REPARE THERAPEUTICS

Insight that enriches. Precision that empowers.

Lunresertib MYTHIC Clinical Trial Update

October 13, 2023

Agenda

Welcome & Introduction
Lloyd M. Segal, President & CEO

Lunresertib Preliminary MYTHIC Monotherapy & Combination Therapy Clinical Trial Results
Timothy Yap, MBBS, PhD, FRCP, Principal Investigator, MYTHIC Trial

Conclusions & Lunresertib Development Plan
Maria Koehler, MD, PhD, Chief Medical Officer

Upcoming Catalysts
Lloyd M. Segal, President & CEO

Q&A
Repare Therapeutics Leadership & Dr. Yap

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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 initiation, timing, progress and results of our current and future preclinical studies and clinical trials, including specifically our clinical trials of lunresertib (RP-6306) and camonsertib; the expected timing of program updates and data disclosures; the timing of filing INDs and other regulatory documents; the timing and likelihood of seeking regulatory approval for our product candidates; the competitive landscape for our product candidates; our ability to identify and develop additional product candidates using our SNIPRx platform; and our estimates regarding expenses, future revenue, capital requirements, cash runway and needs for additional financing.

These forward-looking statements reflect our current beliefs and expectations. Many factors may cause differences between current expectations and actual results, including the duration and impact of the COVID-19 pandemic on our business and market volatility, unexpected safety or efficacy data observed during preclinical or clinical studies, clinical site activation rates or clinical trial enrollment rates that are lower than expected, changes in expected or existing competition, changes in the regulatory environment, and unexpected litigation or other disputes. These and other risks are described more fully in our filings with the Securities and Exchange Commission (“SEC”), including the “Risk Factors” section of our Quarterly Report on Form 10-Q filed with the SEC on August 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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Developing Next-Generation Precision Oncology Therapeutics

Differentiated and expanding clinical-stage pipeline

- **Lunresertib: First-in-class oral PKMYT1 inhibitor (Phase 1/2)**
- Camonsertib: ATR inhibitor (Partnered with Roche)
- Additional near-term clinical programs
- Potential across multiple tumor types

Proprietary CRISPR-enabled SNIPRx platform

- Focused on genomic instability and DNA damage repair within cancer cells

Multiple clinical catalysts expected in 2023 and 2024

Cash runway into 2026

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Lunresertib:

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

- **Combination therapy achieved strong anti-tumor activity** across multiple tumor types and tested genotypes; 33% overall response at preliminary RP2D (N=18)
- **50% RECIST response observed** in camonsertib combination in largest cohort (gynecological tumors) at preliminary RP2D (N=10)
- **Proof of concept established** for monotherapy and camonsertib combination in MYTHIC Phase 1 trial
- **Large, genomically defined potential patient population** ~90K addressable population **including CCNE1, FBXW7 and PPP2R1A**
- **Validated preclinical synergy hypothesis and patient selection approach** from proprietary SNIPRx platform
- **Encouraging safety and tolerability profile observed** for oral monotherapy and combination therapy

RP2D, recommended phase 2 dose

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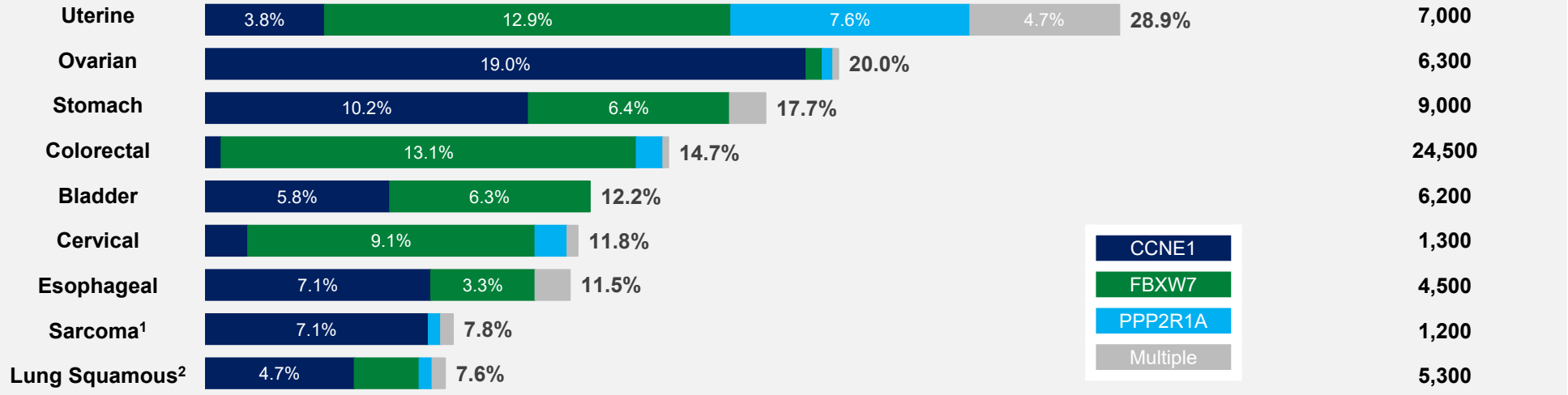
Addressing unmet need in critical patient populations

~90K patients
across tumor types;
~65K among top tumors

CCNE1 amplification or
inactivating mutations
in **FBXW7** and **PPP2R1A**

Genetic alterations **largely mutually exclusive**

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



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

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Lunresertib Preliminary Monotherapy & Combination Therapy Clinical Trial Results

Timothy Yap, MBBS, PhD, FRCP, Principal Investigator, MYTHIC Trial

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Study principal investigator: Timothy Yap, MBBS, PhD, FRCP

Medical Oncologist and Physician-Scientist at the University of Texas, MD Anderson Cancer Center

- Professor, Department for Investigational Cancer Therapeutics (Phase 1 Program)
- Vice President, Head of Clinical Development in the Therapeutics Division
- Primary research focuses on the first-in-human and combinatorial development of molecularly targeted agents and immunotherapies, and their acceleration through clinical studies using novel predictive and pharmacodynamic biomarkers
- Main interests include the targeting of the DNA damage response with novel therapeutics, such as ATR and PARP inhibitors, as well as the development of novel immuno-therapeutics
- BSc degree in Immunology and Infectious Diseases and MD from Imperial College London, UK

Speaker disclosures: Timothy Yap, MBBS, PhD, FRCP

I have the following relevant financial relationships to disclose:

- **Employee of:** University of Texas MD Anderson Cancer Center, where I am Vice President, Head of Clinical Development in the Therapeutics Discovery Division, which has a commercial interest in DDR and other inhibitors (IACS30380/ART0380 was licensed to Artios)
- **Consultant for:** AbbVie, Acrivon, Adagene, Almac, Aduro, Amphista, Artios, Astex, AstraZeneca, Athena, Atrin, Avenzo, Avoro, Axiom, Baptist Health Systems, Bayer, Beigene, BioCity Pharma, Blueprint, Boxer, Bristol Myers Squibb, C4 Therapeutics, Calithera, Cancer Research UK, Carrick Therapeutics, Circle Pharma, Clovis, Cybrexa, Daiichi Sankyo, Dark Blue Therapeutics, Diffusion, Duke Street Bio, 858 Therapeutics, EcoR1 Capital, Ellipses Pharma, EMD Serono, Entos, F-Star, Genesis Therapeutics, Genmab, Glenmark, GLG, Globe Life Sciences, GSK, Guidepoint, Ideaya Biosciences, Idience, Ignyta, I-Mab, ImmuneSensor, Impact Therapeutics, Institut Gustave Roussy, Intellisphere, Jansen, Kyn, MEI pharma, Mereo, Merck, Merit, Monte Rosa Therapeutics, Natera, Nested Therapeutics, Nexys, Nimbus, Novocure, Odyssey, OHSU, OncoSec, Ono Pharma, Onxeo, PanAngium Therapeutics, Pegascy, PER, Pfizer, Piper-Sandler, Pliant Therapeutics, Prolynx, Radiopharma Theranostics, Repare, resTORbio, Roche, Ryvu Therapeutics, SAKK, Sanofi, Schrodinger, Servier, Synnovation, Synthis Therapeutics, Tango, TCG Crossover, TD2, Terremoto Biosciences, Tessellate Bio, Theragnostics, Terns Pharmaceuticals, Tolremo, Tome, Thryv Therapeutics, Trevarx Biomedical, Varian, Veeva, Versant, Vibliome, Voronoi Inc, Xinthera, Zai Labs and ZielBio
- **Grant/Research support from:** Acrivon, Artios, AstraZeneca, Bayer, Beigene, BioNTech, Blueprint, BMS, Boundless Bio, Clovis, Constellation, Cyteir, Eli Lilly, EMD Serono, Forbius, F-Star, GlaxoSmithKline, Genentech, Haihe, Ideaya ImmuneSensor, Insilico Medicine, Ionis, Ipsen, Jounce, Karyopharm, KSQ, Kyowa, Merck, Mirati, Novartis, Pfizer, Ribon Therapeutics, Regeneron, Repare, Rubius, Sanofi, Scholar Rock, Seattle Genetics, Tango, Tesaro, Vivace and Zenith
- **Stockholder in:** Seagen

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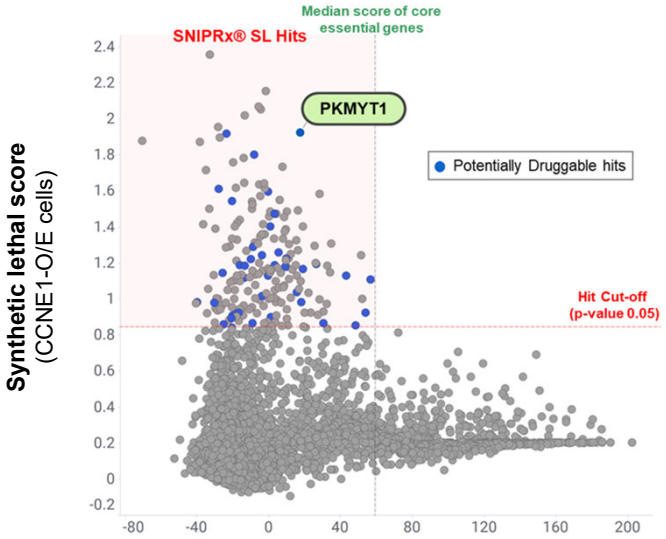
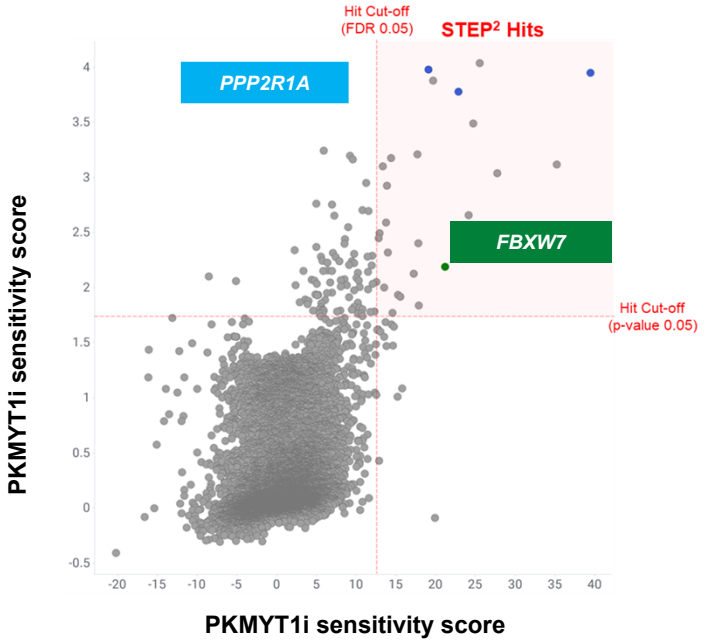
PKMYT1 was identified as a strong synthetic lethal partner to *CCNE1* amplification[1]

Cyclin E overexpression (O/E) drives premature S-phase entry, overloads the DNA replication machinery, resulting in genome instability

Genome-wide CRISPR-Cas9 screen



Chemogenomic screen identified novel sensitizers to PKMYT1i



FBXW7 Inactivating mutations in *FBXW7*, E3 ubiquitin ligase, increase cyclin E levels and replication stress.

PPP2R1A Hotspot inactivating mutations in PP2A phosphatase increase replication stress.

[1]Gallo et al. CCNE1 amplification is synthetic lethal with PKMYT1 kinase inhibition. Nature. 2022; 604 (7907): 749-756.
SNIPRx SL hits are LoF mutations that are essential for fitness in CCNE1-O/E cells but not their wild type counterparts. STEP² (SNIPRx Targeted Expansion of Patient Populations) hits are LOF mutations that are essential for fitness in lunresertib treated cells but not the vehicle treated controls. PKMYT1, protein kinase, membrane associated tyrosine/threonine 1; SNIPRx, SyNthetic Lethal Interactions for Precision Therapeutics platform; PP2A, protein phosphatase 2A.

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Lunresertib: Potent and selective first-in-class PKMYT1 inhibitor

	Parameter	Lunresertib
Potency	Enzyme potency (IC_{50}, nM)	3
	HCC1569 CDK1 T14 phosphorylation (IC_{50}, nM)	20
	HCC1569 cell viability (EC_{50}, nM)	19
	PKMYT1 selectivity over WEE1 (cell-based)	>100-fold
ADME Properties	CYP inh (3A4, 2D6, 2C9, 1A2, 2C19)	all >30 µM
	Hepatocytes: rat, dog, human Cl_{int} (µL/min/10^6cells)	28, <6, <6
	Human plasma protein binding	79%
	Rat PK (%F, $t_{1/2}$)	44%, 2.6h
	Dog PK (%F, $t_{1/2}$)	74%, 5.5h

Lunresertib profile:

- Highly potent and selective inhibitor
- PanLabs Lead Profiling screen on 68 assays showed no significant activity at 10 µM
- No activity (>100 µM) in patch clamp assays for hERG, hNaV1.5, and hCaV1.2 ion channels
- Favorable pre-clinical PK profile
- Low potential for clinical drug-drug interactions

ADME, absorption, distribution, metabolism, excretion; CDK, cyclin-dependent kinase; $_cCl_{int}$, intrinsic clearance CYP inh, cytochrome P inhibition; EC_{50}, half maximal effective concentration; F, bioavailability; h, hour; IC_{50}, half-maximal inhibitory concentration; min, minute; PK, pharmacokinetics; PKMYT1, protein kinase, membrane associated tyrosine/threonine 1; Thr, threonine.

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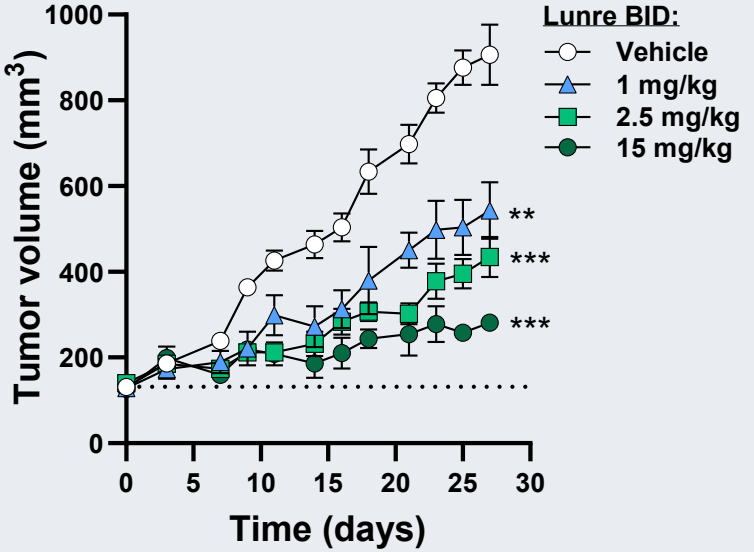
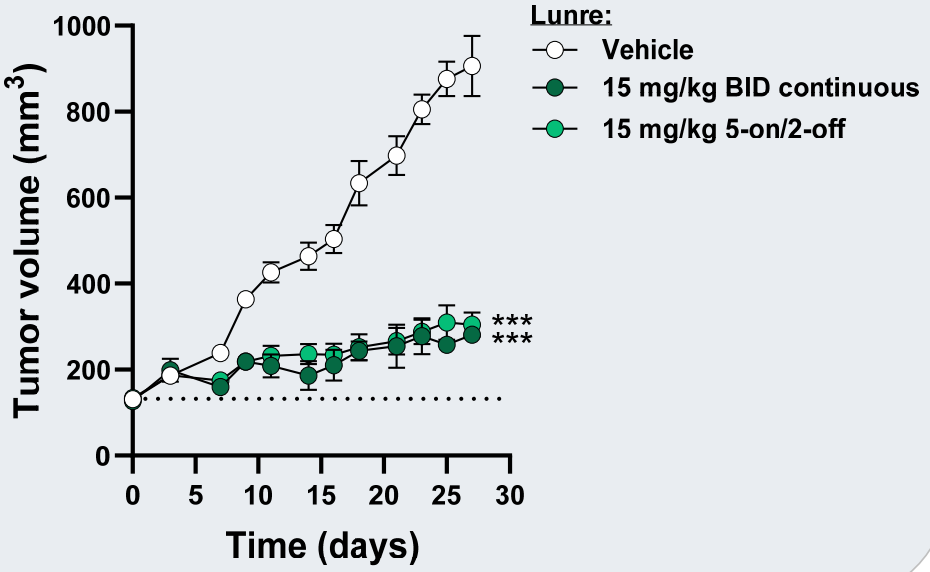
Lunresertib monotherapy inhibits xenograft growth across doses and schedules

HCC1569 CCNE1 amplified Breast Cancer CDX model





5-on/2-off, 5 days on / 2 days off; BID, twice daily; Lunre, lunresertib.

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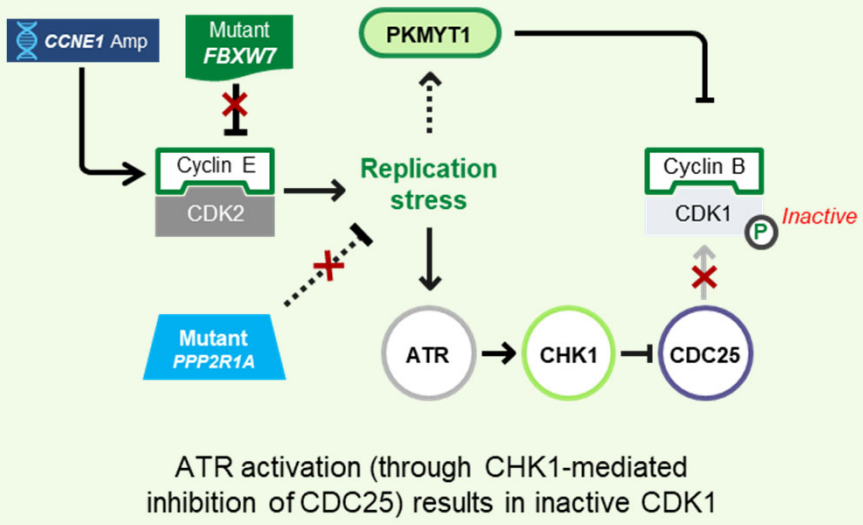
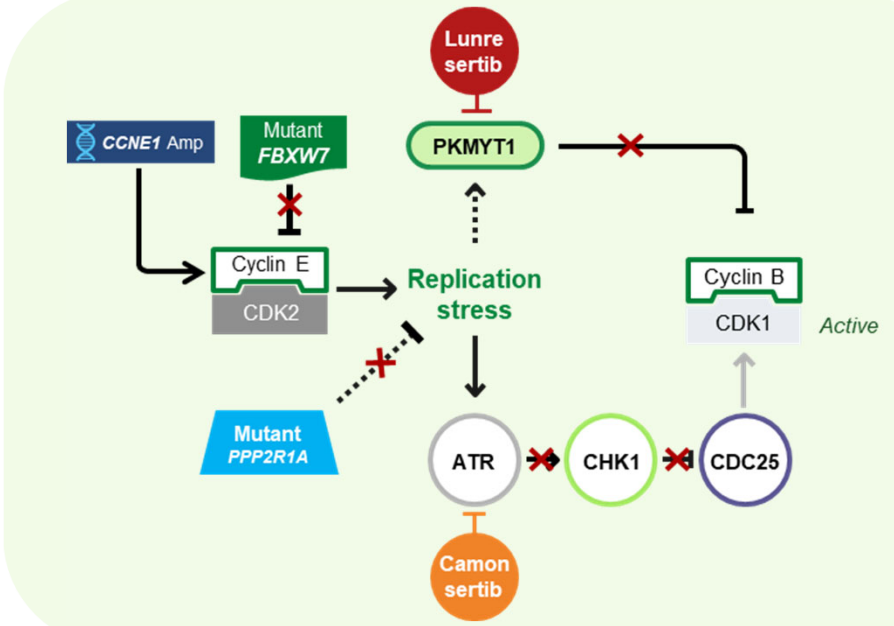
PKMYT1 and ATR inhibitors synergize to enhance anti-tumor activity[1]

Lunresertib-sensitizing alterations engage ATR through replication stress



Combination of ATR and PKMYT1 inhibition enhances CDK1 activation and premature mitosis



[1]ANE poster B057: Gallo et al. Preclinical development of PKMYT1 and ATR inhibitor combinations. ATR, ataxia telangiectasia and Rad-3 related; CDC25, cell division cycle-25; CDK, cyclin-dependent kinase; CHK1, checkpoint kinase 1; PKMYT1, protein kinase, membrane associated tyrosine/threonine 1.

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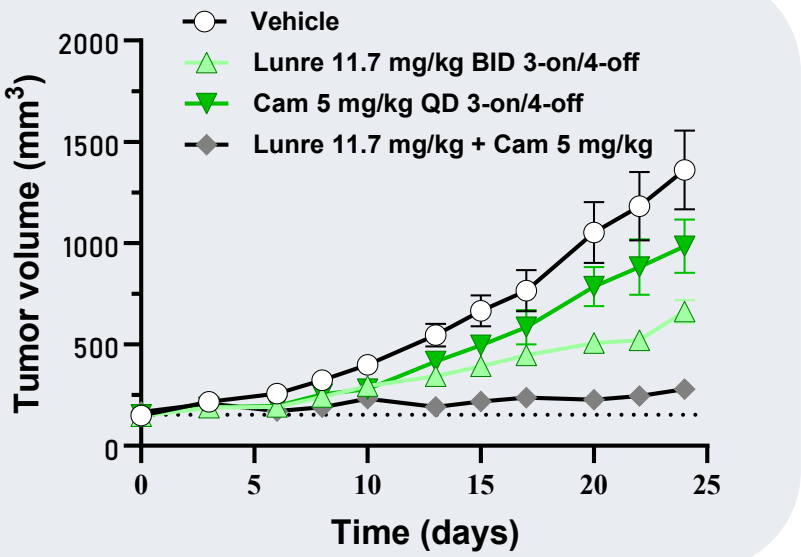
Lunresertib and camonsertib combination treatment is active in *CCNE1* amplified or *FBXW7* altered tumor models

Combination treatment drives tumor regressions at sub-efficacious single-agent doses

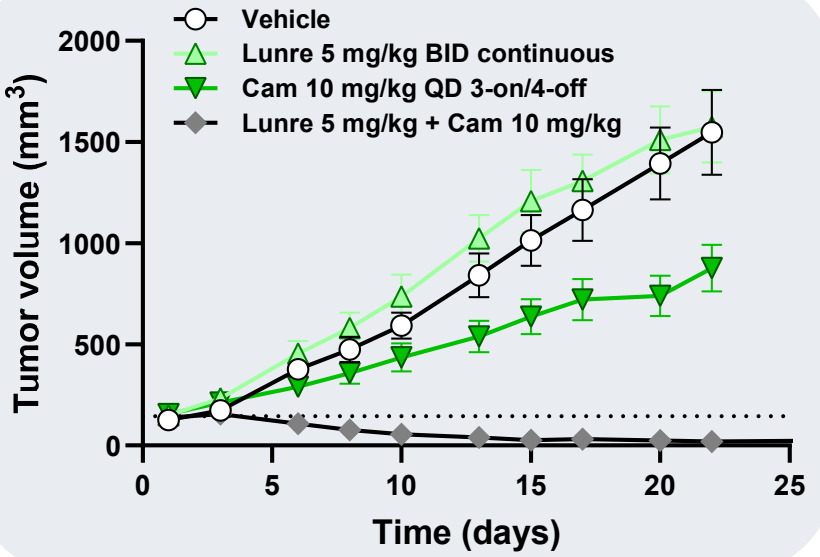
OVCAR3 Ovarian Cancer

CCNE1 amplified CDX model



DLD1 Colorectal Cancer

FBXW7 Knockout CDX model



Camonsertib alone has limited activity in *CCNE1* and *FBXW7* altered *PDX* models*

**Additional internal Repare data, not shown. Free drug exposure of 5-10 mg/kg dose in mouse (AUC or Cmin) are comparable to that at the respective human RP2Ds. 5-on/2-off, 5 days on / 2 days off; 3-on/4-off, 3 days on / 4 days off; AUC, area under the curve; BID, twice daily; Cam, camonsertib; Lunre, lunresertib; QD, once daily; RP2D, recommended phase 2 dose.*

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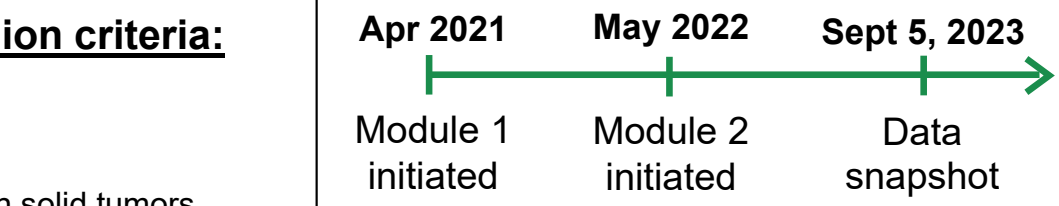
MYTHIC: PKMYT1 inHIbition for the treatment of Cancers (N=126)

Inclusion criteria:

- Patients ≥12 y with solid tumors resistant/intolerant to standard therapy
- Local NGS report (tissue or plasma)*
- Tumors with *CCNE1* amplification**, deleterious *FBXW7* or *PPP2R1A* alterations***
- ECOG PS of 0-2
- Hgb ≥ 9 g/dL
- Platelets ≥ 100 K/uL
- ANC ≥ 1.5 K/uL

Study is ongoing *NCT04855656*



Module 1:
Single agent lunresertib
67 patients

Module 2:
Lunresertib with camonsertib
59 patients

✓ **Primary endpoints:**

- Safety and tolerability
- RP2D, schedule

✓ **Other endpoints:**

- PK
- PD in paired tumor biopsies
- Preliminary antitumor activity
- Kinetics of ctDNA

** NGS report centrally reviewed and annotated by Precision Oncology Decision Support (PODS) Group at MDACC. ** CCNE1 amplification (Copy number ≥6). *** Up to 5 patients with endometrial cancer without these alterations were eligible in Module 1. ANC, absolute neutrophil count; ctDNA, circulating tumor DNA; ECOG PS, Eastern Cooperative Oncology Group Performance Status; Hgb, hemoglobin; NGS, next generation sequencing; PD, pharmacodynamics; PK, pharmacokinetics; RP2D, recommended phase 2 dose.*

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MYTHIC: Patient demographics

Similar patient characteristics in monotherapy and combination therapy cohorts

Parameter	(Lun alone) N=67	(Lun + Cam) N= 59
Sex, n (%)		
Male	17 (25.4)	15 (25.4)
Female	50 (74.6)	44 (74.6)
Age (years)		
Median (range)	60 (15, 81)	65 (16, 81)
≥65 years, n (%)	25 (37.3)	30 (50.8)
ECOG PS[a], n (%)		
0	21 (31.3)	23 (39.0)
1/2	44 (65.7) /1 (1.5)	35 (59.3) / 0
Prior lines of therapy, n (%)		
0	1 (1.5)	0
1-2	21 (31.3)	24 (40.7)
3-4	25 (37.3)	24 (40.7)
≥5	20 (29.9)	11 (18.6)
Prior platinum, n (%)	58 (86.6)	51 (86.4)

Parameter	(Lun alone) N=67	(Lun + Cam) N=59
Tumor types, n (%)		
Endometrial[b]	23 (34.3)	17 (28.8)
Colorectal	11 (16.4)	13 (22.0)
Ovarian	11 (16.4)	11 (18.6)
Breast	3 (4.5)	3 (5.1)
Lung	0	3 (5.1)
Other[c]	19 (28.4)	12 (20.3)
Most common genotypes[d], n (%)		
CCNE1	31 (46.3)	20 (33.9)
FBXW7	21 (31.3)	23 (39.0)
PPP2R1A	12 (17.9)	13 (22.0)
PPP2R1A and CCNE1	0	1 (1.7)
PPP2R1A and FBXW7	1 (1.5)	1 (1.7)
FBXW7 and CCNE1	0	1 (1.7)
Unselected endometrial[e]	2 (3)	0

[a]One each, pediatric patient in monotherapy and combination with Lansky Performance Status score 80 and 90, respectively. [b]Includes uterine serous carcinoma, carcinosarcoma, clear cell carcinoma, endometrioid [c]Other tumor types in monotherapy: esophageal (n=2), head and neck (n=3), leiomyosarcoma (n=2), osteosarcoma (n=3) and one each (bladder, brain, cervical, gallbladder, GI, gastroesophageal junction, kidney, melanoma, vulvar); combination therapy: gastroesophageal (n=2), bile duct (n=2), pancreatic (n=2), one each (cervical, liver, melanoma, osteosarcoma, upper GI, and vulvar). [d]4 patients in lun + cam cohort also had ATRi-sensitizing alterations: 2 biallelic and 2 of unknown allelic status. [e]Endometrial patients without CCNE1, FBXW7, or PPP2R1A mutation.

Cam, camonsertib; ECOG PS, Eastern Cooperative Oncology Group Performance Status; GI, gastrointestinal; Lun, lunresertib.

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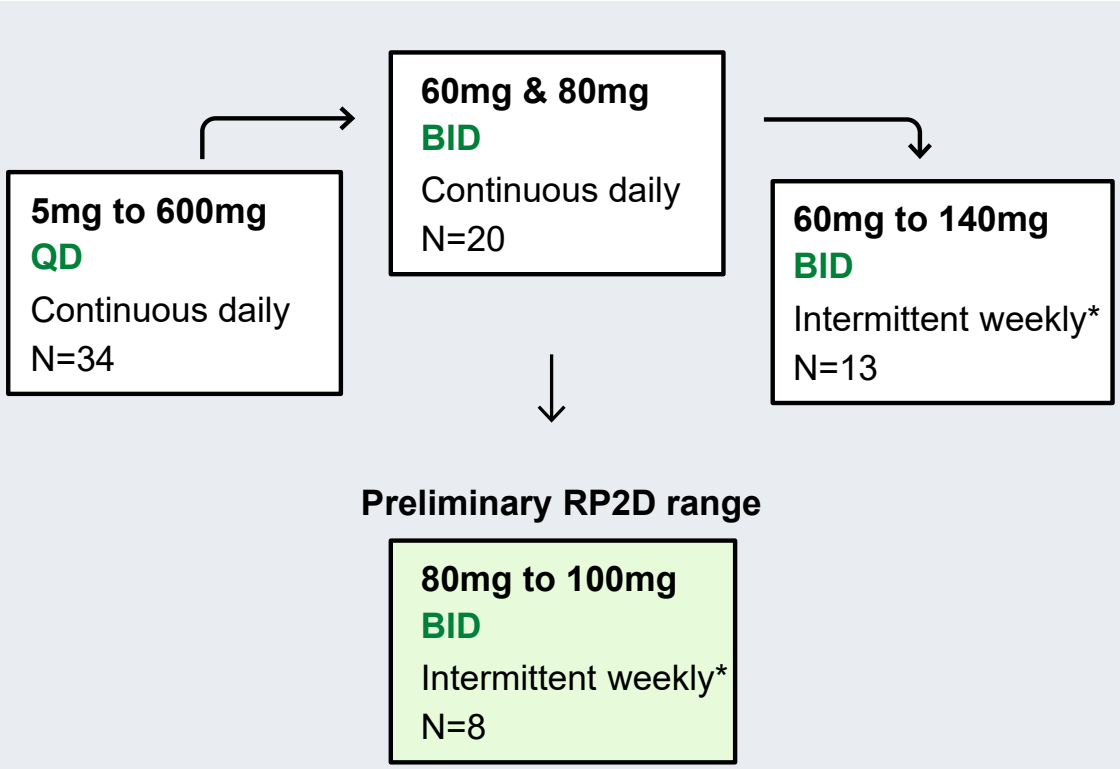
Multiple doses/schedules of lunresertib tested



- **Adaptive BOIN design, sufficient cohort sizes to establish MTD/RP2D**
- **QD dose tested first, once half-life known, BID dose was then tested**
- **Continuous and intermittent schedules showed similar activity in preclinical efficacy models**
- **DLT: reversible rash**
- **Intermittent weekly schedule minimized rash****
- **Exposure with and without food was similar at preliminary RP2D**

** 5 days on/2 days off and 3 days on / 4 days off were evaluated. ** Investigation of the mechanism of rash ongoing*
BID, twice daily; BOIN, bayesian optimal interval; DLT, dose-limiting toxicity; MTD, maximum tolerated dose; QD, once daily; RP2D, recommended phase 2 dose

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Lunresertib monotherapy: Treatment related adverse events (TRAEs)

Limited and reversible low-grade toxicity in monotherapy is encouraging for combination therapies

TRAEs in ≥15% of patients, n (%)	All Patients N=67			Preliminary RP2D 80-100mg BID-I N=8		
	All Grades	**G3**	**G4**	**All Grades**	**G3**	**G4**
Rash*	23 (34.3)	5 (7.5)	**0**	4 (50.0)	0	**0**
Nausea/Vomiting	21 (31.3)	1 (1.5)	**0**	2 (25.0)	0	**0**
Anemia	15 (22.4)	4 (6.0)	**0**	1 (12.5)	0	**0**
Fatigue	15 (22.4)	1 (1.5)	**0**	3 (37.5)	0	**0**

- **Safety profile encouraging**
  - Infrequent Grade 3 and no reported Grade 4 TRAEs across all doses evaluated
  - Preliminary RP2D range (80-100mg BID, intermittent) demonstrates encouraging tolerability profile
- **Favorable tolerability, with manageable AEs**
  - Dose reductions limited to 14.9% of patients
  - *Rash** improves, as early as 48 hours, with supportive care or lunresertib interruption

** Rash terms included: dermatitis contact, eczema, erythema, flushing, pruritis, rash, rash erythematous, rash maculopapular, rash pruritic, skin exfoliation. BID-I, twice daily, intermittent; G, grade; RP2D, recommended phase 2 dose.*

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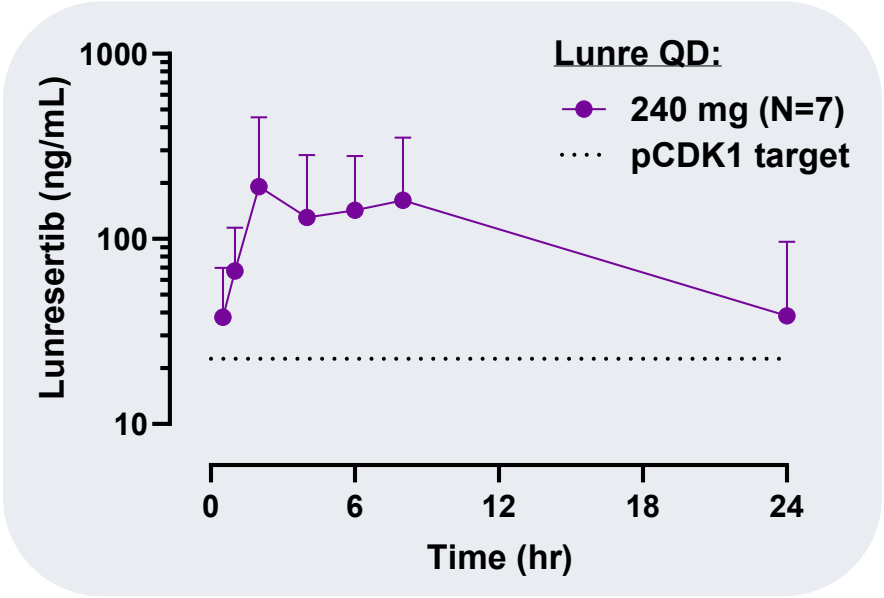
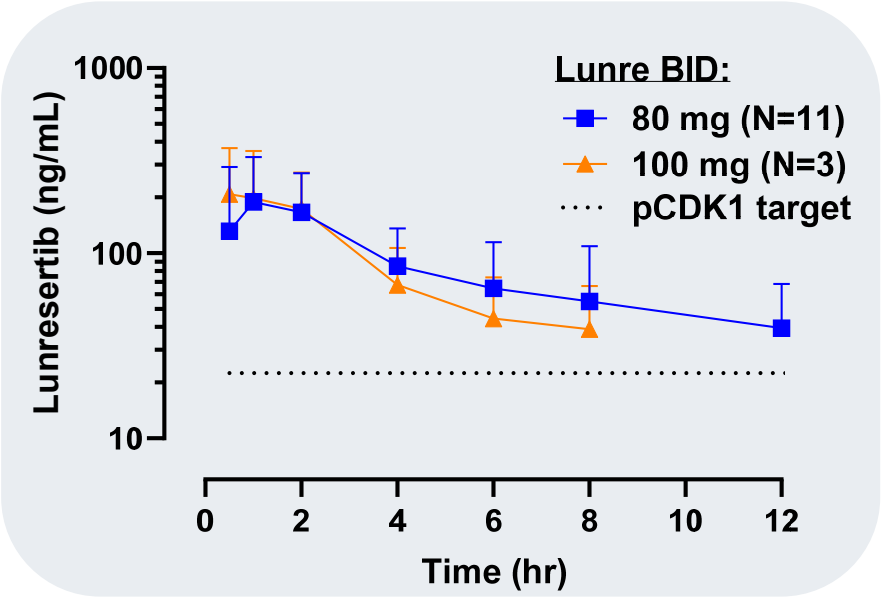
Target PK exposures achieved with lunresertib

Cycle 1 - Day 1 PK at 240 mg QD



Cycle 1 - Day 1 PK at 80 and 100 mg BID



- Human lunresertib PK is linear up to daily doses of 160-240 mg with a half-life of ~9 hours
- PK exposures similar between QD and BID schedules and exceeded the target exposure for inhibition of pCDK1

BID, twice daily; Conc, concentration; pCDK1, phosphorylated cyclin dependent kinase 1; PK, pharmacokinetic; QD, once daily; RP2D, recommended phase 2 dose.

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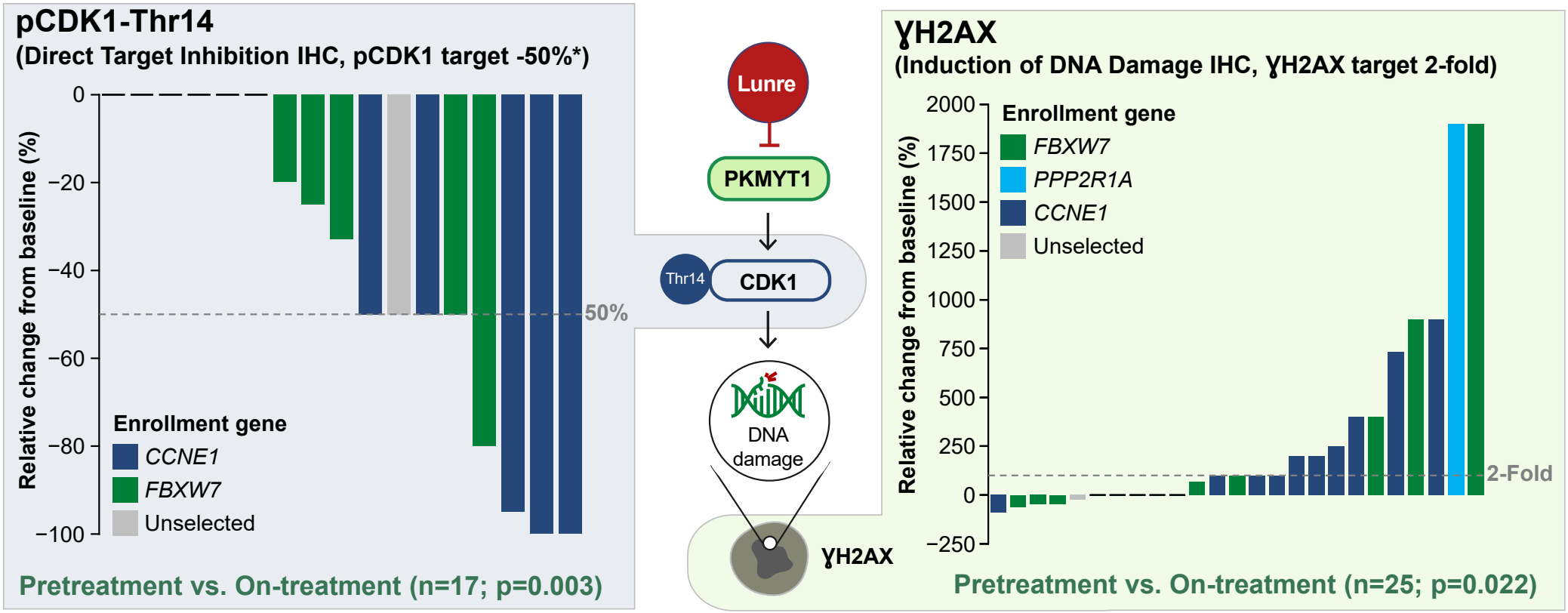
Lunresertib monotherapy mechanism of action confirmed in paired biopsies



Due to assay differences, IHC ~50% target inhibition corresponds to ~80% inhibition by ELISA when maximal tumor growth inhibition in preclinical models was recorded. P-values generated using paired samples with Wilcoxon sign rank test comparing +3% pCDK1 and γH2AX positive cells pre-treatment vs on-treatment. CDK1, cyclin-dependent kinase 1; ELISA, enzyme linked immunosorbent assay; IHC, immunohistochemistry; Lunre, lunresertib; pCDK1, phosphyorylated cyclin-dependent kinase 1; PKMYT1, protein kinase, membrane associated tyrosine/threonine 1; Thr, threonine.

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Anti-tumor activity with lunresertib monotherapy

One RECIST responder

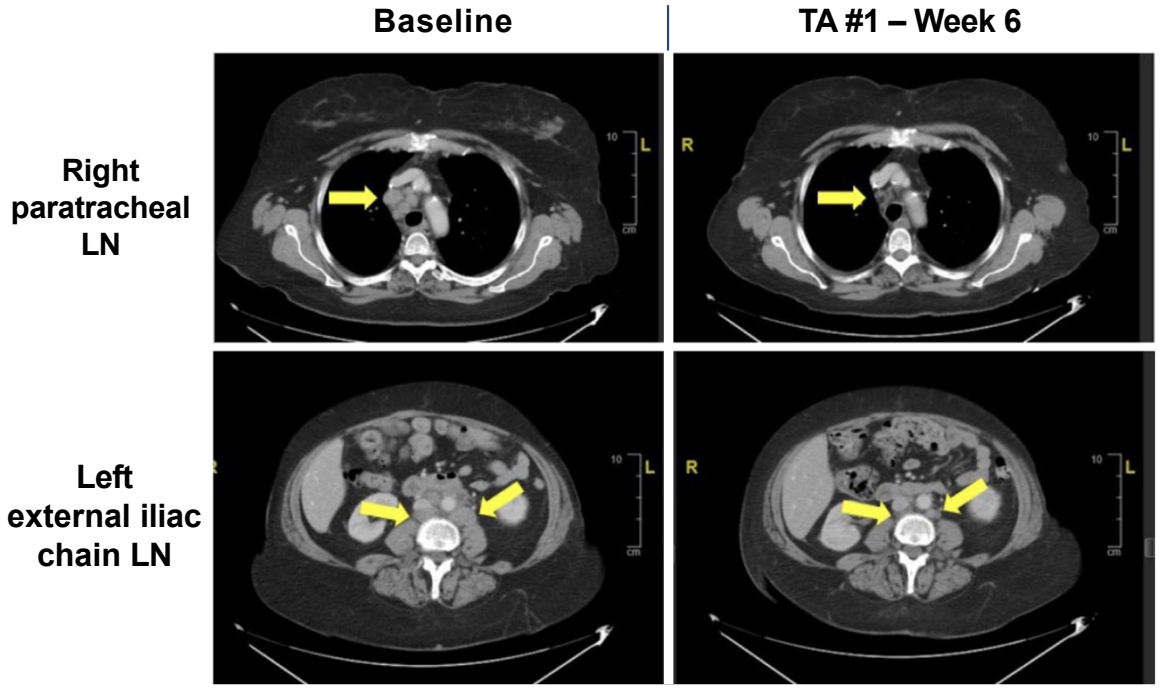
Female
73 years old

Metastatic recurrent uterine carcinosarcoma

FBXW7 & PPP2R1A Mutations

3 prior lines of therapy

Lunresertib:
80mg BID-I



- Overall response: cPR (RECIST)
- RECIST target lesion decrease -41%
- Received therapy for 8.3 months

Further, 7 patients with <30% tumor shrinkage, and 2 patients with PFS > 6 and 14 months, respectively

BID-I, twice daily, intermittent; cPR, confirmed partial response; LN, lymph node; RECIST, Response Evaluation Criteria in Solid Tumors; PFS, progression free survival; RP2D, recommended phase 2 dose; TA, tumor assessment.

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MYTHIC: PKMYT1 inHIbition for the treatment of Cancers (N=126)

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- Local NGS report (tissue or plasma)*
- Tumors with ***CCNE1*** amplification**, deleterious ***FBXW7*** or ***PPP2R1A*** alterations
- ECOG PS of 0-1
- Hgb ≥ 10 g/dL
- Platelets ≥ 100 K/uL
- ANC ≥ 1.5 K/uL

Study ongoing *NCT04855656*

Apr 2021 — Module 1 initiated

May 2022 — Module 2 initiated

Sept 5, 2023 — Data snapshot

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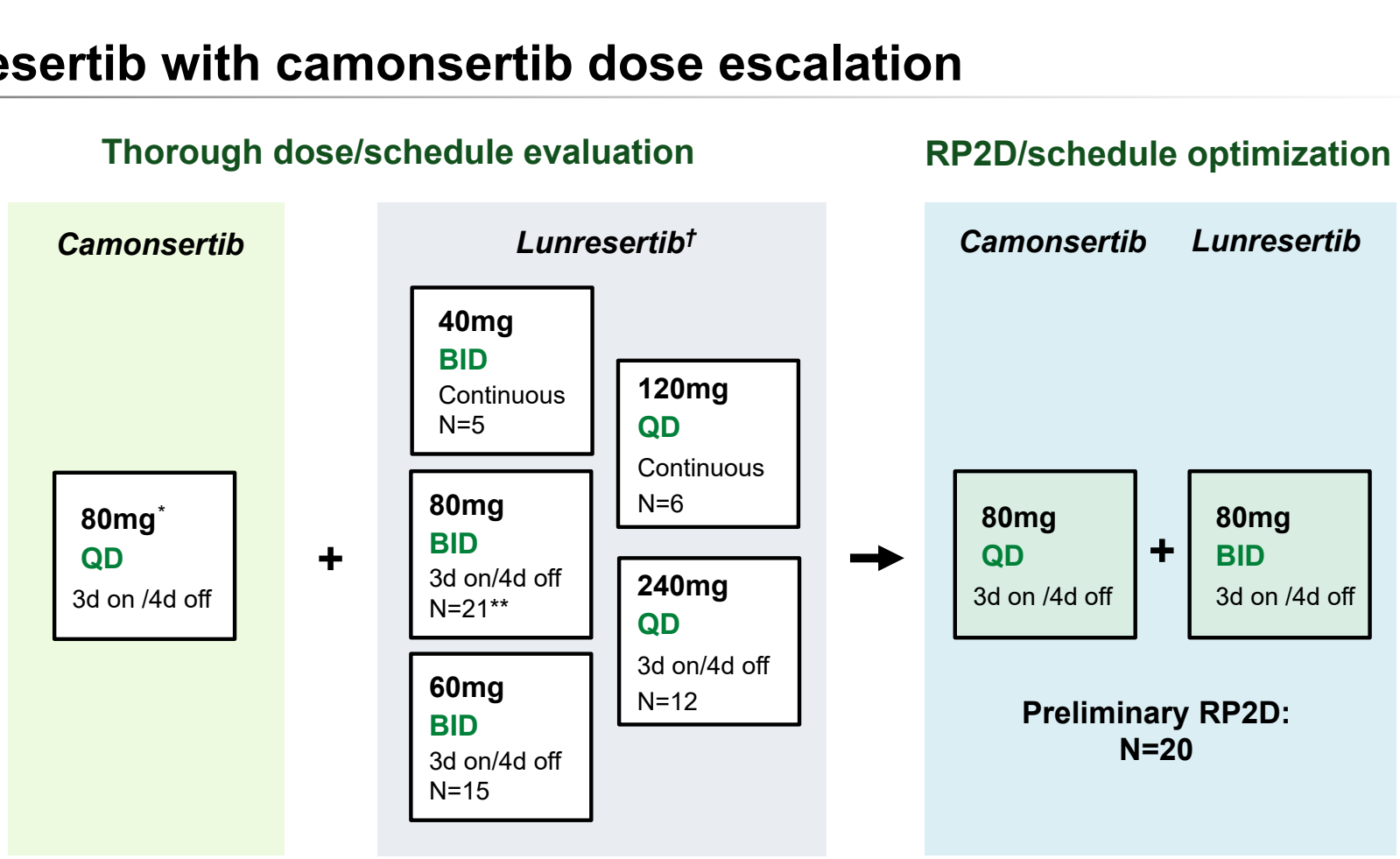
- Preliminary antitumor activity
- Kinetics of ctDNA

** NGS report centrally reviewed and annotated by Precision Oncology Decision Support (PODS) Group at MDACC. ** CCNE1 amplification (Copy number ≥6). ANC, absolute neutrophil count; ctDNA, circulating tumor DNA; ECOG, Eastern Cooperative Oncology Group; Hgb, hemoglobin; NGS, next generation sequencing; PD, pharmacodynamics; PK, pharmacokinetics; RP2D, recommended phase 2 dose.*

REPARE THERAPEUTICS

Lunresertib with camonsertib dose escalation



*† Tested doses derived from single agent exposures values. * Of the 59 patients, 57 were given 80mg and 2 patients received 120mg of camonsertib. ** One patient started at the daily dose of lunresertib 80mg QD 3 d on/ 4d off and was later escalated to 80mg BID. BID, twice daily; d, days; QD, once daily; RP2D, recommended phase 2 dose*

REPARE THERAPEUTICS

Lunresertib + camonsertib: Treatment related adverse events (TRAEs)

TRAEs in ≥15% of patients, n (%)	All Patients N=59			Preliminary RP2D N=20		
	All Grades	G3	G4	All Grades	G3	G4
Anemia	40 (67.8)	25 (42.4)	0	13 (65.0)	9 (45.0)	0
Nausea/Vomiting	38 (64.4)	0	0	9 (45.0)	0	0
Fatigue	24 (40.7)	0	0	5 (25.0)	0	0
Rash*	23 (39.0)	1 (1.7)	0	7 (35.0)	0	0
Leukopenia	12 (20.3)	2 (3.4)	0	3 (15.0)	0	0
Neutropenia	11 (18.6)	7 (11.9)	2 (3.6)	3 (15.0)	2 (10.0)	0
Headache	9 (15.3)	0	0	3 (15.0)	0	0

- **At the preliminary RP2D:**
  - No Grade 4 TRAEs
  - *Anemia* was the most common TRAE
    - Likely due to synergy and ATRi effect[1]
    - Grade 3 anemia detected early (< 6w) in patients with high-risk features†; others had later onset (> 6w)
    - Did not lead to discontinuations
    - Usually improved with 1w drug hold
  - *Nausea/vomiting*, alleviated with food

- Combination therapy DLT: anemia, rash/mucositis, and neutropenia
- **Preliminary RP2D: lunresertib 80 mg BID + camonsertib 80 mg QD; both 3d on/ 4d off**
  - Weekly or 2 weeks on / 1 week off **— schedule optimization ongoing**
  - Dose of camonsertib is ~50% lower than the monotherapy RP2D

[1] *Rosen et al. Development of a practical nomogram for personalized anemia management in patients treated with ataxia telangiectasia and Rad3-related (ATR) inhibitor camonsertib. [in press: Clinical Cancer Research 2023].*

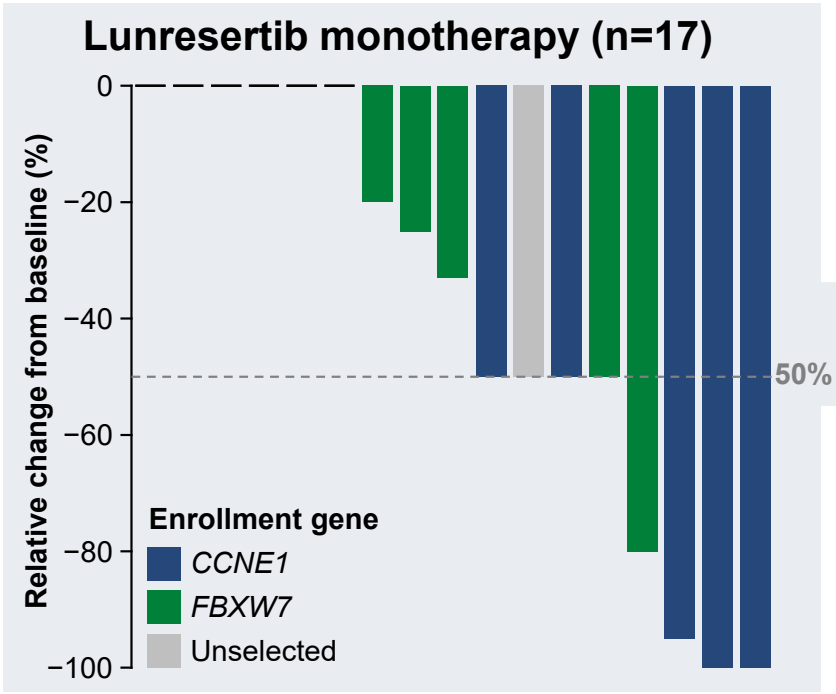
**Rash terms included: dermatitis contact, eczema, erythema, flushing, pruritis, rash, rash erythematous, rash maculopapular, rash pruritic, skin exfoliation.*

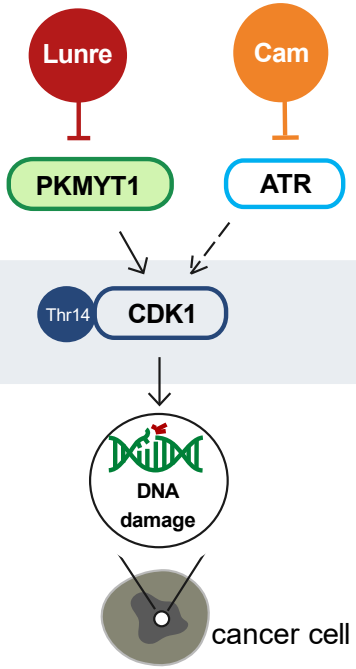
† median values at entry: Hb = 10.7g/dl, previous therapies = 4, median age = 59 y,

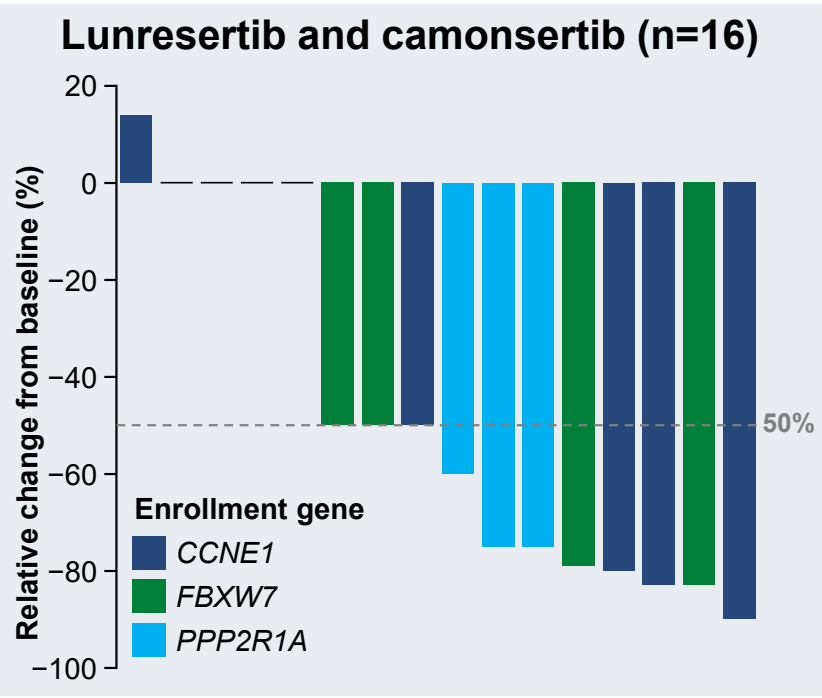
ATRi, ataxia telangiectasia and Rad3-related inhibitor; BID, twice daily; G, grade; Hbg, hemoglobin; QD, once daily; RP2D, recommended phase 2 dose; TRAE, treatment-related adverse events; w, week.

REPARE THERAPEUTICS

Direct target inhibition (pCDK1-Thr14) is enhanced with combination treatment







- **More tumors had a 50% pCDK1 reduction with combination (69%, 11/16) compared to monotherapy (47%, 8/17)**

**Due to assay differences, IHC ~50% target inhibition corresponds to ~80% inhibition by ELISA when maximal tumor growth inhibition in preclinical models was recorded. ATR, ataxia telangiectasia and Rad-3 related; Cam, camonsertib; CDK1, cyclin-dependent kinase 1; Lunre, lunresertib; pCDK1, phosphyorylated cyclin-dependent kinase 1; PKMYT1, protein kinase, membrane associated tyrosine/threonine 1; Thr, threonine.*

REPARE THERAPEUTICS

Responses to combination observed across tumor types and lunresertib-sensitizing alterations

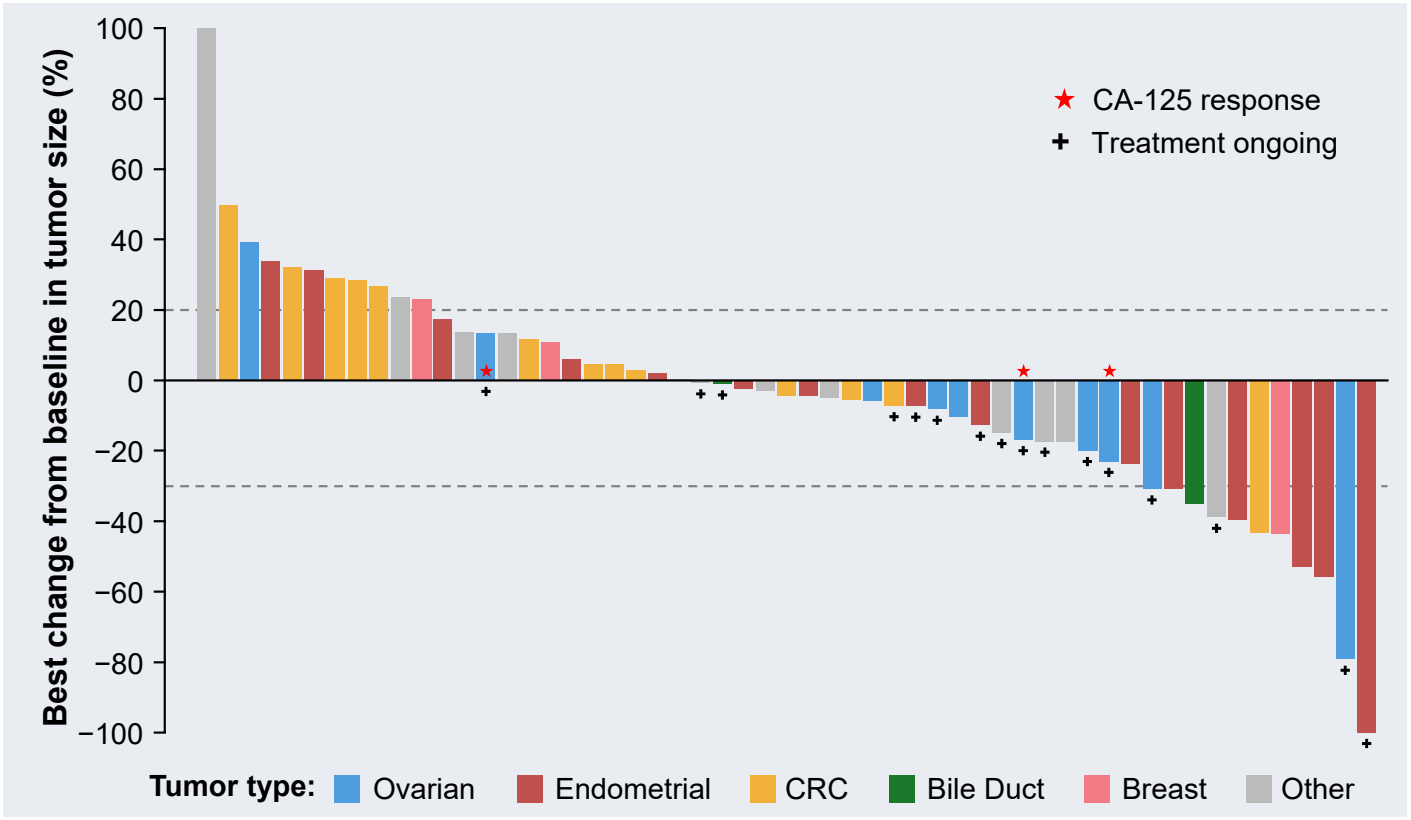
Tumor type	Genotype	Response	Best % change in TL from BL	Therapy (weeks)	Lines of prior Tx/ prior platinum
Endometrial	*PPP2R1A/FBXW7*	cPR	-55.9	30.4	3/Y
	PPP2R1A/CCNE1	cPR	-53.0	18.1	2/Y
	FBXW7	cPR*	-100.0	11.1+	3/Y
	FBXW7	uPR	-39.6	16.0	3/Y
	FBXW7	uPR*	-44.7	11.4+	3/Y
Ovarian	*CCNE1*	cPR*	-70.2	21.4+	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

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

** 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.*

REPARE THERAPEUTICS

Frequent and deep tumor reductions with lunre + cam combination across multiple tumor types



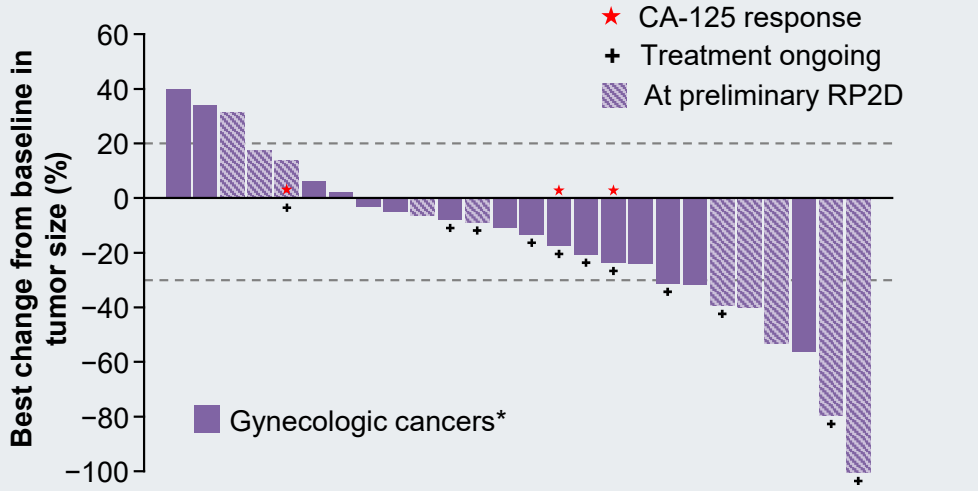
- **In evaluable patients*, across all tumors/doses:**
  - OR: 23.6% (n=55)
  - CBR: 41.8% (n=55)
  - MRR: 50.0% (n=24)
- **At preliminary RP2D, across all tumors:**
  - OR: 33.3% (n=18)
  - CBR: 50.0% (n=18)

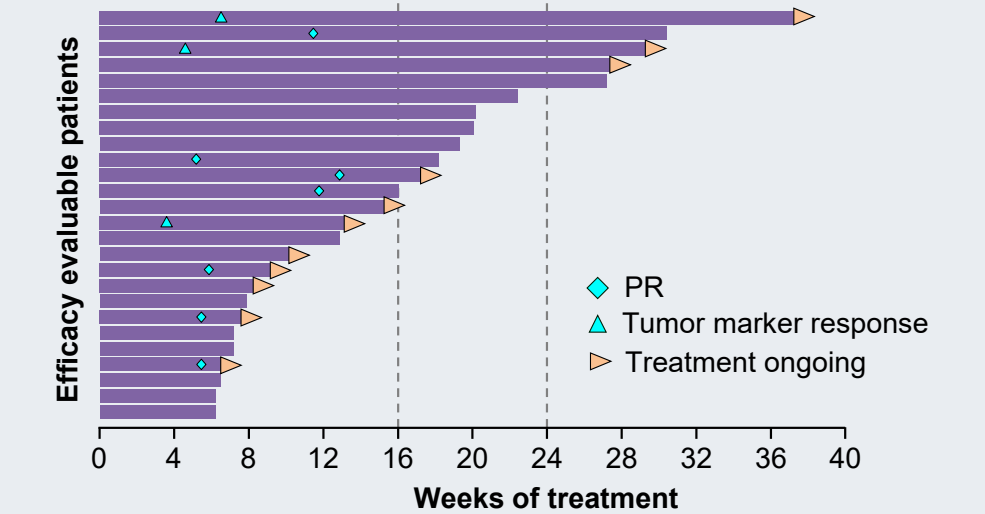
**Efficacy evaluable patients only (≥1 post-baseline tumor assessment). Other tumor types include cervical (n=1), esophageal (n=1), GI (n=1), liver (n=1), lung (n=3), melanoma (n=1), osteosarcoma (n=1), pancreatic (n=2), and upper GI (n=1). CBR: overall response or time on treatment ≥ 16 wk w/o progression; 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.*

REPARE THERAPEUTICS

Most patients with gynecologic cancers had tumor reductions with combination treatment

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





Across all doses (n=26):

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

At preliminary RP2D (n=10):

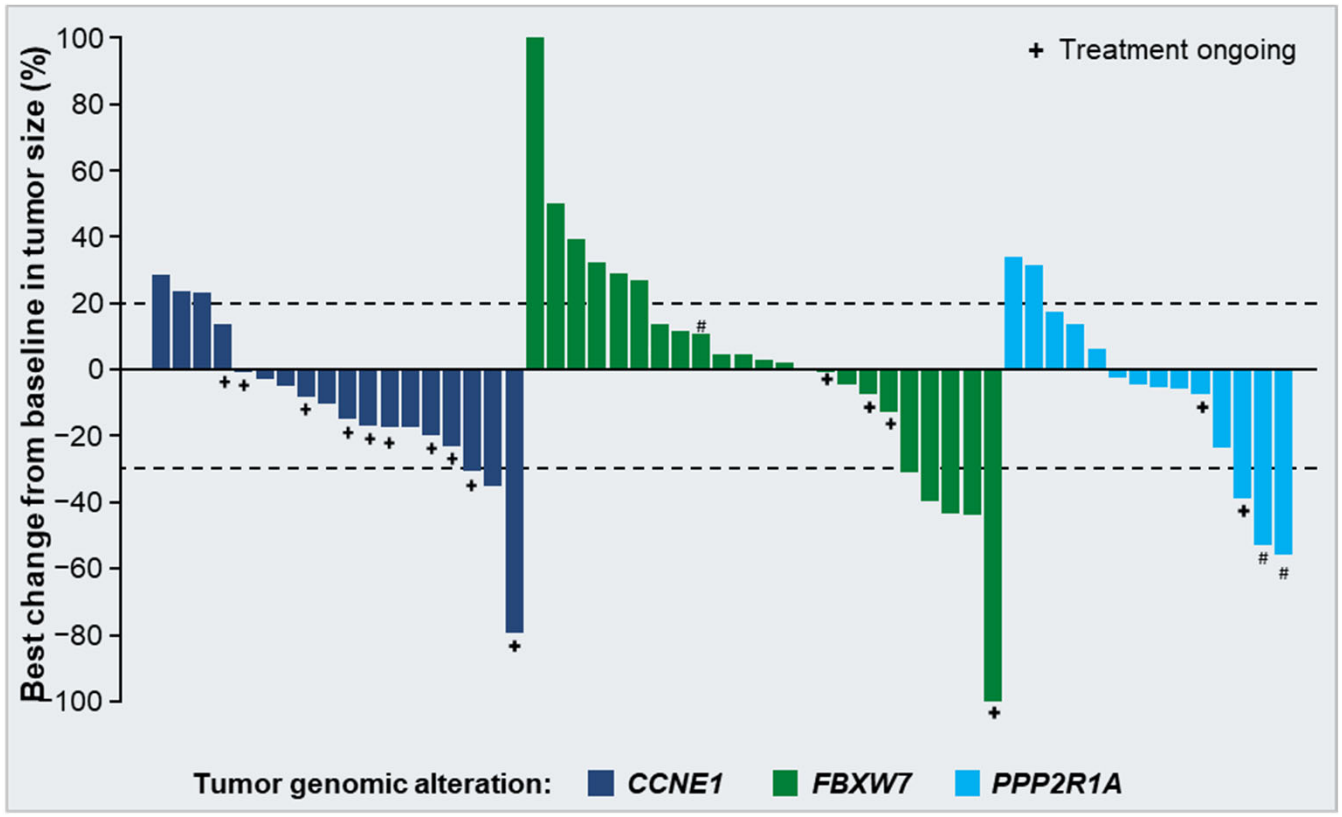
- Overall response: 60%; RECIST Response: 50%
- CBR: 70%

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

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

REPARE THERAPEUTICS

Meaningful tumor reductions across lunresertib-sensitizing alterations

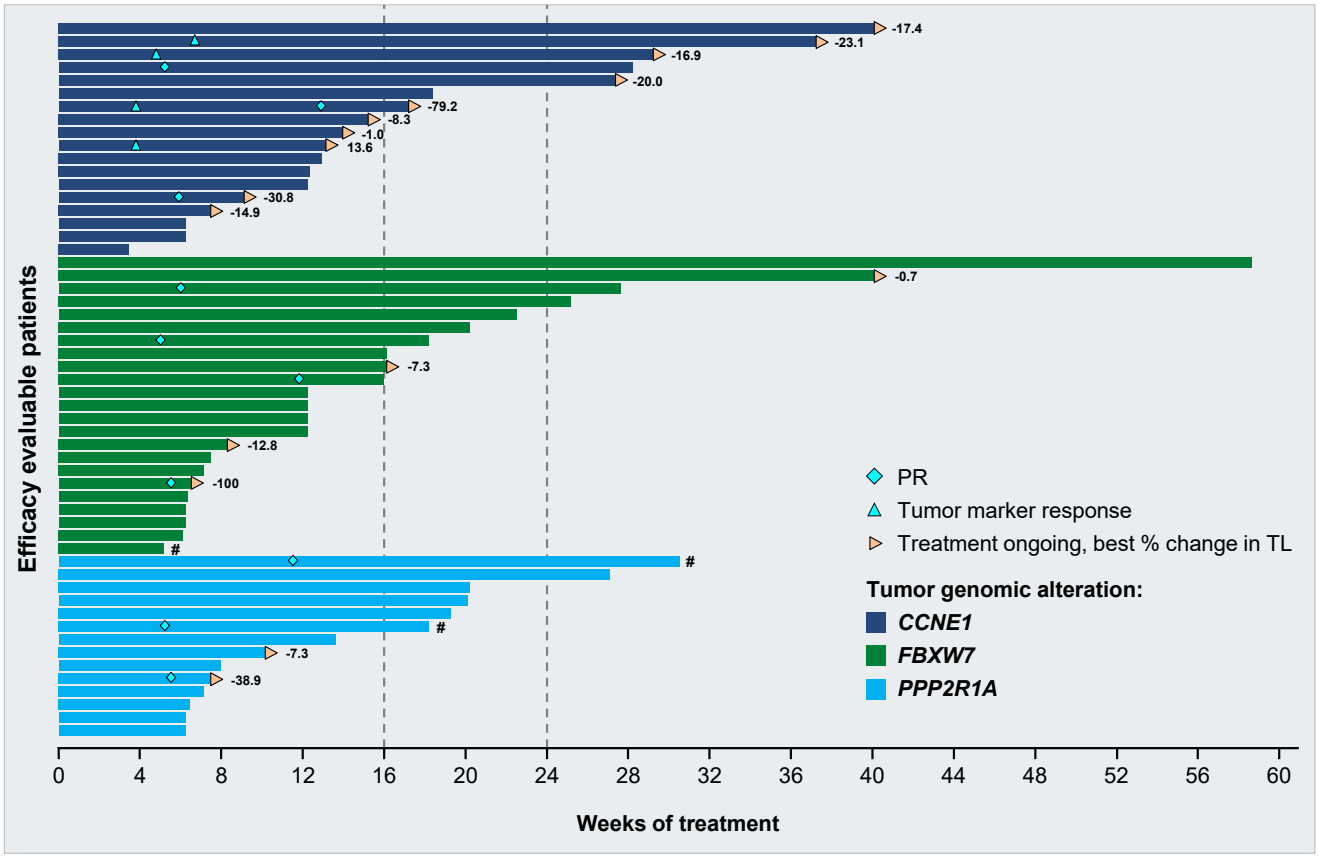


- **OR across all genotypes:**
  - 33.3% in *CCNE1* (n=18)
  - 17.4% in *FBXW7* (n=23)
  - 21.4% in *PPP2R1A* (n=14)
- **CBR is promising across genotypes:**
  - 44% in *CCNE1* (n=18)
  - 35% in *FBXW7* (n=23)
  - 50% in *PPP2R1A* (n=14)
- **MRR:**
  - 40% in *CCNE1* (n=10)
  - 44% in *FBXW7* (n=9)
  - 80% in *PPP2R1A* (n=5)

 # patients with lunresertib-sensitizing co-alterations: 1 each (FBXW7/CCNE1, PPP2R1A/CCNE1, and PPP2R1A/FBXW7). Data represent the efficacy evaluable patient population with ≥ 1 post-baseline tumor assessment. CBR, clinical benefit rate; MRR, molecular response rate; OR, *overall response based on RECIST or GCIG CA-125 response.*

REPARE THERAPEUTICS

Clinical benefit: Combination treatment across lunresertib-sensitizing alterations and doses



- **OR across all genotypes:**
  - 33.3% in *CCNE1* (n=18)
  - 17.4% in *FBXW7* (n=23)
  - 21.4% in *PPP2R1A* (n=14)
- **CBR is promising across genotypes:**
  - 44% in *CCNE1* (n=18)
  - 35% in *FBXW7* (n=23)
  - 50% in *PPP2R1A* (n=14)
- **Treatment ongoing in 16 patients**
- **Efficacy and tolerability assessments continue to optimize RP2D in tumor- and alteration-selected expansions**

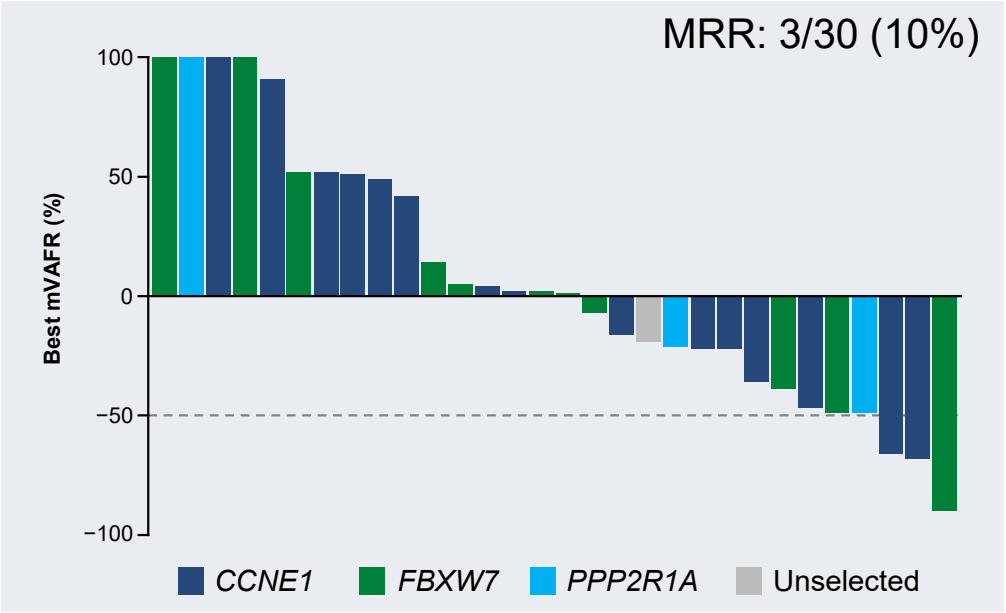
 # patients with lunresertib-sensitizing co-alterations : 1 each (FBXW7/CCNE1, PPP2R1A/CCNE1, and PPP2R1A/FBXW7). Data represent the efficacy evaluable patient population (≥ post-baseline tumor assessment). CBR, clinical benefit rate; OR, overall response based on RECIST or GCIG CA-125 response; PR, partial response; TL, target lesion; RP2D, recommended phase 2 dose.

REPARE THERAPEUTICS

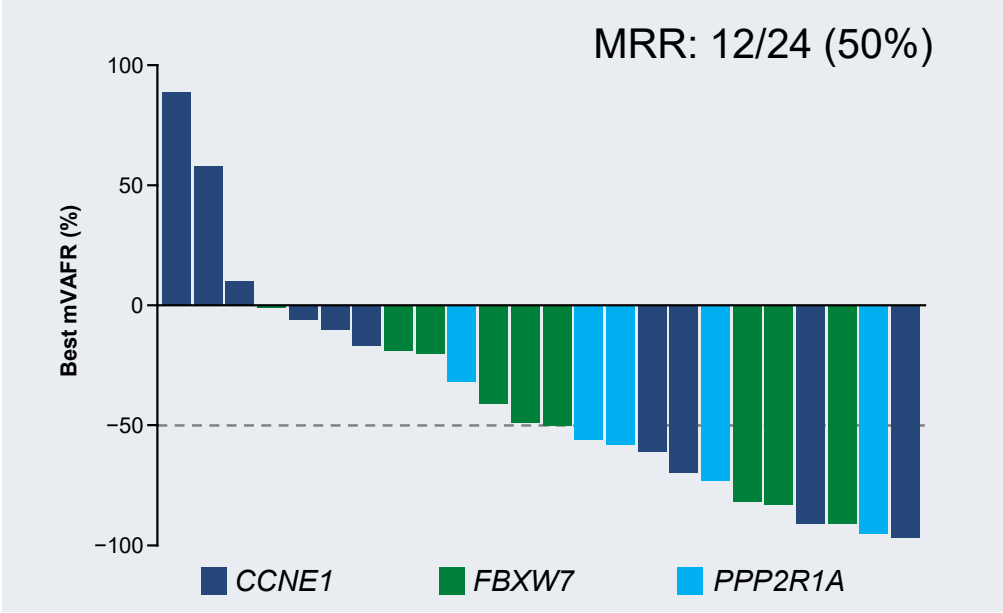
Significantly higher molecular responses confirm the benefit of combination treatment

Molecular responses were observed across lunresertib-sensitizing molecular alterations[1]

Lunresertib monotherapy



Lunresertib + camonsertib



Molecular response rate in combination therapy was significantly higher than with monotherapy (*p*=0.003)

[1]ANE poster B057: Gallo et al. Molecular response: ≥ 50% decline in mVAF assessed by Tempus xF and Tempus xF+ gene panels for patients with detectable somatic alterations in monotherapy and combination therapy, respectively; best mVAFR capped at +100%. p-value of monotherapy vs. combination therapy determined using chi-squared test. MRR, molecular response rate; mVAFR, mean variant allele frequency ratio.

REPARE THERAPEUTICS

Early response in recurrent FBXW7 mutated colorectal adenocarcinoma

Male
63 years old

Recurrent colorectal adenocarcinoma

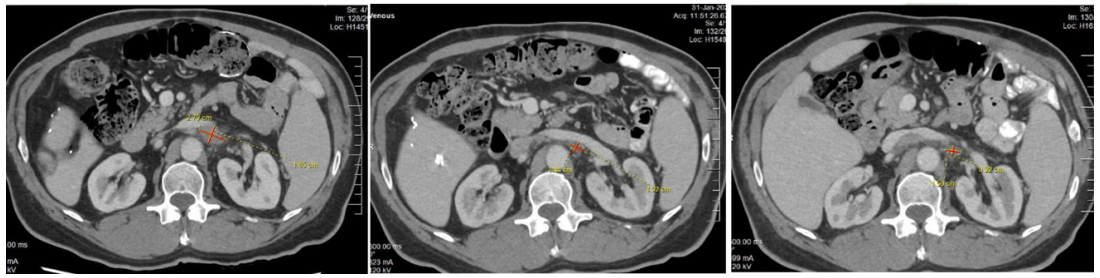
FBXW7
Mutation

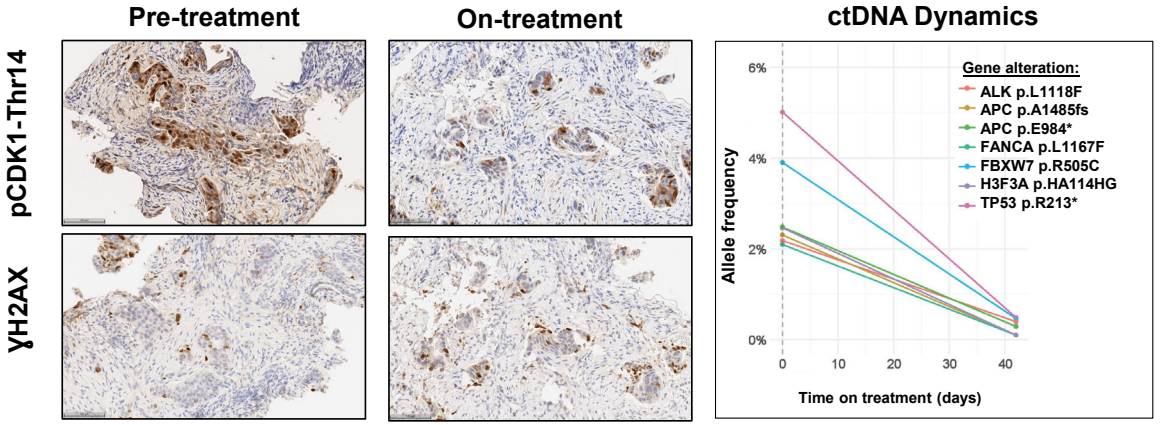
TP53 mut

3 prior lines of therapy

Lunre 240mg QD 3/4
Cam 80mg QD 3/4

Left para-aortic lymph node





- Overall response: cPR (RECIST)
- RECIST target lesion decrease -43.3%
- Received therapy for 27.6 weeks

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

REPARE THERAPEUTICS

Gradual response heralded by CA-125 decrease; recurrent *CCNE1* amplified ovarian cancer

Female
56 years old

High grade serous ovarian carcinoma

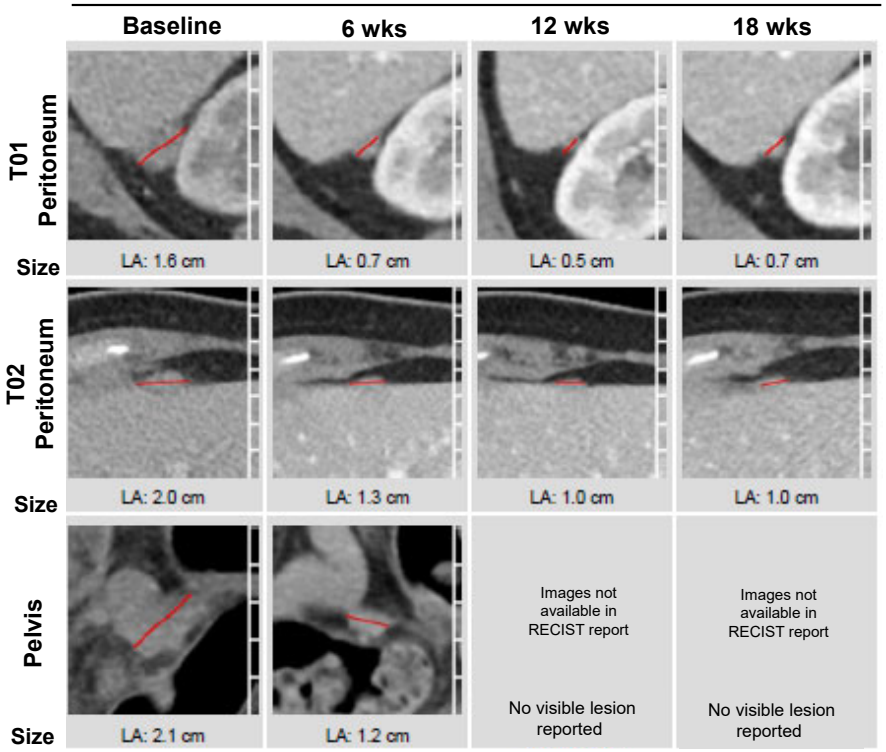
CCNE1
Amplification

TP53 mut

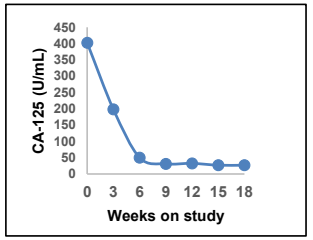
2 prior lines of therapy

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

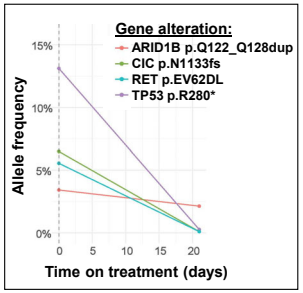
Tumor assessment



CA-125 dynamics



ctDNA dynamics



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

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

REPARE THERAPEUTICS

Prompt response in recurrent cervical carcinosarcoma with a PPP2R1A mutation

Female
66 years old

Recurrent cervical carcinosarcoma

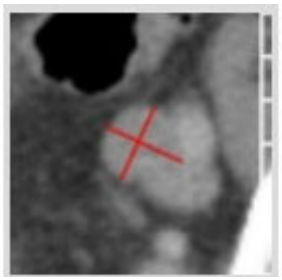
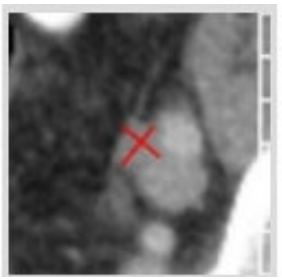
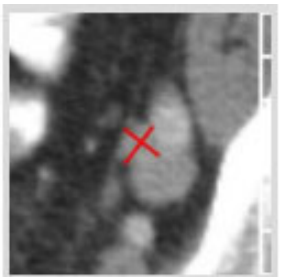
PPP2R1A
Mutation

MYC amp
TP53 mut

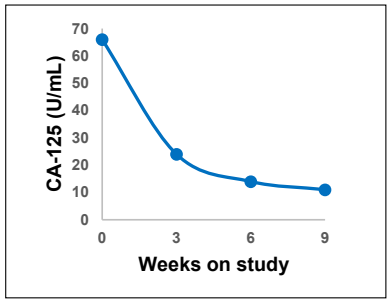
1 prior line of therapy

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

Tumor assessment

	Baseline	6 weeks	12 weeks
T01 Lymph node external iliac left			

CA-125 dynamics



- Overall response: cPR (RECIST)
- RECIST target lesion decrease -44.4%
- Therapy ongoing at 11 weeks

3/4, 3 days on/4 days off; BID, twice daily; CN, copy number; cPR, confirmed partial response; RECIST, Response Evaluation Criteria in Solid Tumors; QD, once daily; RP2D, recommended phase 2 dose; TA, tumor assessment.

REPARE THERAPEUTICS

Conclusions & Lunresertib Development Plan

Maria Koehler, MD, PhD, Chief Medical Officer

REPARE THERAPEUTICS

Lunresertib:

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

MONOTHERAPY

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

Recommended Phase 2 dose: 80 to 100mg twice daily in intermittent schedule

CAMONSERTIB COMBINATION THERAPY

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

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

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

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

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

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

REPARE THERAPEUTICS

Lunresertib + camonsertib combination therapy (additional data)

MYTHIC is a dose finding Phase 1 study: Preliminary RP2D range identified, schedule optimization ongoing. RP2D is important; only 18 pts were treated at preliminary RP2D range.

Anemia is the primary tolerability issue to alleviate. Our experience* and our emerging understanding of the anemia promises a range of simple solutions for patients.

Gynecological cancers are the largest trial population with strongest signal so far. We expect a robust signal at refined dose and schedule with increasing patient numbers.

We are highly interested in multiple other tumors. Numerous opportunities and nothing is off the table.

**Rosen et al. Development of a practical nomogram for personalized anemia management in patients treated with ataxia telangiectasia and Rad3-related (ATR) inhibitor camonsertib. [in press: Clinical Cancer Research 2023]. RP2D, recommended phase 2 dose.*

REPARE THERAPEUTICS

Treatment at preliminary RP2D increases efficacy

Gynecologic cancers provide most robust example of criticality of sufficient exposure

Gynecologic Cancers Only: N (%)	RP2D (N=10)	Non-RP2D (N=16)
Overall Response (RECIST/CA-125)	6 (60.0%)	4 (25.0%)
RECIST response (confirmed+unconfirmed) **	5 (50.0%)	2 (12.5%)
CBR	7 (70.0%)	8 (50.0%)
Therapy Ongoing Without PD	5 (50%)	5 (31.3%)

Most doses were below daily RP2D exposure

More patients still ongoing at RP2D level

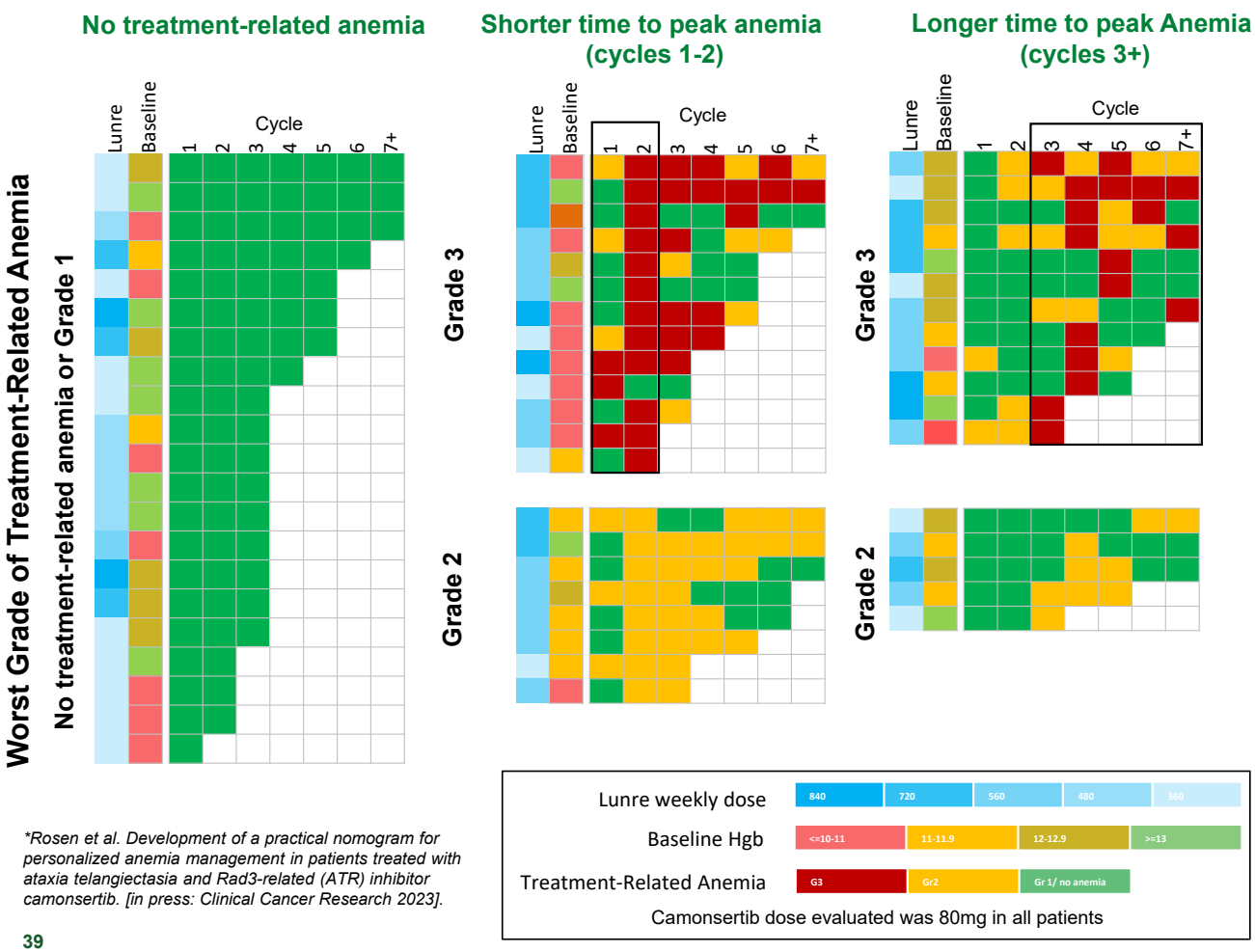
Patient split between RP2D and Non-RP2D reflects thorough dose finding; only most recent patients at RP2D exposures.

Enrollment now open in multiple tumor expansions with RP2D optimization

**Efficacy evaluable patients (>=1 post-baseline tumor assessment); Sept 5 database; Gyn includes endometrial, ovarian, and cervical.*
*** additional endometrial cancer with uPR after data base lock for total of 6 RECIST responders.*

REPARE THERAPEUTICS

Anemia patterns understood and manageable



**Rosen et al. Development of a practical nomogram for personalized anemia management in patients treated with ataxia telangiectasia and Rad3-related (ATR) inhibitor camonsertib. [in press: Clinical Cancer Research 2023].*

Anemia likely a result of synergistic combination effect

Mostly a sole, manageable event, suggestive of narrow bone marrow effect

Dose optimization and individualized patient management now in place:

1) Maintain RP2D weekly in patients without anemia
2) Early onset: schedule adjustment
3) Late onset: “on demand” modifications

Gr 3 anemia at RP2D reflects higher risk population

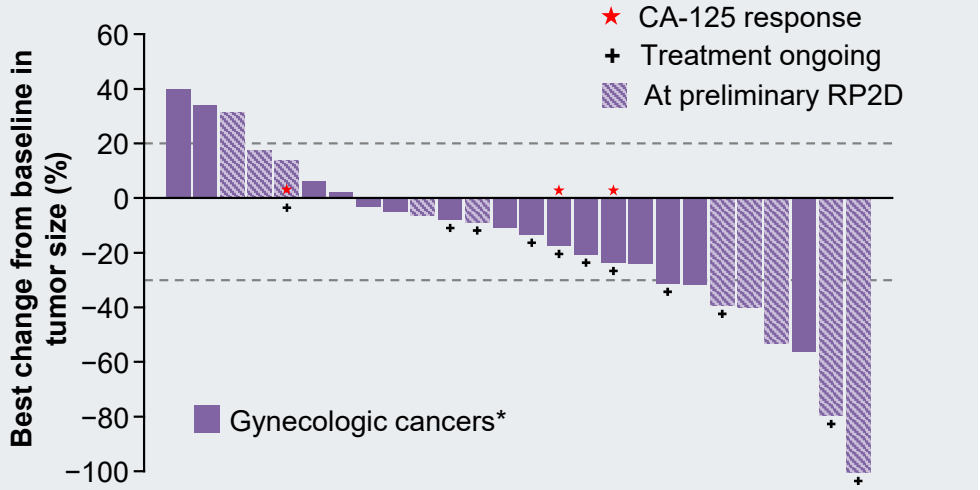
- 8/9 pts w Gr3 anemia entered study with anemia; median Hb=10.7g/dL
- Median age 59y, 3 were >70 years old
- Median previous therapies was 4

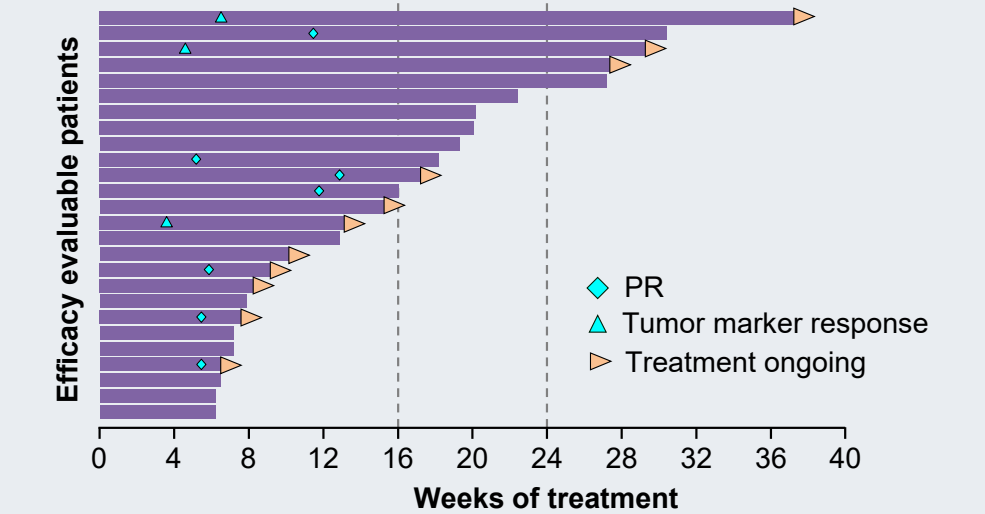
Assessment of this approach and dose/schedule optimization is ongoing

REPARE THERAPEUTICS

Most patients with gynecologic cancers had tumor reductions with combination treatment

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





Across all doses (n=26):

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

At preliminary RP2D (n=10):

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

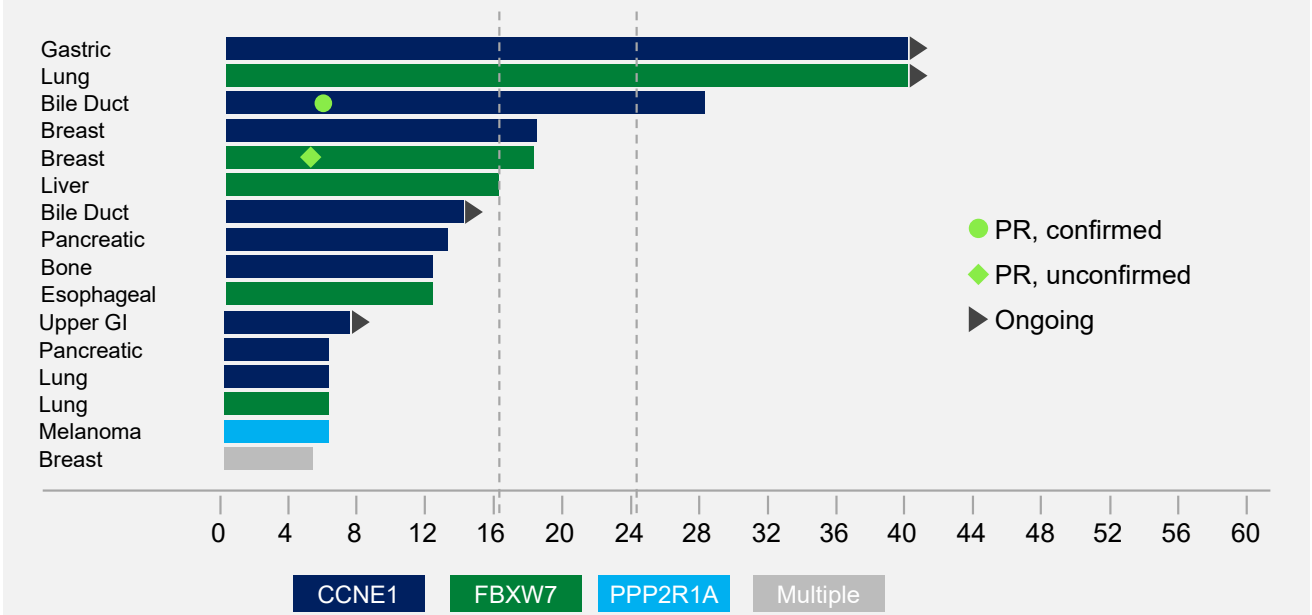
- Patients had 1-9 prior therapies (median=3); treatment ongoing in 11 patients; enrollment in expansion cohorts at RP2D continues

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

REPARE THERAPEUTICS

Opportunity across multiple tumor types: emerging signals from Phase 1 trial – non gynecologic tumors

Time on treatment by tumor type (>=1 post-baseline tumor assessment)



Multiple development options: Additional investigation ongoing

Small #pts in 11 different tumors

1/3 of patients with NSCLC have 10m PFS

1/3 of patients with upper GI cancer have 10m PFS

1/2 of patients with cholangio: cPR

1/3 of patients with breast cancer: uPR, continuous target lesion shrinkage

CRC of keen interest: N=13, only 4 at RP2D, one cPR, 4 treated >16 weeks, including one for >1 year

REPARE THERAPEUTICS

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**
- **MINOTAUR: + FOLFIRI**
- **IST: + CCTG[1]**
- **IST: + Carbo/paclitaxel[2]**
- **4 collaboration trials in advanced discussion**

Determine RP2D dose / schedule

Progress to late-stage trials

Future Opportunities

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

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

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

REPARE THERAPEUTICS

MYTHIC trial: Key takeaways and next steps

Validated lunresertib mechanism of action and SNIPRx preclinical patient selection approach

Safety, tolerability, early efficacy signals confirmed in camonsertib combination therapy

50% RECIST response observed in camonsertib combination in 10 pts in largest cohort (gynecological tumors) at preliminary RP2D, underscoring high opportunity in other tumor types we are now enrolling

Clear understanding of anemia pattern facilitates patient friendly, simple management; Update 2024

MYTHIC trial expanded to evaluate combination therapy in patients with select tumor types and genomic alterations; Expect to report additional data in 2H 2024

Oncology and patient communities taking high interest in emerging data accelerating the expansion of lunresertib development as MYTHIC moves ahead

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Upcoming Catalysts

Lloyd M. Segal, President & CEO

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Upcoming milestones

2H 2023

Camonsertib Phase 2
TAPISTRY trial initiation

Lunresertib + carboplatin/paclitaxel
combination Phase 1
IST initiation

RP-1664 and RP-3467 (Polθi)
focused investor event

1H 2024

RP-1664
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)

REPARE THERAPEUTICS

Q&A

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President & CEO

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Principal Investigator, MYTHIC Trial

Maria Koehler, MD, PhD
Chief Medical Officer

Mike Zinda, PhD
Chief Scientific Officer

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Insight that enriches. Precision that empowers.

Lunresertib MYTHIC Clinical Trial Update

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