Correlating Expression of NaPi2b and Folate Receptor Alpha (FRα) in High-Grade Serous Ovarian Cancer (HGSOC)

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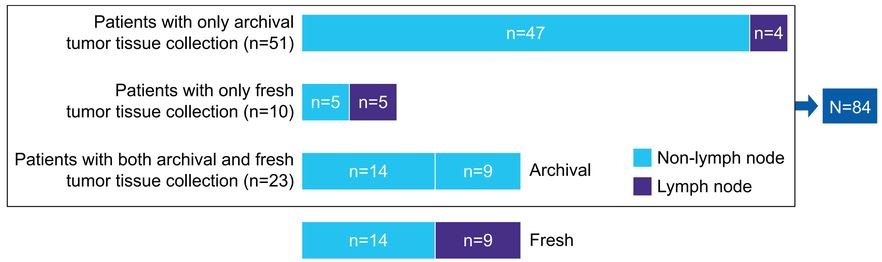
BACKGROUND

- Platinum-resistant ovarian cancer (PROC) is marked by a high unmet medical need, with single-agent chemotherapy as the SOC providing an ORR of ≈12%[1,2]
  - Most ovarian tumors that respond to frontline treatment recur and eventually become platinum resistant
  - There are few treatment options currently available for patients with PROC and for most patients, the clinical outcome to treatment is poor
- Biomarker-driven therapies are increasingly being utilized and studied for potential use in gynecologic cancers, including PROC[3]
  - Upifitamab rilsodotin (UpRi) is a late-stage, first-in-class NaPi2b-targeting antibody-drug conjugate (ADC) with a novel scaffold-linker-payload that is designed to enable high drug-to-antibody ratio and a controlled bystander effect[4,5]
    - Available data suggest approximately 60% of patients with HGSOC have NaPi2b-positive tumors (TPS ≥75 by IHC)[6,7]
  - Mirvetuximab soravtansine, a folate receptor alpha (FRα)-targeting ADC, received accelerated approval by the FDA for patients with FRα-positive PROC who have received 1–3 prior lines of therapy[8,9]
    - Available data suggest approximately 30% of patients with HGSOC have FRα-positive tumors (PS2+ ≥75% by IHC)[10]
- Understanding the relationship between the expression of different biomarkers in HGSOC is important to evaluate potential treatment options or sequencing for patients
- Here we evaluate NaPi2b and FRα RNA expression correlation in HGSOC samples

METHODS

Sample Collection

- Tumor samples were obtained from 84 patients from the UpRi Phase 1b expansion (EXP) study (NCT03319628)[11]
- For patients with both archival and fresh tumor samples, only archival data were included as prior studies suggest concordance between archival and fresh tissue[12]



Expression Correlation Analysis

- Tumor samples were analyzed for RNA expression via Nanostring (770 immune-focus genes from IO 360 panel + 30 customized ADC-related genes)
- The cutoffs for determining positive vs negative RNA expression for NaPi2b and FRα were based on the following assumptions:
  - 60% of samples with highest NaPi2b RNA expression were considered NaPi2b positive (the remaining 40% of samples were considered negative), based on approximately 60% of patients with HGSOC patients having NaPi2b-positive tumors by IHC (TPS ≥75)[6,7]
  - 30% of samples with highest FRα RNA expression were considered FRα positive (the remaining 70% of samples were considered negative), based on approximately 30% of patients with HGSOC patients having FRα-positive tumors by IHC (PS2+ ≥75%)[10]
- A correlation analysis was performed to assess the overlap between NaPi2b and FRα RNA expression
- Another correlation analysis was performed to evaluate the association between NaPi2b protein expression by IHC using data from the Phase 1b EXP study and RNA expression by Nanostring analysis

RESULTS

NaPi2b and FRα RNA Expression Correlation Analysis

- 21% (n=18) of samples had both NaPi2b-positive and FRα-positive RNA expression (by Nanostring)
- 32% (n=27) of samples had both NaPi2b-negative and FRα-negative RNA expression (by Nanostring)
- No statistically significant association was observed (Chi-squared test, *P*=0.129)

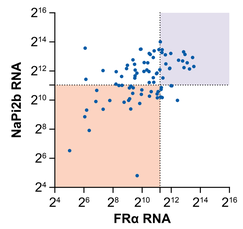


Figure 1. Correlation analysis of NaPi2b (*SLCA34A2*) RNA expression and FRα (*FOLR1*) RNA expression by Nanostring. Dashed lines indicate cutoffs for positive (higher) vs negative (lower) expression.

n (%)		FRα RNA	
		Negative (lower 70%)	Positive (upper 30%)
NaPi2b RNA	Positive (upper 60%)	32 (38.1)	18 (21.4)
	Negative (lower 40%)	27 (32.1)	7 (8.3)

Chi-squared test, *P*=0.129, no significant association

NaPi2b Protein and RNA Expression Correlation Analysis

- 45% (n=38) of samples had positive NaPi2b expression for both RNA (by Nanostring) and protein (by IHC)
- 24% (n=20) of samples had negative NaPi2b expression for both RNA (by Nanostring) and protein (by IHC)
- There was a 69% agreement between NaPi2b RNA and IHC and a statistically significant association was observed (Chi-squared test, *P*=0.001)

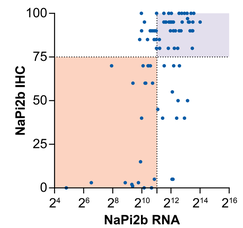


Figure 1. Correlation analysis for NaPi2b protein expression by IHC (TPS) and NaPi2b (*SLCA34A2*) RNA expression by Nanostring. Dashed lines indicate cutoffs for positive (higher) vs negative (lower) expression.

n (%)		NaPi2b RNA	
		Negative (lower 40%)	Positive (upper 60%)
NaPi2b IHC	Positive (TPS ≥75)	14 (16.7)	38 (45.2)
	Negative (TPS <75)	20 (23.8)	12 (14.3)

Chi-squared test, *P*=0.001

CONCLUSIONS

- In this analysis, with limited sample size, no statistically significant correlation was observed between NaPi2b and FRα RNA expression
  - 21% of the samples showed overlapping NaPi2b and FRα RNA positivity; 38% of samples were RNA NaPi2b positive and FRα negative
  - Additional research is warranted to evaluate the correlation between FRα and NaPi2b protein expression via IHC
- General NaPi2b prevalence in HGSOC and the correlation between NaPi2b RNA and IHC suggest that NaPi2b may be a rational biomarker to integrate in RNA tumor panel testing
- This research provides further insight into biomarker expression and correlation in HGSOC, which is clinically informative as novel treatments continue to be integrated into this space

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ADC, antibody-drug conjugate; EXP, dose expansion; FDA, Food and Drug Administration; HGSOC, high-grade serous ovarian cancer; IHC, immunohistochemistry; NaPi2b, sodium-dependent phosphate transporter 2b; ORR, objective response rate; PROC, platinum-resistant ovarian cancer; *SLC34A2*, solute carrier family 34 member 2; SOC, standard of care; TPS, tumor proportion score; UpRi, upifitamab rilsodotin.

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