AACR-NCI-EORTC International Conference on
MOLECULAR TARGETS AND CANCER THERAPEUTICS
October 11-15, 2023 | Hynes Convention Center | Boston, MA

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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AACR American Association for Cancer Research® | NIH NATIONAL CANCER INSTITUTE | EORTC European Organisation for Research and Treatment of Cancer

Disclosure Information

Molecular Targets and Cancer Therapeutics
October 11-15, 2023 | Boston, MA

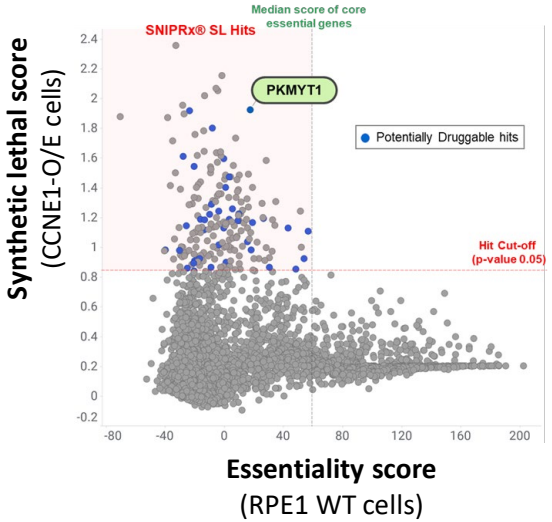
Timothy A. Yap

- **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

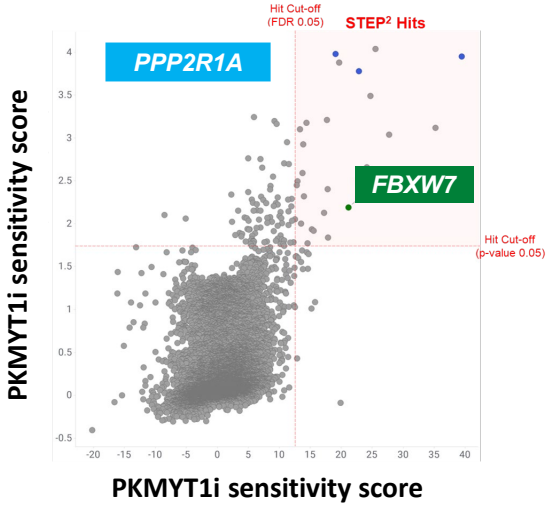
PKMYT1 was identified as a strong synthetic lethal partner to *CCNE1* amplification[1]

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.

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

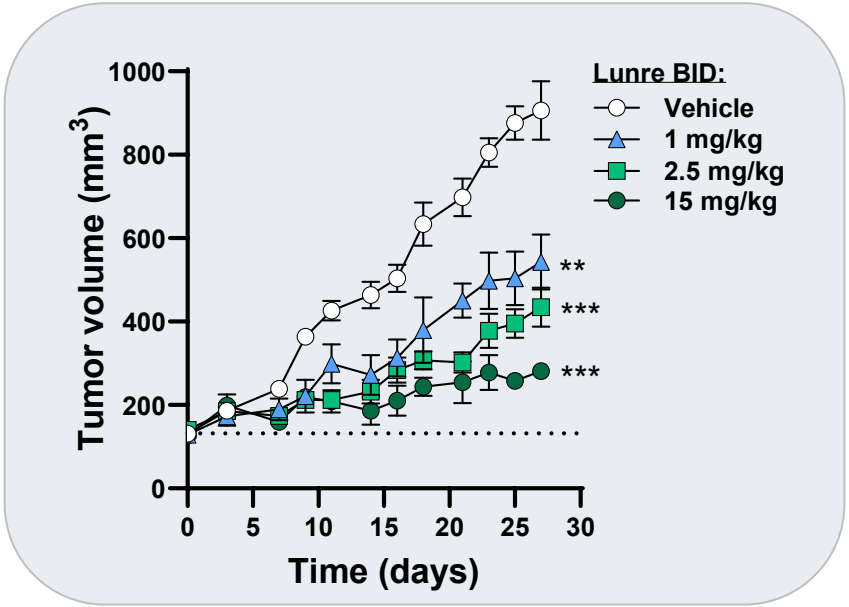
Lunresertib profile:

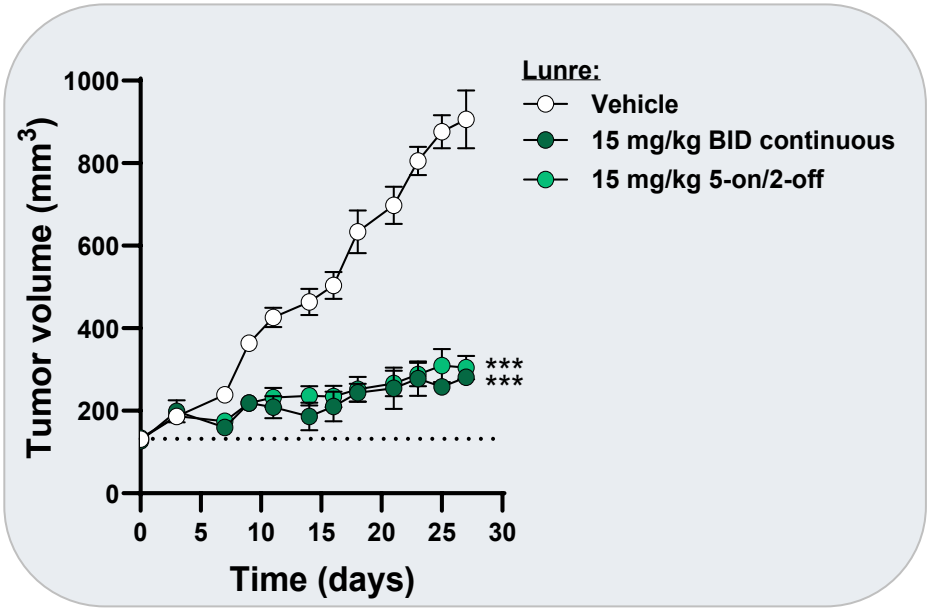
- Highly potent and selective inhibitor
- PanLabs Lead Profiling screen on 68 assays showed no significant activity at 10 µM
- No activity (>100 µM) in patch clamp assays for hERG, hNaV1.5, and hCaV1.2 ion channels
- Favorable pre-clinical PK profile
- Low potential for clinical drug-drug interactions

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.

Lunresertib monotherapy inhibits xenograft growth across doses and schedules

HCC1569 *CCNE1* amplified Breast Cancer CDX model

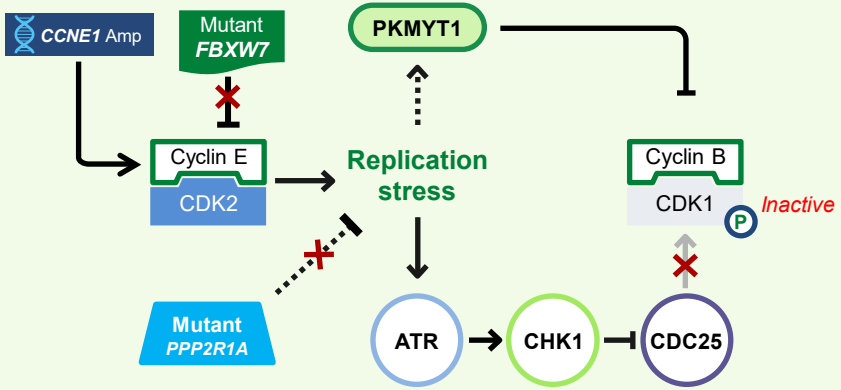




5-on/2-off, 5 days on / 2 days off; BID, twice daily; Lunre, lunresertib.

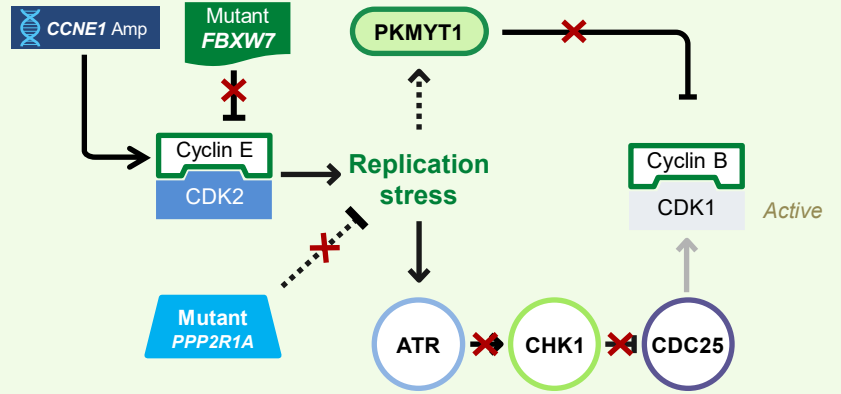
PKMYT1 and ATR inhibitors synergize to enhance anti-tumor activity[1]

Lunresertib-sensitizing alterations engage ATR through replication stress



ATR activation (through CHK1-mediated inhibition of CDC25) results in inactive CDK1

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

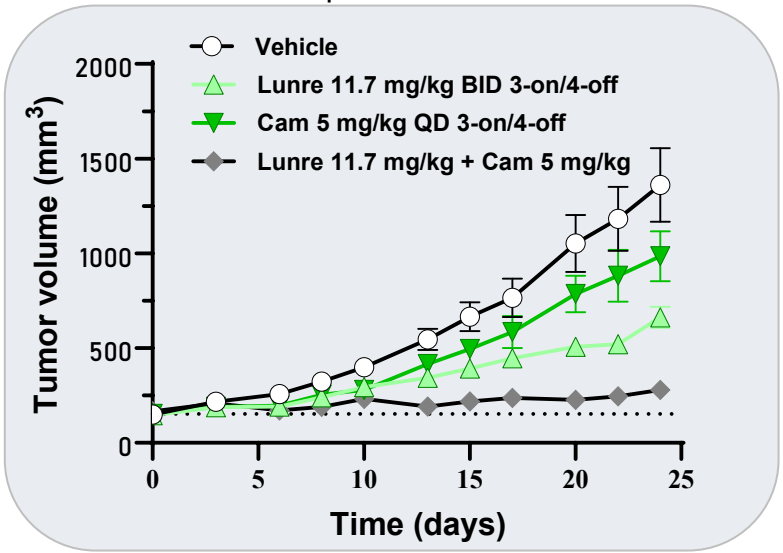


[1] ANE poster B057: Gallo *et al.* Preclinical development of PKMYT1 and ATR inhibitor combinations. ATR, ataxia telangiectasia and Rad-3 related; CDC25, cell division cycle-25; CDK, cyclin-dependent kinase; CHK1, checkpoint kinase 1; PKMYT1, protein kinase, membrane associated tyrosine/threonine 1.

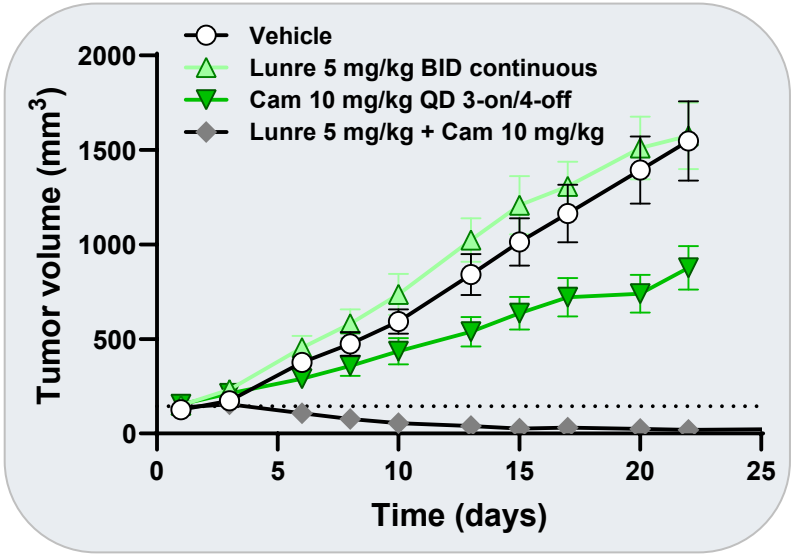
Lunresertib and camonsertib combination treatment is active in *CCNE1* amplified or *FBXW7* altered tumor models

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*

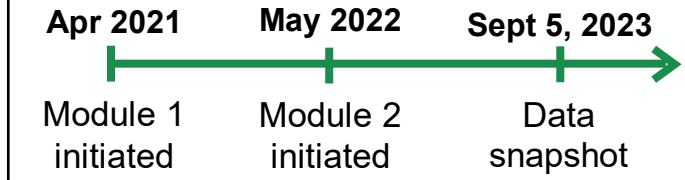
* Additional internal Repare data, not shown. Free drug exposure of 5-10 mg/kg dose in mouse (AUC or C_{min}) are comparable to that at the respective human RP2Ds. 5-on/2-off, 5 days on / 2 days off; 3-on/4-off, 3 days on / 4 days off; AUC, area under the curve; BID, twice daily; Cam, camonsertib; Lunre,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

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 objectives:

- Safety and tolerability
- RP2D, schedule

✓ Other objectives:

- 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.

MYTHIC: Patient demographics

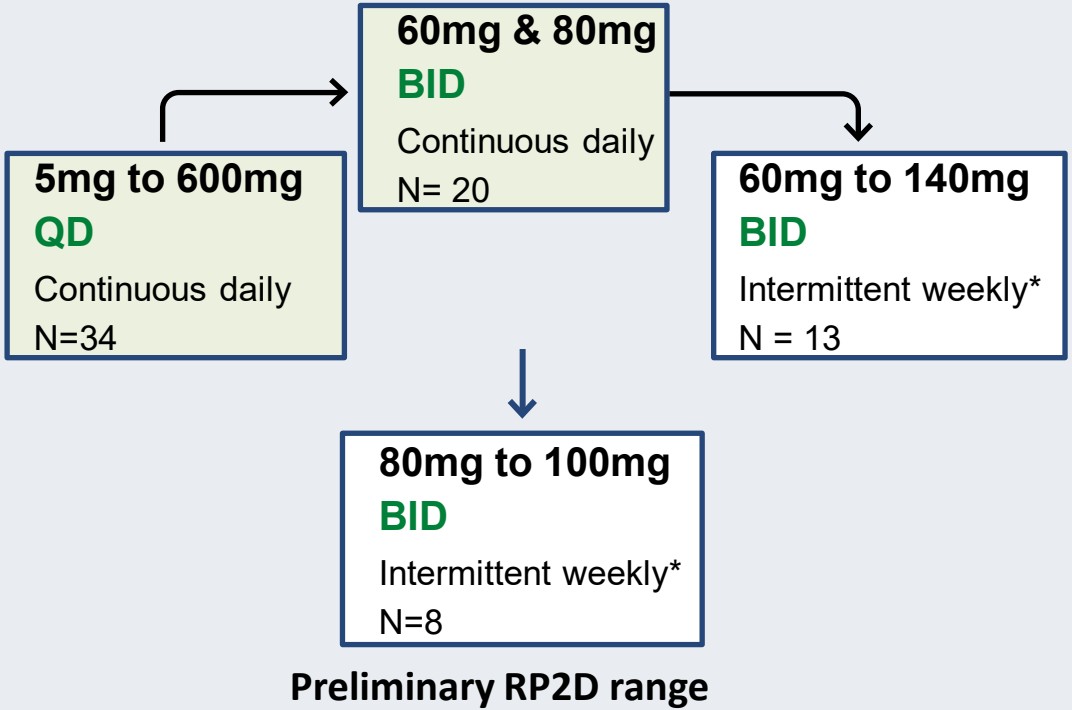
Similar patient characteristics in monotherapy and combination therapy cohorts

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.

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 was 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

Lunresertib monotherapy: Treatment related adverse events (TRAEs)

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

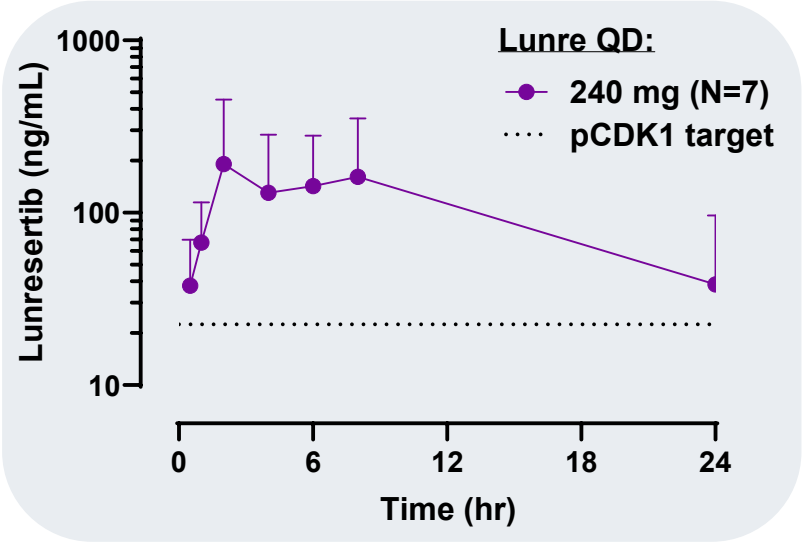
TRAEs in ≥ 15% of patients, n (%)	All Patients N=67			Preliminary RP2D range 80-100mg BID-I N=8		
	All Grades	G3	G4	All Grades	G3	G4
Rash*	23 (34.3)	5 (7.5)	**0**	4 (50.0)	0	**0**
Nausea/Vomiting	21 (31.3)	1 (1.5)	**0**	2 (25.0)	0	**0**
Anemia	15 (22.4)	4 (6.0)	**0**	1 (12.5)	0	**0**
Fatigue	15 (22.4)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

- **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

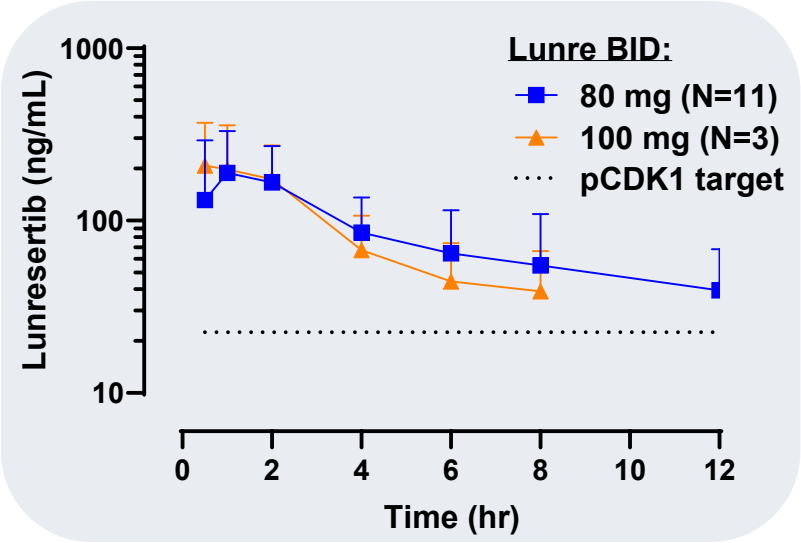
* Rash terms included: dermatitis contact, eczema, erythema, flushing, pruritis, rash, rash erythematous, rash maculopapular, rash pruritic, skin exfoliation. BID-I, twice daily, intermittent; G, grade; RP2D, recommended phase 2 dose.

Target PK exposures achieved with lunresertib

Cycle 1 - Day 1 PK at 240 mg QD



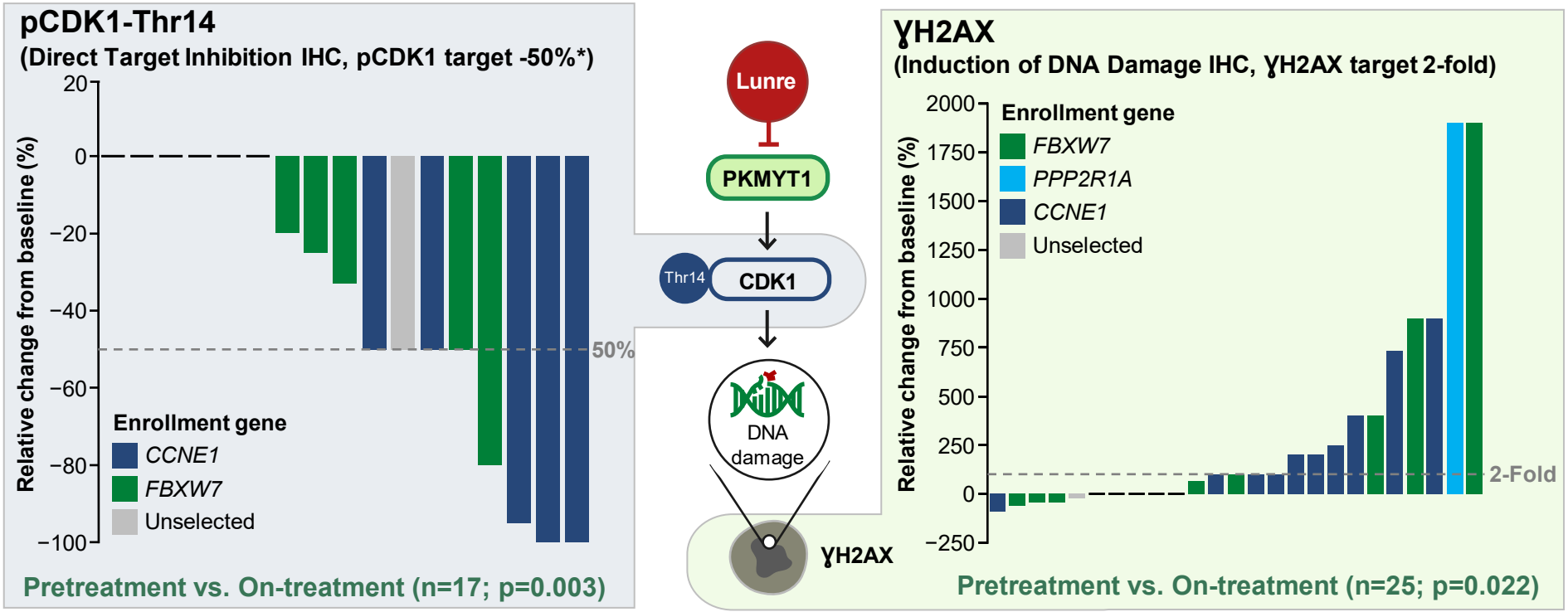
Cycle 1 - Day 1 PK at 80 and 100 mg BID



- 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.

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, phosphorylated cyclin-dependent kinase 1; PKMYT1, protein kinase, membrane associated tyrosine/threonine 1; Thr, threonine.

Anti-tumor activity with lunresertib monotherapy

One RECIST responder

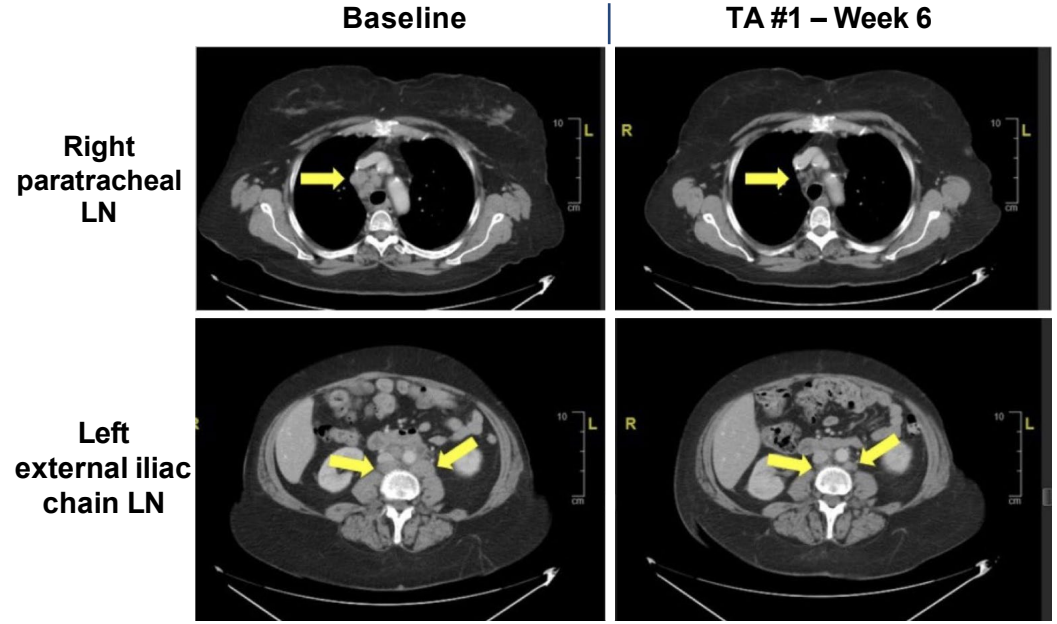
Female
73 years old

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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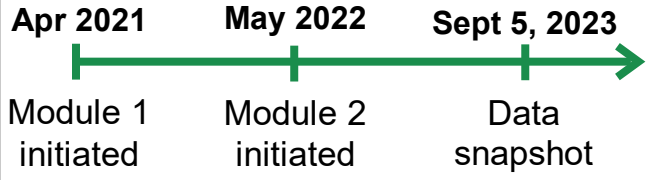
Study ongoing *NCT04855656*



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Lunresertib with camonsertib dose escalation

Thorough dose/schedule evaluation

Camonsertib

80mg* **QD** 3d on /4d off

+

Lunresertib†

40mg **BID** Continuous N= 5

80mg **BID** 3d on/4d off N=21**

60 mg **BID** 3d on/4d off N=15

120mg **QD** Continuous N=6

240mg **QD** 3d on/4d off N=12

→

RP2D/schedule optimization

Camonsertib

80mg **QD** 3d on /4d off

+

Lunresertib

80mg **BID** 3d on /4d off

Preliminary RP2D: N=20

† 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.

Lunresertib + camonsertib: Treatment related adverse events (TRAEs)

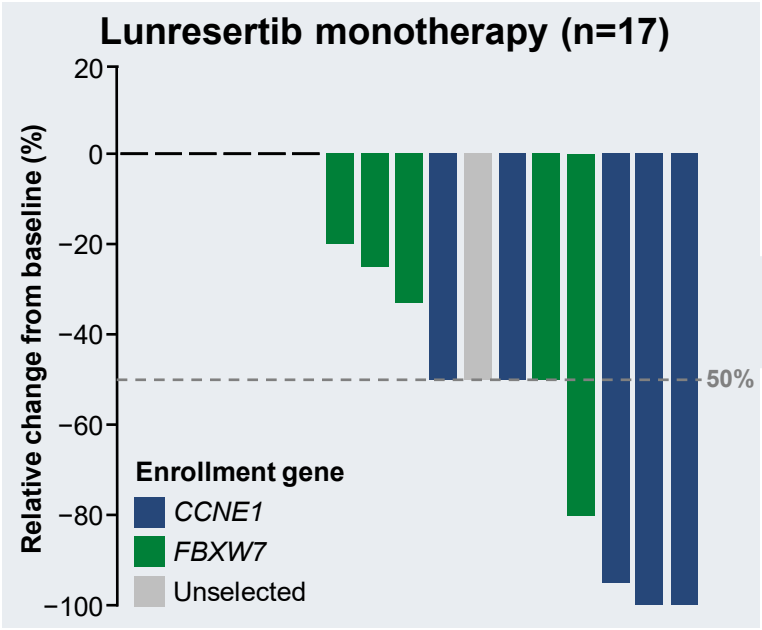
TRAEs in ≥15% of patients, n (%)	All Patients N=59			Preliminary RP2D N=20		
	All Grades	G3	G4	All Grades	G3	G4
Anemia	40 (67.8)	25 (42.4)	0	13 (65.0)	9 (45.0)	0
Nausea/Vomiting	38 (64.4)	0	0	9 (45.0)	0	0
Fatigue	24 (40.7)	0	0	5 (25.0)	0	0
Rash*	23 (39.0)	1 (1.7)	0	7 (35.0)	0	0
Leukopenia	12 (20.3)	2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

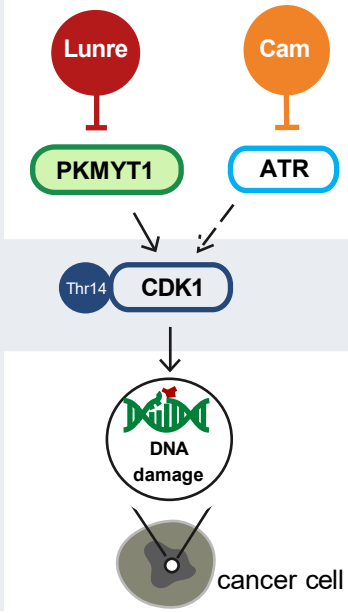
- **At the preliminary RP2D:**
  - No Grade 4 TRAEs
  - *Anemia* was the most common TRAE
    - Likely due to synergy and ATRi effect[1]
    - Grade 3 anemia detected early (< 6w) in patients with high-risk features†; others had later onset (> 6w)
    - Did not lead to discontinuations
    - Usually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

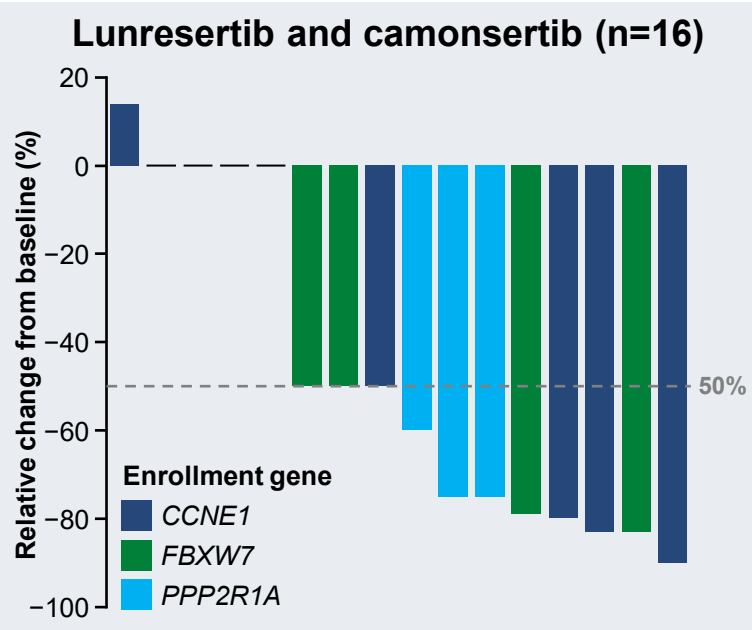
- Combination therapy DLTs: anemia, rash/mucositis, and neutropenia
- **Preliminary RP2D: lunresertib 80 mg BID + camonsertib 80 mg QD; both 3 d on/ 4 d off**
  - Weekly or 2 weeks on / 1 week off — **schedule optimization ongoing**
  - Dose of camonsertib is ~50% lower than the monotherapy RP2D

[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: Hgb = 10.7g/dl, previous therapies = 4, and 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.

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, phosphorylated cyclin-dependent kinase 1; PKMYT1, protein kinase, membrane associated tyrosine/threonine 1; Thr, threonine.

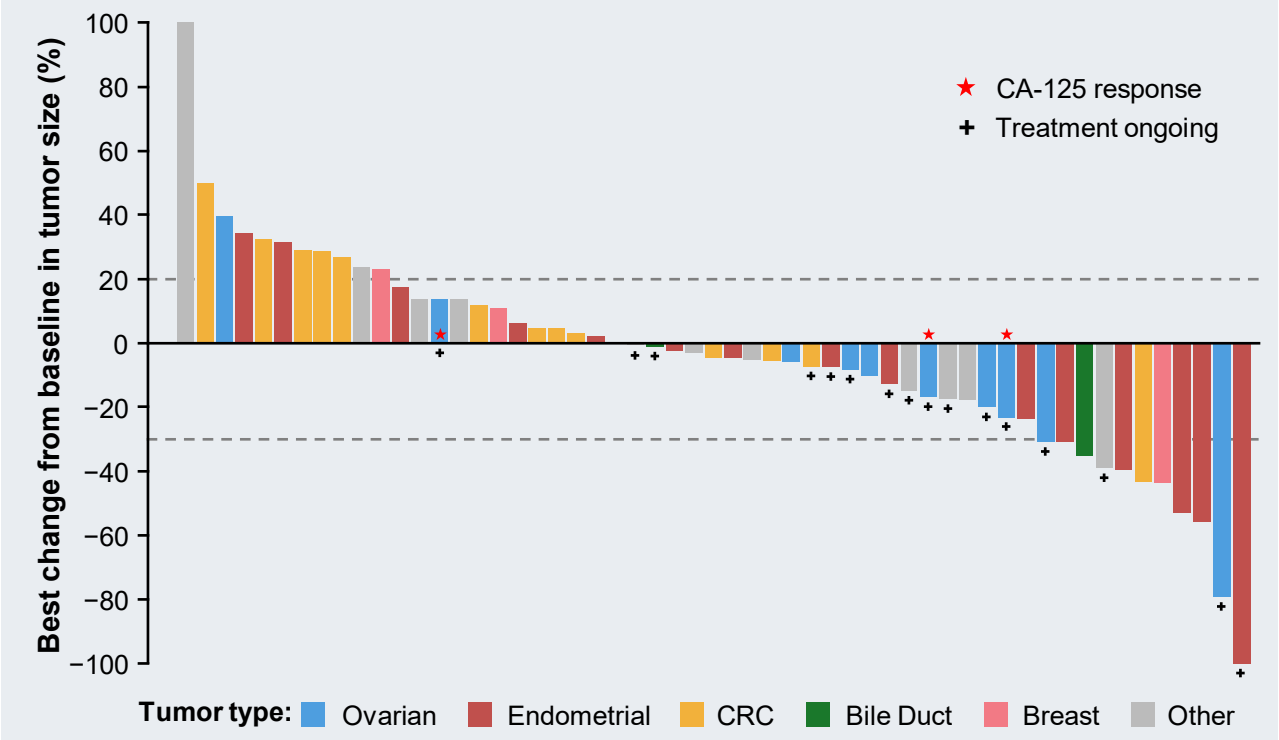
Responses to combination observed across tumor types and lunresertib-sensitizing alterations

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. BL, baseline; cPR, confirmed partial response; RECIST, Response Evaluation Criteria in Solid Tumors; TL, target lesion; Tx, treatment; uPR, unconfirmed partial response.

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

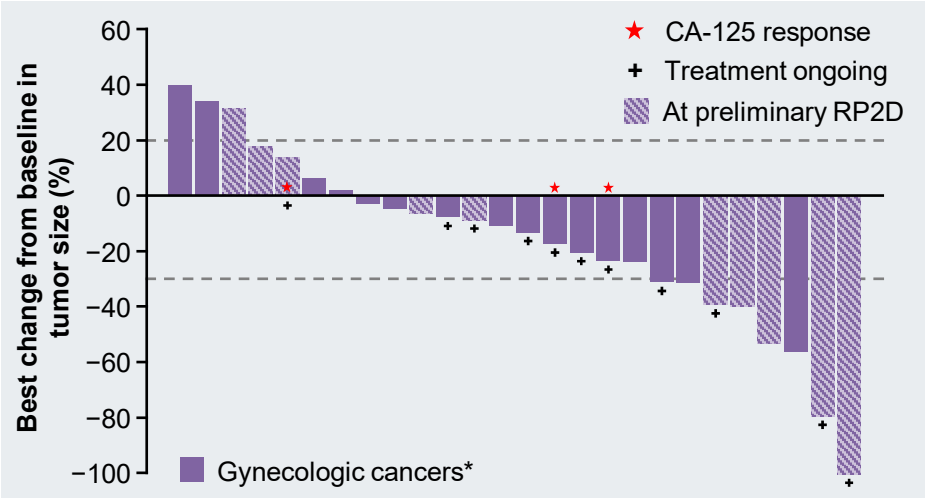


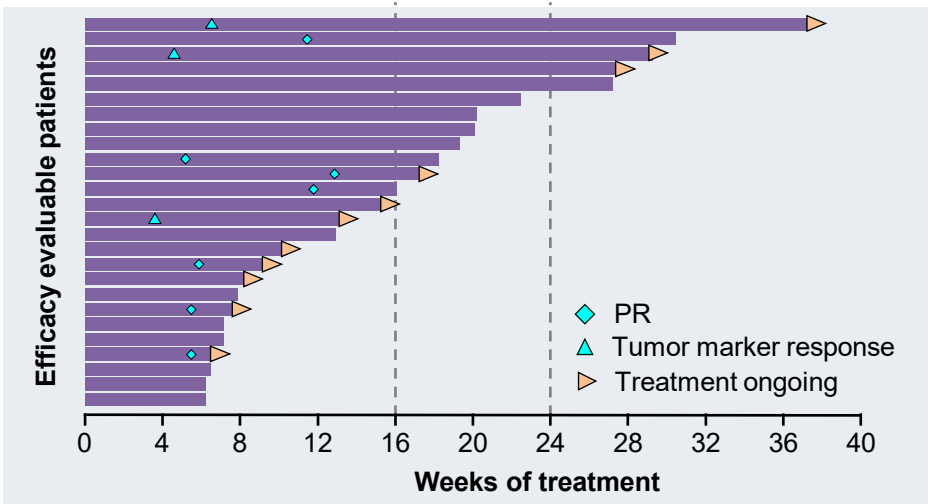
- **In evaluable patients*, across all tumors, all doses:**
  - OR: 23.6% (n=55)
  - CBR: 41.8% (n=55)
  - MRR: 50.0% (n=24)
- **At preliminary RP2D, across all tumors:**
  - OR: 33.3% (n=18)
  - CBR: 50.0% (n=18)

*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). CBR: overall response or time on treatment ≥ 16 wk w/o progression; CRC, colorectal cancer; RECIST, Response Evaluation Criteria in Solid Tumors (RECIST) Gynecological Cancer InterGroup (GCIG); MRR, molecular response rate; OR, overall response based on RECIST or GCIG CA-125 response; RP2D, recommended phase 2 dose.

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%)

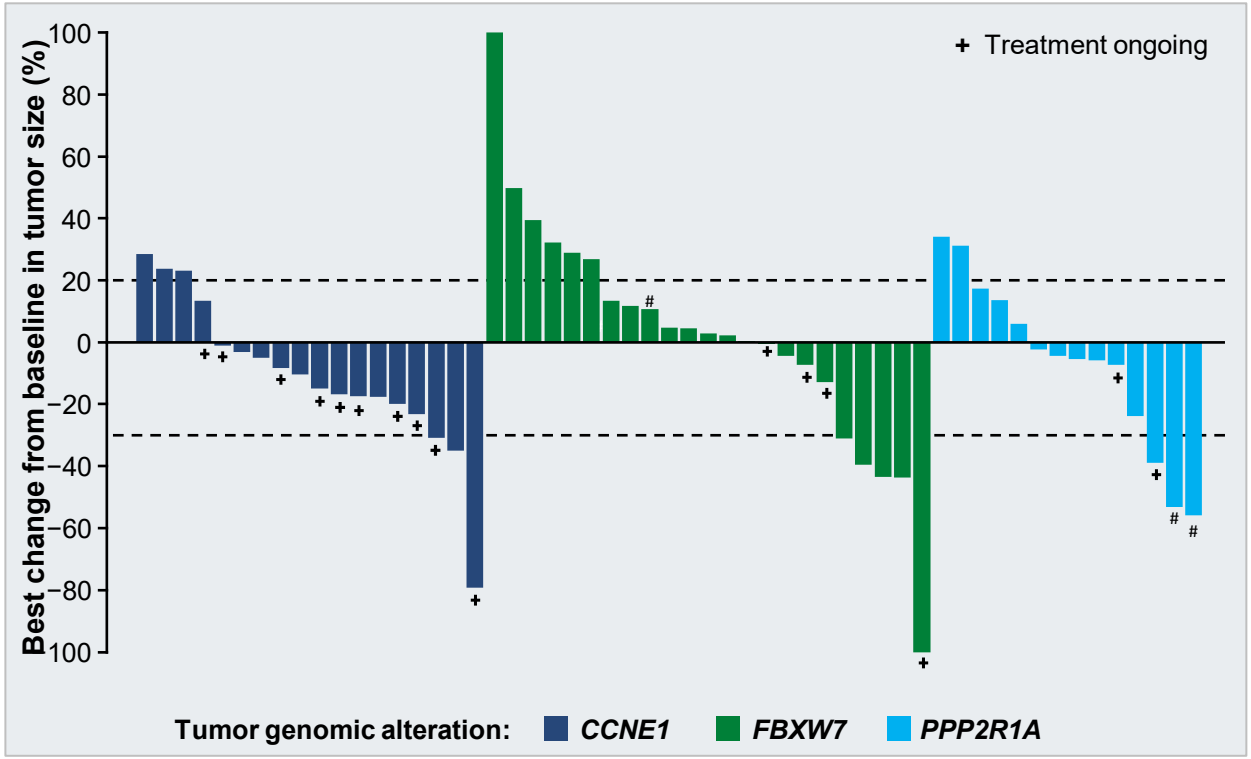
At preliminary RP2D (n=10):

- 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.

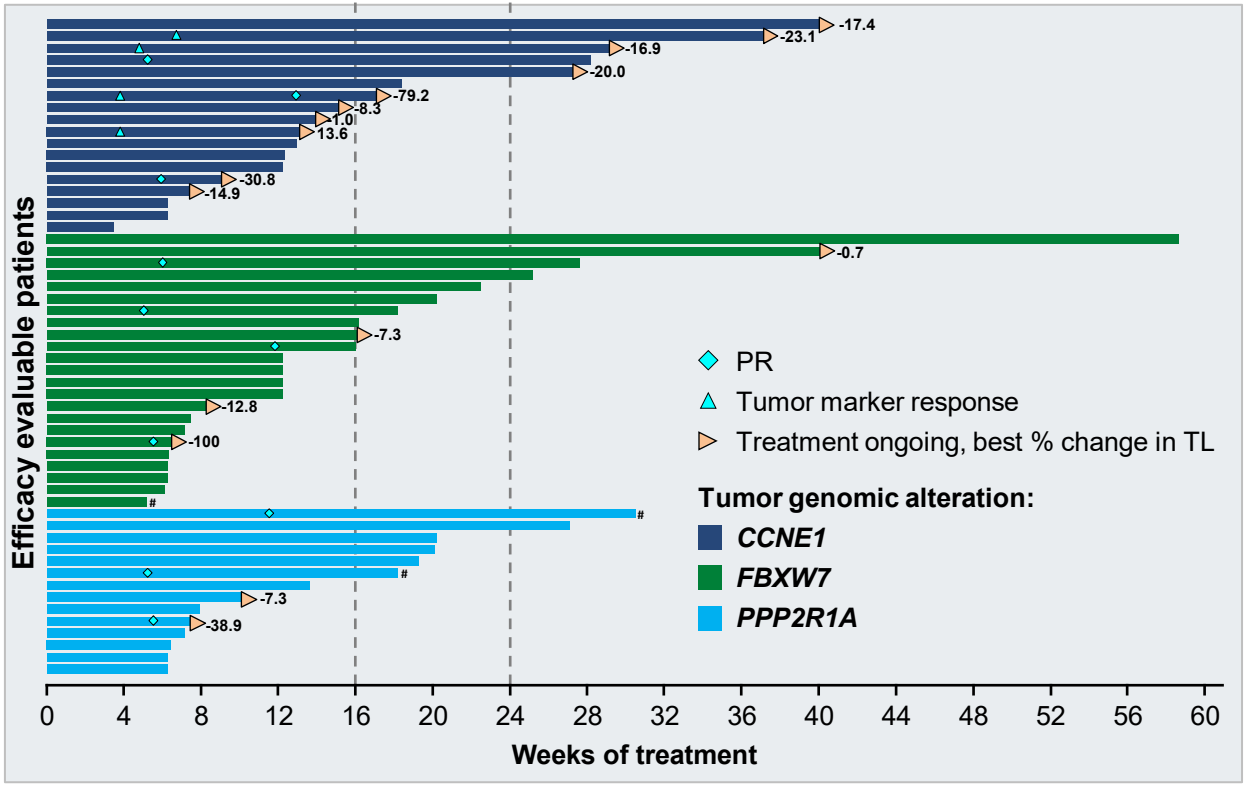
Meaningful tumor reductions across lunresertib-sensitizing alterations



- **OR across all genotypes:**
  - 33.3% in *CCNE1* (n=18)
  - 17.4% in *FBXW7* (n=23)
  - 21.4% in *PPP2R1A* (n=14)
- **CBR promising across genotypes:**
  - 44% in *CCNE1* (n=18)
  - 35% in *FBXW7* (n=23)
  - 50% in *PPP2R1A* (n=14)
- **MRR: evaluation ongoing**
  - 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.

Clinical benefit with combination treatment across lunresertib-sensitizing alterations and doses



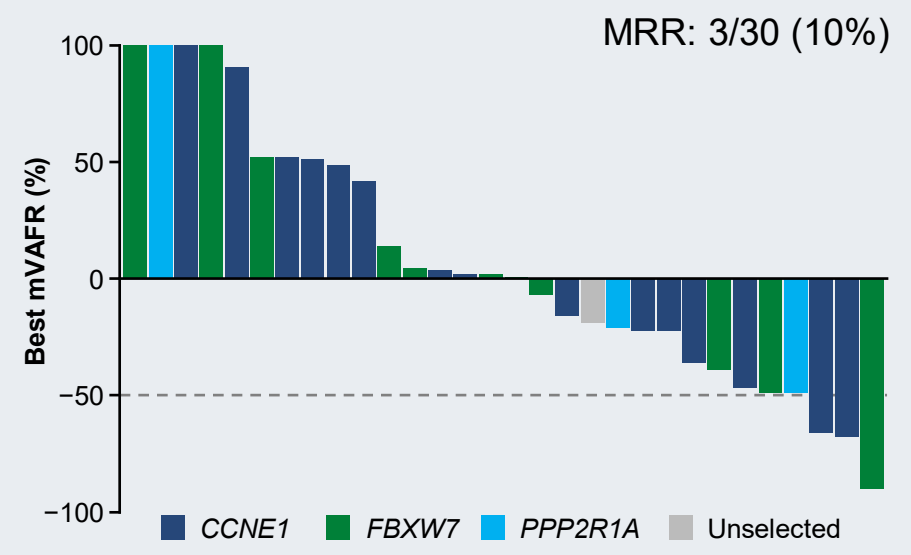
- **OR across all genotypes:**
  - 33.3% in *CCNE1* (n=18)
  - 17.4% in *FBXW7* (n=23)
  - 21.4% in *PPP2R1A* (n=14)
- **CBR is promising across genotypes:**
  - 44% in *CCNE1* (n=18)
  - 35% in *FBXW7* (n=23)
  - 50% in *PPP2R1A* (n=14)
- **Treatment ongoing in 16 patients**
- **Efficacy and tolerability 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 (≥ 1 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.

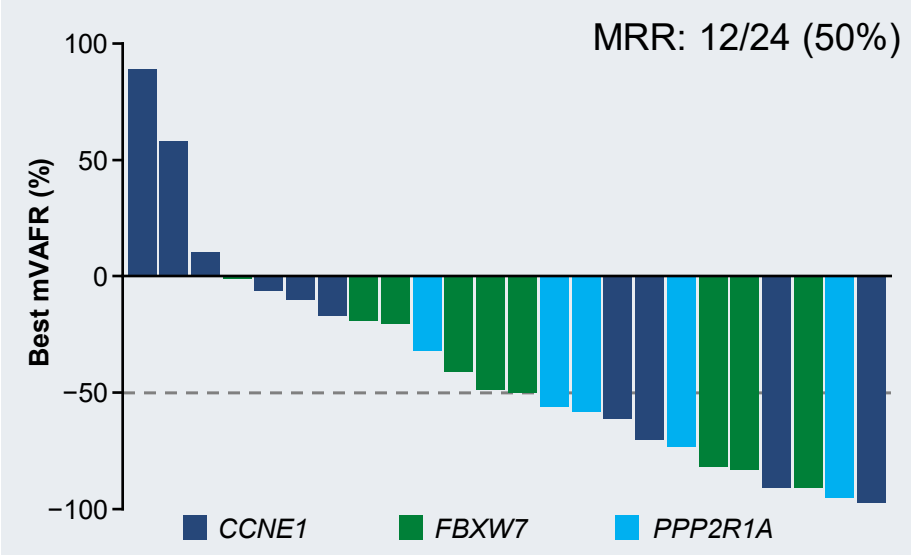
Significantly higher molecular responses confirm the benefit of combination treatment

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

Lunresertib monotherapy



Lunresertib + camonsertib



Molecular response rate with 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.

Early response in recurrent *FBXW7* mutated colorectal adenocarcinoma

Male
63 years old

Recurrent colorectal adenocarcinoma

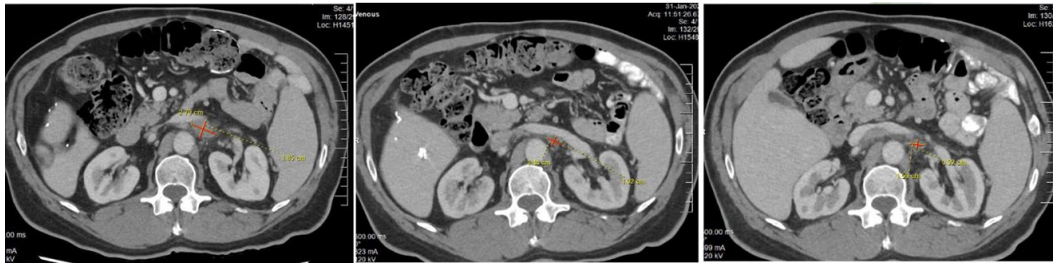
FBXW7
mutation

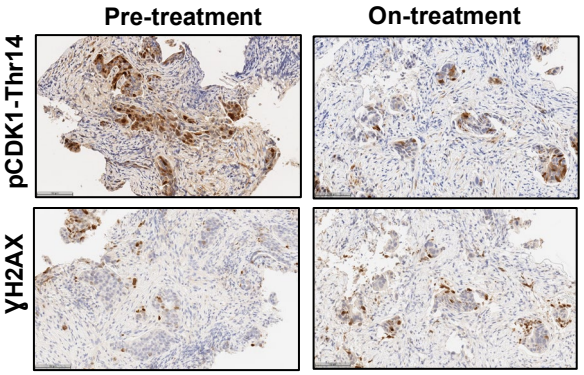
TP53 mut

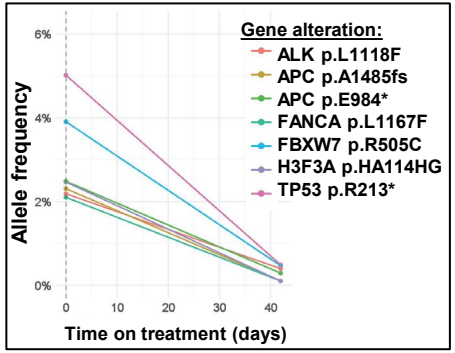
3 prior lines of therapy

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.

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

Female
56 years old

High grade serous ovarian carcinoma

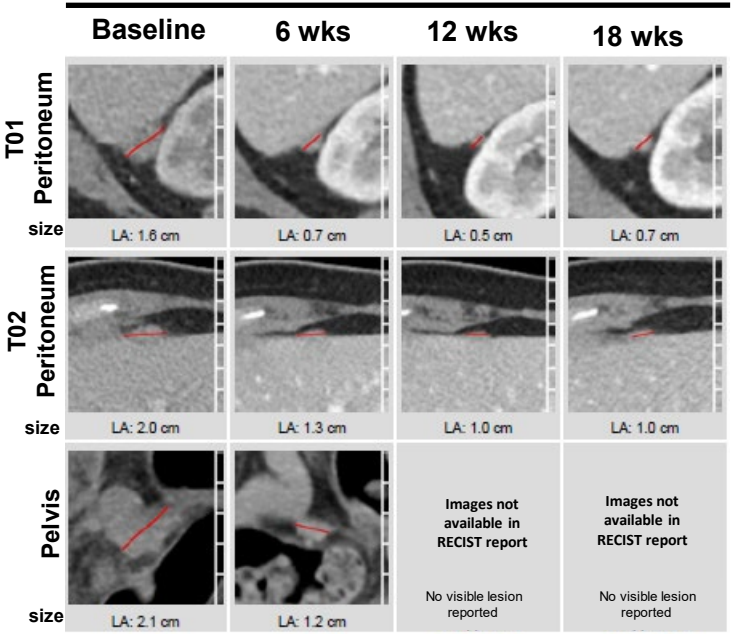
CCNE1 amplification

TP53 mut

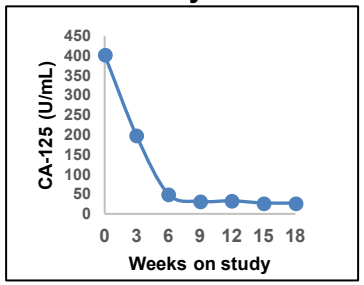
2 prior lines of therapy

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

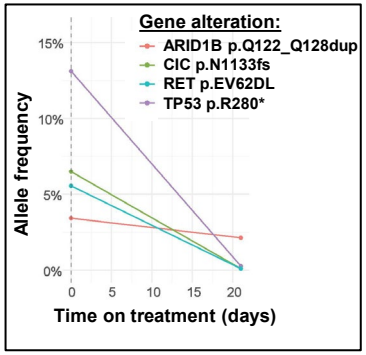
Tumor assessment



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; wks, weeks.

Prompt response in recurrent cervical carcinosarcoma with a *PPP2R1A* mutation

Female
66 years old

Recurrent cervical carcinosarcoma

PPP2R1A mutation

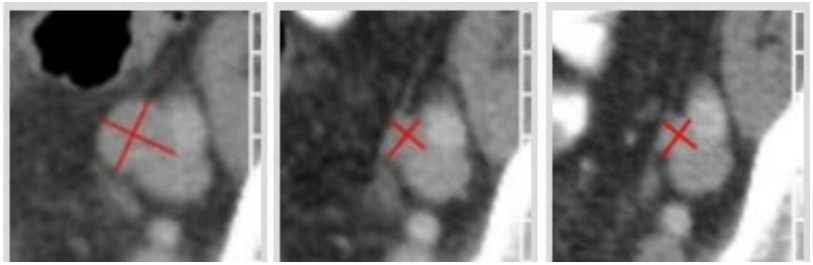
MYC amp
TP53 mut

1 prior line of therapy

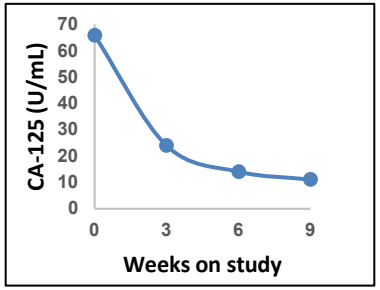
RP2D
Lunre 80mg BID 3/4
Cam 80mg QD 3/4

Tumor assessment

Left external iliac lymph node



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; cPR, confirmed partial response; RECIST, Response Evaluation Criteria in Solid Tumors; QD, once daily; RP2D, recommended phase 2 dose.

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 preliminary RP2D (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**

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