

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

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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* (FR α), *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

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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 FR α alpha high tumors)² and weekly paclitaxel/bevacizumab/pembrolizumab in PDL1+ 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*), folate receptor alpha (FR α), 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 the novel topoisomerase I inhibitor CPT116 via a stable, cleavable linker that enhances intracellular delivery and limits systemic exposure

Methods

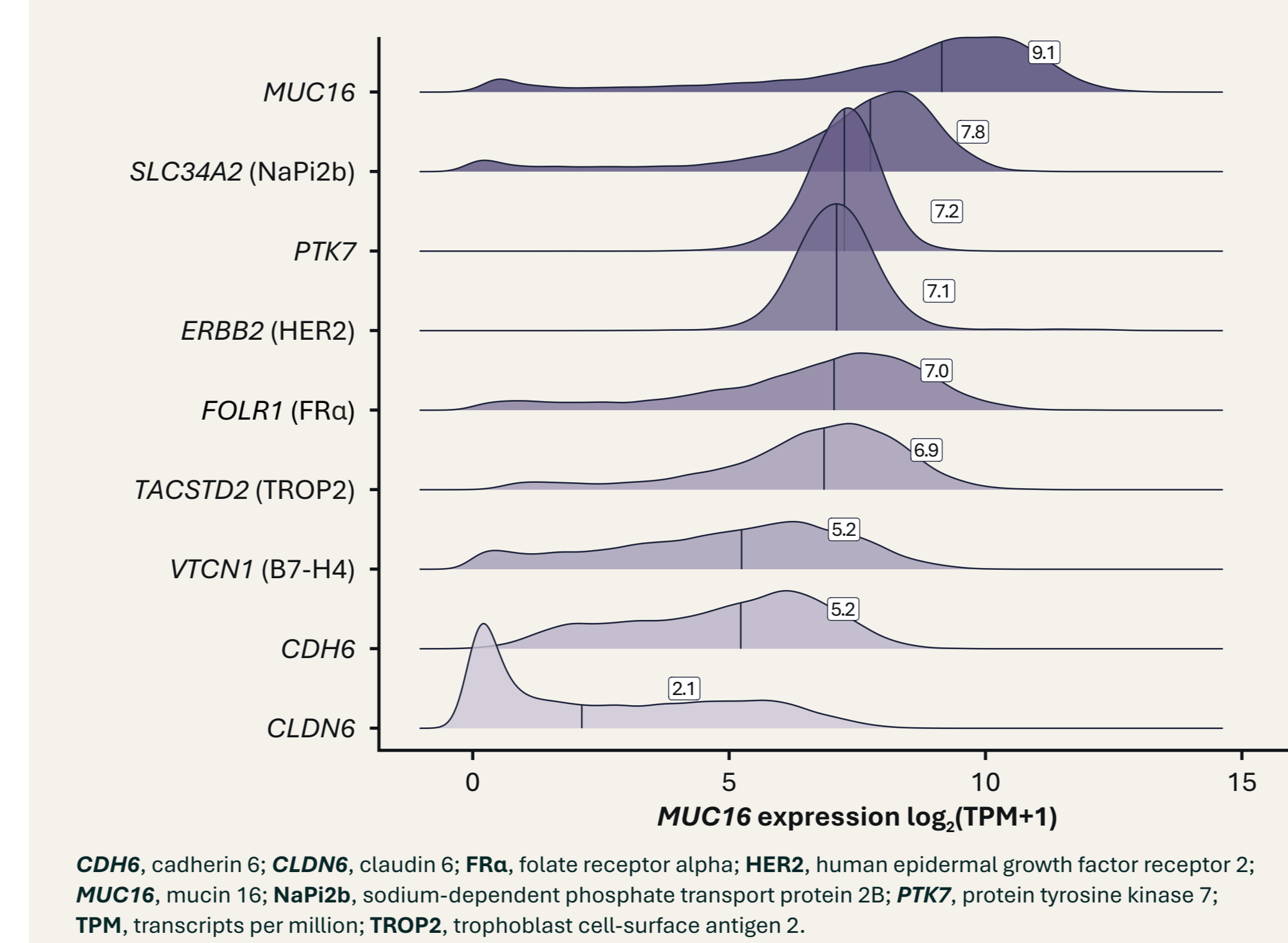
- » RNA-sequencing data from a real-world database (Tempus AI, Inc., Chicago, IL, USA) were utilized to explore gene expression across histologic subtypes of ovarian cancer and in PROC versus PSOC
- Platinum-refractory/resistant disease was defined as any progression event (progression, recurrence, metastasis, 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* [FR α], 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* (FR α), and *TACSTD2* (TROP2)

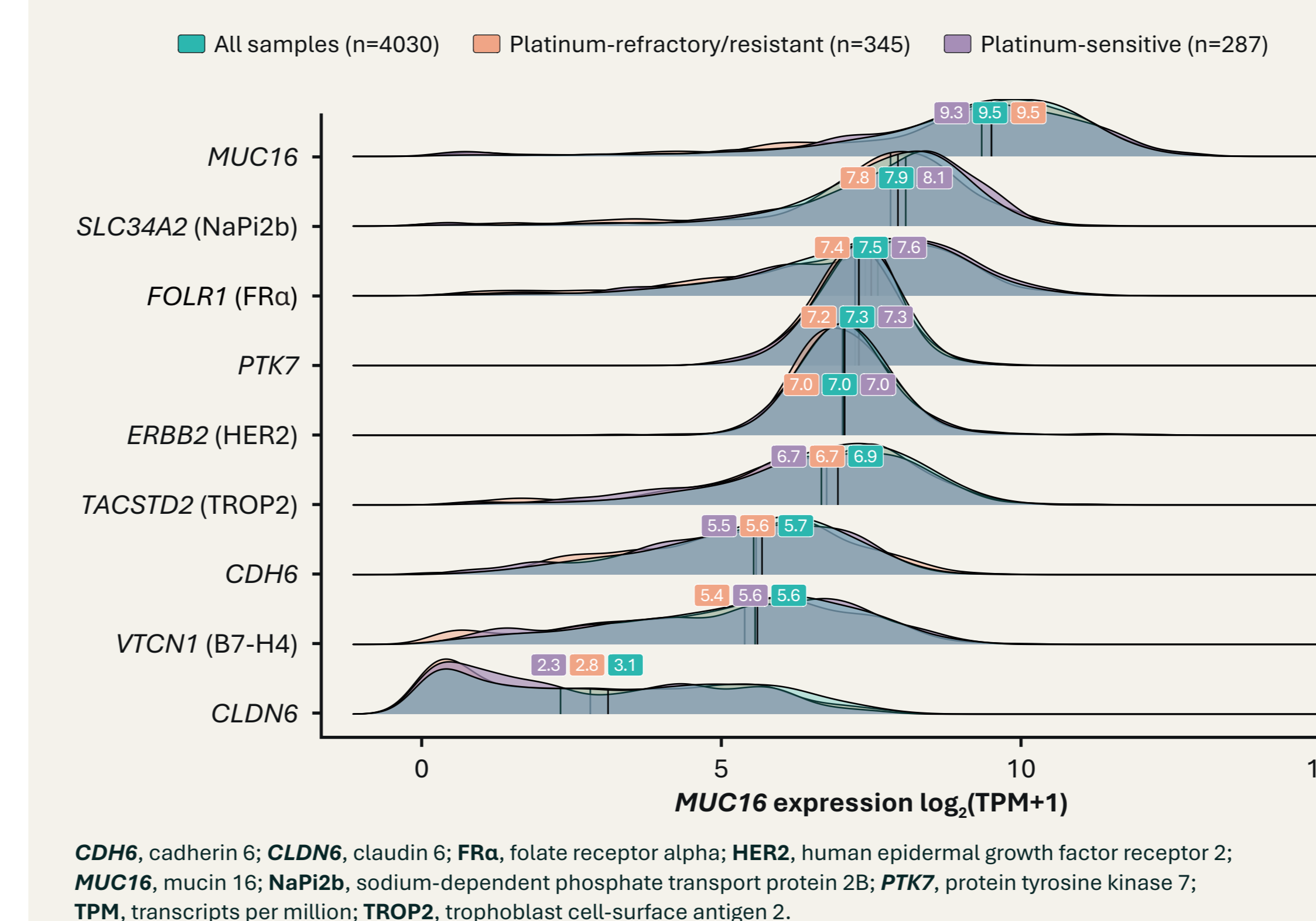
FIGURE 1. *MUC16* mRNA Expression Relative to Other Therapeutic Targets



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* (FR α ; 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* (FR α ; 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



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* (FR α ; 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

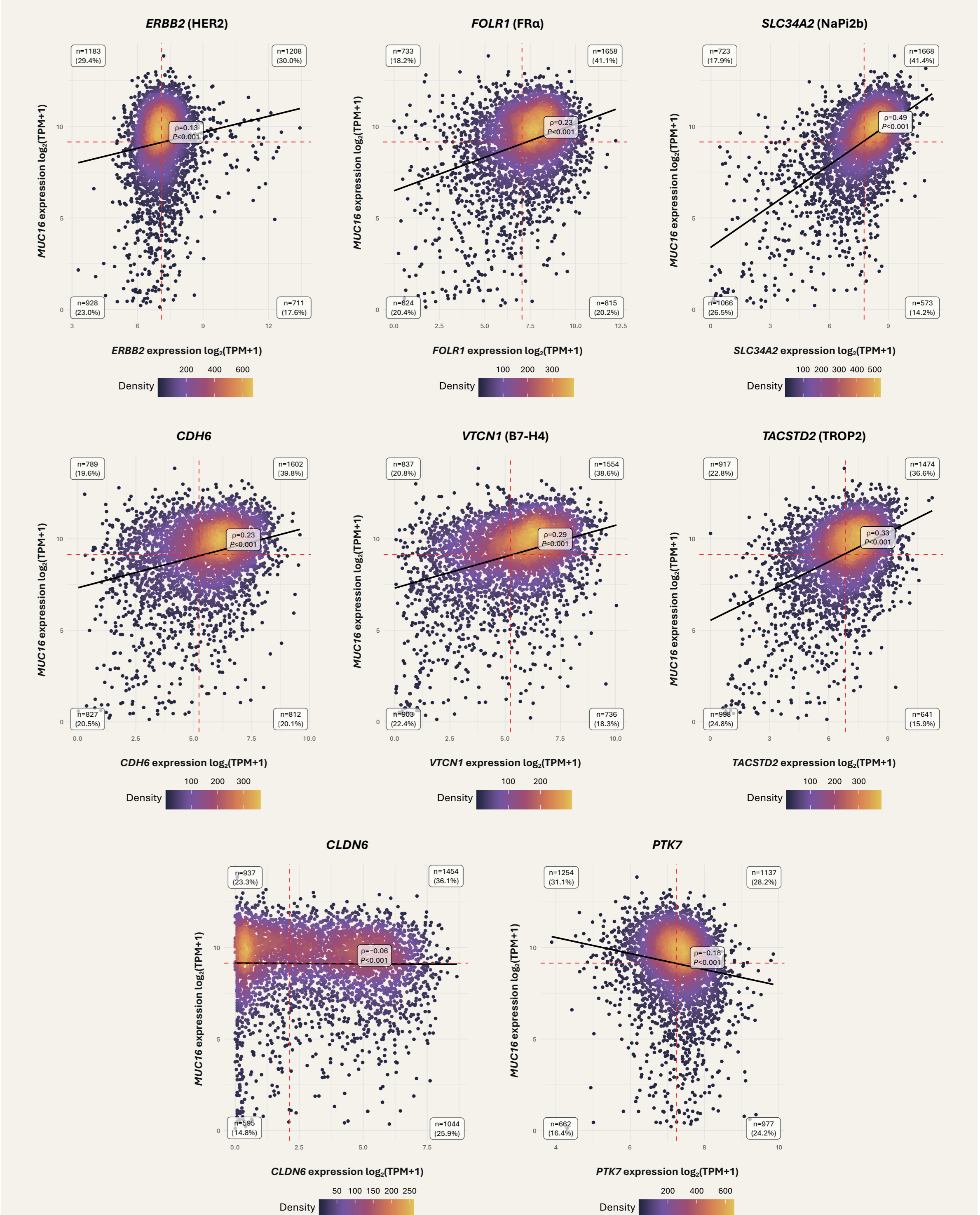


FIGURE 4. Co-Expression of *MUC16* mRNA With Other Therapeutic Targets in High-Grade Serous Ovarian Carcinoma: Correlation Coefficients Overall and in Metastatic Tumor Samples

