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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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)
- **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 amplification¹

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


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.

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: Potent and selective first-in-class PKMYT1 inhibitor

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

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; Cl_{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

Lunresertib-sensitizing alterations engage ATR through replication stress

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

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

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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.
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.
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

* 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.

Primary objectives:
- Safety and tolerability
- RP2D, schedule

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

Module 1:
Single agent lunresertib

- Initiated Apr 2021
- 67 patients

Module 2:
Lunresertib with camonsertib

- Initiated May 2022
- 59 patients

Data snapshot Sept 5, 2023
### Similar patient characteristics in monotherapy and combination therapy cohorts

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Lun alone N=67</th>
<th>Lun + Cam N=59</th>
<th>Parameter</th>
<th>Lun alone N=67</th>
<th>Lun + Cam N=59</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex, n (%)</strong></td>
<td></td>
<td></td>
<td><strong>Tumor types, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>17 (25.4)</td>
<td>15 (25.4)</td>
<td>Endometrial&lt;sup&gt;b&lt;/sup&gt;</td>
<td>23 (34.3)</td>
<td>17 (28.8)</td>
</tr>
<tr>
<td>Female</td>
<td>50 (74.6)</td>
<td>44 (74.6)</td>
<td>Colorectal</td>
<td>11 (16.4)</td>
<td>13 (22.0)</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
<td>Ovarian</td>
<td>11 (16.4)</td>
<td>11 (18.6)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>60 (15, 81)</td>
<td>65 (16, 81)</td>
<td>Breast</td>
<td>3 (4.5)</td>
<td>3 (5.1)</td>
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<tr>
<td>≥65 years, n (%)</td>
<td>25 (37.3)</td>
<td>30 (50.8)</td>
<td>Lung</td>
<td>0</td>
<td>3 (5.1)</td>
</tr>
<tr>
<td>**ECOG PS&lt;sup&gt;a&lt;/sup&gt;, n (%)</td>
<td></td>
<td></td>
<td>Other&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>21 (31.3)</td>
<td>23 (39.0)</td>
<td>19 (28.4)</td>
<td>12 (20.3)</td>
<td></td>
</tr>
<tr>
<td>1/2</td>
<td>44 (65.7) / 1 (1.5)</td>
<td>35 (59.3) / 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Prior lines of therapy, n (%)</strong></td>
<td></td>
<td></td>
<td>Most common genotypes&lt;sup&gt;d&lt;/sup&gt;, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1 (1.5)</td>
<td>0</td>
<td><strong>CCNE1</strong></td>
<td>31 (46.3)</td>
<td>20 (33.9)</td>
</tr>
<tr>
<td>1-2</td>
<td>21 (31.3)</td>
<td>24 (40.7)</td>
<td><strong>FBXW7</strong></td>
<td>21 (31.3)</td>
<td>23 (39.0)</td>
</tr>
<tr>
<td>3-4</td>
<td>25 (37.3)</td>
<td>24 (40.7)</td>
<td><strong>PPP2R1A</strong></td>
<td>12 (17.9)</td>
<td>13 (22.0)</td>
</tr>
<tr>
<td>≥5</td>
<td>20 (29.9)</td>
<td>11 (18.6)</td>
<td><strong>PPP2R1A and CCNE1</strong></td>
<td>0</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>Prior platinum, n (%)</td>
<td>58 (86.6)</td>
<td>51 (86.4)</td>
<td><strong>PPP2R1A and FBXW7</strong></td>
<td>1 (1.5)</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>FBXW7 and CCNE1</strong></td>
<td>0</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Unselected endometriale</td>
<td>2 (3)</td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>a</sup>One each, pediatric patient in monotherapy and combination with Lansky Performance Status score 80 and 90, respectively. <sup>b</sup>Includes uterine serous carcinoma, carcinosarcoma, clear cell carcinoma, endometrioid. <sup>c</sup>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, gastrointestinal 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). <sup>d</sup>4 patients in lun + cam cohort also had ATRi-sensitizing alterations: 2 biallelic and 2 of unknown allelic status. **Endometrial patients without CCNE1, FBXW7, or PPP2R1A mutation.** Cam, camonsertib; ECOG PS, Eastern Cooperative Oncology Group Performance Status; GI, gastrointestinal; Lun, lunresertib.
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

Multiple doses/schedules of lunresertib tested

5mg to 600mg QD
Continuous daily N=20

60mg & 80mg BID
Continuous daily N=20

60mg to 140mg BID
Intermittent weekly* N = 13

80mg to 100mg BID
Intermittent weekly* N=8

Preliminary RP2D range

* 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

<table>
<thead>
<tr>
<th>TRAEs in ≥ 15% of patients, n (%)</th>
<th>All Patients N=67</th>
<th>Preliminary RP2D range 80-100mg BID-I N=8</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>G3</td>
</tr>
<tr>
<td>Rash*</td>
<td>23 (34.3)</td>
<td>5 (7.5)</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>21 (31.3)</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>Anemia</td>
<td>15 (22.4)</td>
<td>4 (6.0)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>15 (22.4)</td>
<td>1 (1.5)</td>
</tr>
</tbody>
</table>

- **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 erythematosus, rash maculopapular, rash pruritic, skin exfoliation. BID-I, twice daily, intermittent; G, grade; RP2D, recommended phase 2 dose.
Target PK exposures achieved with lunresertib

- 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

**pCDK1-Thr14**
(Direct Target Inhibition IHC, pCDK1 target -50%*)

**ƔH2AX**
(Induction of DNA Damage IHC, ƔH2AX target 2-fold)

*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. 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.

Enrollment gene
- **CCNE1**
- **FBXW7**
- **PPP2R1A**
- **Unselected**

**Relative change from baseline (%)**

Pretreatment vs. On-treatment (n=17; p=0.003)

Pretreatment vs. On-treatment (n=25; p=0.022)
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.
### 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 0-1
- Hgb ≥ 10 g/dL
- Platelets ≥ 100 K/uL
- ANC ≥ 1.5 K/uL

**Study ongoing** NCT04855656

**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). 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.
Thorough dose/schedule evaluation

Camonsertib

- 80mg
  - QD
  - 3d on/4d off
  - N=5

Lunresertib†

- 40mg
  - BID
  - Continuous
  - N=5

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

- 120mg
  - QD
  - Continuous
  - N=5

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

Camonsertib

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

Lunresertib

- 80mg
  - QD
  - 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)

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

**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

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\(^\dagger\) 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  
linresertib-sensitizing alterations

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Genotype</th>
<th>Response</th>
<th>Best % change in TL from BL</th>
<th>Therapy (weeks)</th>
<th>Lines of prior Tx/ prior platinum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrial</td>
<td>$PPP2R1A/FBXW7$</td>
<td>cPR</td>
<td>-55.9</td>
<td>30.4</td>
<td>3/Y</td>
</tr>
<tr>
<td></td>
<td>$PPP2R1A/CCNE1$</td>
<td>cPR</td>
<td>-53.0</td>
<td>18.1</td>
<td>2/Y</td>
</tr>
<tr>
<td></td>
<td>$FBXW7$</td>
<td>cPR*</td>
<td>-100.0</td>
<td>11.1+</td>
<td>3/Y</td>
</tr>
<tr>
<td></td>
<td>$FBXW7$</td>
<td>uPR</td>
<td>-39.6</td>
<td>16.0</td>
<td>3/Y</td>
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<tr>
<td></td>
<td>$FBXW7$</td>
<td>uPR*</td>
<td>-44.7</td>
<td>11.4+</td>
<td>3/Y</td>
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<tr>
<td></td>
<td>$CCNE1$</td>
<td>cPR*</td>
<td>-70.2</td>
<td>21.4+</td>
<td>2/Y</td>
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<tr>
<td></td>
<td>$CCNE1^\dagger$</td>
<td>cPR*</td>
<td>-30.8</td>
<td>12.6+</td>
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<tr>
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<td>CA-125</td>
<td>-16.9</td>
<td>29.0+</td>
<td>9/Y</td>
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<tr>
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<td>37.0+</td>
<td>2/Y</td>
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<td>CA-125</td>
<td>13.6</td>
<td>12.9+</td>
<td>5/Y</td>
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<td>Colorectal</td>
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<td>Breast</td>
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<td>uPR</td>
<td>-43.8</td>
<td>18.1</td>
<td>2/N</td>
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* 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 $^\dagger$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.

RECIST and tumor marker responses occurred early despite heavily pre-treated, relapsed/refractory patient population
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%)
  - Patients had 1-9 prior therapies (median=3); treatment ongoing in 11 patients; enrollment in expansion cohorts at RP2D continues

At preliminary RP2D (n=10):
- Overall response: 60%; RECIST Response: 50%
- CBR: 70%

* 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

Lunresertib monotherapy

MRR: 3/30 (10%)

Lunresertib + camonsertib

MRR: 12/24 (50%)

Molecular response rate with combination treatment was significantly higher than with monotherapy ($p=0.003$)

1 ANE poster B057: Gallo et al. Molecular response: $\geq 50\%$ 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

### Overall response:
cPR (RECIST)

### RECIST target lesion decrease
-43.3%

### Received therapy for
27.6 weeks

**Gene alteration:**
- ALK p.L1118F
- APC p.A1485fs
- APC p.E984*
- FANCA p.L1167F
- FBXW7 p.R505C
- H3F3A p.HA114HG
- TP53 p.R213*

### Allele frequency

### Time on treatment (days)

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

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

CA-125 dynamics
ctDNA dynamics
Gene alteration:
- ARID1B p.Q122_Q128dup
- CIC p.N1133fs
- RET p.EV62DL
- TP53 p.R280*

Tumor assessment

Baseline 6 wks 12 wks 18 wks

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<th>6 wks</th>
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<th>12 wks</th>
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<table>
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</table>

Images not available in RECIST report
No visible lesion reported

CA-125 (U/mL)

Weeks on study

No visible lesion reported

Allele frequency

Time on treatment (days)

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

**Tumor assessment**

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

**CA-125 dynamics**

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
Acknowledgements

The authors would like to thank all patients and caregivers, and all investigators involved in this study

Participating MYTHIC Sites study coordinators for their contribution
- Hansini Krishna; Desirae Dufner; Jessica Johnson; Ileana Gutierrez – University of Texas MD Anderson Cancer Center
- Maxwell Blanch; Lydia Bosque-Hamilton; Ava Greenberg – Dana-Farber Cancer Institute
- Andrea Standish; Kristina Powell; Diego Rodriguez; Katherine Ouellette; Kimberly Zola – Perelman School of Medicine University of Pennsylvania
- Ashley Marie Rodriguez – Memorial Sloan Kettering Cancer Center
- Emily Roth; Ryann Damaso; Deborah Good; Brittney Pollard; Molly Murphy – Rhode Island Hospital / Lifespan Cancer Center
- Vivian Feng – Princess Margaret Cancer Centre, Toronto, Canada
- Nadia Kamp Nielsen; Cecilia Sonander Westphal; Sally Johanna Agren – Rigshospitalet, Copenhagen, Denmark
- Cherie Peterson – University of Utah Huntsman Cancer Institute
- Allie Gordon; Sydney Korstad; Katlyn Kraft; Casey Ezell – Washington University School of Medicine
- Priscilla Stève – Yale School of Medicine
- Lucas Angles; Paola Cruz – Columbia University Irving Medical Center

Members of the Repare Clinical Study Team

Precision Oncology Decision Support (PODS) Group at the University of Texas MD Anderson Cancer Center

ProPharma Group, Clinical Research Organization (CRO)
- Alissa Moody and the team of CRAs

This study was funded by Repare Therapeutics