REPARE THERAPEUTICS

Insight that enriches. Precision that empowers.

Corporate Presentation

May 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, camonsertib, RP-1664, and preclinical studies of RP-3467; 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-Q filed with the SEC on May 7, 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, proprietary 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

- Key readouts from ongoing trials
- New clinical entries (PLK4 and Polθ ATPase inhibitors)

Strong balance sheet

- Cash and investments of ~$237M[1] fund operations to mid-2026
- Multiple clinical catalysts in that timeframe

[1] *As of March 31, 2024.*

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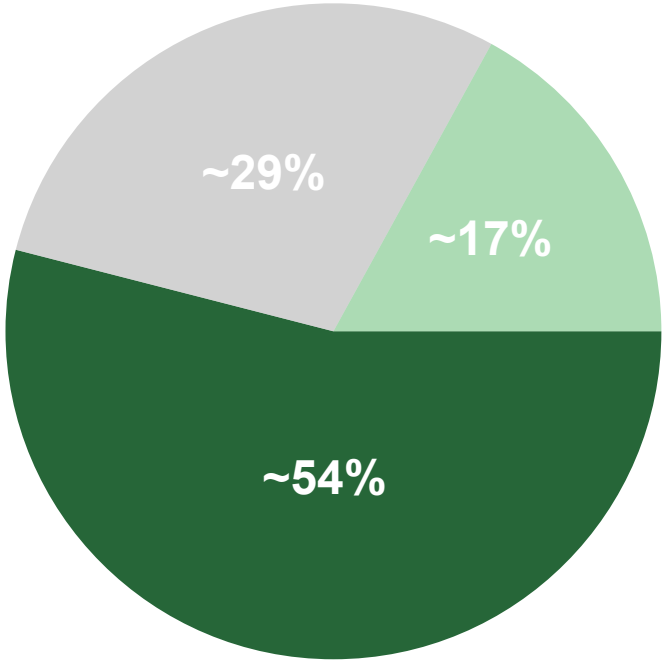
Targeting the untargetable through synthetic lethality

Precision oncology last 20 years:
Targetable gain of function (e.g., EGFR)



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Focused on 71% untapped target space, conventionally untargetable

- **Gain of function (e.g., CCNE1, 17%)**
- **Loss of function (no known driver; e.g., BRCA1, 54%)**

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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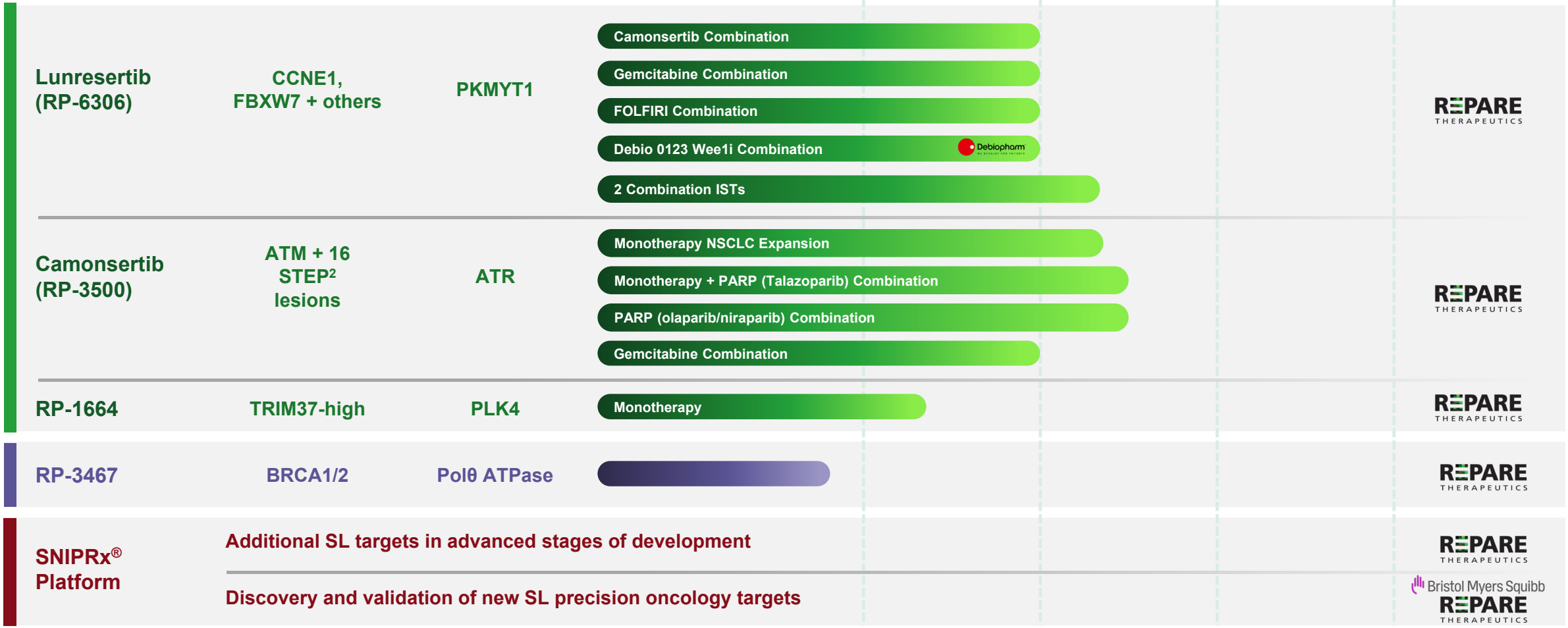
Expanding pipeline of precision oncology therapeutics



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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

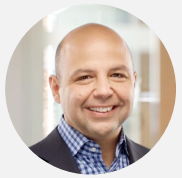
Kim A. Seth, PhD
Chief Business Officer

Pfizer · Goldman Sachs

Daniel Bélanger
Head of Human Resources

ADARE PHARMA SOLUTIONS · APTALIS

Scientific Founders

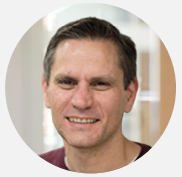


Daniel Durocher, PhD

- 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 addressable patient population of ~90k

- 50% RECIST response in camonsertib combination in gynecological tumors

Anti-tumor activity observed

- Across multiple tumor types and genotypes
- POC in patients established
- FDA agreed with RP2D; safe and well tolerated

Repare discovered synthetic lethality of PKMYT1 inhibition

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

Supported preclinical synergy hypothesis and patient selection approach from proprietary SNIPRx platform

POC, proof of concept; RP2D, recommended Phase 2 dose.

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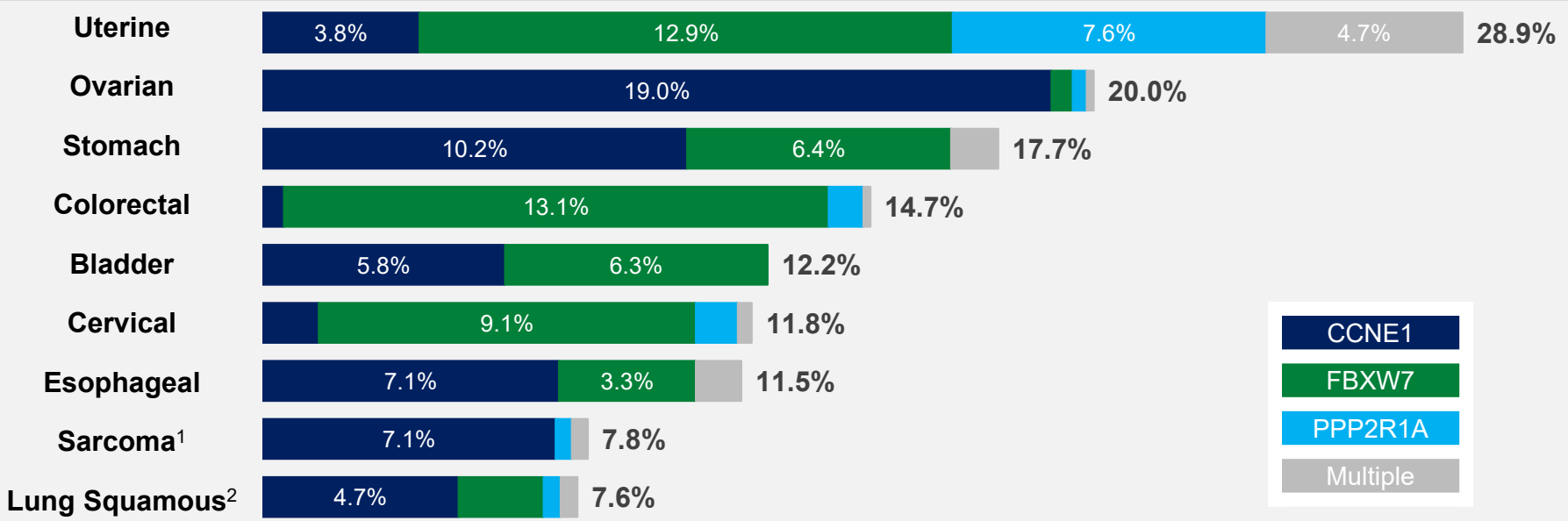
Large, genomically defined potential patient population

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

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



** 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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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

Multiple Investigator Sponsored Trials (CCTG[1], Carbo/paclitaxel[2])

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] *Standard of care ("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 observed 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)

Dose/schedule optimization complete; RP2D of lunresertib 80mg twice daily and camonsertib 80mg once daily

MONOTHERAPY

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

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

OR, overall response; CBR, clinical benefit rate.

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Key updates since ENA 2023; registrational decision on track

Registrational decision on track in gyn expansions in Q4 2024

Continuing trends of patient response and benefit

Grade 3 anemia reduced from 45% to 25% at RP2D with **updated dosing**

- 2 weeks on / 1 week off for patients with low Hg, otherwise weekly

FDA agreed with RP2D

Efficacy assessment is ongoing, continues to be **promising and on track** to be shared by end of Q4 2024

Data is expected to include **~20-30 patients per histology (ovarian and endometrial) at RP2D**

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Lun + 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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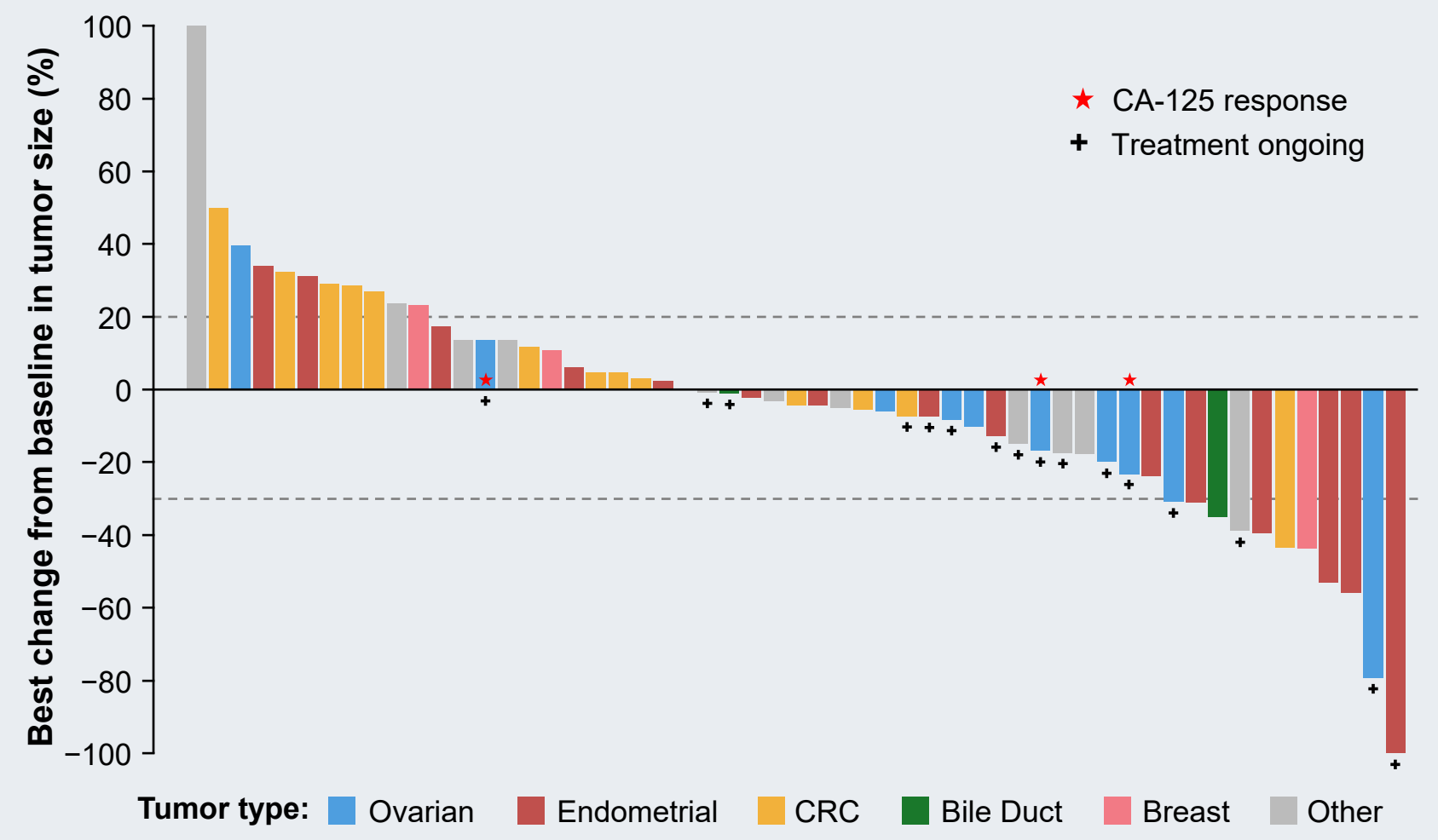
Frequent and deep tumor reductions observed with lun + cam



- **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; lun, lunresertib.*

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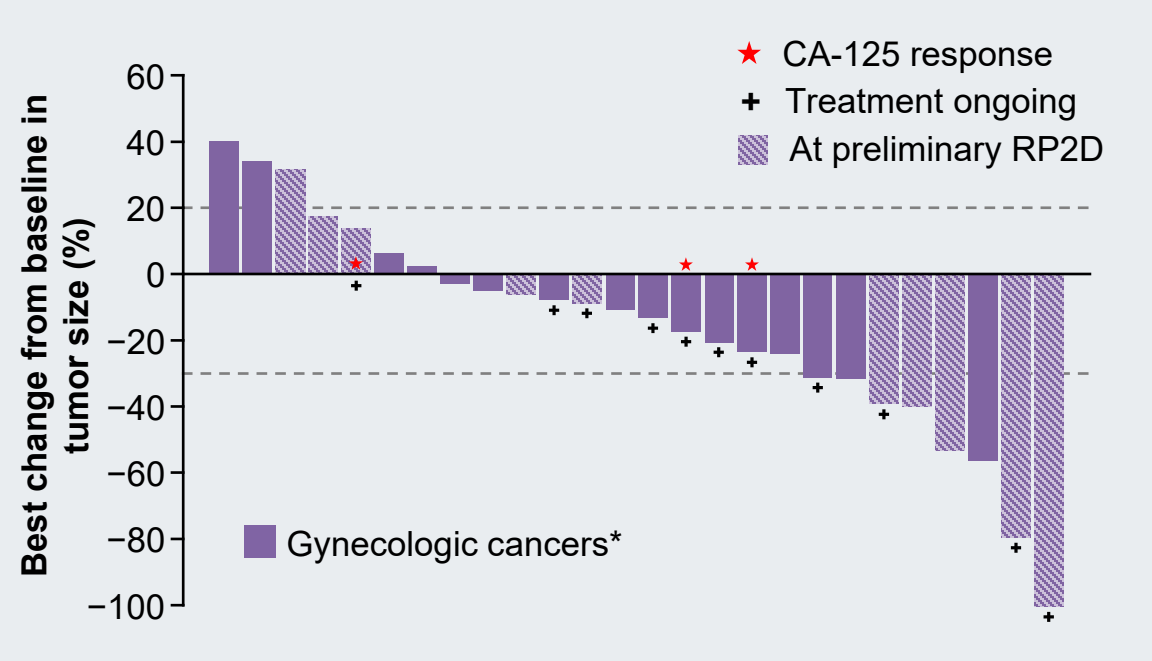
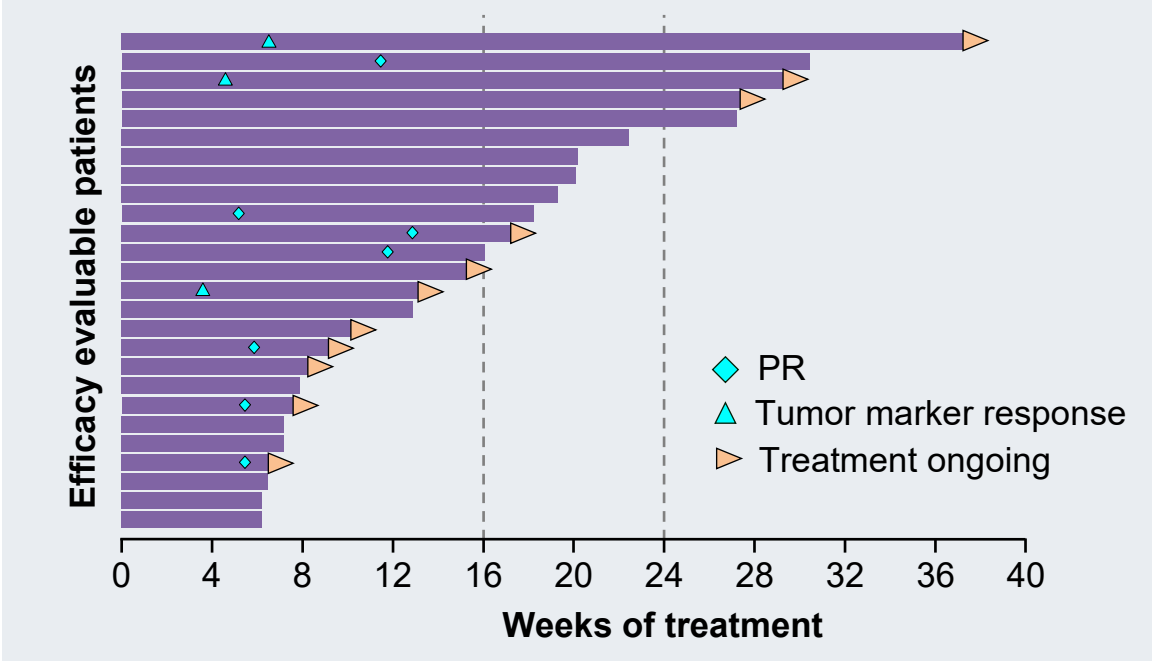
Combination treatment effective in gynecologic tumors

Meaningful tumor reductions, durable clinical benefit observed in heavily pre-treated patients to date





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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Significant improvement in anemia observed with updated dosing

RP2D: lunresertib 80mg BID + camonsertib 80mg QD 3d/4d

Selected hematologic TRAEs, n (%)	RP2D (ENA Cutoff)[a] N=20			RP2D (Cohort Post ENA) N=44		
	All Grades	Gr3	Gr4	All Grades	Gr3	Gr4
Anemia	13 (65.0)	9 (45.0)	0	29 (65.9)	11 (25.0)	0
Leukopenia	3 (15.0)	0	0	9 (20.5)	3 (6.8)	0
Neutropenia	3 (15.0)	2 (10.0)	0	7 (15.9)	5 (11.4)	0
Thrombocytopenia	0	0	0	0	0	0

Updated dosing strategy reduced Grade 3 anemia by ~half
Hematologic safety profile similar to commercial SL agents
No thrombocytopenia observed

[a] *ENA data cutoff of September 2023. TRAEs, treatment-related adverse events.*

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Continued favorable safety profile observed to date

TRAEs in ≥10% of patients, n (%)	Lun+Cam RP2D N=65[a] All Grades	Gr3	Gr4
Nausea/Vomiting	34 (52.3)	0	0
Rash[a]	26 (40.0)	1 (1.5)	0
Fatigue	18 (27.7)	1 (1.5)	0
Stomatitis	18 (27.7)	4 (6.2)	0
Decreased appetite	13 (20.0)	0	0
Diarrhea	10 (15.4)	0	0
Headache	7 (10.8)	0	0
Constipation	5 (7.7)	0	0

- **Patient demographics remain comparable:**
  - Entry Hg
  - Gender and age
  - Prior lines and therapies
  - ECOG
  - Histologies and DOT
- **Differences in anemia rates likely a result of the updated dosing strategy**

FDA agreement on RP2D
No FDA comments raised about safety profile observed in lun + cam combination

[a] *Data as of March 2024; all patients treated at exposures consistent with RP2D at any time of the trial. DOT, duration of treatment.*

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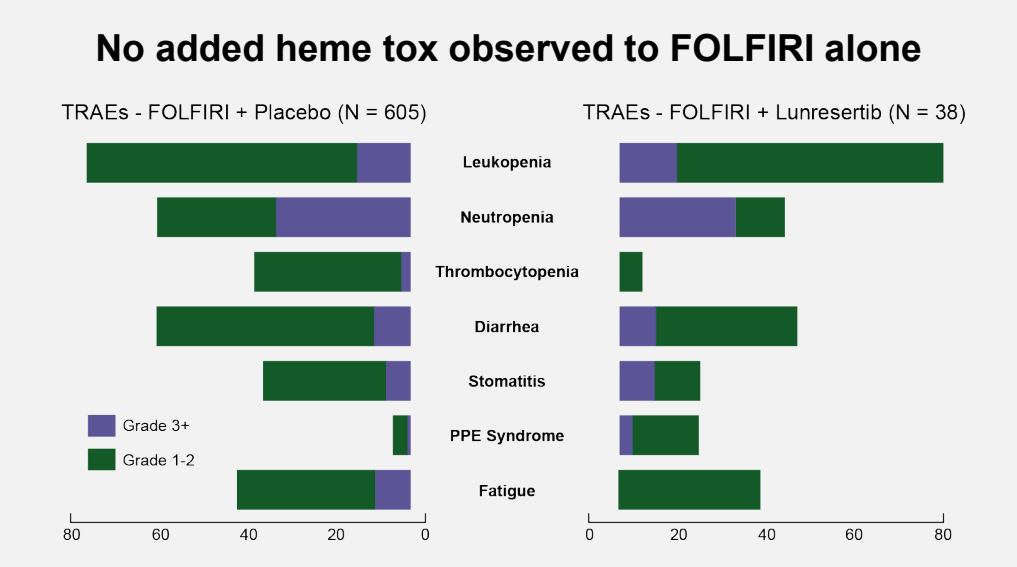
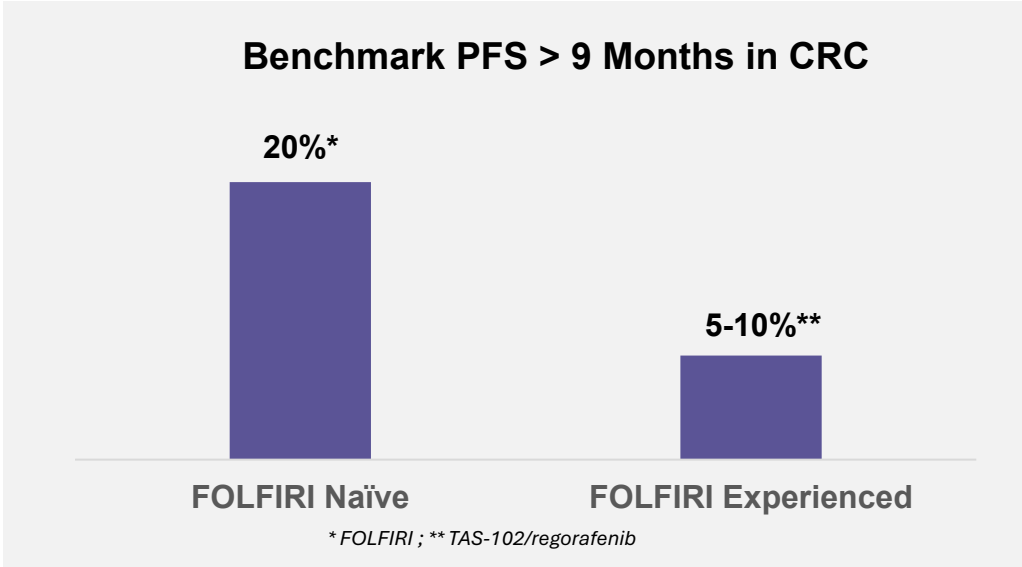
Lun + FOLFIRI combination promising

MINOTAUR demonstrating overall favorable tolerability and early signal in CRC and other GI tumors

- Favorable tolerability: lunresertib given continuously daily (QD), demonstrating promising tolerability profile vs. other FOLFIRI combinations
- No new toxicities observed; no treatment withdrawals at RP2D
- Focus on potential for duration of treatment advantage in both FOLFIRI-naïve and experienced patients





Full data to be shared at ESMO GI in June 2024

Source: Clarivate-Decision Resources Group,

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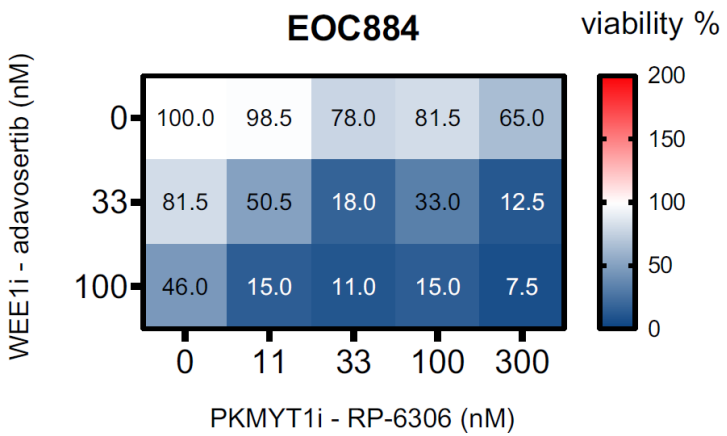
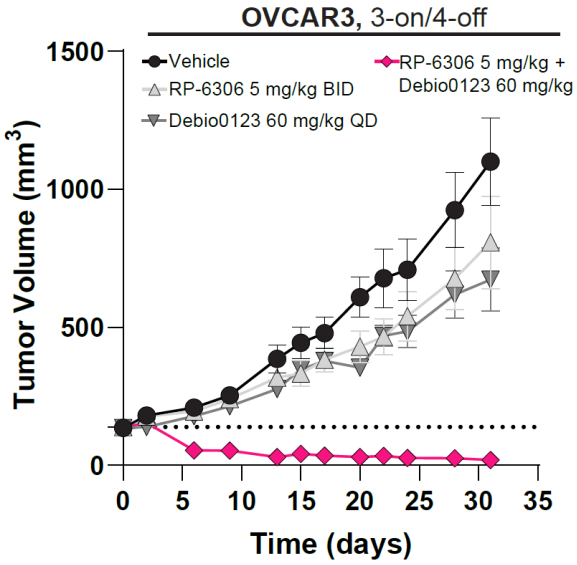
First clinical trial inhibiting both PKMYT1 and WEE1

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



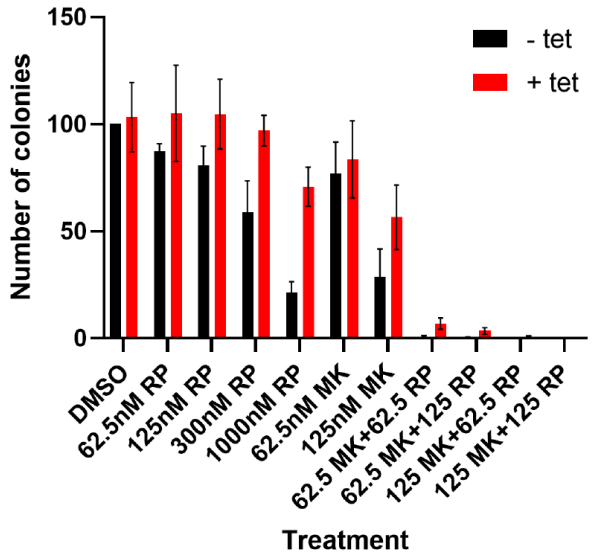
Combination synergistically eradicates ovarian cancer cells and organoid models at a low doses…

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.

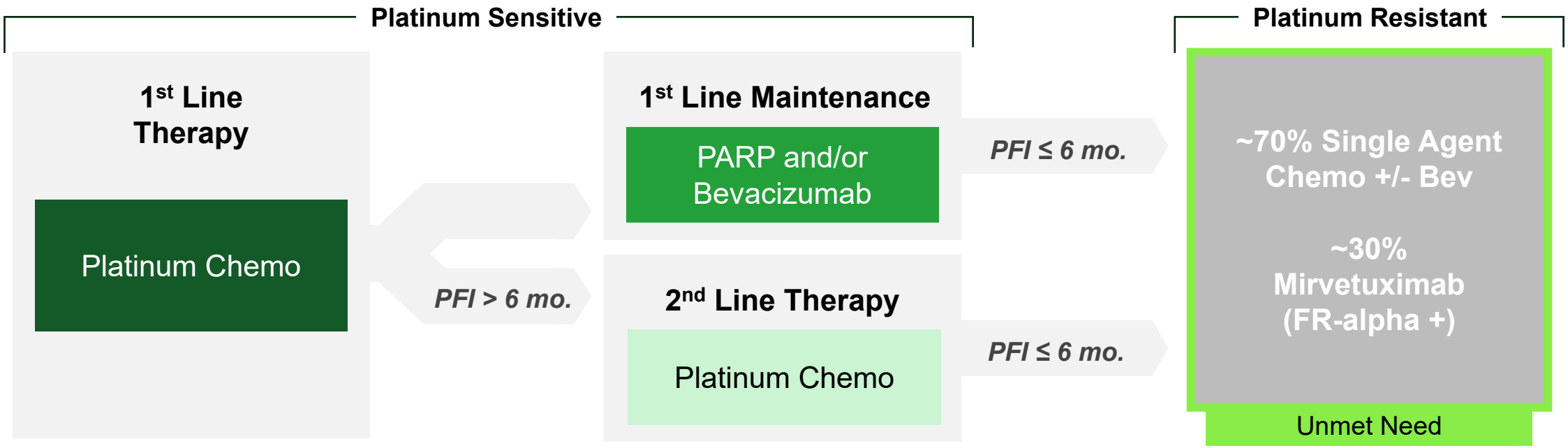


… and overcomes resistance to MK-1775 (adavosertib) mediated by tet-induced Myt1 upregulation

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

Platinum-resistant ovarian cancer (PROC) market opportunity

Unmet need remains significant for platinum resistant patients



Chemo + Bevacizumab[1]	Single Agent Chemo[1,2]	Mirvetuximab[2]
28% ORR	13 - 16% ORR	42% ORR
6.8 mo. PFS	3.4 - 4.0 mo. PFS	5.6 mo. PFS
16.6 mo. OS	12.8 - 13.3 mo. OS	16.5 mo. OS

~2,900 2L+ Patients
with CCNE1[3]

1 Chemo+Bevacizumab vs Chemo (AURELIA); Source: Bevacizumab FDA Label
2 Mirvetuximab vs Chemo (MIRASOL); Source: Mirvetuximab FDA Label, ASCO 2023. Mirvetuximab is approved for ~1/3 of PROC patients who are folate receptor positive.
3 Eligible Patients in US and EU4/UK Based On Company Estimates from TCGA and GENIE, 2L+ (2L - 5L)
PFI, progression-free interval.

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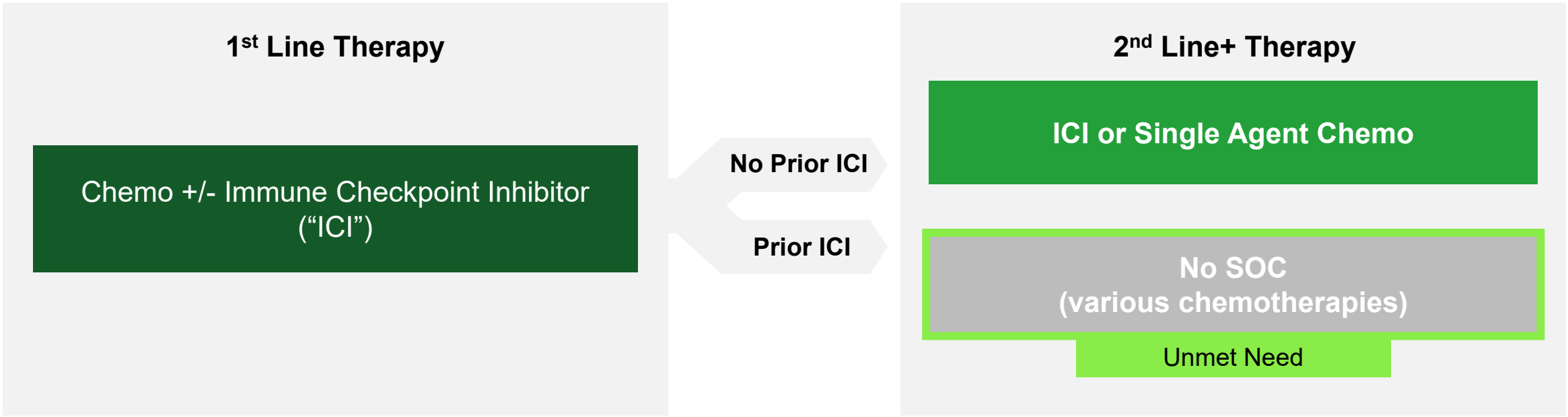
Endometrial cancer market opportunity

Evolving 1L SOC towards Chemo + ICI creating large unmet need in future 2L+ setting



Single Agent Chemo[1,2]

15 - 16% ORR

3.8 - 4.0 mo. PFS

12.0 - 12.3 mo. OS

~3,600 2L+ Patients

with CCNE1, FBXW7, or PPP2R1A[3]

1 Lenvatinib/Pembrolizumab vs Single Agent Chemo (KEYNOTE-775); Source: Lenvatinib FDA Label
2 Ixabepilone vs Paclitaxel or Doxorubicin; McMeekin S. Gynecologic Oncology 2015 https://doi.org/10.1016/j.ygyno.2015.04.026
3 Eligible Patients in US and EU4/UK Based On Company Estimates from TCGA and GENIE, 2L+ (2L - 5L)

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Metastatic CRC is a large market opportunity for MINOTAUR

Unmet need in 2L+ oxaliplatin-treated mCRC patients

1st Line Therapy

Oxaliplatin-based Chemotherapy +/- VEGF

2nd Line+ Therapy

Irinotecan-based Chemotherapy +/- VEGF
KRAS Inhibitors (KRAS G12C)
Encorafenib + Cetuximab (BRAF V600)

Unmet Need

FOLFIRI+ VEGF[1,2,4]

13 - 20% ORR
5.7 - 9.2 mo. PFS
13.3 - 21.4 mo. OS

FOLFIRI[1,2,3]

11 - 15% ORR
4.5 - 5.6 mo. PFS
11.7 - 13.8 mo. OS

~11,300 2L+ Patients
with FBXW7[5] (~13% of CRC)

G7 Colorectal Cancer market:
>$8B today (>$10B by 2032)

1 FOLFIRI+Aflibercept vs FOLFIRI (VELOUR); Source: Aflibercept FDA Label
2 FOLFIRI+Ramucirumab vs FOLFIRI (RAISE); Source: Ramucirumab FDA Label, Lancet 2015
3 Napabucasin+FOLFIRI vs FOLFIRI+Bevacizumab (CanStem303C); Source: Shah M. Clinical Colorectal Cancer 2022
4 Panitumumab+FOLFIRI vs FOLFIRI+Bevacizumab (SPIRITT); Source: Hecht JR. Clinical Colorectal Cancer 2015
5 Eligible Patients in US and EU4/UK Based On Company Estimates from TCGA and GENIE, 2L+ (2L - 5L)

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Camonsertib (RP-3500)

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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 observed in ovarian cancer

Global development and commercialization rights **wholly-owned** by Repare

- Rapid monotherapy signal confirmation in **NSCLC**

NSCLC, non-small cell lung cancer.

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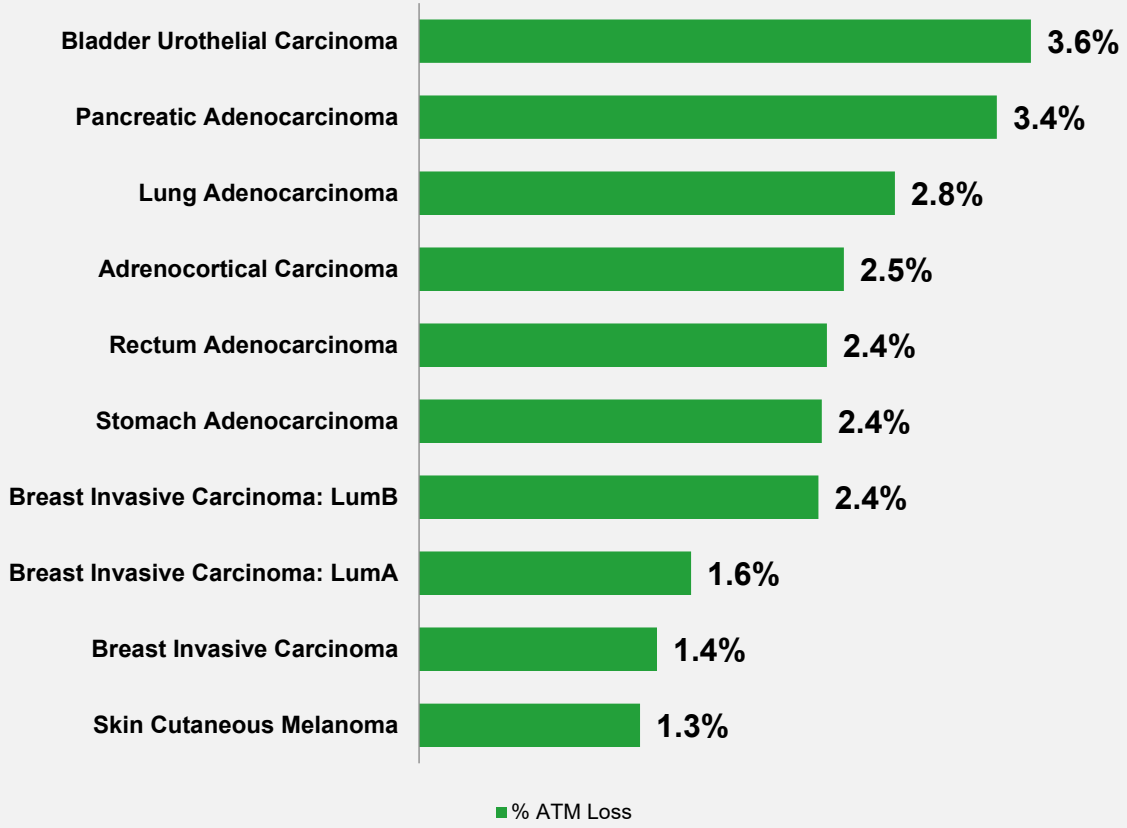
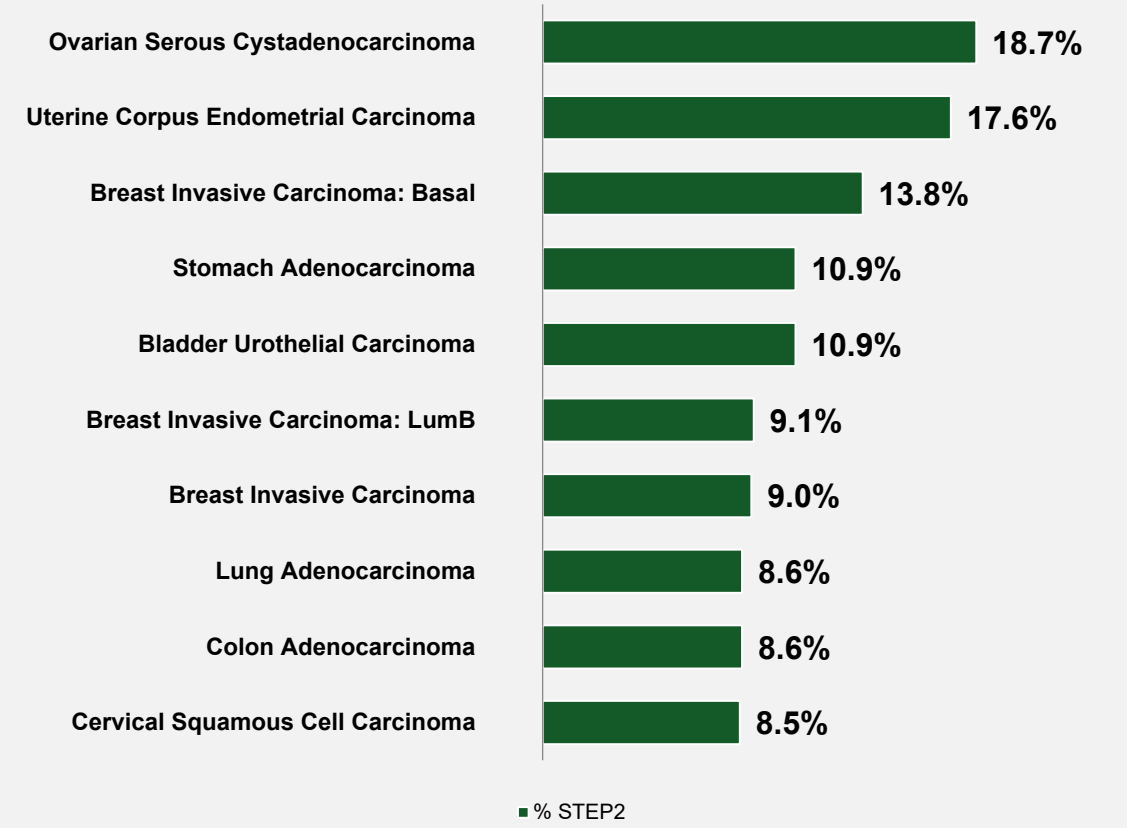
Potential across significant additional patient populations

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

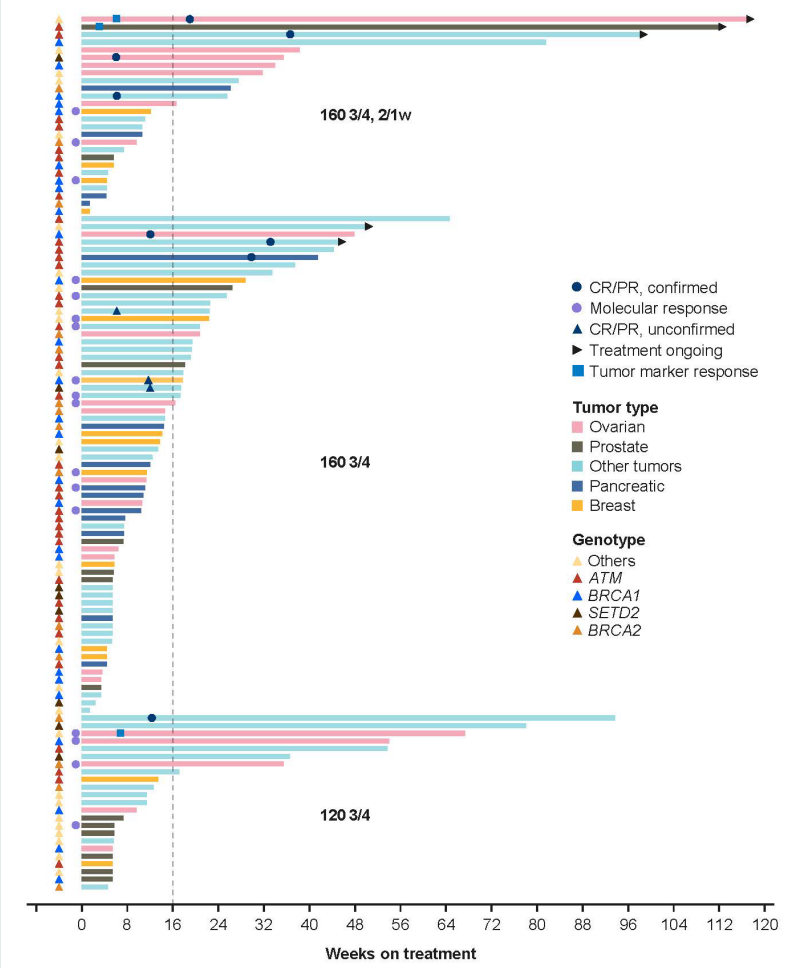


** TCGA; Not weighted for tumor prevalence*

REPARE THERAPEUTICS

Updated camonsertib monotherapy data in ATM*m* tumors

- **Updated data continues to support ATR-ATM synthetic lethality thesis across various tumor types and genotypes**
- **114 total efficacy evaluable patients treated at 3 efficacious dose levels**
- **36 patients enrolled with ATM alterations**
  - 4 with responses and treatment durations 41-112+ weeks
  - 9/36 (25%) total with Tx duration >6 months

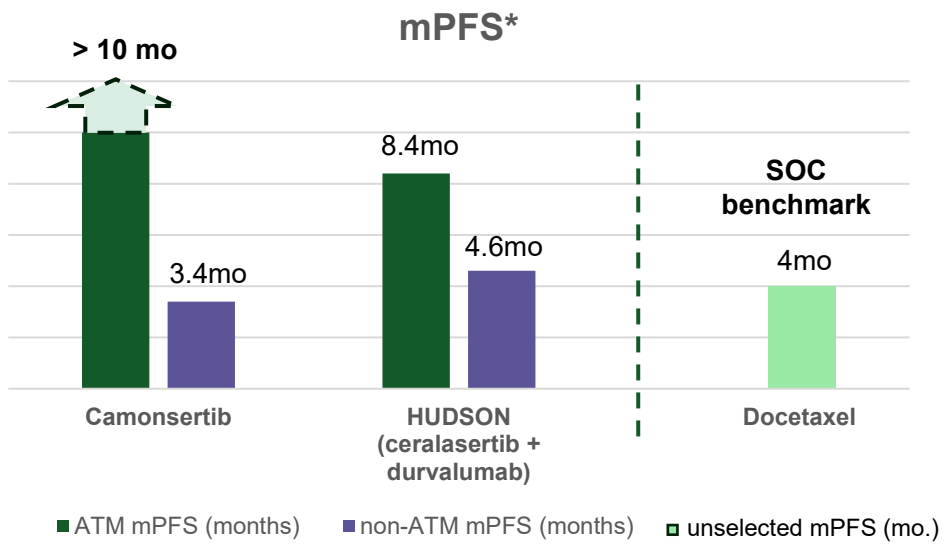


REPARE THERAPEUTICS

Camonsertib: rapid monotherapy signal confirmation in NSCLC

- **>12 months durability observed in >20% of patients with ATMm tumors treated with camonsertib monotherapy**
- **ATMm NSCLC (~4% of NSCLC) an attractive opportunity**
  - Camonsertib monotherapy signal potentially offers rapid and cost-efficient path to PoC with ~15-20 more patients within TRESR
  - 11 NSCLC patients (4 with ATMm) highlight improved mPFS in ATMm NSCLC vs non-ATMm
  - AstraZeneca HUDSON Ph2 data subset (ATR + PD-L1 post IO) further supports ATMm hypothesis in NSCLC
  - ATMm tumors do not have better outcomes in NSCLC
- **TRESR open to enrollment; data expected in 2025, with potential for expansion**
- **IO collaborations beyond monotherapy an obvious, substantial opportunity**

Promising Camonsertib mPFS in NSCLC



** mPFS of 4.6 months reported for both primary resistance and acquired resistance cohorts in the biomarker non-matched group, as reported in Besse, B. et al. Biomarker-directed targeted therapy plus durvalumab in advanced non-small-cell lung cancer: a phase 2 umbrella trial. Nature Medicine. 13 February 2024 (HUDSON trial).*

REPARE THERAPEUTICS

Camonsertib NSCLC market opportunity

Significant unmet need for non-biomarker driven NSCLC patients

Non-Biomarker Driven Patients
1st Line Therapy

Chemoimmunotherapy
Immunotherapy (PD-L1)

2nd Line+ Therapy

Single Agent Chemotherapy +/- VEGF
Immunotherapy (PD-L1)

Unmet Need

Biomarker Driven Patients
(EGFR, ALK, KRAS, ROS, etc.)
1+ Lines of Biomarker Driven Therapies

Ramucirumab + Chemo[2]
23% ORR
4.5 mo. PFS
10.5 mo. OS

Single Agent Chemo[1,2]
13 - 14% ORR
3.0 - 4.0 mo. PFS
9.1 - 9.6 mo. OS

~5,300 2L+ Patients
with ATM[3]

1 Atezolizumab vs Chemo (OAK); Source: Atezolizumab FDA Label
2 Ramucirumab+Chemo vs Chemo (REVEL); Source: Ramucirumab FDA Label
3 Eligible Patients in US and EU4/UK Based On Company Estimates from TCGA and GENIE, 2L+ (2L - 5L)

REPARE THERAPEUTICS

RP-1664

REPARE THERAPEUTICS

RP-1664

First-in-class,
oral PLK4 inhibitor

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

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

Actively enrolling in **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 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*

REPARE THERAPEUTICS

Compelling synthetic lethal rationale for targeting PLK4

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

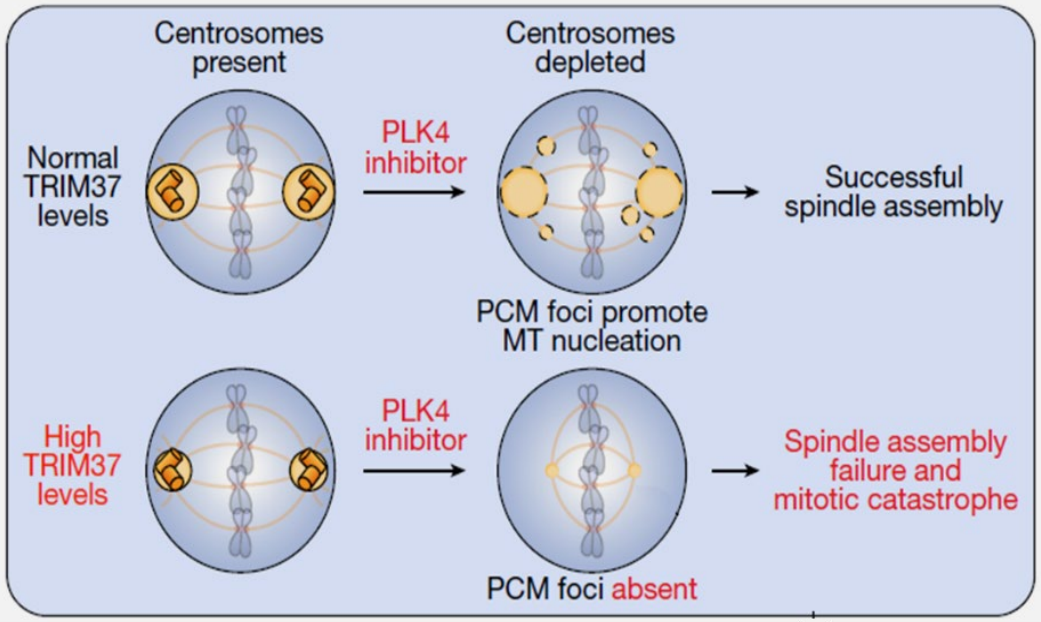
Centrosomes use centrioles and pericentriolar material (PCM) for mitotic spindle formation

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)

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

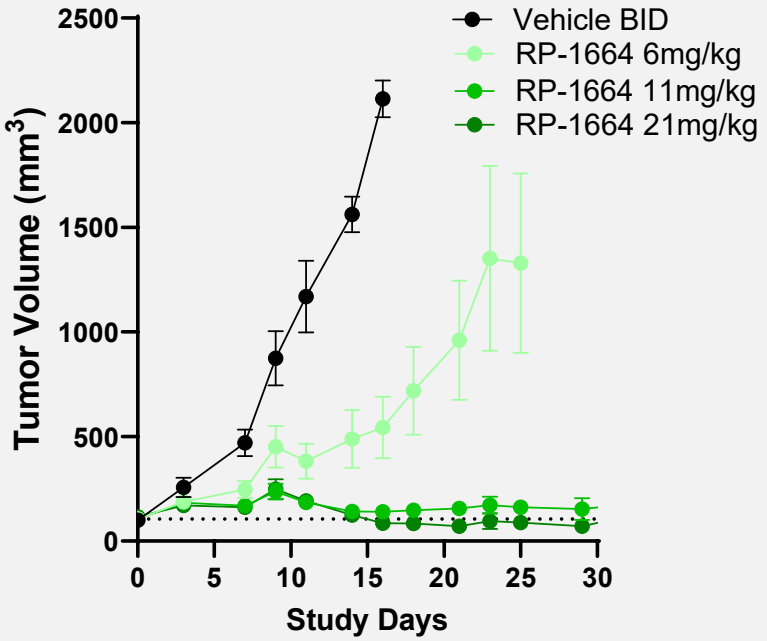
[1] CFI-400945 and EXEL-7871. *Source: internal data and Exelixis corporate presentation*

REPARE THERAPEUTICS

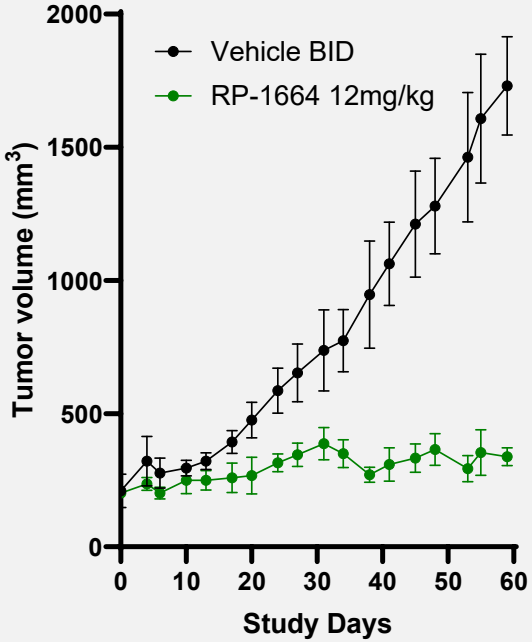
Robust monotherapy efficacy across solid tumor PDX/CDX models

Monotherapy drives tumor stasis to regression in TRIM37-high models

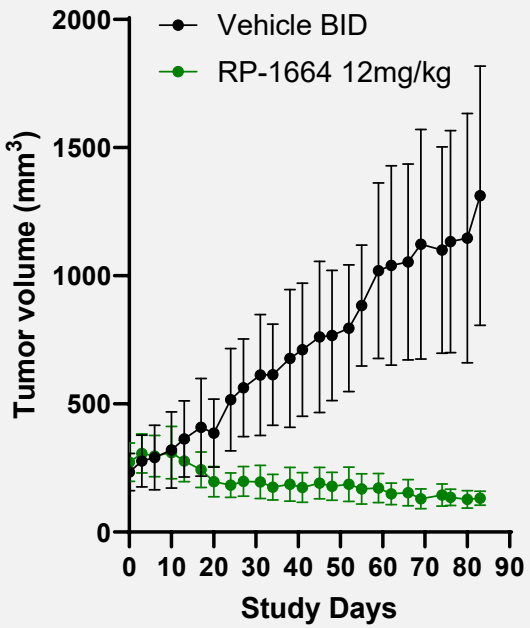
Breast (Triple Negative) CDX



Breast (ER positive) PDX



NSCLC PDX

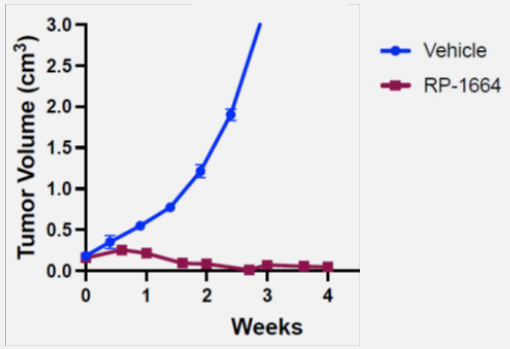


REPARE THERAPEUTICS

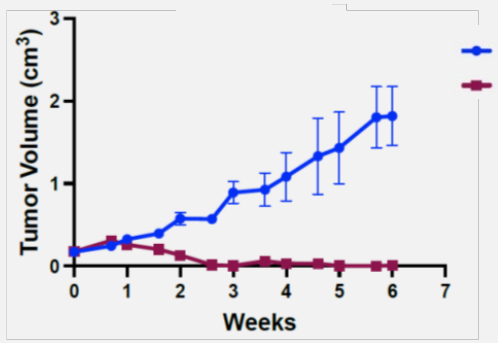
Highly efficacious as monotherapy in neuroblastoma models

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

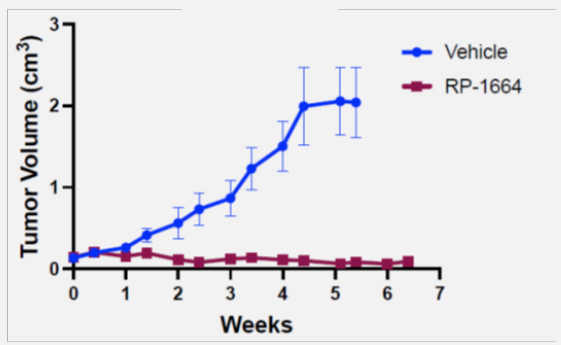
COG-N-424X



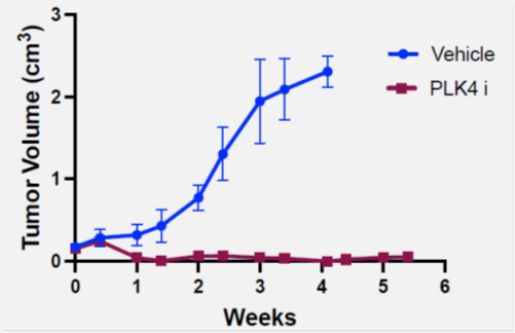
COG-N-421



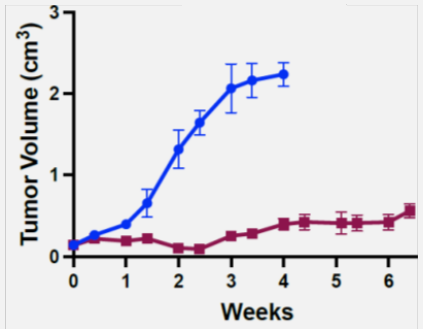
NBSD



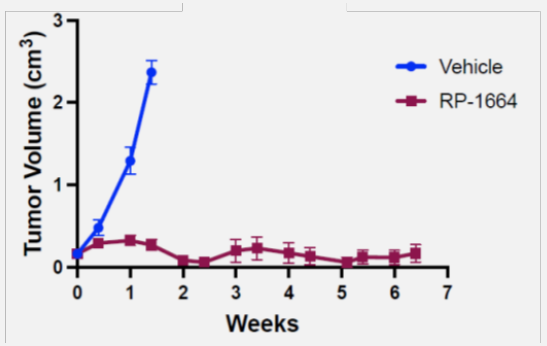
Felix



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 started: 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 potential for **combination efficacy** without added toxicity

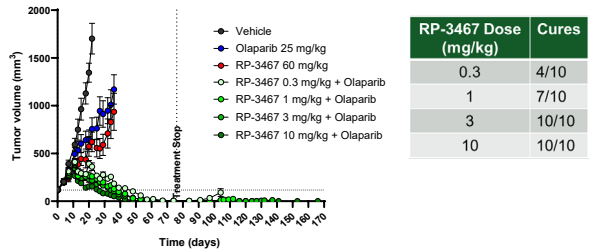
RP-3467 capable of **complete regressions** and synergies in **PARPi resistance** preclinical models

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

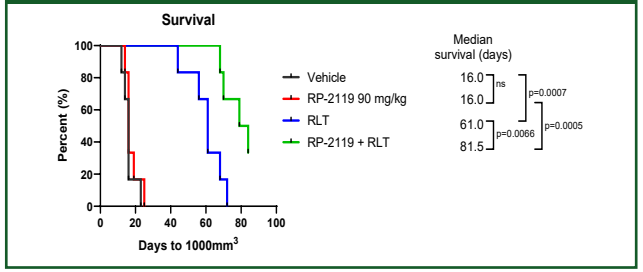
REPARE THERAPEUTICS

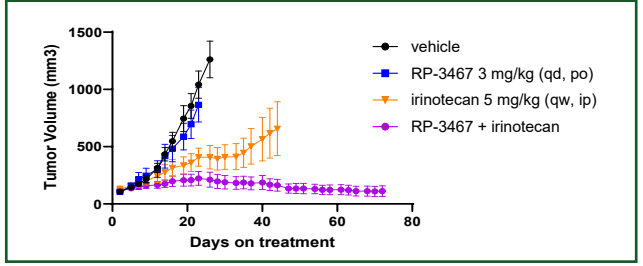
RP-3467 clinical plan: multiple potential Phase 1/2 trials

Phase 1 Trial	Phase 1/2 Trials	Preclinical Results	Global Market Segment
Initiation expected in H2 2024 **Goal: PK, safety and RP2D**	**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 unselected 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**



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



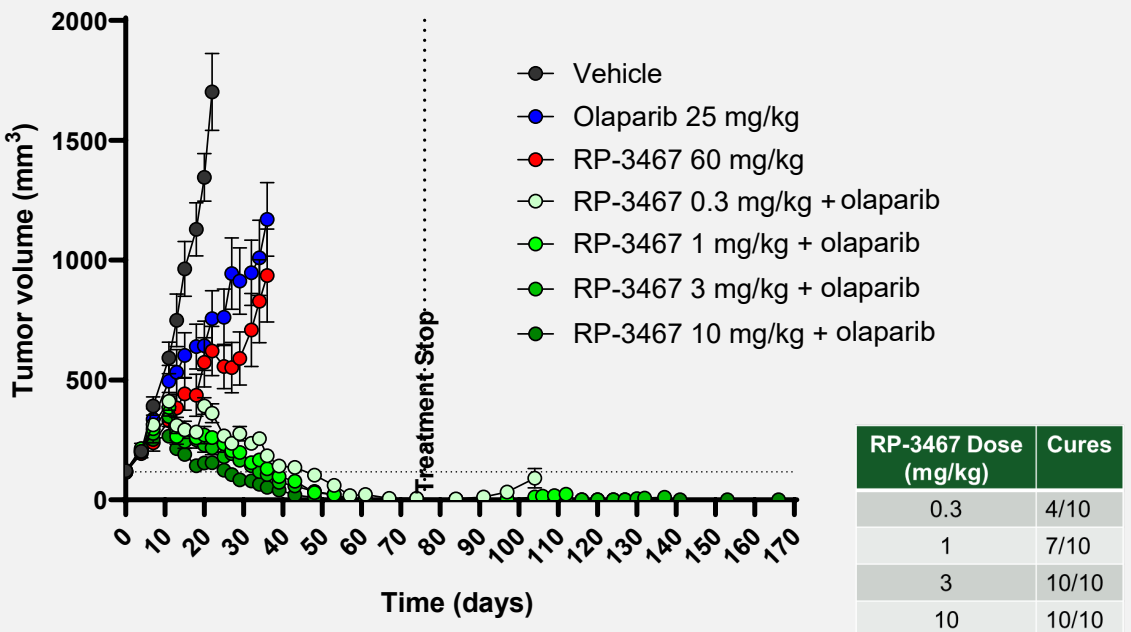


REPARE THERAPEUTICS

Profound, durable synergy observed with PARP inhibition

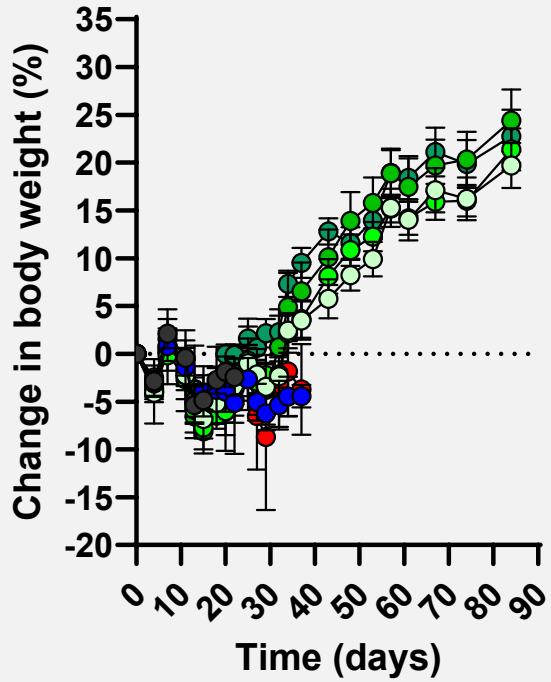
Deep/durable complete regressions observed across a wide dose range and well tolerated

HCT116 BRCA2 -/-



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

Body Weight



REPARE THERAPEUTICS

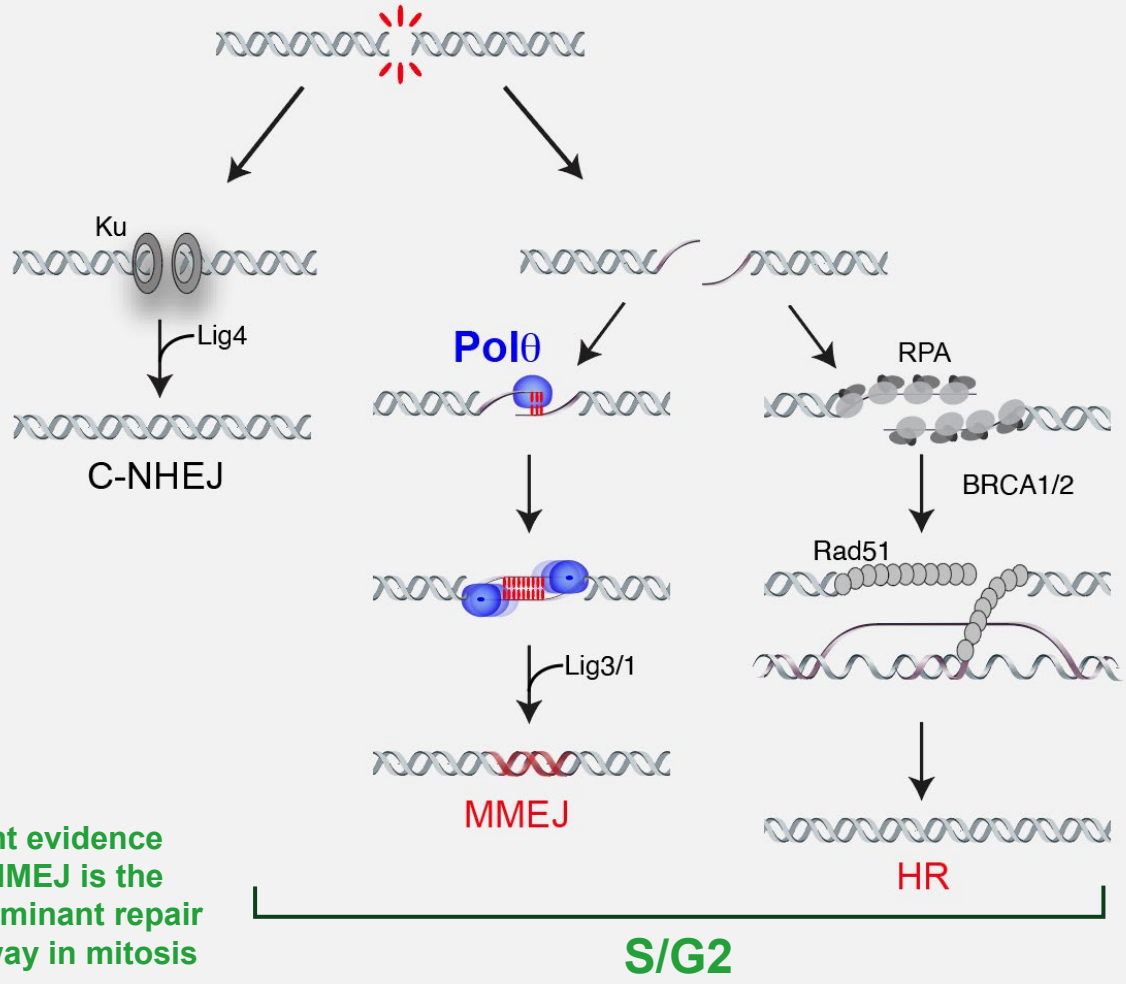
Polθ: uniquely promising therapeutic target

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

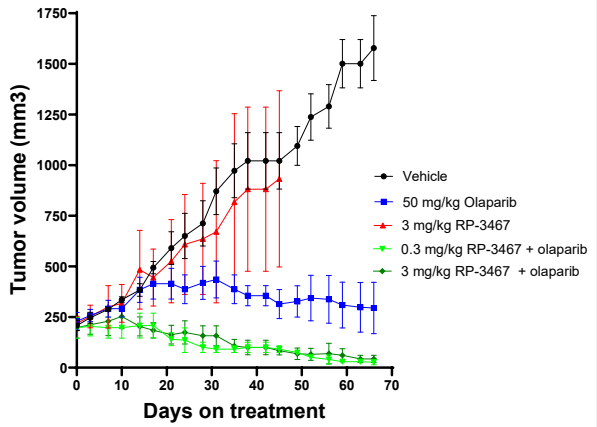
REPARE THERAPEUTICS

Target profile: potent, tolerable, capable of complete regressions

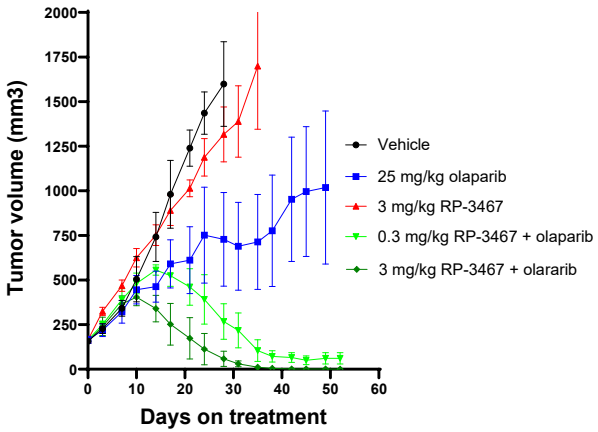
	Parameter	RP-3467
Potency	Polθ ATPase Enzyme IC_{50}	<0.25 nM
	CETSA cellular target engagement IC_{50}	5 nM
	Cell proliferation DLD1 / HCT116 (BRCA2mt) EC_{50}	4 / 7 nM
Selectiv.	Off-target ATPase (HELQ, WRN, BLM) IC_{50}	> 10 µM
	Off-target Polθ polymerase domain IC_{50}	> 100 µM
ADME	Human Hepatocyte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

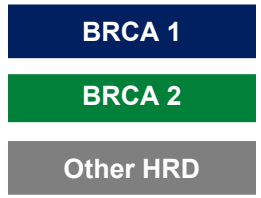
REPARE THERAPEUTICS

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)*

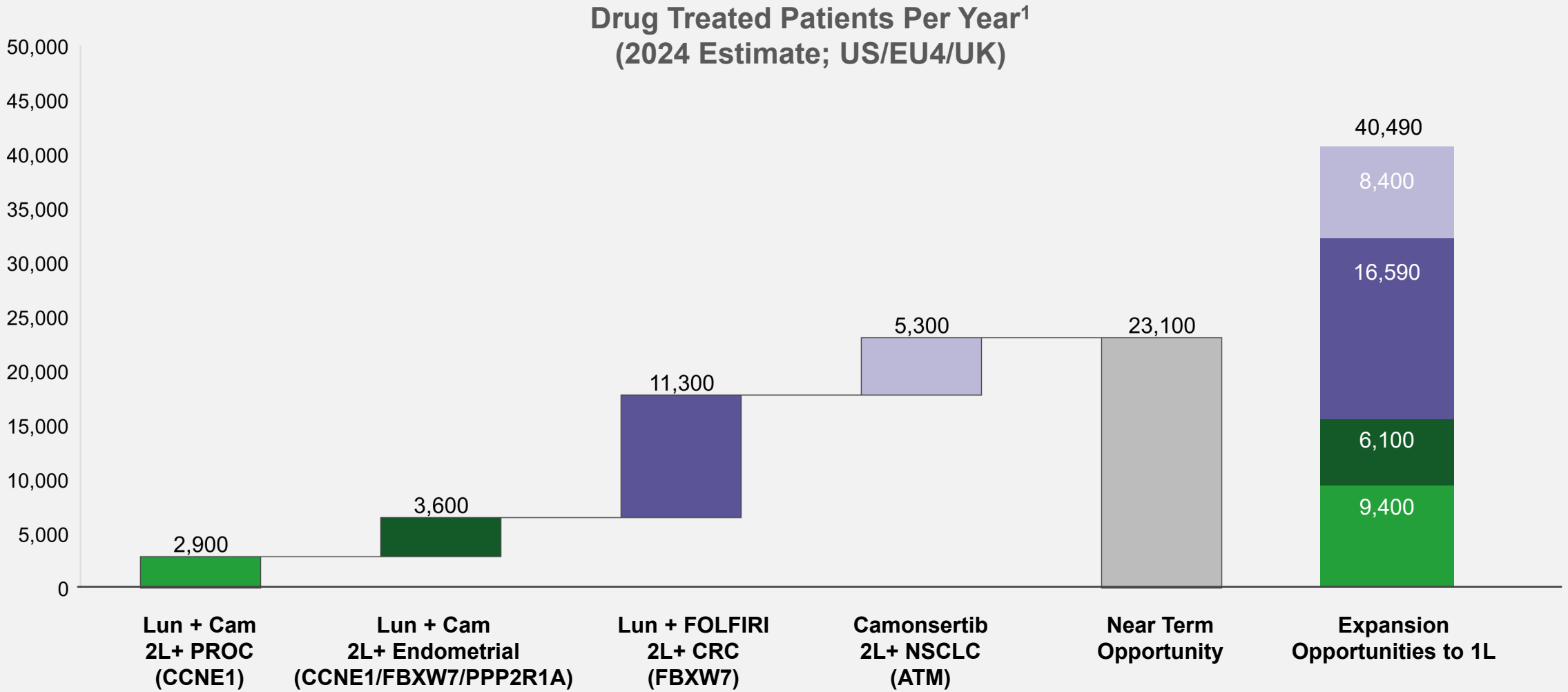
Tumor type	Prevalence of gene of interest	PARP-naïve opportunity (1L)	PARP-resistant opportunity (2L)
Ovarian	10.7% / 5.6% / 6.4% — 22.7%	7,700	3,500
Castrate-Resistant Prostate	5.9% — 8.2%	5,100	2,400
HER2- Breast**	3.7%	2,900	1,600
Pancreatic**	2.6%	1,700	500



** 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

Multiple potential market opportunities for near term milestones



1 Eligible Patients Based On Company Estimates from TCGA and GENIE; Source: Drug Treated patients from CernerEnviza/CancerMpact

REPARE THERAPEUTICS

Recent and expected milestones

1H 2024

✓ **RP-1664 (PLK4i)** clinical trial initiation

✓ **Lunresertib + Debio 0123** combination Ph1/1b clinical trial initiation

✓ Regained **camonsertib** rights

Initial **lunresertib + FOLFIRI** combination Ph1 data at ESMO GI in June

2H 2024

Camonsertib monotherapy expansion to NSCLC in TRESR

RP-3467 Ph1 clinical trial initiation

Lunresertib + camonsertib expansion cohort data in ovarian and endometrial in Q4

2025

Lunresertib + Debio 0123 combination data

Camonsertib monotherapy data in NSCLC

Initiate first **pivotal trial** for **lun+cam** in 2025

REPARE THERAPEUTICS

Developing Next-Generation Precision Oncology Medicines

Differentiated, proprietary 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

- Key readouts from ongoing trials
- New clinical entries (PLK4 and Polθ ATPase inhibitors)

Strong balance sheet

- Cash and investments of ~$237M[1] fund operations to mid-2026
- Multiple clinical catalysts in that timeframe

[1] *As of March 31, 2024.*

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Insight that enriches. Precision that empowers.

Corporate Presentation

May 2024