2024 ESMO GASTROINTESTINAL CANCERS
Annual Congress

# PHASE 1 STUDY OF THE PKMYT1 INHIBITOR LUNRESERTIB (LUNRE) IN COMBINATION WITH FOLFIRI IN ADVANCED GASTROINTESTINAL CANCERS (MINOTAUR STUDY)

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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

# DECLARATION OF INTERESTS

## Elisa Fontana

Employee of Hospital Corporation of America (HCA) International

**Honoraria**:

Repare Therapeutics, CARIS Life Science, Seagen, Sapience, BicycleTx Ltd (conference attendance);

Astellas, Pfizer (Advisory Board)

**Leadership roles**:

European Organisation for Research and Treatment of Cancer (EORTC), Gastrointestinal Tactical Coordinating Group (GITCG) secretary (2021–2023)

ASCO Annual Meeting Scientific Programme Committee GI cancers, Colorectal and Anal Track (2024–2026)

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# LUNRE AND IRI SYNERGIZE TO ENHANCE DNA DAMAGE AND ANTI-TUMOR ACTIVITY

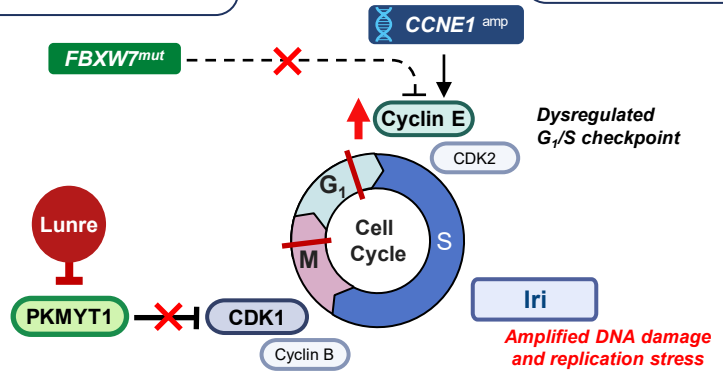
***CCNE1*$^{amp}$ and deleterious *FBXW7*$^{mut}$ present in ~20% of GI cancers are associated with poor prognoses[1-3] and have no matched targeted therapies**

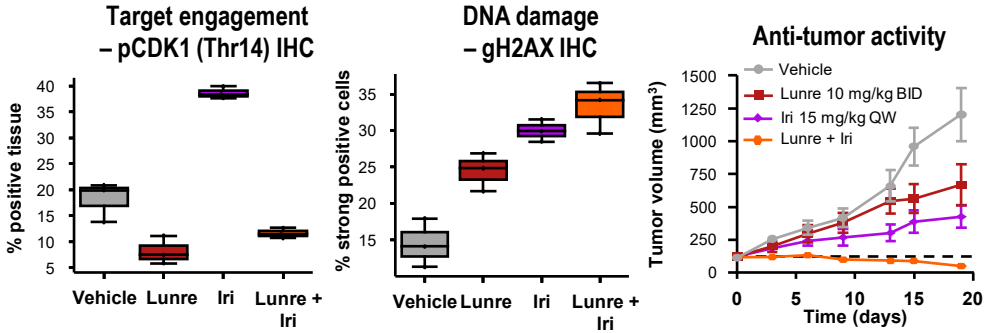
**Lunre, a well-tolerated, first-in-class PKMYT1i, is synthetically lethal with *CCNE1*$^{amp}$ or deleterious *FBXW7*$^{mut}$ [4,5]**

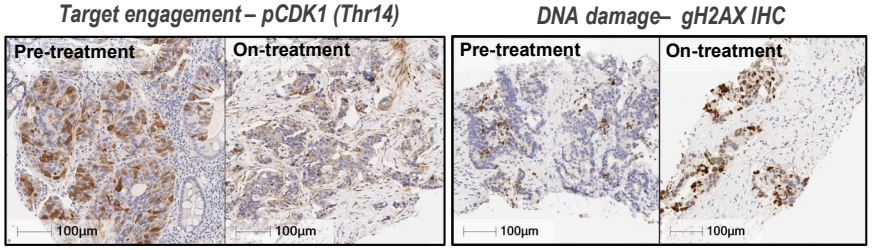
**Lunre abrogates iri-induced CDK1 phosphorylation causing premature entry into mitosis with extensive DNA damage, enabling synergistic anti-tumor activity**

***FBXW7*$^{mut}$ prevalence[1]**
CRC – 13.1%
Esophageal – 7.1%
Gastric – 10.2%

***CCNE1*$^{amp}$ prevalence[1]**
CRC – 0.5 %
Esophageal – 7.1%
Gastric – 6.4%




*DLD FBXW7-/- tumor-bearing animals (CB-17 SCID, n=7 per group) were treated with single agents lunre (10 mg/kg, BID, PO daily), Iri (15 mg/kg, IP, QW), or the combination and assessed for anti-tumor activity and tumor PD biomarker modulation via evaluation of pCDK-Thr14 and γH2AX by IHC in tumor samples tissue samples collected on day 2 (26 hours after treatment initiation, n=3 animals per treatment group). Paired pre- and on-treatment biopsies were collected on the MINOTAUR study those collected within the window achieving exposure above $IC_{90}$ were evaluable for target engagement and showed declines in pCDK-Thr14 levels. DNA damage induction confirms pathway engagement. amp, amplification; BID, twice daily; CCNE1, cyclin E1; CDC25, cell division cycle-25; CDK, cyclin-dependent kinase; CHK1, checkpoint kinase 1; CRC, colorectal cancer; FBXW7, F-box and WD repeat domain containing 7; g, gamma; GI, gastrointestinal; H, histone; IHC, immunohistochemistry; iri, irinotecan; lunre, lunresertib; mut, mutated; p, phosphorylated; Ph, phase; PKMYT1, protein kinase, membrane-associated tyrosine/threonine; SCID, severe combined immunodeficiency; Thr, threonine; QW, once weekly.*

# MINOTAUR: STUDY DESIGN AND DEMOGRAPHICS

(PK**M**YT1 **IN**hibitor and F**O**LFIRI **T**re**A**tment of solid T**U**mo**R**s)

## Key inclusion criteria

- Locally advanced or metastatic GI or other solid tumors
- Measurable disease by RECIST v1.1
- Local NGS report (tissue or plasma-based)
- ***CCNE1*** amplification[a] or deleterious ***FBXW7*** alterations (centrally reviewed[b])
- Prior iri permitted

Study is ongoing, closed to enrollment: ***NCT05147350***

## Design and objectives

Lunre (dose escalation) + FOLFIRI

✓ **Primary:**

- Safety and tolerability
- RP2D and schedule

✓ **Secondary and exploratory:**

- Pharmacokinetics
- Preliminary antitumor activity
- Pharmacodynamics
- ctDNA monitoring

## Demographics

| Parameter, n (%) | CRC (N=18) | Other tumors[c] (N=20) | Total (N=38) |
|---|---|---|---|
| **Sex** | | | |
| Male | 12 (66.7) | 9 (45.0) | 21 (55.3) |
| **Age** (years) | | | |
| Median (range) | 55.0 (33–75) | 57.5 (31–78) | 55.5 (31–78) |
| ≥65 years | 5 (27.8) | 7 (35.0) | 12 (31.6) |
| **ECOG status** | | | |
| 0 | 8 (44.4) | 10 (50.0) | 18 (47.4) |
| 1 | 10 (55.6) | 10 (50.0) | 20 (52.6) |
| **Prior LoT** | | | |
| 0–2 | 7 (38.9) | 14 (70.0) | 21 (55.3) |
| 3+ | 11 (61.1) | 6 (30.0) | 17 (44.7) |
| **Prior iri** | 13 (72.2) | 5 (25.0) | 18 (47.4) |
| **Prior platinum** | 17 (94.9) | 20 (100) | 37 (97.4) |
| ***RAS/BRAF*** | | | |
| WT[d] | 4 (22.2) | 13 (65) | 17 (44.7) |
| *RAS*$^{mut}$ [e] | 14 (77.8) | 7 (35) | 21 (55.3) |
| *BRAF*$^{mut}$ | 0 (0) | 0 (0) | 0 (0) |
| **Enrollment gene** | | | |
| *FBXW7* | 18 (100.0) | 8 (40.0) | 26 (68.4) |
| *CCNE1* | 0 (0) | 12 (60.0) | 12 (31.6) |

*[a]Copy number ≥6. [b]NGS report centrally reviewed and annotated by Precision Oncology Decision Support (PODS) Group at MDACC. [c]Other tumor types include anal (n=2), bile duct (n=3), esophageal (n=4), gastric (n=5), jejunal (n=1), pancreatic (n=3), and neuroendocrine (originating from the intestinal tract; n=2). [d]Includes WT RAS and RAF. [e]Includes single nucleotide variants and/or amplifications in KRAS and NRAS. ANC, absolute neutrophil count; CCNE1, cyclin E1; CRC, colorectal; ctDNA, circulating tumor DNA; ECOG, Eastern Cooperative Oncology Group; FBXW7, F-box and WD repeat domain containing 7; FOLFIRI, folinic acid, fluorouracil, and irinotecan hydrochloride; iri, irinotecan; GI, gastrointestinal; LoT, lines of therapy; mut, mutation; NGS, next-generation sequencing; pts, patients; RECIST, response evaluation criteria in solid tumors; RP2D, recommended phase II dose; WT, wild-type.*

# SAFETY PROFILE CONSISTENT WITH FOLFIRI ALONE

**RP2D established at 60mg BID, continuous daily dosing**

- **Lunre 40–240mg continuous and 160–240mg 3 days on/4 days off were evaluated**
- No safety-related treatment discontinuation or Gr3+ TRAEs at RP2D

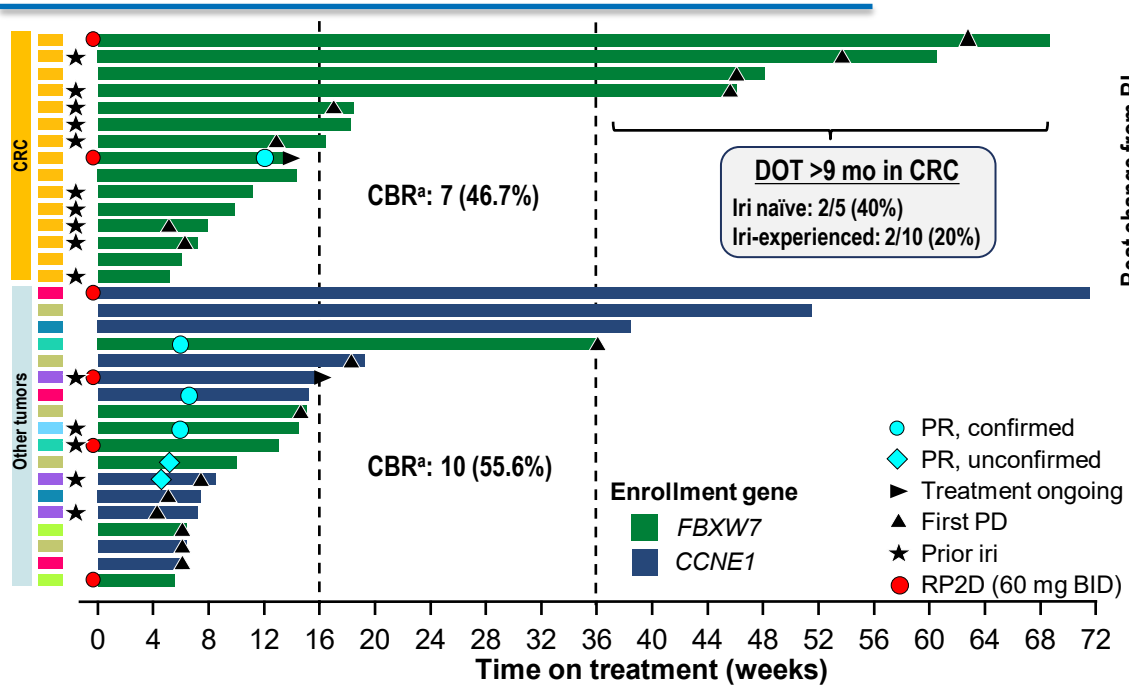
**Safety profile consistent with FOLFIRI alone[a,6,7]**

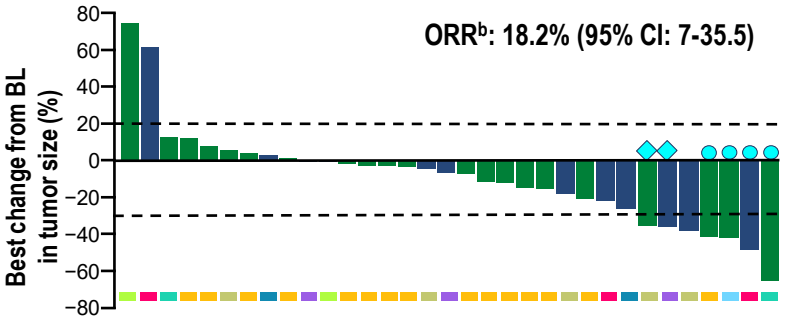
- Neutropenia was the most common Gr3+ hematologic TRAE
  - Similar rate to FOLFIRI alone (30% vs 31.6%)[a,6,7]
  - Reversible and preventable with FOLFIRI interruption and/or dose modifications

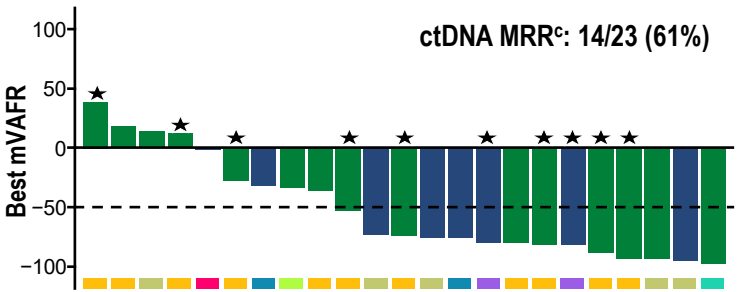
| | All patients N=38 | |
|---|---|---|
| **TRAEs in ≥ 15% of patients, n (%)** | **All Grades** | **Gr3+[b]** |
| Nausea/Vomiting | 21 (55.3) | 1 (2.6) |
| Neutropenia | 16 (42.1) | 12 (31.6) |
| Diarrhea | 15 (39.5) | 2 (5.3) |
| Mucosal inflammation | 15 (39.5) | 2 (5.3) |
| Fatigue | 13 (34.2) | 0 (0) |
| Rash[c] | 12 (31.6) | 0 (0) |
| Alopecia | 8 (21.1) | 1 (2.6) |
| Leukopenia | 8 (21.1) | 5 (13.2) |
| Anemia | 7 (18.4) | 2 (5.3) |
| PPE syndrome | 7 (18.4) | 1 (2.6) |
| Stomatitis | 7 (18.4) | 3 (7.9) |
| Taste disorder | 6 (15.8) | 0 (0) |

*[a]Data extracted from the control arm of the randomized phase III VELOUR study. [b]Grade 4 TRAEs: neutropenia in 3 (7.9%) patients. [c]Rash terms include maculo-popular, pruritis, rash, skin exfoliation, erythema, dermatitis contact, eczema, flushing, rash erythematous, and rash pruritic. BID, twice daily; d, day;* FOLFIRI, folinic acid, fluorouracil, and irinotecan hydrochloride; *gr, grade; lunre, lunresertib; PPE, palmar-plantar erythrodyxaesthesia; RP2D, recommended phase II dose; TRAE, treatment-related adverse event.*

# PROLONGED CLINICAL BENEFIT AND ROBUST ANTI-TUMOR ACTIVITY OBSERVED, INCLUDING IN PATIENTS WITH PRIOR IRI




**Tumor type:** Anal | Bile duct | Colorectal | Esophageal | Gastric | Jejunal | Neuroendocrine | Pancreatic

[a]*CBR was defined as the best overall response of CR or PR according to RECIST 1.1 criteria or duration of treatment ≥16 weeks without (denoted by dashed line).* [b]ORR was defined as the best response of confirmed CR or PR, unconfirmed CR or PR, or tumor marker response according to RECIST v1.1 criteria. [c]ctDNA MR was defined as a ≥50% decline in ctDNA (denoted by dashed line). *For DOT and tumor reduction data as of 6June24 and represent the efficacy evaluable population (≥1 post-baseline tumor assessment; n=33). ctDNA MR data as of 07May2024 using the Tempus xF+ liquid biopsy panel. Patients with no variants detected at baseline were deemed as non-monitorable for this analysis (n=7). BID, twice daily; BL, baseline; CBR, clinical benefit rate; CCNE1, cyclin E1; PR, partial response; CRC, colorectal cancer; DOT, duration of treatment; FBXW7, F-box and WD repeat domain-containing 7; iri, irinotecan; mo, months; MRR, molecular response rate; mVAFR, mean variant allele frequency rate; ORR, overall response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; RP2D, recommended phase II dose.*

# PROLONGED TUMOR RESPONSE IN PATIENT WITH ANAL CARCINOMA

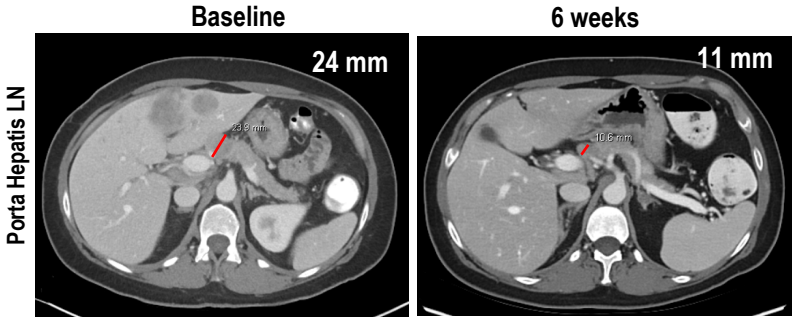
**Case description:**

- 59-year-old female patient with anal carcinoma with *FBXW7* mutation, high cyclin E
- History of 3 prior treatments; no prior iri

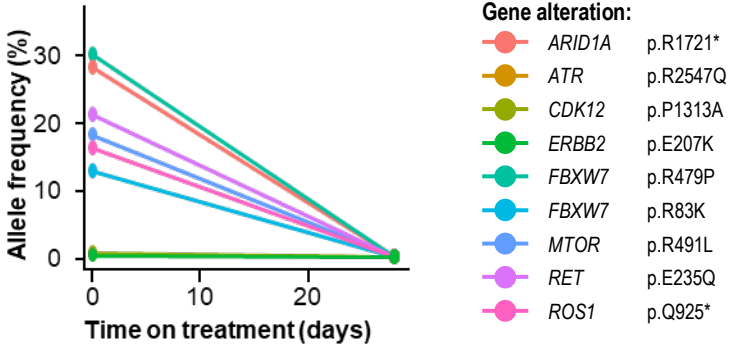
**Study treatment:** Lunre: 120mg BID 3 days on/4 days off and iri: 180mg/m$^2$; 5FU 2400mg/m$^2$; LV 400mg/m$^2$

- **Duration of treatment:** 9 months
- **Response:**
  - PR (confirmed), initially at 6 weeks
  - Best target lesion decrease from baseline: –65.2%
  - Molecular Response at 4 weeks: –98%

**Tumor assessment[a]**




**ctDNA dynamics[b]**




[a]*Representative CT scans from screening (baseline) and 6 weeks on study. Bar represents 150mm.* [b]*ctDNA analysis of allele frequency over time. 5-fluorouracil; BID, twice daily; d, days; CT, computed tomography; ctDNA, circulating tumor DNA; FBXW7, F-box and WD repeat domain-containing 7; FOLFIRI, folinic acid, fluorouracil, and irinotecan hydrochloride; iri, irinotecan; LN, lymphnode; lunre, lunresertib; LV, leucovorin; PR, partial response.*

# PROLONGED STABLE DISEASE IN PATIENT WITH CRC AND PRIOR IRI

**Case description:** 67-year-old male patient with CRC with *KRAS* and *FBXW7* mutations

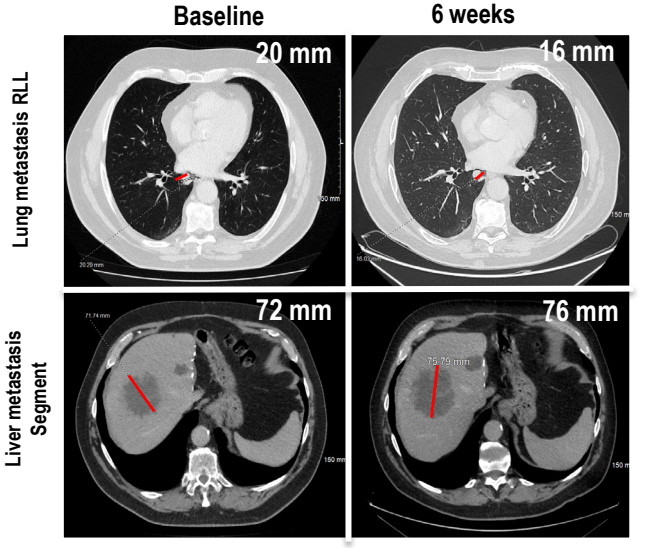
**Prior therapies:**

- Neoadjuvant CAPOX, primary and liver resection, adjuvant CAPOX – PD within 5 months
- FOLFIRI x 5 cycles with PD
- Trifluridine/tipiracil x 3 cycles with PD

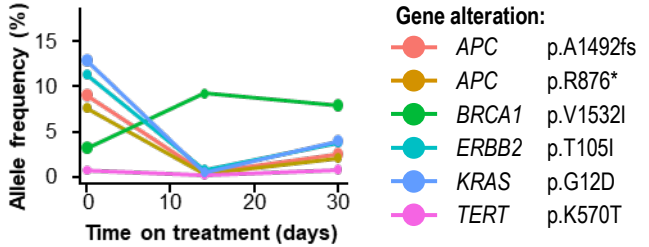
**Study treatment:** Lunre: 240mg QD continuous and iri: 180mg/m$^2$; LV 400mg/m$^2$; 5FU infusion 2400mg/m$^2$

- **Duration of treatment:** 46 weeks
- **Response:**
  - SD with decrease from baseline: –1.3%
  - Molecular Response at 2 weeks: –74%

**Tumor assessment[a]**




**ctDNA dynamics[b]**




*[a]Representative CT scans from screening (baseline) and 6 weeks post treatment. Red line indicates tumor and bar represents 150mm. [b]ctDNA analysis of allele frequency over time. 5FU, 5-fluorouracil; CAPOX, capecitabine and oxaliplatin; CRC, colorectal cancer; CT, computed tomography; ctDNA, circulating tumor DNA; FBXW7, F-box and WD repeat domain-containing 7; FOLFIRI, folinic acid, fluorouracil, and irinotecan hydrochloride; iri, irinotecan; lunre; lunresertib; LV, leucovorin; PD, progressive disease; QD, once weekly; SD, stable disease.*

# CONCLUSIONS

In the first evaluation of this novel combination, standard FOLFIRI and daily lunre were well tolerated
- The hematologic safety profile was consistent with that reported for FOLFIRI alone
- Low-grade, reversible rash was consistent with lunre monotherapy experience

Preliminary RP2D was established as 60mg BID continuous daily lunre plus standard FOLFIRI, with no Gr3+ TRAEs or TRAEs leading to discontinuation observed at RP2D

Promising efficacy in a heavily pretreated *CCNE1*$^{amp}$ and *FBXW7*$^{mut}$ population known to be associated with a poor prognosis
- 6 partial responses, regardless of prior iri exposure (ORR: 18.2%)
- Patients with CRC had prolonged clinical benefit with 40% of iri-naïve patients receiving treatment >9 months

This promising targeted treatment combination in high-risk GI tumors that harbor *CCNE1*$^{amp}$ or *FBXW7*$^{mut}$ warrants further exploration in a randomized phase II study

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