

MUC16 As a Therapeutic Target: Advancing Antibody-Drug Conjugates for Ovarian Cancer Treatment



ANNUAL MEETING
ON WOMEN'S CANCER

SAN JUAN, PR
APRIL 10-13, 2026

1544

David M. O'Malley¹; Michael J. Birrer²; Ursula A. Matulonis³; Kathleen N. Moore⁴; Fernanda B. Musa⁵; Maria M. Rubinstein⁶; Ritu Salani⁷; Dayana Delgado⁸; Lennart Langouche⁹; David Dornan⁹; Kathleen S. Keegan⁹; David J. Lennon⁹; Ashwini B. Pai⁹; Robert L. Coleman¹⁰

¹The Ohio State University and James Comprehensive Cancer Center, Columbus, OH, USA; ²University of Arkansas for Medical Sciences, Little Rock, AR, USA; ³Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; ⁴Stephenson Oklahoma Cancer Center, Oklahoma City, OK, USA; ⁵Providence-Swedish Cancer Institute, Seattle, WA, USA; ⁶Memorial Sloan Kettering Cancer Center, New York, NY, USA; ⁷University of California Los Angeles Health, Los Angeles, CA, USA; ⁸Tempus AI, Chicago, IL, USA; ⁹Whitehawk Therapeutics, Morristown, NJ, USA; ¹⁰Texas Oncology, The Woodlands, TX, USA

Objectives

The aims of this study were to quantify *MUC16* RNA expression across ovarian cancer histologic subtypes and in PROC versus PSOC high-grade serous carcinoma, and to compare *MUC16* expression with that of other therapeutic targets in late-stage development

Conclusions

- » *MUC16* mRNA expression was substantially higher than that of genes encoding other ADC targets that are in late-stage development for ovarian cancer
- » In high-grade serous ovarian carcinoma, *MUC16* expression remained high irrespective of platinum-sensitivity status
- » In high-grade serous ovarian carcinoma, *MUC16* defines an independent population, as suggested by the weak correlations in mRNA expression between *MUC16* and *FOLR1* (FRα), *ERBB2* (HER2), *VTCN1* (B7-H4), *CDH6*, *CLDN6*, and *PTK7*
 - This population may benefit from *MUC16*-targeted therapy due to uniquely high *MUC16* expression
- » These results support *MUC16* as a promising target for the treatment of ovarian cancer

REFERENCES

- Li H, et al. *Genes Dis.* 2025;13:101801.
- Moore KN, et al. *N Engl J Med.* 2023;389:2162-74.
- Colombo N, et al. Presented at ESMO Congress 2025. Abstract LBA3.
- Narayana RVL and Gupta R. *Oncogene.* 2025;44:2343-56.
- He J, et al. *Int J Gynecol Cancer.* 2025;35:10197-10.
- Kato M, et al. *Front Mol Med.* 2025;5:1661016.
- Giamougiannis P, et al. *Carcinogenesis.* 2021;42:327-43.
- Yang N, et al. *BMC Cancer.* 2025;25:294.

ACKNOWLEDGMENTS and DISCLOSURES

This study was sponsored by Whitehawk Therapeutics, Morristown, NJ, USA. Data generation and data analysis were provided by Lennart Langouche and Dayana Delgado of Tempus AI, Chicago, IL, USA. Medical writing support was provided by Farhana Burnett, PhD, CMPP, of Twist Medical, and funded by Whitehawk Therapeutics.

Corresponding author: David M. O'Malley (David.O'Malley@osumc.edu)

David M. O'Malley reports consulting/advisory roles for AbbVie, AstraZeneca, Corecept Therapeutics, DualityBio, GlaxoSmithKline, GOG Foundation, Merck, Novocure, Pfizer, Regeneron, Sutro Biopharma, Verastem, and Zentalis; and institutional research funding from AbbVie, AbbVie/Stemcentrx, Acerta Pharma, Advaxis, Agenus, Ajinomoto, Alkermes, Amgen, Aravive, Arcus Biosciences, Array BioPharma, AstraZeneca, Ayala, Bayer, BBI Healthcare, BeiGene USA, Boston Biomedical, Bristol Myers Squibb, Cerulean Pharma, Clovis Oncology, Daiichi Sankyo, Deciphera Pharma, Eisai, EMD Serono, Ergomed, Exelixis, Genentech/Roche, Genmab, GlaxoSmithKline, GOG Foundation, Immunogen, Incyte, Invance Biotherapeutics, Karyopharm Therapeutics, Leap Therapeutics, Ludwig Institute for Cancer Research, Merck, Mersana, Nektar, Nikang, Novartis, NovoCure, OncoQuest, OSI, PF Argemum IP Holdings, Pfizer, PharmaMar, Precision Therapeutics, PTC Therapeutics, Rain Therapeutics, Regeneron, Roche, Sanofi, SeaGen, Shasqi, Sumitomo Dainippon Pharma Oncology Inc, Sutro Biopharma, Tesaro, Verastem, Xynomic, and Zentalis.

For disclosures of co-authors, please refer to the abstract.

Background

- » High-grade serous ovarian carcinoma is an aggressive subtype of ovarian cancer with poor prognosis; it is also the most common subtype of ovarian cancer—accounting for ~70% of cases¹
- » Among patients with ovarian cancer who are treated with platinum-based chemotherapy, ~70% will relapse and develop platinum-refractory/resistant ovarian cancer (PROC)¹
- » Platinum-resistant tumors are currently defined as those that progressed during or within 6 months of completion of platinum-based chemotherapy. Expected response rates in PROC are improving with recent approvals of mirevetuximab (42% overall response rate [ORR]) in folate receptor alpha (FRα)-high tumors² and weekly paclitaxel/bevacizumab/pembrolizumab in PD-L1+ tumors (ORR 53%).³ For tumors without these biomarkers, the ORR with cytotoxic chemotherapy ranges from 10% to 15% defining an area of high unmet need¹
- » Antibody-drug conjugates (ADCs) represent a promising therapeutic strategy, with treatments in late-stage development directed at several targets; these include mucin 16 (*MUC16*), sodium-dependent phosphate transport protein 2B (*NaPi2b*), FRα, human epidermal growth factor receptor 2 (HER2), cadherin 6 (*CDH6*), B7-H4, trophoblast cell-surface antigen 2 (*TROP2*), claudin 6 (*CLDN6*), and protein tyrosine kinase 7 (*PTK7*)⁴⁻⁶

- » *MUC16* is an attractive target due to its high expression in ovarian tumors versus normal tissue and its association with tumor proliferation and disease progression^{7,8}
 - Data from public databases demonstrate that *MUC16* RNA expression and *MUC16* protein abundance are correlated, and both are significantly increased in ovarian tumor tissue relative to normal tissue⁸
- » HWK-016 is an investigational, next-generation ADC that targets membrane-bound *MUC16*. It comprises a monoclonal antibody conjugated to a novel topoisomerase I inhibitor via a stable, cleavable linker that enhances intracellular delivery and limits systemic exposure

Methods

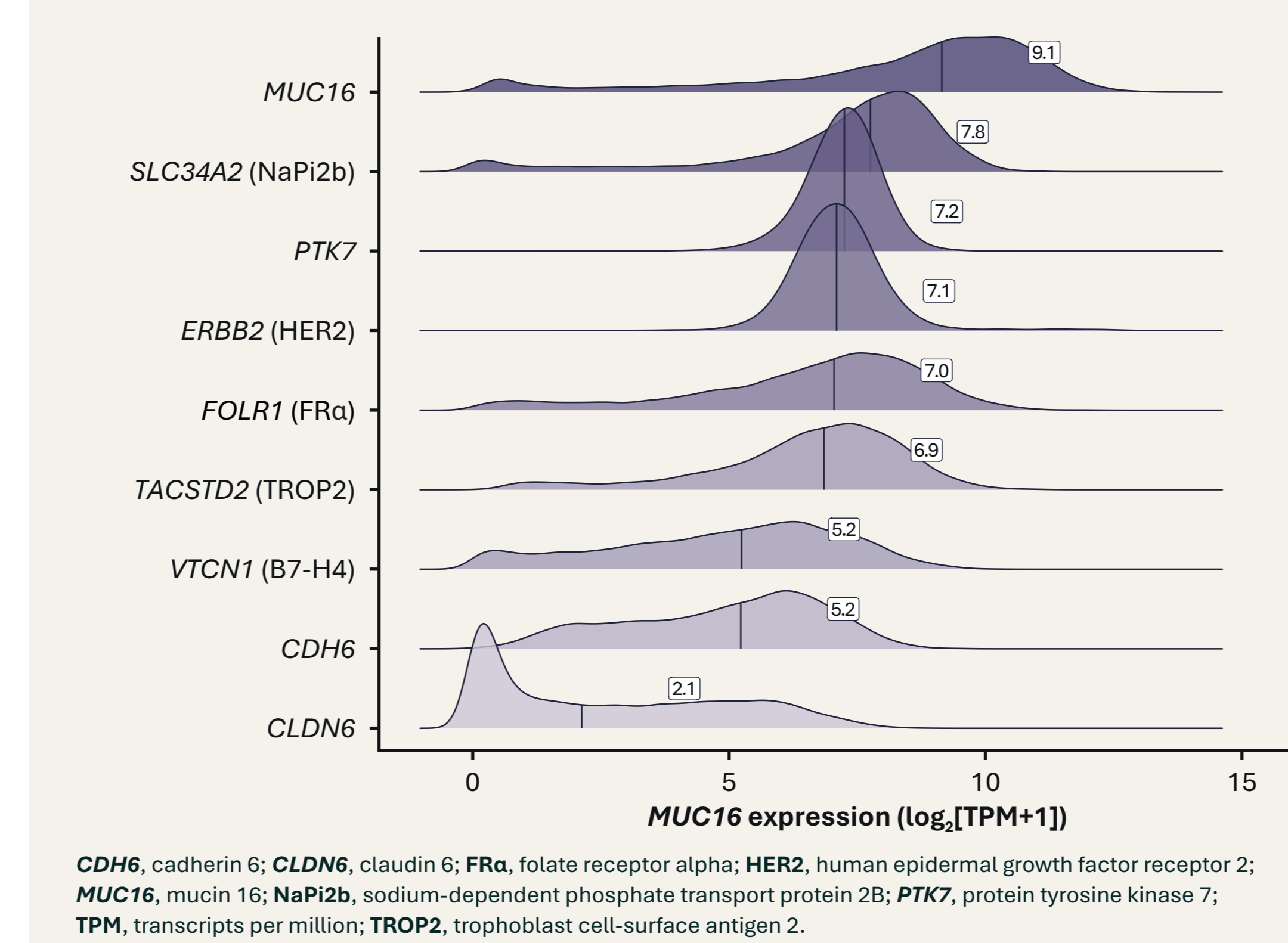
- » RNA-sequencing data from a real-world database (Tempus AI, Inc., Chicago, IL, USA) were used to explore gene expression across ovarian cancer subtypes and in PROC versus platinum-sensitive ovarian cancer (PSOC)
 - Platinum-refractory/resistant disease was defined as any progression event (progression, recurrence, metastasis, or death) or proxy (start of non-platinum/non-maintenance line) within 6 months of starting (refractory) or ending (resistant) platinum therapy. Platinum-sensitive disease required no such event or proxy within 6 months of ending platinum therapy
 - Gene-expression data were derived from a whole-transcriptome RNA-sequencing panel (Tempus xR) capturing 20,000 genes
- » Median mRNA expression was reported as $\log_2(\text{transcripts per million [TPM]}+1)$
- » Co-expression of *MUC16* mRNA with other ADC targets was assessed using Spearman's correlation

Results

MUC16 EXPRESSION IS HIGHER THAN THAT OF OTHER THERAPEUTIC TARGETS IN OVARIAN CANCER

- » Gene expression in nine histologic subtypes of ovarian cancer was analyzed using 7235 tumor samples from 6906 patients. Tumor samples were considered unique, even when derived from the same patient
- » Of the tested biomarkers, *MUC16* showed the highest median expression across samples with $\log_2(\text{TPM}+1)$ of 9.1, which represented 2- to >100-fold higher median expression than other biomarkers (*SLC34A2* [*NaPi2b*], 3-fold; *PTK7*, 4-fold; *ERBB2* [HER2], 4-fold; *FOLR1* [FRα], 4-fold; *TACSTD2* [TROP2], 5-fold; *VTCN1* [B7-H4], 15-fold; *CDH6*, 15-fold; *CLDN6*, 126-fold) (Figure 1)
 - The distribution of *MUC16* expression mirrored that of *SLC34A2* (*NaPi2b*), *FOLR1* (FRα), and *TACSTD2* (TROP2)

FIGURE 1. *MUC16* mRNA Expression Relative to Other Therapeutic Targets

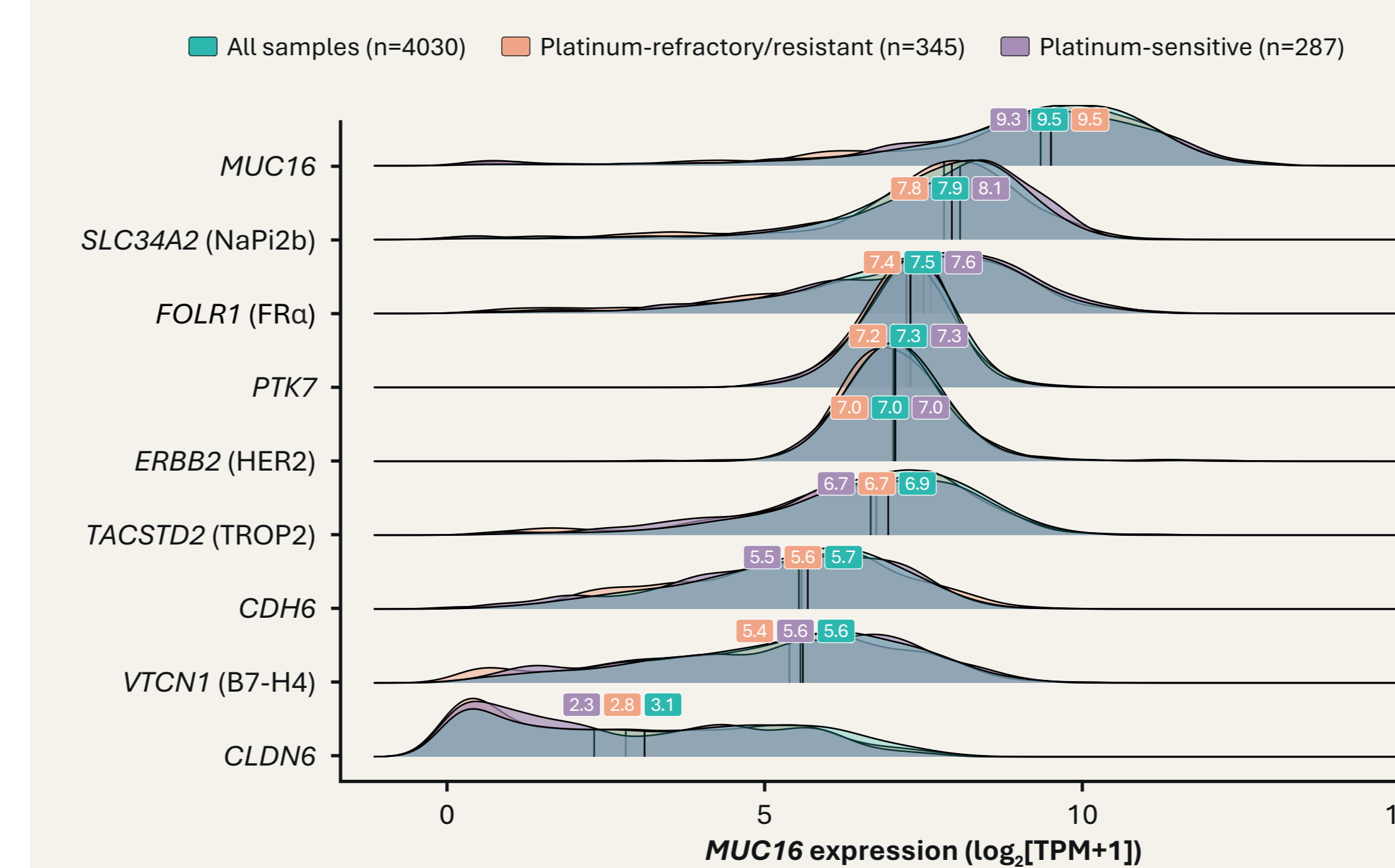


CDH6, cadherin 6; *CLDN6*, claudin 6; *FRα*, folate receptor alpha; *HER2*, human epidermal growth factor receptor 2; *MUC16*, mucin 16; *NaPi2b*, sodium-dependent phosphate transport protein 2B; *PTK7*, protein tyrosine kinase 7; *TPM*, transcripts per million; *TROP2*, trophoblast cell-surface antigen 2.

MUC16 MRNA EXPRESSION REMAINS HIGH IN HIGH-GRADE SEROUS OVARIAN CARCINOMA IRRESPECTIVE OF PLATINUM-SENSITIVITY STATUS

- » In high-grade serous ovarian carcinoma tumor samples, median *MUC16* mRNA expression was high overall (9.5 [n=4030]) and in both PROC (9.5 [n=345]) and PSOC (9.3 [n=287]), and it remained higher than all other tested biomarkers when stratified by platinum-sensitivity status (Figure 2)
 - In PROC tumor samples, *MUC16* expression was 3- to 104-fold higher than that of *SLC34A2* (*NaPi2b*; 3-fold), *FOLR1* (FRα; 4-fold), *PTK7* (5-fold), *ERBB2* (HER2; 6-fold), *TACSTD2* (TROP2; 7-fold), *CDH6* (15-fold), *VTCN1* (B7-H4; 17-fold), and *CLDN6* (104-fold)
 - In PSOC tumor samples, *MUC16* expression was 2- to 128-fold higher than that of *SLC34A2* (*NaPi2b*; 2-fold), *FOLR1* (FRα; 3-fold), *PTK7* (4-fold), *ERBB2* (HER2; 5-fold), *TACSTD2* (TROP2; 6-fold), *CDH6* (14-fold), *VTCN1* (B7-H4; 13-fold), and *CLDN6* (128-fold)

FIGURE 2. Gene-Expression Distributions in High-Grade Serous Ovarian Carcinoma Overall and by Platinum-Sensitivity Status

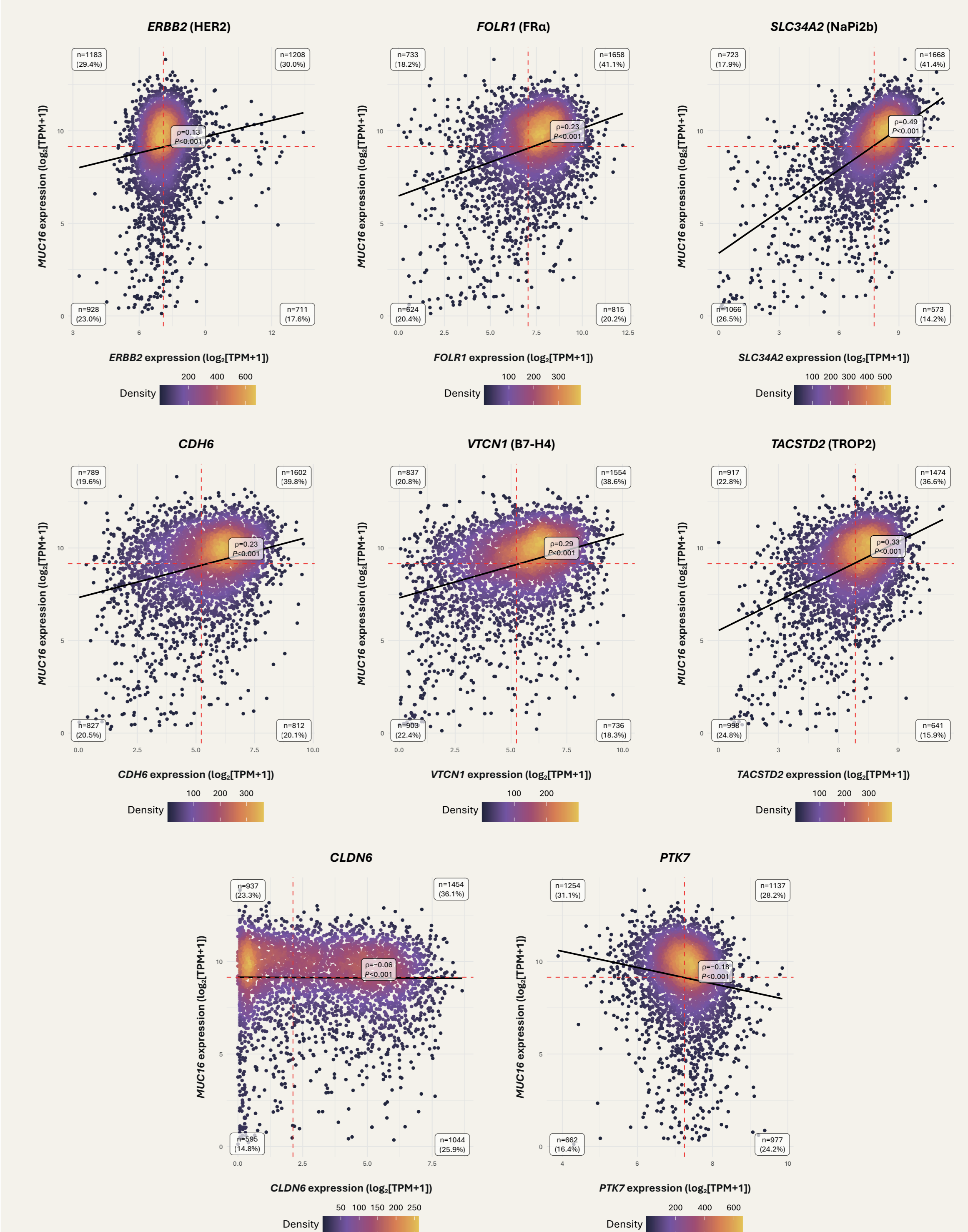


CDH6, cadherin 6; *CLDN6*, claudin 6; *FRα*, folate receptor alpha; *HER2*, human epidermal growth factor receptor 2; *MUC16*, mucin 16; *NaPi2b*, sodium-dependent phosphate transport protein 2B; *PTK7*, protein tyrosine kinase 7; *TPM*, transcripts per million; *TROP2*, trophoblast cell-surface antigen 2.

MUC16 DEFINES AN INDEPENDENT POPULATION THAT MAY BENEFIT FROM *MUC16*-TARGETED THERAPY DUE TO UNIQUELY HIGH *MUC16* EXPRESSION

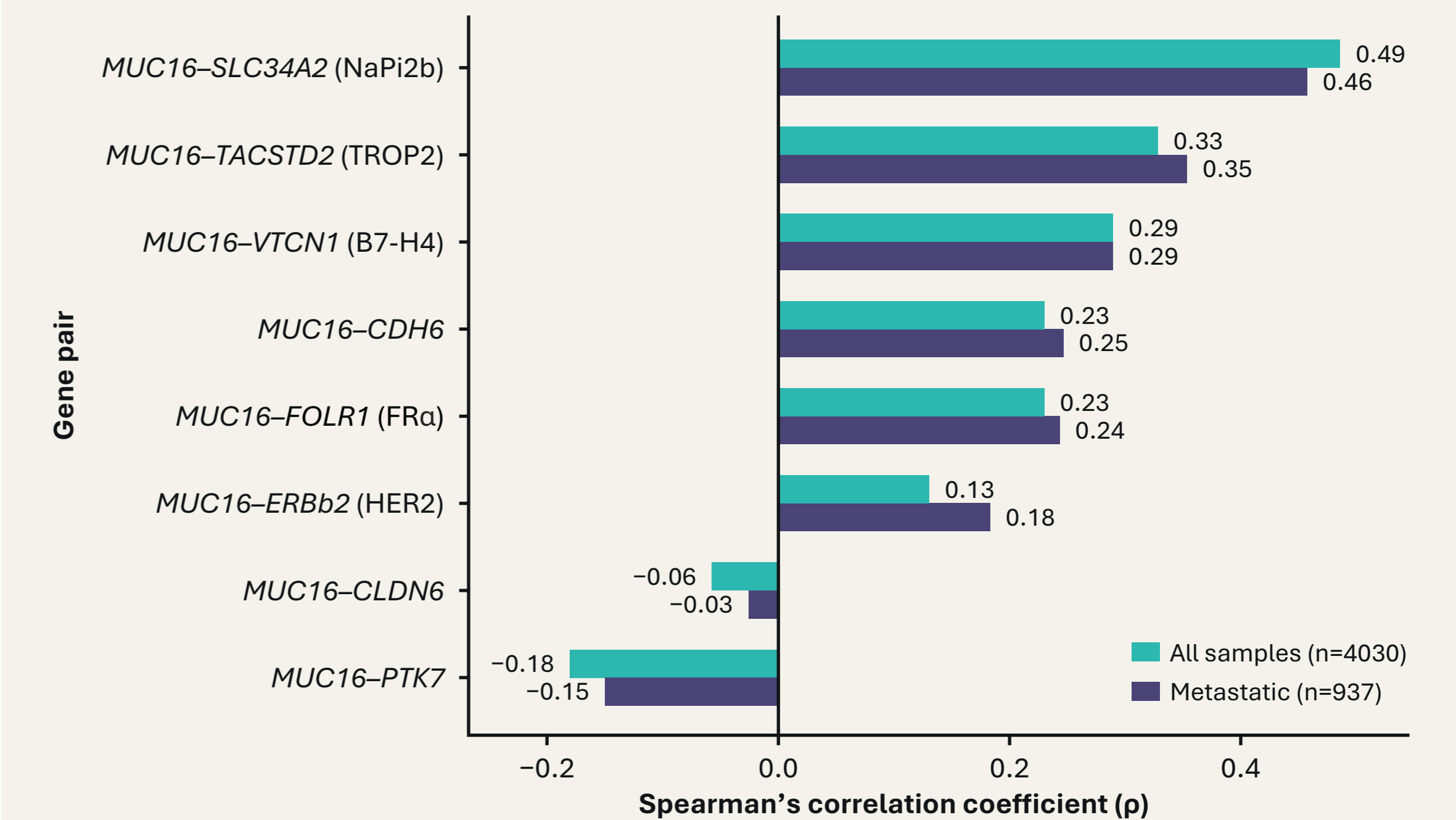
- » In high-grade serous ovarian carcinoma tumor samples, *MUC16* expression was weakly correlated with expression of *ERBB2* (HER2; Spearman's rho [ρ]=0.13), *FOLR1* (FRα; ρ=0.23), *CDH6* (ρ=0.23), *VTCN1* (B7-H4; ρ=0.29), *CLDN6* (ρ=-0.06), and *PTK7* (ρ=-0.18) (Figure 3)
 - *MUC16* mRNA showed moderate co-expression with *SLC34A2* (*NaPi2b*; ρ=0.49) and *TACSTD2* (TROP2; ρ=0.33)
- » Correlations in gene expression were similar when limited to metastatic tumor samples (n=937) (Figure 4)

FIGURE 3. Co-Expression of *MUC16* mRNA With Other Therapeutic Targets in High-Grade Serous Ovarian Carcinoma



CDH6, cadherin 6; *CLDN6*, claudin 6; *FRα*, folate receptor alpha; *HER2*, human epidermal growth factor receptor 2; *MUC16*, mucin 16; *NaPi2b*, sodium-dependent phosphate transport protein 2B; *PTK7*, protein tyrosine kinase 7; ρ, Spearman's rho; *TPM*, transcripts per million; *TROP2*, trophoblast cell-surface antigen 2.

FIGURE 4. Co-Expression of *MUC16* mRNA With Other Therapeutic Targets in High-Grade Serous Ovarian Carcinoma: Correlation Coefficients Overall and in Metastatic Tumor Samples



CDH6, cadherin 6; *CLDN6*, claudin 6; *FRα*, folate receptor alpha; *HER2*, human epidermal growth factor receptor 2; *MUC16*, mucin 16; *NaPi2b*, sodium-dependent phosphate transport protein 2B; *TROP2*, trophoblast cell-surface antigen 2.