Dynamic changes in folate receptor alpha scoring in ovarian surface epithelial carcinomas and treatment implications

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Background

- Folate receptor alpha (FRα) is the target of several antibody drug conjugates including mirvetuximab soravtansine-gynx (MIRV).
- FRα expression may be dynamic, with some FRα-high tumors converting to FRα-low (Manning 2024, Martin 2024).
- FRα expression and MIRV outcomes are established in high-grade serous ovarian carcinoma (HGSOC), but little is known about non-HGSOC histologies.
- Compared to immunohistochemistry (IHC), RNA-sequencing (seq) may better represent FRα status, and in turn, MIRV time on treatment (ToT)

Objectives

1. **Understand FRα expression over time**
2. **Assess concordance of FRα expression between IHC and RNA-seq**
3. **Evaluate associations of FRα IHC vs RNA-seq with MIRV treatment duration in non-HGSOCs**

Methods

- EOC samples with FRα IHC and whole-transcriptome RNA-seq at Caris Life Sciences were identified.
- FRα high (+) was defined as ≥2+ membrane staining in ≥75% of viable cells. IHC H-scores were calculated as: FRα IHC intensity X% stained cells.
- Patient (pt)-matched samples from subsequent biopsies were concordant if both samples had the same IHC result (FRα+ or –) and discordant if IHC result differed.
- Overall survival and MIRV ToT were inferred from claims data and reported as median durations or hazard ratios (HR) [95% confidence interval] from Kaplan-Meier or Cox proportional hazard models, respectively.

Results

1) FRα IHC is associated with biopsy location

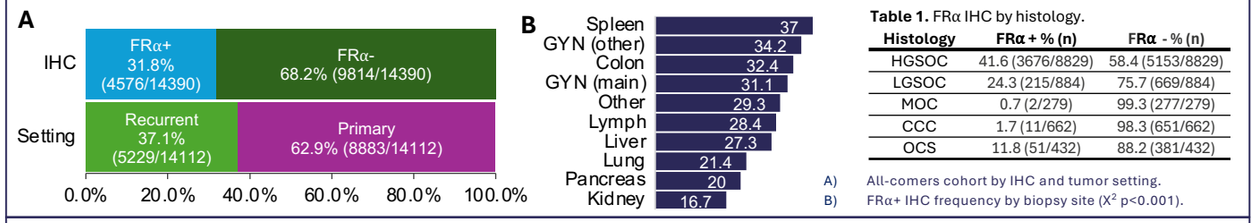
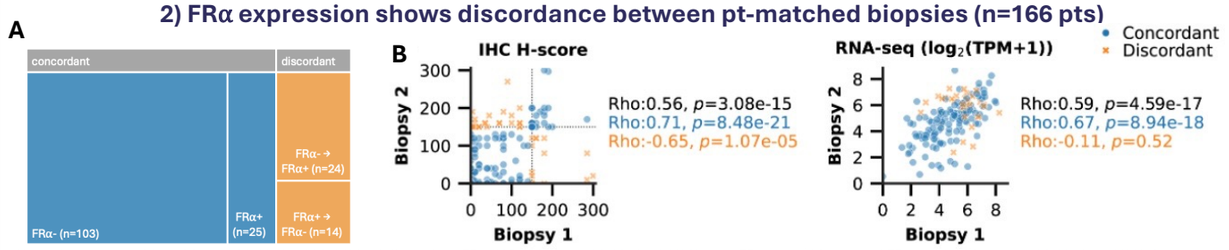


Table 1. FRα IHC by histology.

Histology	FRα + % (n)	FRα - % (n)
HGSOC	41.6 (3676/8829)	58.4 (5153/8829)
LGSOC	24.3 (215/884)	75.7 (669/884)
MOC	0.7 (2/279)	99.3 (277/279)
CCC	1.7 (11/662)	98.3 (651/662)
OCS	11.8 (51/432)	88.2 (381/432)

A) All-comers cohort by IHC and tumor setting.
B) FRα+ IHC frequency by biopsy site (X^2 p<0.001).

2) FRα expression shows discordance between pt-matched biopsies (n=166 pts)



A) Among pts with >1 biopsy, 22.9% (n=38/166) had discordant FRα IHC. Of these, 63.2% (n=24/38) were FRα- at 1st biopsy and FRα+ at 2nd biopsy, vs 36.8% (n=14/38) that were FRα+ at 1st and FRα- at 2nd biopsy.
   i. Among pts with FRα - on 1st biopsy, median FRα IHC% was 5 (0.5-30 IQR) in those that remained FRα - at 2nd biopsy and 35 (9-50 IQR) in those that became FRα +.
B) Correlation of FRα IHC H-scores and RNA-seq between 1st and 2nd biopsies. Among concordant samples, both IHC and RNA-seq show strong positive correlation between biopsies.

3) FRα discordant and concordant samples demonstrate molecular and histologic differences

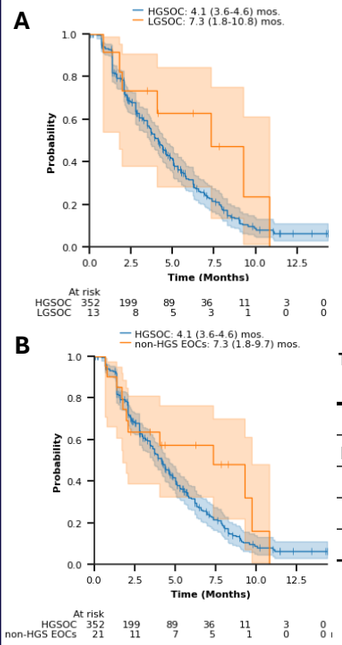
Table 2. Clinicodemographic and molecular feature comparisons among n=166 pts with >1 biopsy (n=344 samples).

Variable	Description	Concordant	Discordant	Statistic	p
Age	Median age (range)	65.5 (24 - 86)	65.0 (39 - 84)	MWU	0.923
Bx Site				Chi-square	0.583
Histology	HGSOC	78.9% (202/256)	82.9% (63/76)	Fisher's Exact	0.022
	CCC	7.4% (19/256)	0.0% (0/76)		
	LGSOC	5.9% (15/256)	11.8% (9/76)		
	OCS	3.9% (10/256)	5.3% (4/76)		
	MOC	2.7% (7/256)	0.0% (0/76)		
	EC	1.2% (3/256)	0.0% (0/76)		
IHC	ER+	37.3% (91/244)	56.9% (41/72)	Chi-square	0.003
NGS	KRAS-mut	5.3% (13/244)	0.0% (0/74)	Fisher's Exact	0.044

Variable	Description	FRα+ %(n) IHC cohort	FRα- %(n) IHC cohort	Statistic	p
Histology	HGSOC	76.2% (186/244)	89.8% (79/88)	Fisher's Exact	<0.05
	CCC	7.8% (19/244)	0.0% (0/88)		
	LGSOC	7.4% (18/244)	6.8% (6/88)		
	OCS	4.5% (11/244)	3.4% (3/88)		
	MOC	2.9% (7/244)	0.0% (0/88)		

CCC, Clear Cell Carcinoma; LGSOC, low-grade serous ovarian carcinoma; OCS, ovarian carcinosarcoma; MOC, mucinous adenocarcinoma; EC, endometrioid carcinoma

4) MIRV ToT does not vary among histologies



A) HGSOC vs LGSOC (HR=0.58, [0.28-1.26] p=0.17)

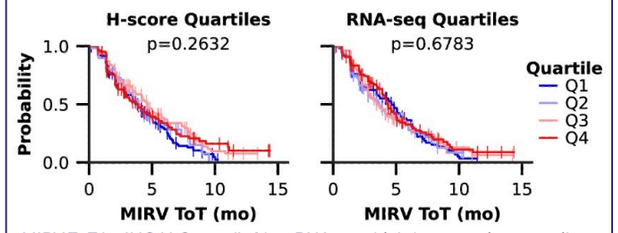
B) HGSOC vs non-HGSOC (HR=0.68, [0.38-1.21] p=0.19)

Table 3. MIRV ToT by histology.

Histology (n)	Median ToT
LGSOC (13)	7.3 [1.8-10.8]
HGSOC (352)	4.1 [3.6-4.6]
MOC (1)	2.1 [2.1-2.1]
EC (2)	1.7 [1.7-NR]
OCS (4)	1.4 [0.7-9.7]

Results

5) FRα expression not associated with MIRV ToT

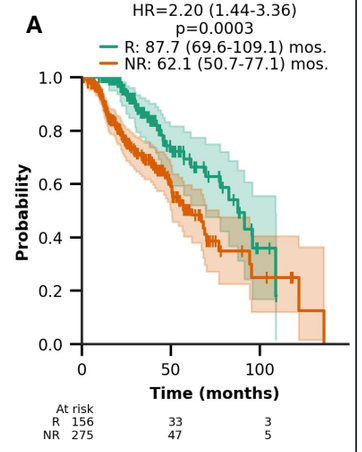


MIRV ToT by IHC H-Score (left) or RNA-seq (right) expression quartiles (Q1, lowest; Q4, highest quartiles)

6) MIRV ToT associated with OS, not FRα RNA-seq

All EOC pts were stratified based on MIRV ToT into:
- R ≥ median (4.14) mo
- NR < median (4.14) mo

A) OS between R and NR cohorts.



Not shown:
- No differences in race (p=0.19), ethnicity (p=0.74), genetic ancestry (p=0.17) or histology (p=0.59) between R and NR cohorts
- No difference in median RNA-seq between R and NR cohorts (204.7 TPM vs 185.4 TPM; MWU p=0.96)

Conclusions

- **FRα expression is dynamic** and varies by biopsy site. Discordance of FRα expression between biopsies may be as high as 23%.
- **There are molecular differences between FRα concordant and discordant samples**, which may have clinical implications.
- **Further optimization of the threshold defining FRα+ by IHC may lead to better prediction of response to MIRV**
- **RNA-seq may not predict MIRV ToT** as there was no significant difference in FRa expression between patients whose ToT was longer. However, further evaluations are needed.