Characterizing FOLR1 expression in Low Grade Serous Ovarian Carcinoma

Tullia Rushton[1], Harris B. Krause[2], Andrew Elliott[2], Anthony Karnezis[3], Michael Toboni[4], Premal H. Thaker[5], David Braxton[6], Matthew Oberley[2], David M. Gershenson[7], Deborah K. Armstrong[1]

[1]Johns Hopkins University, Baltimore, MD; [2]Caris Life Sciences, [3]University of California-Davis, Davis, CA; [4]University of Alabama at Birmingham, Birmingham, AL; [5]Washington University in St. Lous, St. Louis, MO; [6]Hoag Health, Newport Beach, CA; [7]University of Texas MD Anderson Cancer Center, Houston, TX

Background

- Targeted therapy in folate receptor alpha (FOLR1)-positive high grade serous ovarian carcinoma (HG) is now a mainstay for platinum-resistant disease.
- The rate of FOLR1-positivity in low grade serous ovarian carcinoma (LG) is unknown.
- We compared the genomic and transcriptomic landscapes in FOLR1-positive/negative LG in comparison to its HG counterpart.

Methods

- LG (N = 281) and HG (N = 5086) tumors were tested at Caris Life Sciences (Phoenix, AZ) with NextGen Sequencing on DNA (592 genes or whole exome) and RNA (whole transcriptome).
- PD-L1+ (22C3, TPS > 1%) and FOLR1 (Positive [F+], ⩾ 2+, ⩾75%) expression was assessed by IHC.
- Mutations were defined as pathogenic SNVs/indels (-Mt).
- A transcriptomic signature associated with MAPK pathway activation (MPAS) was applied.
- Fisher's exact/χ^2 and Mann-Whitney U tests were applied as appropriate ($p < .05$, adjusted for multiple comparisons).
- Real-world overall survival (OS) was obtained from insurance claims and Kaplan-Meier estimates were calculated for molecularly defined patients.
- This study was reviewed by the Johns Hopkins Medicine IRB and determined to qualify as exempt human subjects research.

Results

LG tumors have a lower rate of FOLR1+ as compared to HG

(A)

IHC	FOLR1 Positive 2+, ≥75%	FOLR1 Medium 2+, >74-50%	FOLR1 Low 2+, 49-25%	FOLR1 Negative < 2 or <25%
HG	43.5% (2213/5086)	11.8% (598/5086)	12.8% (652/5086)	31.9% (1623/5086)
LG	24.6% (69/281)	16.0% (45/281)	13.2% (37/281)	46.3% (130/281)

(B)

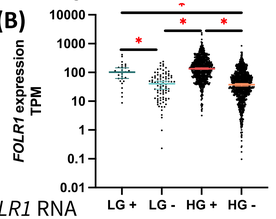

Figure 1: **(A)** Prevalence of FOLR expression by IHC. **(B)** *FOLR1* RNA expression (transcripts per million, TPM) in low-grade and high-grade ovarian tumors that are FOLR1 IHC positive and FOLR1 IHC negative. Red asterisks indicate statistical significance ($p < 0.05$).

LG tumors are enriched for mutations in the MAPK pathway

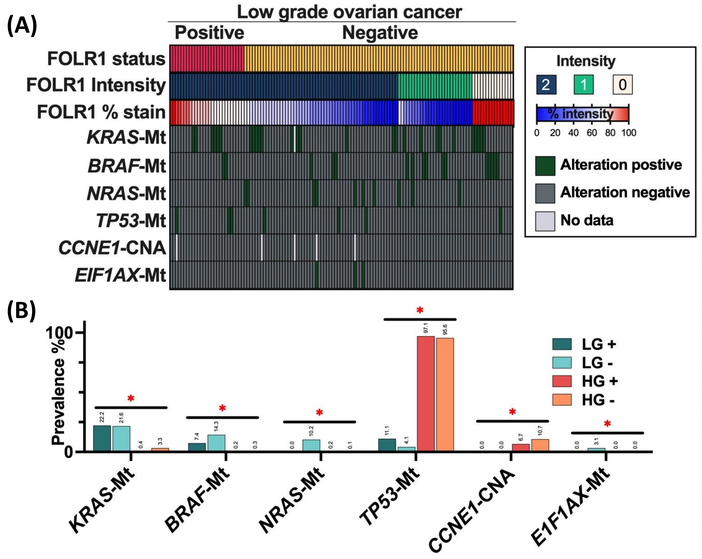

Figure 2:
(A) Heatmap of low-grade ovarian tumors showing FOLR1 IHC status, staining intensity and % stain in addition to key alterations (-MT: SNV/indel pathogenic mutations, CNA: copy number amplification)
(B) Prevalence of alterations that were significantly different between the four investigated cohorts. Red asterisks indicate statistical significance ($p < 0.05$).

LG tumors have increased activation of the MAPK pathway

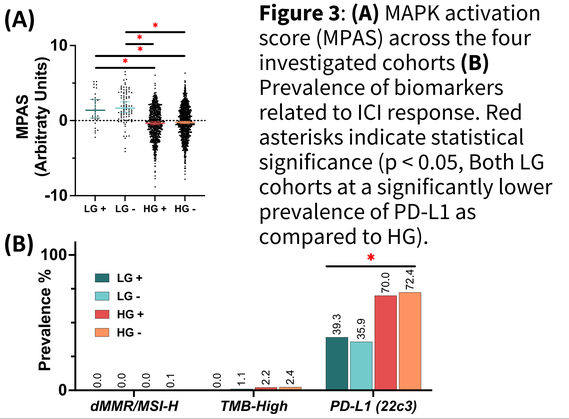

Figure 3: **(A)** MAPK activation score (MPAS) across the four investigated cohorts **(B)** Prevalence of biomarkers related to ICI response. Red asterisks indicate statistical significance ($p < 0.05$, Both LG cohorts at a significantly lower prevalence of PD-L1 as compared to HG).

HG+ tumors have an increased OS as compared to HG-

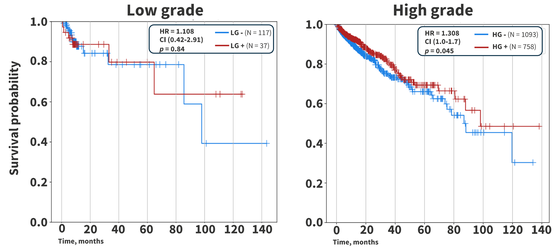

Figure 4: Overall survival between FOLR1 – vs + low grade or high-grade ovarian tumors. None of the tumors are from individuals who received mirvetuximab soravtansine. Median survival of each group was: LG- 98.0 months, LG+ not yet reached, HG- 86.8 months, HG+ 98.1 month.

Study Highlights

- 25% of LG tumors were FOLR1 positive
- MAPK activation was significantly higher in LG tumors when compared to HG, yet no difference between LG F+ and F- tumors was observed.
- The opposite pattern was observed for KRAS-Mt, BRAF-Mt,

Conclusions

Though less prevalent than in HG disease, a notable portion of LG tumors were FOLR1+, which suggests that FOLR1 expression in LG could be a viable target for this rare histology, particularly in the recurrent setting.

Contact Dr. Tullia Rushton (trushto1@jhu.edu) for additional information

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