NaPi2b Expression in High-Grade Serous Ovarian Cancer: Results From Combined Data Sets

Susana Banerjee,[1] Debra L Richardson,[2] Nicole Concin,[3] Bradley J Monk,[4] Mansoor Raza Mirza,[5] Robert L Coleman,[6] Isabelle Ray-Coquard,[7] Bhavana Pothuri,[8] Christian Marth,[9] Leslie DeMars,[10] Chelsea Bradshaw,[10] Caroline DiCristo,[10] Rebecca Mosher,[10] Ronny Drapkin[11]

[1]Royal Marsden NHS Foundation Trust, London, United Kingdom; [2]Division of Gynecologic Oncology, Stephenson Cancer Center, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA; [3]Department of Gynaecology and Obstetrics, Innsbruck Medical University, Innsbruck, Austria; [4]HonorHealth University of Arizona, Creighton University, Phoenix, AZ, USA; [5]Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark; [6]US Oncology Research, Texas Oncology, The Woodlands, TX, USA; [7]University Claude Bernard Lyon I and the Centre Léon Bérard, Lyon, France; [8]NYU Langone Health, Perlmutter Cancer Center and NYU Grossman School of Medicine, New York, NY, USA; [9]Innsbruck Medical University, Innsbruck Austria; [10]Mersana Therapeutics, Cambridge, MA, USA; [11]Department of Obstetrics and Gynecology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

BACKGROUND

- NaPi2b is a sodium-dependent phosphate transporter broadly expressed in high-grade serous ovarian cancer (HGSOC), with limited expression in normal tissues[1–3]
  - NaPi2b is the target of the antibody-drug conjugate (ADC) upifitamab rilsodotin (UpRi), which is under clinical investigation for the treatment of HGSOC in the platinum-sensitive and platinum-resistant space[3]
  - Safety and efficacy results from a Phase 1b study of UpRi in patients with platinum-resistant HGSOC have been presented[4]
- **Prevalence of NaPi2b-positive HGSOC tumors and NaPi2b expression over time in HGSOC has not been well characterized**
- Understanding the expression of NaPi2b over time and the effect of treatment on expression is critical to biomarker-targeted therapy

METHODS

Three Sets of HGSOC Tissue Samples Were Collected

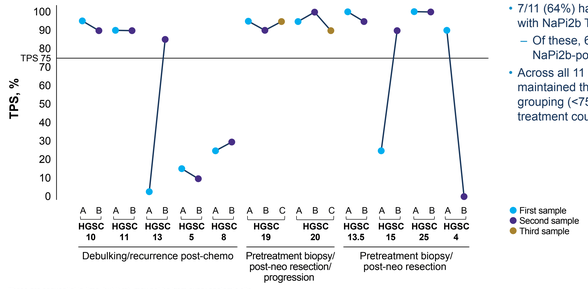
Longitudinal tissue series	Primary and synchronous metastatic paired samples	Fresh and archival samples
N=11 patients	**N=18 pairs**	**N=56 patients**
Samples were collected at multiple timepoints throughout disease course	Samples were collected synchronously from primary and metastatic lesions	Matched metachronous samples were obtained from patients in the Phase 1b dose expansion study of UpRi
Samples were obtained from Ovarian Cancer Research Center Tumor BioTrust Collection (RRID SCR_02287) at University of Pennsylvania and had well-annotated treatment history	Samples were procured from tissue banks	Freshly biopsied and/or archival tissue samples were collected from the UpRi Phase 1b study (NCT03319628)

- NaPi2b expression was assessed by QualTek Molecular Laboratories (Discovery Life Sciences) using an immunohistochemistry (IHC) Good Laboratory Practices assay and assigned a tumor proportion score (TPS)
  - In a separate retrospective analysis, TPS of ≥75 was shown to identify patients with a higher likelihood of response and was thus determined as the cutoff used to define "NaPi2b positive"[5]
  - Data has been presented in part previously at IGCS 2022[6,7]

RESULTS

LONGITUDINAL TISSUE SERIES[6,7]

NaPi2b Expression in Matched Samples Over Disease Course (N=11)



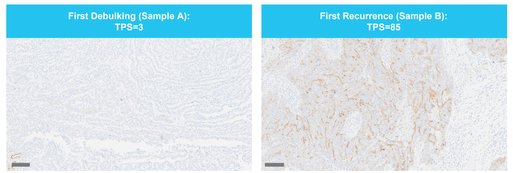
These are sequential in time, but "first" may not be from ovary anatomic site.

- 7/11 (64%) had an initial biopsy with NaPi2b TPS ≥75
  - Of these, 6/7 (86%) maintained NaPi2b-positive status
- Across all 11 patients, 8 (73%) maintained the same TPS grouping (<75 or ≥75) over their treatment course

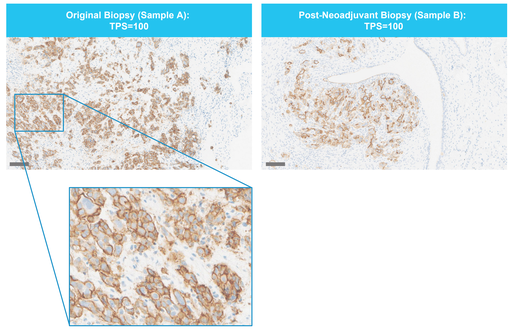
RESULTS (cont'd)

Representative IHC of Matched HGSOC Tissue Samples[6,7]

HGSC 13



HGSC 25



Higher power view of Sample A from HGSCD 25 showing TPS=100

Scale bars = 100 µm

SYNCHRONOUS PRIMARY/ METASTATIC PAIRS[6,7]

- NaPi2b expression between synchronous primary and metastatic tissue pairs had a concordance rate of 72%
  - 13/18 pairs (72%) had the same NaPi2b expression status (TPS ≥75 vs TPS <75) across primary and metastatic samples
  - 7/18 (39%) primary tumor samples were NaPi2b positive
  - 10/18 (56%) metastatic tumor samples were NaPi2b positive

FRESH VS ARCHIVAL TISSUE SAMPLES[6,7]

- Overall, 64% of samples (36/56) were deemed NaPi2b positive based on either fresh or archival tissue[4]
- The concordance between fresh and archival tissues was 75% (42/56)
  - 76% (22/29) maintained NaPi2b-positive status between archival and fresh tissues
  - 74% (20/27) maintained NaPi2b-negative status between archival and fresh tissues
- The concordance between archival and fresh tissues is not affected by the interval between archival and fresh tissue sample collection
  - 11 patients were NaPi2b positive based on archive samples that were aged <2 years; at fresh biopsy, 8 remained NaPi2b positive (73%)
  - 18 patients were NaPi2b positive based on archival samples that were aged ≥2 years; at fresh biopsy, 14 remained NaPi2b positive (78%)

NaPi2b Expression Concordance Between Fresh and Archival Tissues[6,7]

		Archival samples (N=56)		
		NaPi2b high (TPS ≥75)	NaPi2b low (TPS <75)	Total (archival samples)
Fresh samples (N=56)	NaPi2b high (TPS ≥75)	22 (39.3%)	7 (12.5%)	**29 (52%)**
	NaPi2b low (TPS <75)	7 (12.5%)	20 (35.7%)	**27 (48%)**
	Total (fresh samples)	**29 (52%)**	**27 (48%)**	

22/56 samples maintained high and 20/56 samples maintained low NaPi2b expression between fresh and archival samples for a concordance of 75% (42/56)

Kappa = 0.5 (0.27, 0.73, moderate agreement).
Percentages shown are based on a denominator of 56.

NaPi2b Expression Concordance Between Fresh and Archival Tissues Based on Timing of Archival Sample Collection

		Archival samples aged <2 years (n=29)		
		NaPi2b high (TPS ≥75)	NaPi2b low (TPS <75)	Total
Fresh samples	NaPi2b high (TPS ≥75)	8 (27.6%)	4 (13.8%)	**12 (41%)**
	NaPi2b low (TPS <75)	3 (10.3%)	14 (48.3%)	**17 (59%)**
	Total	**11 (38%)**	**18 (62%)**	

Total concordance: 76% (22/29)

Percentages shown are based on a denominator of 29.

		Archival samples aged ≥2 years (n=27)		
		NaPi2b high (TPS ≥75)	NaPi2b low (TPS <75)	Total
Fresh samples	NaPi2b high (TPS ≥75)	14 (51.9%)	3 (11.1%)	**17 (63%)**
	NaPi2b low (TPS <75)	4 (14.8%)	6 (22.2%)	**10 (37%)**
	Total	**18 (67%)**	**9 (33%)**	

Total concordance: 74% (20/27)

Percentages shown are based on a denominator of 27.

CONCLUSIONS[6,7]

- NaPi2b is a biomarker that appears to be highly expressed in the majority of HGSOC tumors **(59[8]–64%)**
- These assessments suggest that NaPi2b expression remains stable **over time**, **between sites**, and **throughout treatment**, with a concordance from **72–75%**
- Findings show high concordance between fresh and archival tissue samples, with no difference based on interval between sample collection, which **support the use of archival tissue for NaPi2b biomarker analysis**
- Analysis of NaPi2b expression in the UPLIFT trial will be presented in the future
- Overall, these findings support the rationale of NaPi2b testing early in the disease course and provide evidence that NaPi2b is a rational biomarker to consider for drug development in HGSOC

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ADDITIONAL INFORMATION

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ADC, antibody-drug conjugate; HGSOC, high-grade serous ovarian cancer; HGSC, high-grade serous carcinoma; IHC, immunohistochemistry; NaPi2b, sodium-dependent phosphate transport protein 2B; TPS, tumor proportion score; UpRi, upifitamab rilsodotin.

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