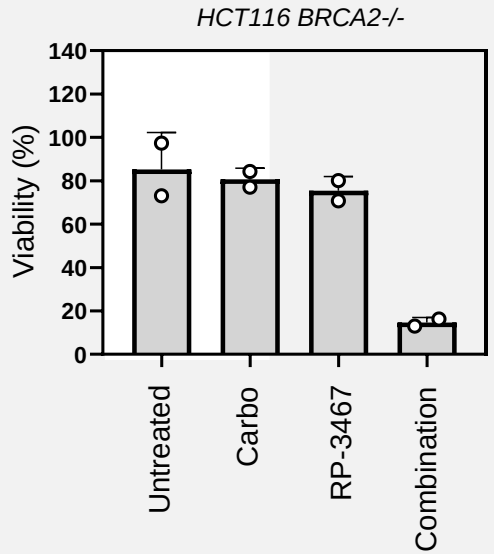
Homologous recombination proficient tumors treated with one dose of RLT and 4 weeks of Polθi

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

REPARE THERAPEUTICS

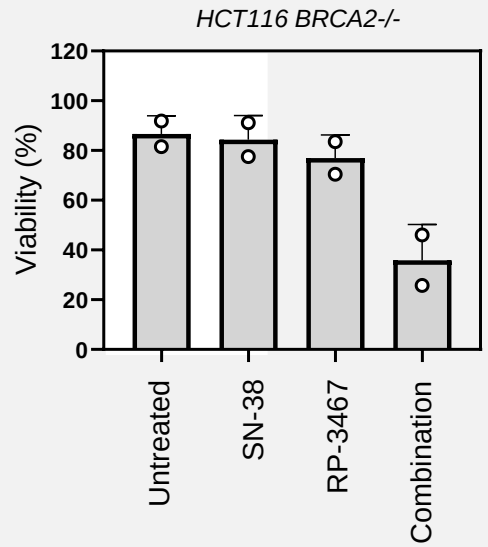
Synergizes with dsDNA break inducing chemotherapy

Combo RP-3467 & Carboplatin



Carbo: 111 nM
PolQi RP-3467: 1.23 nM

Combo RP-3467 & SN-38



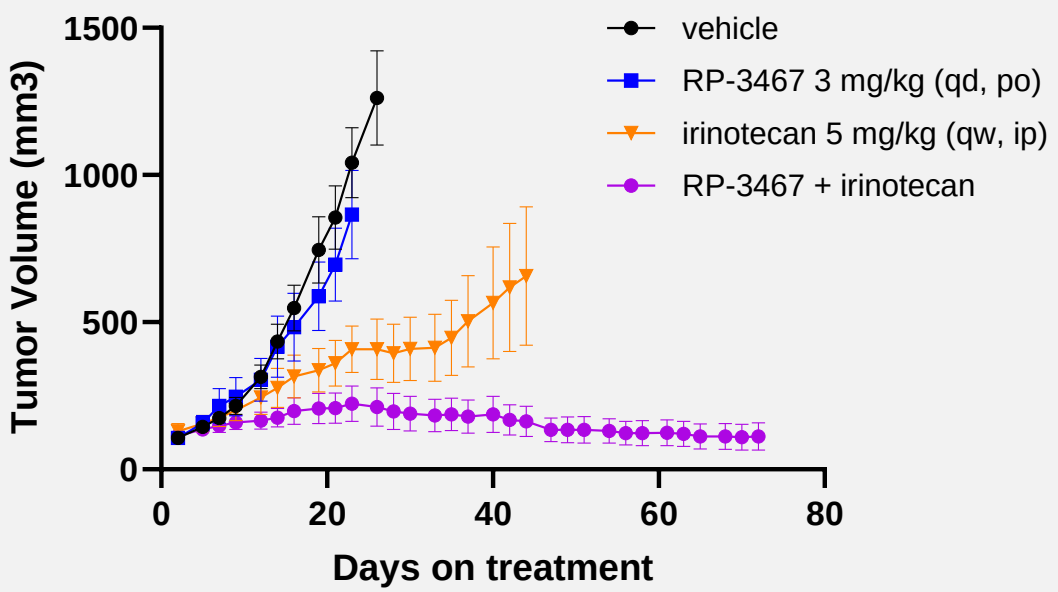
SN-38: 0.022 nM
PolQi RP-3467: 1.23 nM

- **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**

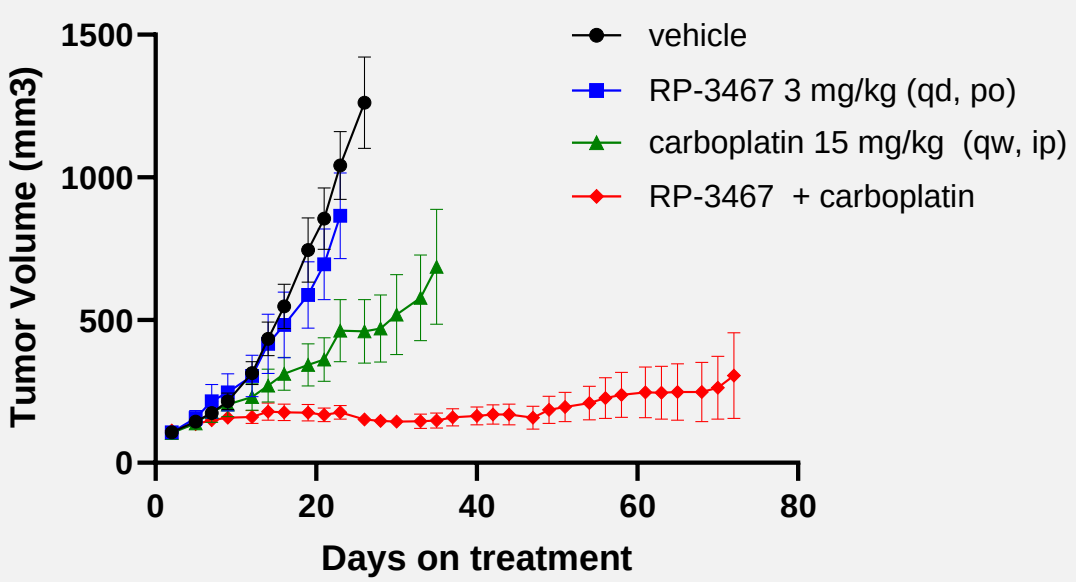
REPARE THERAPEUTICS

Clear *in vivo* combination benefit with chemo – No additional tox

HCT116 BRCA2 -/- (Irinotecan combo)



HCT116 BRCA2 -/- (Carboplatin combo)



- **Sensitizes to carboplatin and irinotecan and is well tolerated in combination (no changes in BW over single agents alone)**

REPARE THERAPEUTICS

RP-3467 Clinical Plan

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)**

REPARE THERAPEUTICS

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**

* PARPi and ADC market estimate: Decision Resources Group, RLT market estimate: *Ostuni E and Taylor MRG (2023) Commercial and business aspects of alpha radioligand therapeutics. Front.Med.9:1070497. doi:10.3389/fmed.2022.1070497*

Upcoming Catalysts

REPARE THERAPEUTICS

Upcoming milestones

2H 2023

Camonsertib Phase 2
TAPISTRY 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)

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Q&A

Lloyd M. Segal
President & CEO

Mike Zinda, PhD
Chief Scientific Officer

Maria Koehler, MD, PhD
Chief Medical Officer

Steve Forte, CPA
Chief Financial Officer

Philip Herman
Chief Commercial, Portfolio Development Officer

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Insight that enriches. Precision that empowers.

RP-1664 & RP-3467 Update Conference Call

November 15, 2023