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Poster number: B156

MYTHIC: First-in-human biomarker-driven phase I trial of first-in-class PKMYT1 inhibitor lunresertib alone and with ATR inhibitor camonsertib in solid tumors with *CCNE1* amplification or deleterious alterations in *FBXW7* or *PPP2R1A*

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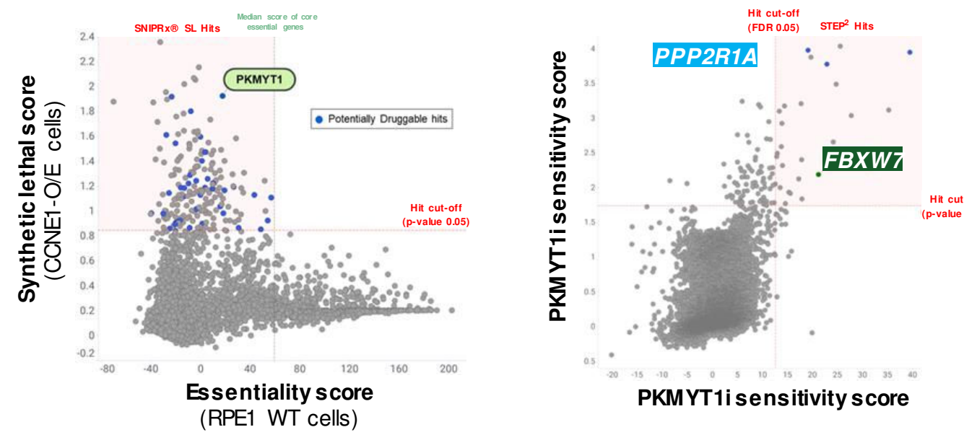
Background

- Cyclin E1 overexpression (O/E) drives premature S-phase entry and overloads the DNA replication machinery, resulting in genome instability; with no approved therapies, this is an area of high unmet need in the clinic
- Lunresertib (RP-6306) is a first-in-class inhibitor of the membrane-associated tyrosine- and threonine-specific Cdc2-inhibitory kinase (PKMYT1) that disrupts the G2/M checkpoint leading to premature mitosis and catastrophic DNA damage in the context of Cyclin E1 O/E
- Additionally, PKMYT1 inhibition was identified to be synthetic lethal (SL) with *FBXW7* and *PPP2R1A* in chemical genomic screens[1,2]
- Camonsertib, a potent ATRi with demonstrated clinical activity, is SL with genomic alterations affecting the DNA damage response distinct from those leading to lunresertib sensitivity[3,4]
- Combination of PKMYT1 and ATR inhibition is hypothesized to enhance CDK1 activation and premature mitosis in the context of lunresertib-sensitizing genomic alterations
- Here, we present preliminary data from a phase 1 study assessing the safety, tolerability, and anti-tumor activity of the first-in-class PKMYT1 inhibitor lunresertib alone and in combination with camonsertib

PKMYT1 identified as a strong SL partner to *CCNE1* amplification[1]

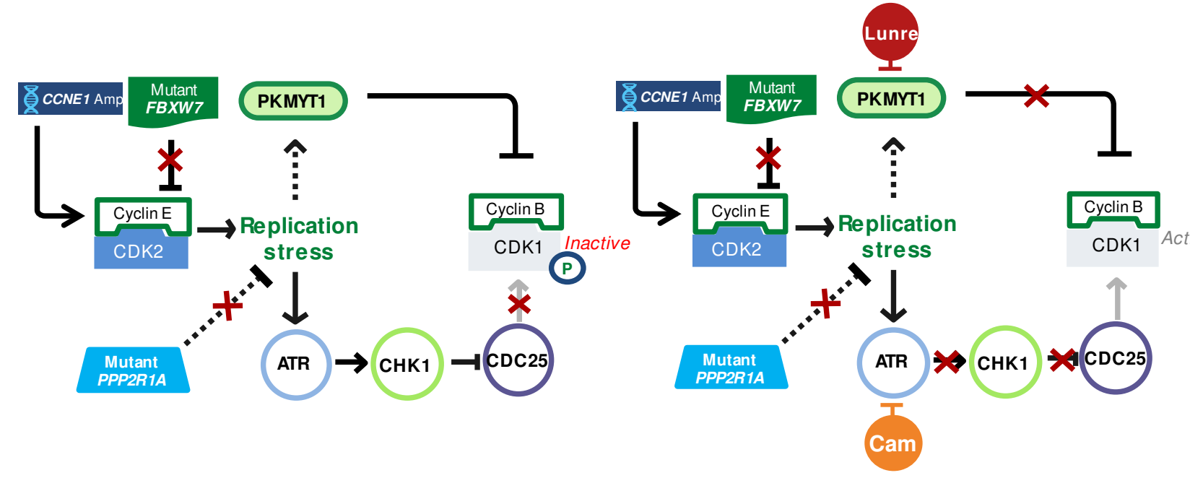


Genome-wide CRISPR-Cas9 screen

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 and ATR inhibitors synergize to enhance antitumor activity[2]



Lunresertib-sensitizing alterations engage ATR through replication stress

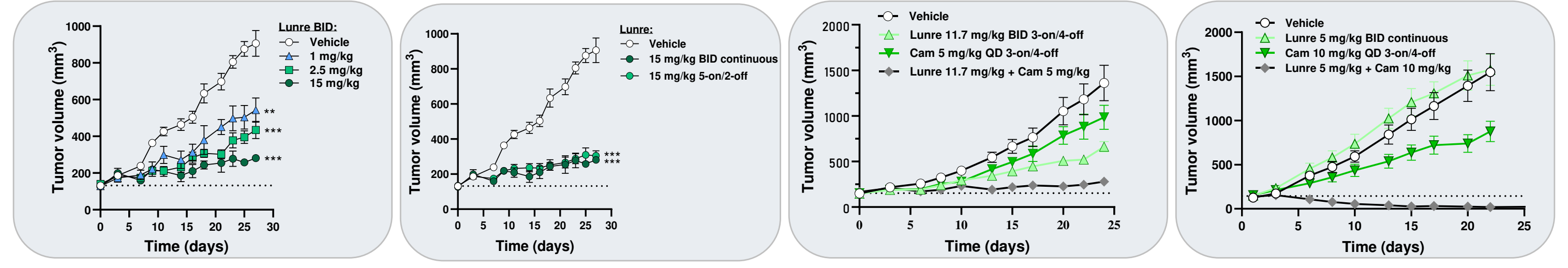
Combination of ATR and PKMYT1 inhibition enhances CDK1 activation and premature mitosis

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

Lunresertib + camonsertib inhibition in xenograft models

HCC1569 *CCNE1* amplified Breast Cancer CDX model | **OVCAR3 Ovarian Cancer** *CCNE1* amplified CDX model | **DLD1 Colorectal Cancer** *FBXW7 Knockout* CDX model



- Lunresertib monotherapy inhibits xenograft growth across doses and schedules
- Combination treatment drives tumor regressions at sub-efficacious single-agent doses
- Camonsertib alone has limited activity in *CCNE1* and *FBXW7* altered *PDX* models, data not shown

Study Design

PKMYT1 inhibition for the treatment of cancers: MYTHIC

Inclusion criteria:

- Patients aged ≥ 12 y with solid tumors resistant/intolerant to standard therapy
- Local NGS report (tissue or plasma)[a]
- Tumors with ***CCNE1*** amplification[b], deleterious ***FBXW7*** or ***PPP2R1A*** alterations[c]
- ECOG PS of 0–2 (Module 1) or 0–1 (Module 2)
- Hgb ≥ 9 g/dL (Module 1) or ≥ 10 g/dL (Module 2)
- Platelets ≥ 100 K/uL
- ANC ≥ 1.5 K/uL

Apr 2021	May 2022	Sep 05, 2023
Module 1 initiated	Module 2 initiated	Data snapshot

Module 1:
Single agent lunresertib
67 patients

Module 2:
Lunresertib with camonsertib
59 patients

Study is ongoing: **NCT04855656**

✓ **Primary endpoints:**

- Safety and tolerability
- RP2D and schedule

✓ **Other endpoints:**

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

[a] NGS report centrally reviewed and annotated by the Precision Oncology Decision Support group at MD Anderson Cancer Center. [b] *CCNE1* amplification (CN ≥ 6). [c] Up to 5 patients with endometrial cancer without these alterations were eligible in Module 1.

Results

MYTHIC: Patient demographics

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

Similar patient characteristics in monotherapy and combination therapy cohorts

[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: bile duct (n=2), gastroesphogeal (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.

Lunresertib monotherapy: Treatment related adverse events (TRAEs)

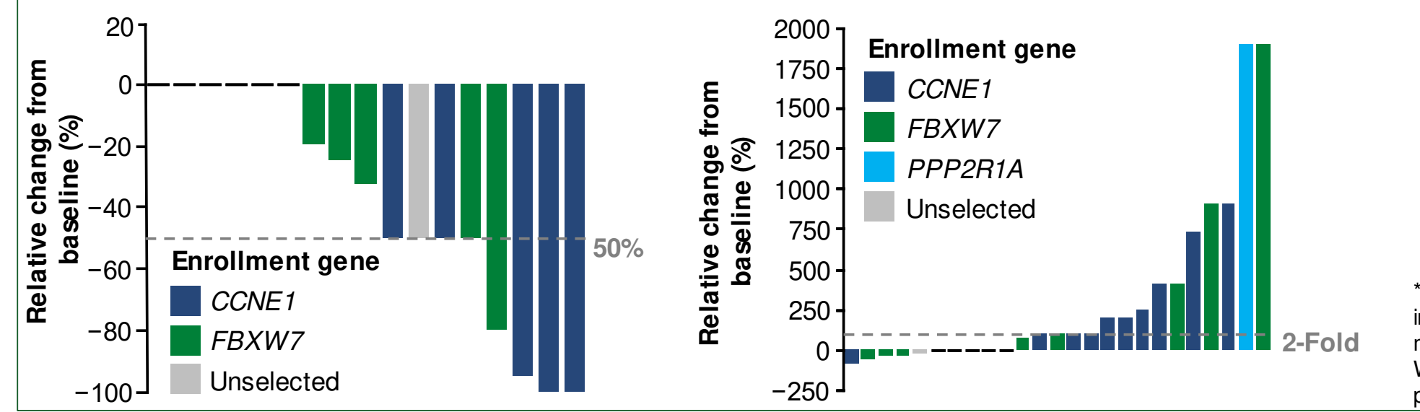
TRAEs in ≥ 15% of patients, n (%)	All Patients N=67			Preliminary RP2D Range 80-100mg BID-I N=8		
	All Grades	G3	G4	All Grades	G3	G4
Rash*	23 (34.3)	5 (7.5)	0	4 (50.0)	0	0
Nausea/Vomiting	21 (31.3)	1 (1.5)	0	2 (25.0)	0	0
Anemia	15 (22.4)	4 (6.0)	0	1 (12.5)	0	0
Fatigue	15 (22.4)	1 (1.5)	0	3 (37.5)	0	0

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

- **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

Lunresertib monotherapy mechanism of action confirmed in paired biopsies

A. pCDK1-Thr14 (Direct Target Inhibition IHC, pCDK1 target -50%*) | **B. ɣH2AX** (Induction of DNA Damage IHC, ɣH2AX target 2-fold)



- **Pretreatment vs. on-treatment of patients on monotherapy**
  - pCDK1-Thr14 (n=17, $p = 0.003$)
  - ɣH2AX (n=25, $p = 0.022$)

*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 ɣH2AX positive cells pre-treatment vs on-treatment.

Lunresertib + camonsertib: 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

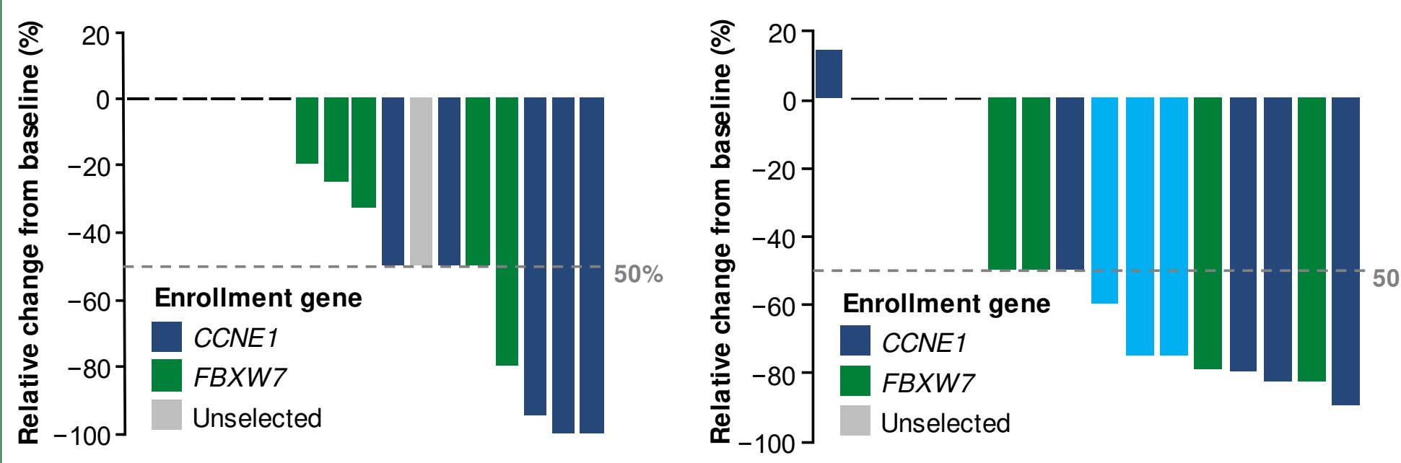
- **At the preliminary RP2D:**
  - No Grade 4 TRAEs
  - *Anemia* was the most common TRAE
    - likely due to synergy and ATRi effect[5]
    - Grade 3 anemia detected early (< 6wks) in patients with high-risk features[†]; others had later onset (> 6wks)
    - did not lead to discontinuations
    - usually improved with 1 wk drug hold
  - *Nausea/vomiting*, alleviated with food

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

* Rash terms included: dermatitis contact, eczema, erythema, flushing, pruritis, rash, rash erythematous, rash maculopapular, rash pruritic, skin exfoliation. [†] Median values at entry: Hgb = 10.7g/dl, previous therapies = 4, and age = 59 y.

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

A. Lunresertib monotherapy (n=17) | **B. Lunresertib + camonsertib (n=16)**



- 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.

Results

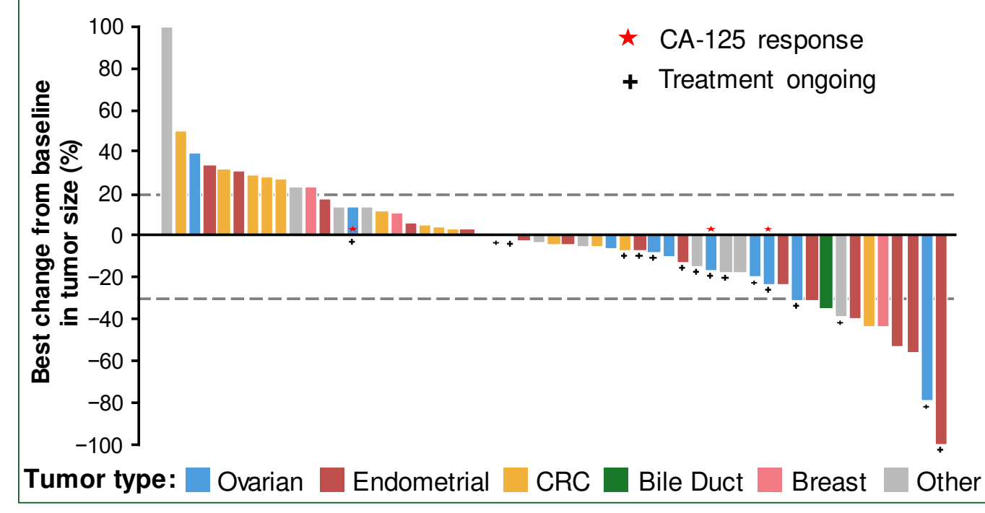
Responses to combination observed across tumor types and lunresertib-sensitizing alterations

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. 10, 2023. Relevant patient tumor co-mutations [†]BRCA1 rearrangement and [‡]BRCA2 biallelic loss. +Treatment ongoing.

Frequent and deep tumor reductions with combination across multiple tumor types

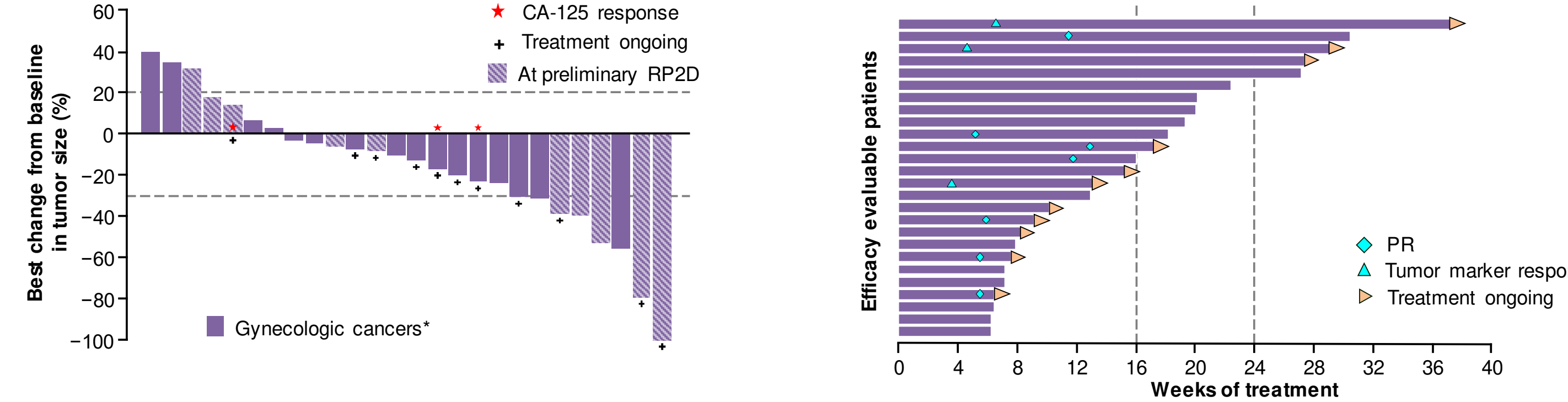


- **In evaluable patients*, across all tumors, all doses:**
  - OR: 23.6% (n=55)
  - CBR: 41.8% (n=55)
  - MRR: 50.0% (n=24)
- **At preliminary RP2D, across all tumors:**
  - OR: 33.3% (n=18)
  - CBR: 50.0% (n=18)

*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).

Most patients with gynecologic cancers had tumor reductions with combination treatment

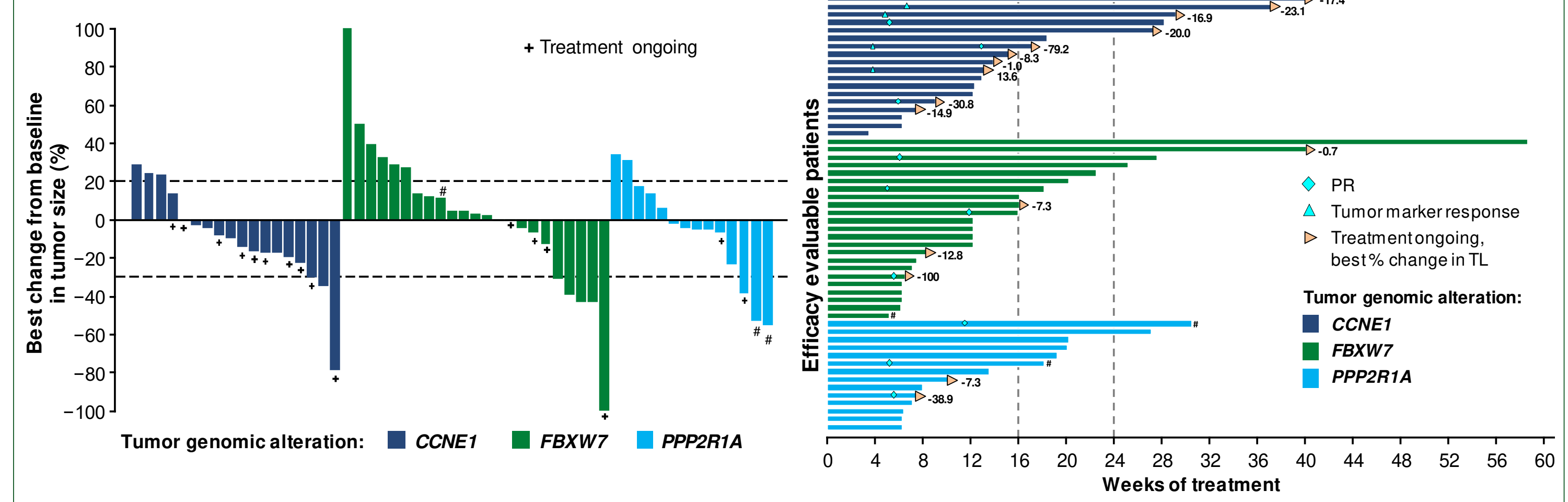
Meaningful tumor reductions and durable clinical benefit observed in heavily pre-treated patients



- **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 continues

* Gynecologic cancers: ovarian, endometrial, and cervical cancers. Data represent the efficacy evaluable patient population (≥1 post-baseline tumor assessment).

Meaningful tumor reductions and clinical benefit across all lunresertib-sensitizing alterations



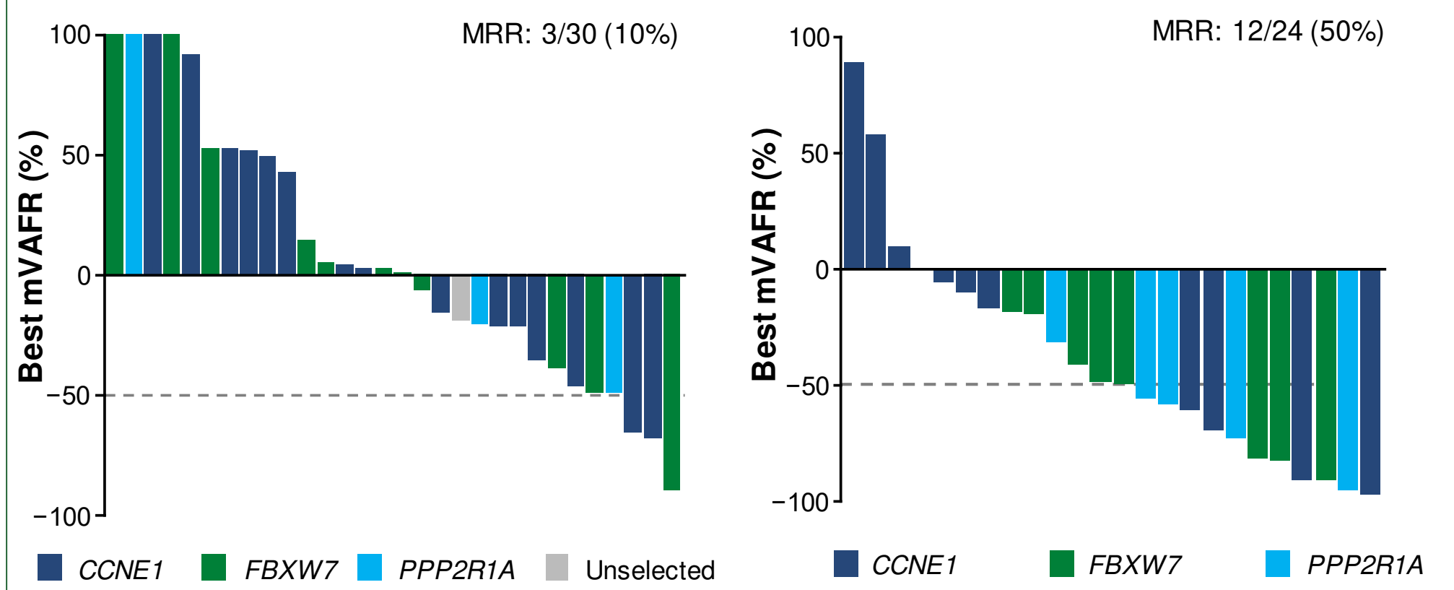
- ORs across all genotypes were 33.3% in *CCNE1* (n=18), 17.4% in *FBXW7* (n=23), and 21.4% in *PPP2R1A* (n=14)
- CBR is promising across genotypes with 44% in *CCNE1* (n=18), 35% in *FBXW7* (n=23), and 50% in *PPP2R1A* (n=14)
- MRR (evaluation ongoing) is 40% in *CCNE1* (n=10), 44% in *FBXW7* (n=9), and 80% in *PPP2R1A* (n=5)
- 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 (≥ 1 post-baseline tumor assessment).

Results

Significantly higher molecular responses confirm the benefit of combination therapy

A. Lunresertib monotherapy | **B. Lunresertib + camonsertib**



- MRs were observed across lunresertib-sensitizing molecular alterations[2]
- MRR with combination therapy was significantly higher compared to monotherapy (p=0.003)

Molecular response: ≥ 50% decline in mVAF assessed by Tempus xF and Tempus xF+ gene panels for patients with detectable somatic alterations in **A**) monotherapy and **B**) combination therapy, respectively; best mVAFR capped at +100%. *p*-value of monotherapy vs. combination therapy determined using chi-squared test.

Conclusions

- **First clinical proof-of-concept for a synthetic lethal strategy with a PKMYT1 inhibitor in patients with molecularly selected cancers**
- **Lunresertib, first-in-class, potent PKMYT1 inhibitor, in cancers with *CCNE1* amplification, *PPP2R1A* and *FBXW7* deleterious mutations**
  - Proof of mechanism established, and preliminary antitumor activity observed
  - Well tolerated with low-grade, transient rash
- **Lunresertib + camonsertib is well tolerated with promising anti-tumor activity across tumors and genomic alterations**
  - Most common TRAE was anemia, likely due to combination synergy
  - Overall response 33.3% at RP2D range (n=18) and 23.6% across all doses (N=55)
  - Overall response 60% in heavily pre-treated gynecologic cancers at preliminary RP2D (n=10) and 38.5% across all doses (n=26)
  - Molecular response rate was 50% in patients with available paired samples (n=24)
  - Schedule optimization in multiple tumors and genomic alterations is ongoing
- **This oral combination may provide a novel therapeutic option in areas of high clinical unmet need**

References

1. *Gallo et al. Nature. 2022; 604 (7907): 749-756.* 2. **ANE poster B057**: Gallo *et al.* Preclinical development of PKMYT1 and ATR inhibitor combinations. 3. **ANE poster B045**: *Rosen et al.* Camonsertib (RP-3500), an ataxia telangiectasia- and Rad3-related kinase inhibitor (ATRi) in combination with low dose gemcitabine (gem) in patients with solid tumors with DNA damage response (DDR) aberrations: Preclinical and Phase 1b results (NCT04497116). *4. Yap TA, et al. Nat Med. 2023 Jun;29(6):1400-1411.* 5. 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].

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Abbreviations

ANC, absolute neutrophil count; ATR, ataxia telangiectasia and Rad-3 related; ATRi, ATR inhibitor; AUC, area under the curve; BID, twice daily; BID-I, twice daily, intermittent; BL, baseline; Cam, camonsertib; CA-125, cancer antigen-125; CBR, clinical benefit rate; CDC25, cell division cycle-25; CDK, cyclin-dependent kinase; CHK1, checkpoint kinase 1; CN, copy number; cPR, confirmed partial response; CRC, colorectal cancer; ctDNA, circulating tumor DNA; ECOG PS, Eastern Cooperative Oncology Group performance status; ELISA, enzyme linked immunoabsorbant assay; FISH, fluorescence *in situ* hybridization; G, grade; GCIG, Gynecological Cancer Intergroup; GI, gastrointestinal; Hgb, hemoglobin; IHC, immunohistochemistry; LN, lymph node; Lunre, lunresertib; M1, module 1; M2, module 2; MRR, molecular response rate; MYTHIC, PKMYT1 inHIbition for the treatment of Cancers; mVAFR, mean variant allele frequency ratio; NGS, next-generation sequencing; O/E, overexpression; OR, overall response based on RECIST or GCIG CA-125 response; PBMC, peripheral blood mononuclear cells; pCDK1, phosphorylated CDK1; PD, pharmacodynamics; PFS, progression free survival; PK, pharmacokinetics; PKMYT1, protein kinase, membrane associated tyrosine/threonine 1; PP2A, protein phosphatase 2A; PR, partial response; PSA, prostate-specific antigen; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended phase 2 dose; SL, synthetic lethal; SNiPDx, SyNthetic lethal Interactions for Precision Diagnostics; SNiPRx, SyNthetic lethal Interactions for Precision Therapeutics platform; TA, tumor assessment; Thr, threonine; TL, target lesion; TRAE, treatment-related adverse event; Tx, treatment; uPR, unconfirmed partial response; wk, week; y, years; 3-on/4-off, 3 days on / 4 days off; 5-on/2-off, 5 days on / 2 days off.

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