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Driver alterations in *FBXW7*, *PPP2R1A*, *CCNE1* confer a poor prognosis in patients with metastatic gynecologic cancers

Poster number: 89

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Introduction

- The combination of lunresertib (lunre), a PKMYT1 inhibitor, and camonsertib, an ATR inhibitor, is currently being studied in patients harboring lunre-sensitizing biomarkers (Lunre BM) including *CCNE1* amplifications or mutations in *FBXW7* or *PPP2R1A* in the phase I MYTHIC trial (NCT04855656)
- *CCNE1* amplifications, which occur in ~30% of platinum-resistant ovarian cancers,[1-3] are well established as a poor prognostic indicator in ovarian cancer,[4-7] but little is known about other Lunre BM in ovarian and endometrial cancers

Key translational questions

- What is the distribution of Lunre BM in ovarian and endometrial cancers?
- What is the prognosis for gynecological malignancies with lunre BM?
- Is presence of a Lunre BM independently prognostic or associated with other poor outcomes indicators?

Lunre-sensitizing alterations are enriched in gynecological malignancies

- Lunre-sensitizing alterations are most highly enriched in gynecological malignancies (**Figure 1A**)
- In MYTHIC, the distribution of individual biomarkers enrolled within gynecological malignancies was consistent with prevalence estimates from TCGA[1] (**Figure 1B**)

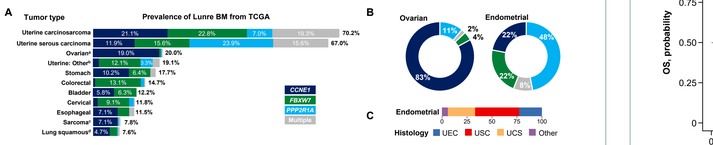


Figure 1: (**A**) Estimated prevalence of Lunre BM from TCGA. (**B**) Distribution of enrollment biomarkers in ovarian and endometrial patients enrolled in the MYTHIC trial. (**C**) Distribution of histologies in endometrial patients enrolled in the MYTHIC trial. [a]Includes only high-grade serous ovarian patients. [b]Uterine Endometrioid Carcinoma and Uterine Mixed Endometrial Carcinoma [c]Soft-tissue sarcoma only. [d]Squamous histology of non-small cell lung cancer only.

- Within ovarian cancer, previous studies have demonstrated an enrichment of *CCNE1* amplification in platinum-resistant patients[1-3] (**Table 1**)
- Ovarian cancer patients with platinum-refractory disease, highly enriched for *CCNE1* amplification, are a subset distinct from homologous recombination deficient (HRD; i.e., *BRCA1/BRCA2*) and thus, a high unmet clinical need[3-5]

Table 1. *CCNE1* amplification frequency in ovarian cancer

Platinum status	Refractory[a]	Resistant[b]	Sensitive
TCGA. *Nature*. 2011[1]	27.6% (n=58)		13.1% (n=130)
Patch A-M, et al. *Nature*. 2015[2]	41% (n=12)	29.7% (n=37)	6.5% (n=31)
Smith P, et al. *Nat Commun*. 2023[3]	58% (n=12)	8.8% (n=114)	

[a]Refractory: Defined as disease progression while on primary platinum treatment or within one month of end of primary platinum treatment
[b]Resistant: Defined as a platinum-free interval of ≤6 months

Methods

Analysis of MSK MetTropism[8,9] dataset

- Clinical and genomic data were obtained from the MSK MetTropism[8,9]
- Patients with metastatic endometrial cancer (UEC, n=478; USC, n=243; UCS, n=174), HGSOC (n=949), and CCOV (n=80) were included (**Figures 2A and 5A**)
- Overall survival (OS) was measured from the time of NGS testing to death and was censored at the last time reported alive
- OS was modeled on Lunre BM status alone or concurrently with p53 status, tumor histology, and MSI status (endometrial only) using multivariate Cox proportional-hazards models

Results: Ovarian cancer

Clinicogenomic landscape of Lunre BM in metastatic ovarian cancer

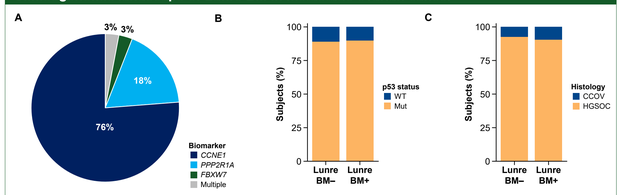
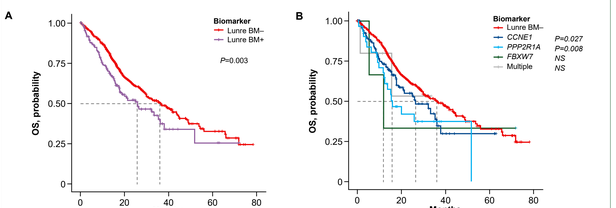


Figure 2: (**A**) Distribution of Lunre BM in metastatic ovarian cancer patients. (**B**) p53 status and (**C**) histology in Lunre BM– and BM+ patients.

Metastatic ovarian cancer patients with Lunre BM+ tumors have poor outcomes



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	Biomarker					
	Lunre BM–	Lunre BM+	*CCNE1*	*PPP2R1A*	*FBXW7*	Multiple
Patients, n	843	174	133	31	5	5
mOS (95% CI), months	36 (30-43)	26 (18-38)	27 (19-38)	16 (12-NR)	12 (5-NR)	NR (16-NR)

Figure 3: Kaplan–Meier survival analysis for metastatic ovarian cancer patients stratified by (**A**) grouped lunre BM status and (**B**) individual lunre BM status. (**C**) mOS in months within patients stratified by grouped and individual lunre BM status. NR = Not Reached, NS= Not significant.

Poor outcomes in metastatic ovarian cancer patients with Lunre BM+ tumors are independent of histology and p53 status

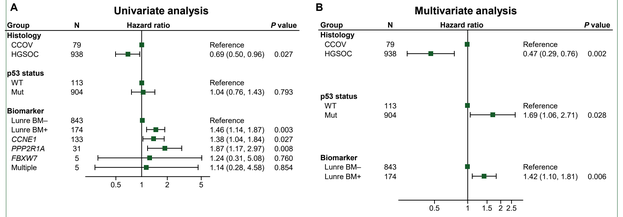


Figure 4: (**A**) Univariate and (**B**) multivariate Cox-proportional hazards models for metastatic ovarian cancer patients.

Results: Endometrial cancer

Clinicogenomic landscape of Lunre BM in metastatic endometrial cancer

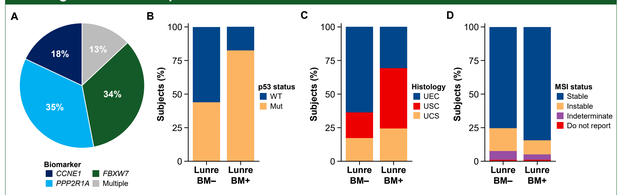
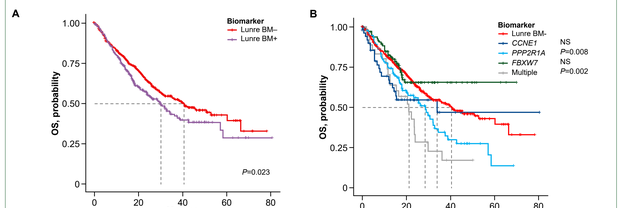


Figure 5: (**A**) Distribution of lunre BM in metastatic endometrial cancer patients. (**B**) p53 status, (**C**) histology, and (**D**) MSI status in lunre BM– and lunre BM+ patients.

Metastatic endometrial cancer patients with Lunre BM+ tumors have poor outcomes



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	Biomarker					
	Lunre BM–	Lunre BM+	*CCNE1*	*PPP2R1A*	*FBXW7*	Multiple
Patients, n	616	277	50	96	94	37
mOS (95% CI), months	41 (31-60)	30 (24-38)	34 (15-NR)	29 (20-34)	NR (NR-NR)	21 (13-30)

Figure 6: Kaplan–Meier survival analysis for metastatic endometrial cancer patients stratified by (**A**) grouped lunre BM status and (**B**) individual lunre BM status. (**C**) mOS in months within patients stratified by grouped and individual lunre BM status. NR = Not Reached, NS= Not significant.

Poor outcomes in metastatic endometrial cancer patients with Lunre BM+ tumors is driven by the association with mutant p53 and non-endometrioid histologies

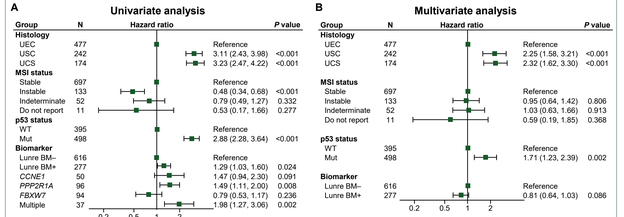
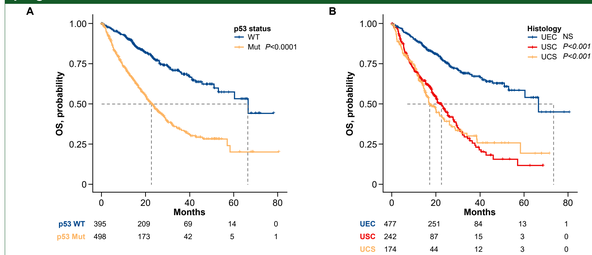


Figure 7: (**A**) Univariate and (**B**) multivariate Cox-proportional hazards models for metastatic endometrial cancer patients.

p53 mutant and high-risk endometrial histologies (enriched for Lunre BM+) have poor prognoses



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	p53 status		Histology		
	WT	Mut	UEC	USC	UCS
Patients, n	395	498	477	242	174
mOS (95% CI), months	66 (53-NR)	23 (20-26)	66 (60-NR)	22 (19-28)	17 (15-24)

Figure 8: Kaplan-Meier survival analysis for metastatic endometrial cancer patients stratified by (**A**) p53 status and (**B**) histology. (**C**) Median overall survival (mOS) in months within patients stratified by p53 status and histology. NR = Not Reached.

Potential limitations of this analysis include:

- Analysis of data from a single academic center is subject to center-specific biases
- *CCNE1* amplification copy number thresholds from MSK-IMPACT® may differ from other commonly used NGS assays
- Important ovarian cancer co-variates, such as platinum sensitivity and HRD status, were not available and likely impact prevalence and clinical outcomes
- Survival analysis was anchored on NGS date; date of diagnosis or relapse may more accurately reflect true prognosis

Conclusions

- In both endometrial and ovarian cancers, Lunre BM+ tumors had worse prognoses compared to Lunre BM– tumors
- Lunre BM+ status was independently associated with poor prognosis in ovarian cancer
- In endometrial cancers, Lunre BM+ status was indirectly associated with poor prognosis due to the enrichment for patients with high-risk histologies (UCS and USC) and genotype (p53 mutant)
  - MSI was largely distinct from the Lunre BM+ population and was associated with better prognosis due to its enrichment in UEC
- Additional treatment solutions are a critical unmet need for this very high-risk population with adverse outcomes

References

1. *Cancer Genome Atlas Research Network. Nature.* 2011;474(7353):609–615. **2.** Patch A-M, et al. *Nature.* 2015;521(7553):489–494. **3.** Smith P, et al. *Nat Commun.* 2023;14(1):4387. **4.** Chan AM, et al. *J Pathol Clin Res.* 2020;6(4):252–262. **5.** Kang E-Y, et al. *Cancer.* 2023;129(5):697–713. **6.** Nakayama N, et al. *Cancer.* 2010;116(11):2621–2634. **7.** Stronach EA, et al. *Mol Cancer Res.* 2018;16(7):1103–1111. **8.** Nguyen B, et al. *Cell.* 2022;185(3):563–575.e11. **9.** https://www.cbioportal.org

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Abbreviations

ATRi, ataxia telangiectasia and Rad-3 related inhibitor; CI, confidence interval; CN, copy number; HGSOC, high-grade serous ovarian carcinoma; HRD, homologous recombination deficient; lunre, lunresertib; Lunre BM, lunresertib-sensitizing biomarkers; MSI, microsatellite instability; MSK-IMPACT, Memorial Sloan Kettering – Integrated Mutation Profiling of Actionable Cancer Targets; MSK-MetTropism, Memorial Sloan Kettering - Metastatic Events and Tropisms; mOS, median overall survival; *mut*, mutated; MYTHIC, PKMYT1 inHibition for the treatment of Cancers; NGS, next-generation sequencing; NR, not reached; OCCC, ovarian clear cell carcinoma; OS, overall survival; PKMYT1, membrane-associated tyrosine- and threonine-specific Cdc2-inhibitory kinase; strata, stratified; UCS, uterine carcinosarcoma; UEC, uterine endometrioid cancer; USC, uterine serous carcinoma; WT, wild-type.

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